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Mary Smith
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SUMMARY

- Induction treatment with infliximab, adalimumab, golimumab, vedolizumab or tofacitinib improves quality of life compared to placebo. Evidence on maintenance therapy is sparse and uncertain. Head-to-head comparisons could enhance confidence in conclusions about differences between drugs in terms of HRQL. – Systematic Review 2018 (23)
- Trials involving direct head to head comparisons of biologics would help determine which biologics provide optimum benefit for HRQL. – Cochrane Database of Systematic Reviews 2015 (77)
- Sample size calculations suggest that adequately powered head-to-head comparative efficacy trials would require greater than 3000 patients. (82)

Comparisons between Infliximab and Ustekinumab

- Cost-Effectiveness Comparison of Ustekinumab, Infliximab, or Adalimumab for the Treatment of Moderate-Severe Crohn’s Disease in Biologic-Naïve Patients. (10)
- Indirect comparisons suggest that infliximab or adalimumab may be preferred first-line agents, and ustekinumab a preferred second-line agent, for induction of remission in patients with moderate-severe CD. Head-to-head trials are warranted. (27)
- Ustekinumab for Treating Moderately to Severely Active Crohn's Disease after Prior Therapy: An Evidence Review Group Perspective of a NICE Single Technology Appraisal.(33)
- Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. (85)

**Comparisons between other drugs**
- Infliximab / Etrolizumab (11)
- Infliximab / Conventional Therapy (14)
- Infliximab / Tacrolimus (22), (45)
- Infliximab / Ciclosporin (37), (63), (66), (70), (71), (97), (98), (105)
- Infliximab / Laparoscopic ileocaecal resection (43)
- Infliximab / Adalimumab (52), (55), (56), (58), (61), (65), (69), (73), (80), (83), (86), (87), (90), (92), (93)
- Infliximab / Golimumab (52), (55), (61), (65), (73), (80)
- Infliximab / Vedolizumab (52), (55), (58), (65)
- Infliximab / Combination Therapy (79), (84), (91), (113)
- Infliximab / Certolizumab (82), (92)
- Infliximab / Corticosteroids (104)
- Infliximab / Azathioprine (113)
- Ustekinumab / Vedolizumab (19), (36)
- Vedolizumab, Tofacitinib (15)

**Genetic Markers**
- Genetic Markers Predict Primary Nonresponse and Durable Response to Anti-Tumor Necrosis Factor Therapy in Ulcerative Colitis. (30)
- Genetic Markers Predict Primary Non-Response and Durable Response to Anti-TNF Biologic Therapies in Crohn's Disease. (54)
- Current and future role of biomarkers in Crohn's disease risk assessment and treatment. (107)

**SEARCH RESULTS**

**NICE GUIDANCE & other guidelines**

Crohn’s Disease Management NG 129

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

ACG Clinical guideline: management of Crohn’s Disease

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1. Medical and surgical management of pediatric perianal crohn's disease: A systematic review.
**Author(s):** Forsdick, Victoria K; Tan Tanny, Sharman P; King, Sebastian K
**Source:** Journal of pediatric surgery; Dec 2019; vol. 54 (no. 12); p. 2554-2558
**Publication Date:** Dec 2019
**Publication Type(s):** Journal Article Systematic Review
BACKGROUND The timely management of pediatric Crohn’s disease (CD), and specifically perianal CD, is important owing to the possible adverse effects on growth, development, and quality of life. Perianal involvement is increasingly common, with up to 62% of pediatric CD patients affected. Presently, literature addressing the management of perianal CD has focused primarily on adults, with findings that cannot always be extrapolated to the pediatric population. We aimed to review the rates of healing, recurrence, and need for surgical intervention in perianal CD to provide evidence-based recommendations for the ideal management in children. 

METHOD We conducted a systematic review of CENTRAL, PubMed, Medline, and EMBASE databases (January 1997-December 2017) in accordance with PRISMA. Two independent reviewers performed data extraction. 

RESULT Ten studies met the inclusion criteria with a combined total of 538 patients. Median study population size was 17 (range 7-276), with a median age at intervention of 13.9 years (range 1-18). Seton placement allowed complete healing in 28.6% of children. Similar results (28.5%) were seen in children undergoing fecal diversion. One study demonstrated complete resolution of fistulizing disease in 70% of children treated with infliximab (IFX). One quarter of patients treated with IFX required further surgical intervention for disease control. Recurrence occurred most frequently in children undergoing Seton placement alone (5/14, 35.7%), compared with IFX (46/197, 23.4%) and combination therapy (12/276, 4.3%). 

CONCLUSION In the pediatric population, a combination of medical and surgical treatment is required to control perianal CD, with fewer side effects. 

LEVEL OF EVIDENCE Level II. 

Database: Medline

2. An updated systematic review and meta-analysis about the safety and efficacy of infliximab biosimilar, CT-P13, for patients with inflammatory bowel disease. 

Author(s): Ebada, Mahmoud Ahmed; Elmatboly, Abdelmagid M; Ali, Ahmed Said; Ibrahim, Ahmed Mohamed; Fayed, Notila; Faisal, Ahmed Faisal; Alkanj, Souad 

Source: International journal of colorectal disease; Oct 2019; vol. 34 (no. 10); p. 1633-1652 

Publication Date: Oct 2019 

Publication Type(s): Meta-analysis Journal Article Systematic Review 

PubMedID: 31492986 

Abstract: OBJECTIVE We aimed to evaluate the efficacy and safety of infliximab biosimilar, CT-P13, for patients with inflammatory bowel disease. METHODS We searched PubMed, Scopus, Ovid, and Web of Science for relevant clinical trials discussing CT-P31 administration for IBD patients either naïve to biological therapy or switched from IFX therapy. Data of the rates of clinical response, clinical remission, and adverse events were extracted and pooled in a random effect model meta-analysis using CMA version 2. RESULT Thirty-two studies with a total of 3464 IBD patients treated with CT-P13 were identified. The pooled rates of clinical response among Crohn’s disease (CD) and ulcerative colitis (UC) at 8-14 weeks were 0.81 (95% CI = 0.72 to 0.87) and 0.68 (95% CI = 0.63 to 0.72), respectively, and at 48-63 weeks were 0.69 (95% CI = 0.48 to 0.85) and 0.54 (95% CI = 0.45 to 0.63) respectively. After switching from IFX to CT-P13, the pooled rates of sustained clinical response among CD and UC at 30-32 weeks were 0.84 (95% CI = 0.57 to 0.96) and 0.96 (95% CI = 0.58 to 0.99), respectively, and at 48-63 weeks were 0.51 (95% CI = 0.22 to 0.79) and 0.83 (95% CI = 0.19 to 0.99) respectively. Moreover, adverse events were reported (CD = 0.10, 95% CI 0.04 to 0.22; UC = 0.18, 95% CI 0.05 to 0.15). CONCLUSION CT-P13 is effective and well tolerated in short and long-term periods. Switching to CT-P13 is recommended for the management of IBD. 

Database: Medline
3. Effects of Ustekinumab on Histologic Disease Activity in Patients With Crohn's Disease.

**Author(s):** Li, Katherine; Friedman, Joshua R; Chan, Daphne; Pollack, Paul; Yang, Feifei; Jacobstein, Douglas; Brodmerkel, Carrie; Gasink, Christopher; Feagan, Brian G; Sandborn, William J; Rutgeerts, Paul; De Hertogh, Gert

**Source:** Gastroenterology; Oct 2019; vol. 157 (no. 4); p. 1019

**Publication Date:** Oct 2019

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Multicenter Study Journal Article Clinical Trial, Phase Iii

**PubMedID:** 31279870

Available at Gastroenterology - from Unpaywall

**Abstract:** BACKGROUND & AIMSAAlthough ustekinumab is an effective therapy for moderate to severe Crohn's disease (CD), its effects on the microscopic manifestations of CD are unknown. METHODS We evaluated the effects of ustekinumab on histologic CD activity in an analysis of data from 251 participants in phase 3 induction and maintenance studies. Two endoscopic biopsy samples were collected at weeks 0, 8, and 44 from the ileum, splenic flexure, and rectum (18 biopsy samples from each patient). Histologic activity was assessed based on global histology activity scores (GHASs). RESULTS At week 8, the mean GHAS was significantly reduced after ustekinumab induction treatment (from 10.4 ± 7.0 to 7.1 ± 5.9; P < .001) but not in patients who received placebo (from 9.2 ± 6.4 to 7.8 ± 6.2). At week 44 in the randomized maintenance therapy population, the mean GHAS remained reduced from week 8 in patients who received subcutaneous ustekinumab (90 mg every 8 weeks; from 7.4 ± 7.7 to 6.1 ± 4.7) but not every 12 weeks (from 7.1 ± 6.2 to 5.2 ± 4.2; P < .0001) but not in those given ustekinumab every 12 weeks (from 6.1 ± 5.7 to 7.2 ± 5.1) or placebo (from 8.2 ± 4.2 to 8.9 ± 6.8). A significantly greater proportion of patients achieved histologic response (≥50% decrease in GHAS from baseline) at week 44 if they received ustekinumab every 8 weeks (50% in the randomized maintenance population and 54% in the pooled maintenance population) compared with every 12 weeks (17% and 39% in the randomized and pooled populations, respectively) or placebo (0% and 22% in the randomized and pooled populations, respectively) (P = .0137 for every 8 weeks vs placebo and P = .3529 for every 12 weeks vs placebo in the randomized population; P = .0168 for every 8 weeks vs placebo and P = .0369 for every 12 weeks vs placebo in the pooled population). Regional and overall mean GHASs correlated with the simple endoscopic score for CD (r = .6255, P < .0001). Multivariate analysis found an association between histologic improvement and endoscopic or histologic burden at baseline. CONCLUSIONS In an analysis of data from participants in phase 3 induction and maintenance trials, we found histologic improvement in a greater proportion of patients given ustekinumab vs placebo. The largest improvements occurred in patients who received ustekinumab maintenance therapy every 8 weeks. ClinicalTrials.gov nos. NCT01369329, NCT01369342, and NCT01369355.

**Database:** Medline


**Author(s):** Dulai, Parambir S; Osterman, Mark T; Lasch, Karen; Cao, Charlie; Riaz, Faisal; Sandborn, William J

**Source:** Digestive diseases and sciences; Sep 2019; vol. 64 (no. 9); p. 2478-2488

**Publication Date:** Sep 2019
BACKGROUND AND AIMSTreatment pathways for ulcerative colitis (UC) and Crohn's disease (CD) are shifting to a more individualized, risk-stratified approach. The perception is that insurance policies may not have implemented this paradigm shift, particularly regarding access to newer agents. We evaluated patient access to advanced therapies by analyzing policy information from the Managed Markets Insight and Technology database.

METHODSCoverage status as of December 2018 for all US lives was queried for adalimumab, infliximab, infliximab-dyyb, tofacitinib, ustekinumab, and vedolizumab by indication (UC and/or CD) and medical or pharmacy coverage benefit. Coverage status was classified by the number of biologic steps before access to specified drug as "No Biologic," "1 Prior Biologic," "2+ Prior Biologics," "Not Covered." Unknown lives were excluded from the analyses.

RESULTSCoverage analysis was available for approximately 302 million lives under each medical and pharmacy benefit. Our analysis indicates that approximately half of covered lives had access to all agents (except tofacitinib) as first-line therapy; two-thirds had access after one biologic exposure. Among newer agents, vedolizumab had the widest coverage. For indications of UC and CD, 81% of known lives had access to vedolizumab with no prior biologic exposure required ("No Biologic"), 95% after "No Biologic" + "1 prior Biologic." Geographic variations were identified for coverage patterns.

CONCLUSIONSThis US-based healthcare policy analysis points to an increased access to advanced therapies for UC and CD. An individualized, risk-stratified treatment approach integrating advanced therapies, including those recently approved, into treatment pathways for UC and CD is feasible.
[95% confidence interval: 1.34, 2.91; p <0.001]) compared with enrolment into the conventional therapy group. No notable risk differences between groups were identified for haematological disorder, autoimmune disorder, malignancy/lymphoproliferative disorder, hepatobiliary disorder or fatality. **CONCLUSIONS** UC patients treated with infliximab had higher risk for serious infection, compared with conventional therapies. No new safety concerns were observed with originator infliximab in the OPUS registry. [ClinicalTrials.gov: NCT00705484].

**Database:** Medline

**6. Analytical and clinical performance evaluation of two POC tests for therapeutic drug monitoring of infliximab.**

**Author(s):** Van den Bossche, Dorien; De Smet, Dieter; Debrabandere, Johan; Vanpoucke, Hilde

**Source:** Clinical chemistry and laboratory medicine; May 2019; vol. 57 (no. 6); p. 856-863

**Publication Date:** May 2019

**Publication Type(s):** Journal Article

**PubMedID:** 30838834

**Abstract:** Background Infliximab (IFX) is an effective therapy in patients with inflammatory bowel disease. Serum IFX trough concentrations correlate well with clinical, biological and endoscopic outcomes. Therefore, therapeutic drug monitoring (TDM) of infliximab is useful for dose optimization and prevention of secondary treatment failure. In the present study, analytical and clinical performance of two point-of-care (POC) tests, RIDA® QUICK IFX Monitoring assay (R-biopharm) and Quantum Blue® Infliximab assay (Bühlmann), have been evaluated and compared to our established enzyme-linked immunosorbent assay (ELISA) (apDia IFX ELISA). Methods Analytical performance was assessed according to the CLSI EP5-A2 protocol using the manufacturer’s kit controls and different serial dilution series. Method comparison with our established ELISA was done using a wide range of consecutive patient samples (n=180). Clinical concordance was evaluated by categorization based on well-known therapeutic cut-off points (3-7 μg/mL). Results The analytical performance of both POC tests was inferior to the established ELISA, but acceptable based on the manufacturer’s quality claims. Eight-point serial dilution confirmed the analytical performance data in the low-level measuring range. Eleven-point serial dilution demonstrated linearity for both POC tests over the studied concentration range. Method comparison with the ELISA showed significant negative proportional bias for the RIDA® QUICK IFX Monitoring assay. However, good correlation and clinical concordance were shown. Quantum Blue® Infliximab assay showed a significant positive proportional and a negative systematic bias in comparison with the ELISA, resulting in overestimation of IFX levels with impact on clinical concordance data. Conclusions Both POC tests have their own specific benefits and drawbacks but are suitable for therapeutic drug monitoring of IFX. However, long-term monitoring of IFX trough levels requires measurement of IFX concentrations with the same assay.

**Database:** Medline

**7. Treatment sequence network meta-analysis in Crohn's disease: a methodological case study.**

**Author(s):** Varu, Abhishek; Wilson, Florence R; Dyrda, Peter; Hazel, Maureen; Hutton, Brian; Cameron, Chris

**Source:** Current medical research and opinion; May 2019; vol. 35 (no. 5); p. 733-756

**Publication Date:** May 2019

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article
OBJECTIVE Several biologic therapies are available for the treatment of mild-to-moderate Crohn’s disease (CD). This network meta-analysis (NMA) aimed to assess the comparative efficacy of ustekinumab, adalimumab, vedolizumab and infliximab in the maintenance of clinical response and remission after 1 year of treatment.

METHODS A systematic literature search was performed to identify relevant randomized controlled trials (RCTs). Key outcomes of interest were clinical response (CD activity index [CDAI] reduction of 100 points; CDAI-100) and remission (CDAI score under 150 points; CDAI < 150). A treatment sequence Bayesian NMA was conducted to account for the re-randomization of patients based on different clinical definitions, the lack of similarity of the common comparator for each trial and the full treatment pathway from the induction phase onwards.

RESULTS Thirteen RCTs were identified. Ustekinumab 90 mg q8w was associated with statistically significant improvement in clinical response relative to placebo and vedolizumab 300 mg. For clinical remission, ustekinumab 90 mg q8w was associated with statistically significant improvement relative to placebo and vedolizumab 300 mg q8w. Findings from sub-population analyses had similar results but were not statistically significant.

CONCLUSIONS The NMA suggest that ustekinumab is associated with the highest likelihood of reaching response or remission at 1 year compared with placebo, adalimumab and vedolizumab. Results should be interpreted with caution because this is a novel methodology; however, the treatment sequence analysis may be the most methodologically sound analysis to derive estimates of comparative efficacy in CD in the absence of head-to-head evidence.

Database: Medline

8. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn’s disease: an international, randomised, double-blind, phase 3 non-inferiority study.

Author(s): Ye, Byong Duk; Pesegova, Marina; Alexeeva, Olga; Osipenko, Marina; Lahat, Adi; Dorofeyev, Andriy; Fishman, Sigal; Levchenko, Olena; Cheon, Jae Hee; Scribano, Maria Lia; Mateescu, Radu-Bogdan; Lee, Kang-Moon; Eun, Chang Soo; Lee, Sang Joon; Lee, Sung Young; Kim, HoUng; Schreiber, Stefan; Fowler, Heather; Cheung, Raymond; Kim, Young-Ho

Source: Lancet (London, England); Apr 2019; vol. 393 (no. 10182); p. 1699-1707

Publication Date: Apr 2019

Publication Type(s): Comparative Study Randomized Controlled Trial Multicenter Study Journal Article Clinical Trial, Phase Iii

PubMedID: 30929895

Available at Lancet (London, England) - from ProQuest (Health Research Premium) - NHS Version

Abstract: BACKGROUND The infliximab biosimilar CT-P13 was approved for use in Crohn’s disease after clinical comparison with originator infliximab in ankylosing spondylitis and rheumatoid arthritis; however, concerns about such indication extrapolation have been expressed. This study investigated whether CT-P13 is non-inferior to infliximab in patients with Crohn’s disease who were naive to biological therapy. METHODS In this randomised, multicentre, double-blind, phase 3 non-inferiority study, we enrolled patients with active Crohn’s disease who had not responded to, or were intolerant to, non-biological treatments. Patients were randomly assigned (1:1:1:1) to receive CT-P13 then CT-P13, CT-P13 then infliximab, infliximab then infliximab, or infliximab then CT-P13, with switching occurring at week 30. Patients received 5 mg/kg CT-P13 or infliximab at weeks 0, 2, 6, and then every 8 weeks up to week 54. The primary endpoint was the proportion of patients with a decrease of 70 points or more in Crohn’s Disease Activity Index (CDAI) from baseline to week 6. A non-inferiority margin of -20% was set (CT-P13 was non-inferior to infliximab if the lower limit of the
two-sided 95% CI for the treatment difference was greater than -20). This trial is registered with ClinicalTrials.gov, number NCT02096861, and is completed.

**FINDINGS**

Between Aug 20, 2014, and Feb 15, 2017, 308 patients were assessed for eligibility, and 220 patients were enrolled: 111 were randomly assigned to initiate CT-P13 (56 to the CT-P13-CT-P13 group and 55 to the CT-P13-infliximab group) and 109 to initiate infliximab (54 to the infliximab-infliximab group and 55 to the infliximab-CT-P13 group). CDAI-70 response rates at week 6 were similar for CT-P13 (77 [69·4%, 95% CI 59·9 to 77·8] of 111) and infliximab (81 [74·3%, 95% CI 65·1 to 82·2] of 109; difference -4·9% [95% CI -16·9 to 7·3]), thereby establishing non-inferiority. Over the total study period, 147 (67%) patients experienced at least one treatment-emergent adverse event (36 [64%] in the CT-P13-CT-P13 group, 34 [62%] in the CT-P13-infliximab group, 37 [69%] in the infliximab-infliximab group, and 40 [73%] in the infliximab-CT-P13 group).

**INTERPRETATION**

This study showed non-inferiority of CT-P13 to infliximab in patients with active Crohn's disease. Biosimilar CT-P13 could be a new option for the treatment of active Crohn's disease.

**FUNDING**

Celltrion, Pfizer.

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9. Absence of Relationship Between Crohn's Disease Activity Index or C-Reactive Protein and Infliximab Exposure Calls for Objective Crohn's Disease Activity Measures for the Evaluation of Treatment Effects at Treatment Failure.

**Author(s):** Edlund, Helena; Grisic, Ana-Marija; Steenholdt, Casper; Ainsworth, Mark A; Brynskov, Jørn; Huisinga, Wilhelm; Kloft, Charlotte

**Source:** Therapeutic drug monitoring; Apr 2019; vol. 41 (no. 2); p. 235-242

**Publication Date:** Apr 2019

**Publication Type(s):** Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 30883516

**Abstract:**

**BACKGROUND**

Circulating infliximab (IFX) concentrations correlate with clinical outcomes, forming the basis of the IFX concentration monitoring in patients with Crohn's disease. This study aims to investigate and refine the exposure-response relationship by linking the disease activity markers "Crohn's disease activity index" (CDAI) and C-reactive protein (CRP) to IFX exposure. In addition, we aim to explore the correlations between different disease markers and exposure metrics.

**METHODS**

Data from 47 Crohn's disease patients of a randomized controlled trial were analyzed post hoc. All patients had secondary treatment failure at inclusion and had received intensified IFX of 5 mg/kg every 4 weeks for up to 20 weeks. Graphical analyses were performed to explore exposure-response relationships. Metrics of exposure included area under the concentration-time curve (AUC) and trough concentrations (Cmin). Disease activity was measured by CDAI and CRP values, their change from baseline/last visit, and response/remission outcomes at week 12.

**RESULTS**

Although trends toward lower Cmin and lower AUC in nonresponders were observed, neither CDAI nor CRP showed consistent trends of lower disease activity with higher IFX exposure across the 30 evaluated relationships. As can be expected, Cmin and AUC were strongly correlated with each other. Contrarily, the disease activity markers were only weakly correlated with each other.

**CONCLUSIONS**

No significant relationship between disease activity, as evaluated by CDAI or CRP, and IFX exposure was identified. AUC did not add benefit compared with Cmin. These findings support the continued use of Cmin and call for stringent objective disease activity (bio-)markers (eg, endoscopy) to form the basis of personalized IFX therapy for Crohn's disease patients with IFX treatment failure.

**Database:** Medline
10. Cost-Effectiveness Comparison of Ustekinumab, Infliximab, or Adalimumab for the Treatment of Moderate-Severe Crohn's Disease in Biologic-Naïve Patients.

**Author(s):** Aliyev, Elmar R; Hay, Joel W; Hwang, Caroline  
**Source:** Pharmacotherapy; Feb 2019; vol. 39 (no. 2); p. 118-128  
**Publication Date:** Feb 2019  
**Publication Type(s):** Journal Article  
**PubMedID:** 30565265  

**Abstract:**  
STUDY OBJECTIVE: Ustekinumab was recently approved by the United States U.S. Food and Drug Administration for the treatment of Crohn's disease. In this analysis, we aimed to compare the cost-effectiveness of ustekinumab, infliximab, or adalimumab for the treatment of moderate-severe Crohn's disease in patients who failed conventional therapy (i.e., corticosteroids and immunomodulators) but were naïve to tumor necrosis factor antagonists (i.e., biologic drugs).  
DESIGN: Cost-effectiveness analysis using a hybrid model structure (decision tree and Markov model).  
MEASUREMENTS AND MAIN RESULTS: A decision tree simulated biologic induction, and a Markov model simulated biologic and conventional therapy maintenance. Cycle length was 2 weeks with a discounted 5-year time horizon and a limited U.S. societal perspective in the base case; results from a payer perspective are also reported. Transition probabilities, direct costs, indirect costs, and utilities were obtained from the literature. To measure relative treatment value (i.e., order of treatment cost-effectiveness), net monetary benefits were reported for a $150,000 willingness-to-pay threshold per quality-adjusted life-year in the base case. Infliximab dominated both adalimumab and ustekinumab, with a net monetary benefit (NMB) of $9943 and $29,798, respectively, in the base case. Adalimumab dominated ustekinumab, with an NMB of $19,855. All biologics yielded similar quality-adjusted life-years (~3.5), whereas costs varied substantially ($50,510, $54,985, and $72,921 for infliximab, adalimumab, and ustekinumab, respectively). The payer perspective, alternate time horizons, and scenario analyses consistently showed infliximab dominance. One-way, threshold, and probabilistic sensitivity analyses confirmed the robustness of these results with respect to all parameters. Although biosimilars were not explicitly modeled as comparators, one-way sensitivity analysis showed that drug acquisition costs could alter relative treatment value but would have to be varied by at least 50%.  
CONCLUSION: For moderate-severe Crohn's disease, infliximab yields significantly more NMBs compared with both adalimumab and ustekinumab. Additional clinical (e.g., empiric dosing, biologic cycling) and quality-of-life (e.g., lost productivity, disutility of home injections) research is needed to allow for model frameworks and parameters that more accurately reflect the nuances of Crohn's disease treatment.  

**Database:** Medline


**Author(s):** Motaghi, Ehsan; Ghasemi-Pirbaluti, Masoumeh; Zabihi, Mohsen  
**Source:** Pharmacological research; Jan 2019; vol. 139; p. 120-125  
**Publication Date:** Jan 2019  
**Publication Type(s):** Research Support, Non-u.s. Gov't Meta-analysis Comparative Study Journal Article Systematic Review  
**PubMedID:** 30395950  

**Abstract:**  
OBJECTIVES: There is still a need to develop new effective medications for the treatment of ulcerative colitis, particularly for patients who are intolerant or resistant to first line therapies. This article compared the efficacy and safety of etrolizumab and infliximab in moderate to severe...
ulcerative colitis. **METHOD** This meta-analysis was performed according to the PRISMA statement protocol. A systematic literature search of three major bibliographic databases (Scopus, PubMed, and Cochrane) was performed until June 30, 2018. This review included studies that evaluated the efficacy of etrolizumab or infliximab in ulcerative colitis and were placebo controlled randomized trials. Pooled data from each treatment were indirectly compared using Bucher’s method. **RESULTS** Seven trials were sufficiently homogeneous to be used for indirect comparison of the induction phase of the treatment. There were no significant differences in clinical remission and serious adverse events between etrolizumab and infliximab. Moreover, adverse events of etrolizumab were significantly less than those of infliximab. However, further trials are required to compare other parameters of efficacy such as the clinical response and mucosal healing of etrolizumab with infliximab in anti-TNF alpha naïve patients.

**Database:** Medline

12. **Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis.**

**Author(s):** Sands BE, Sandborn WJ, Panaccione R et al.

**Source:** N Engl J Med. 2019 Sep 26;381(13):1201-1214

**Abstract:** The efficacy of ustekinumab, an antagonist of the p40 subunit of interleukin-12 and interleukin-23, as induction and maintenance therapy in patients with ulcerative colitis is unknown. **METHODS:** We evaluated ustekinumab as 8-week induction therapy and 44-week maintenance therapy in patients with moderate-to-severe ulcerative colitis. A total of 961 patients were randomly assigned to receive an intravenous induction dose of ustekinumab (either 130 mg [320 patients] or a weight-range-based dose that approximated 6 mg per kilogram of body weight [322]) or placebo (319). Patients who had a response to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned again to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks [172 patients] or every 8 weeks [176]) or placebo (175). The primary end point in the induction trial (week 8) and the maintenance trial (week 44) was clinical remission (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no subscore >1 [range, 0 to 3] on any of the four Mayo scale components). **RESULTS:** The percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg (15.6%) or 6 mg per kilogram (15.5%) was significantly higher than that among patients who received placebo (5.3%) (P<0.001 for both comparisons). Among patients who had a response to induction therapy with ustekinumab and underwent a second randomization, the percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks (38.4%) or every 8 weeks (43.8%) than among those assigned to placebo (24.0%) (P = 0.002 and P<0.001, respectively). The incidence of serious adverse events with ustekinumab was similar to that with placebo. Through 52 weeks of exposure, there were two deaths (one each from acute respiratory distress syndrome and hemorrhage from esophageal varices) and seven cases of cancer (one each of prostate, colon, renal papillary, and rectal cancer and three nonmelanoma skin cancers) among 825 patients who received ustekinumab and no deaths and one case of cancer (testicular cancer) among 319 patients who received placebo. **CONCLUSIONS:** Ustekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe ulcerative...

Author(s): Li K, Friedman JR, Chan D, et al.


Abstract: BACKGROUND & AIMS: Although ustekinumab is an effective therapy for moderate to severe Crohn’s disease (CD), its effects on the microscopic manifestations of CD are unknown. METHODS: We evaluated the effects of ustekinumab on histologic CD activity in an analysis of data from 251 participants in phase 3 induction and maintenance studies. Two endoscopic biopsy samples were collected at weeks 0, 8, and 44 from the ileum, splenic flexure, and rectum (18 biopsy samples from each patient). Histologic activity was assessed based on global histology activity scores (GHASs). RESULTS: At week 8, the mean GHAS was significantly reduced after ustekinumab induction treatment (from 10.4 ± 7.0 to 7.1 ± 5.9; P < .001) but not in patients who received placebo (from 9.2 ± 6.4 to 7.8 ± 6.2). At week 44 in the randomized maintenance therapy population, the mean GHAS remained reduced from week 8 in patients who received subcutaneous ustekinumab (90 mg every 8 weeks; from 7.4 ± 7.7 to 6.1 ± 4.7) but not every 12 weeks (from 5.3 ± 3.9 to 8.7 ± 4.1) or placebo (from 9.2 ± 3.8 to 10.9 ± 7.1). In the pooled (randomized and nonrandomized) maintenance therapy population, histologic improvement continued in patients given ustekinumab every 8 weeks (from 7.1 ± 6.2 to 5.2 ± 4.2; P < .0001) but not in those given ustekinumab every 12 weeks (from 6.1 ± 5.7 to 7.2 ± 5.1) or placebo (from 8.2 ± 4.2 to 8.9 ± 6.8). A significantly greater proportion of patients achieved histologic response (≥50% decrease in GHAS from baseline) at week 44 if they received ustekinumab every 8 weeks (50% in the randomized maintenance population and 54% in the pooled maintenance population) compared with every 12 weeks (17% and 39% in the randomized and pooled populations, respectively) or placebo (0% and 22% in the randomized and pooled populations, respectively) (P = .0137 for every 8 weeks vs placebo and P = .3529 for every 12 weeks vs placebo in the randomized population; P = .0168 for every 8 weeks vs placebo and P = .3069 for every 12 weeks vs placebo in the pooled population). Regional and overall mean GHASs correlated with the simple endoscopic score for CD (r = .6255, P < .0001). Multivariate analysis found an association between histologic improvement and endoscopic or histologic burden at baseline. CONCLUSIONS: In an analysis of data from participants in phase 3 induction and maintenance trials, we found histologic improvement in a greater proportion of patients given ustekinumab vs placebo. The largest improvements occurred in patients who received ustekinumab maintenance therapy every 8 weeks. ClinicalTrials.gov nos. NCT01369329, NCT01369342, and NCT01369355.
**14. Five-year Safety Data From OPUS, a European Observational Safety Registry for Adults With Ulcerative Colitis Treated With Originator Infliximab [Remicade®] or Conventional Therapy.**

**Author(s):** Panés J, Lindsay JO, Teich N, et al.

**Source: J Crohns Colitis. 2019 Sep 19;13(9):1148-1157. doi: 10.1093/ecco-jcc/jjz048.**

**Abstract:** **BACKGROUND AND AIMS:** The Observational Postmarketing Ulcerative colitis Study [OPUS] was conducted to obtain the first long-term [5 years] safety data assessing treatment with originator infliximab versus conventional therapies in patients with ulcerative colitis [UC] in real-world clinical practice. **METHODS:** The OPUS registry was a prospective, non-randomised, observational study that measured adverse events in nine prespecified categories of interest in UC patients whose treatment with either originator infliximab or conventional therapy [defined as initiation or dose-increase of corticosteroids and/or immunosuppressants] was determined by their treating physician. **RESULTS:** Data for 2239 patients were available: N = 1180 enrolled to conventional therapy [including N = 296 who switched to originator infliximab during follow-up] and N = 1059 enrolled to originator infliximab. Patients in the originator infliximab group, compared with the conventional therapy group, had more severe disease at baseline, based on partial Mayo score [PMS]: 46.0% of patients in the originator infliximab group had severe disease (PMS of 7-9 [out of 9]), compared with 30.5% in the conventional therapy group. In adjusted time-to-event analyses, enrolment into the originator infliximab group was associated with a higher risk of serious infection (hazard ratio = 1.98 [95% confidence interval: 1.34, 2.91; p <0.001]) compared with enrolment into the conventional therapy group. No notable risk differences between groups were identified for haematological disorder, autoimmune disorder, malignancy/lymphoproliferative disorder, hepatobiliary disorder or fatality. **CONCLUSIONS:** UC patients treated with infliximab had higher risk for serious infection, compared with conventional therapies. No new safety concerns were observed with originator infliximab in the OPUS registry. [ClinicalTrials.gov: NCT00705484].

**Database:** PubMed

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**15. Tofacitinib for the treatment of moderately to severely active ulcerative colitis: A systematic review, network meta-analysis and economic evaluation.**

**Author(s):** Lohan C., Diamantopoulos A., LeReun C., Wright E., Bohm N., Sawyer L.M.


Background and aims: In the UK, treatments for patients with moderately to severely active ulcerative colitis who have an inadequate response to conventional therapies comprise four biological therapies - the tumour necrosis factor inhibitor (TNFi) agents adalimumab, golimumab and infliximab and the anti-integrin vedolizumab - and an orally administered small molecule therapy, tofacitinib. However, there have been few head-to-head studies of these therapies. This study aimed to compare the clinical and cost-effectiveness of tofacitinib with biological therapies. **Method(s):** A systematic literature review was conducted to identify all relevant randomised controlled trial (RCT) evidence. Clinical response, clinical remission and serious infection rates were synthesised using
network meta-analysis (NMA). The results were used to compare the cost-effectiveness of tofacitinib and biologics with conventional therapy, using a Markov model, which incorporated lifetime costs and consequences of treatment from a UK National Health Service perspective. Analyses were conducted separately for TNFi-naive and TNFi-exposed populations. Result(s): Seventeen RCTs were used in the NMAs. There were no statistically significant differences among biological therapies and tofacitinib for either TNFi-naive or TNFi-exposed patients. In TNFi-naive patients, all therapies were more efficacious than placebo. In TNFi-exposed patients, only tofacitinib was significantly more efficacious than placebo as induction therapy, and only tofacitinib and vedolizumab were significantly more efficacious than placebo as maintenance therapies. There were no significant differences in serious infection rates among therapies. The incremental cost-effectiveness ratios for tofacitinib versus conventional therapy were 21,338 and 22,816 per quality-adjusted life year (QALY) in the TNFi-naive and TNFi-exposed populations, respectively. TNFi therapies were dominated or extendedly dominated in both populations. Compared with vedolizumab, tofacitinib was associated with a similar number of QALYs, at a lower cost. Conclusion(s): Tofacitinib is an efficacious treatment for moderately to severely active ulcerative colitis and is likely to be a cost-effective use of NHS resources. Copyright © 2019 Author(s).

Database: Embase


Author(s): Lorena J.G., David G.S.M., Silvia F.C.

European Journal of Clinical Pharmacy. 21 (2) (pp 96-100), 2019. Date of Publication: April-June 2019.

Ulcerative colitis (UC) is a chronic disease that results in inflammation of gastrointestinal tract. Pivotal GEMINI I clinical trial compares VDZ versus placebo in refractory patients to one or more previous conventional therapies for UC or previous use of anti-TNF. This is a phase III, multicenter, prospective, randomized and double-blind, designed in two phases: induction and maintenance. According to clinical trials, most frequent adverse effects (AE) were headaches, nasopharyngitis, upper respiratory tract infection, arthralgia, nausea, abdominal pain and fatigue. GEMINI I trial studied safety in 895 patients (620 patients with VDZ and 275 with placebo), taking into account non-responders in week 6. Incidence of AE was similar between VDZ and placebo (80% of population in each group), as well as incidence of severe AE (12-13%). VDZ is considered as an effective alternative, in second or third line of treatment of moderate-severe active UC. Copyright © 2019 Rasgo Editorial S.A. All rights reserved.

Database: Embase

17. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease.

Author(s): Gjuladin-Hellon T, Iheozor-Ejiofor Z, Gordon M, Akobeng AK
Background: Crohn’s disease (CD) is a chronic relapsing inflammatory condition and maintenance of remission is a major issue as many patients fail to achieve remission with medical management and require surgical interventions. Purine analogues such as azathioprine (AZA) and 6-mercaptopurine (6-MP) have been used to maintain surgically-induced remission in CD, but the effectiveness, tolerability and safety of these agents remains controversial.

Objectives: To assess the efficacy and safety of purine analogues (AZA and 6-MP) for maintenance of surgically-induced remission in CD.

Search methods: We searched PubMed, MEDLINE, Embase, CENTRAL, and the Cochrane IBD Group Specialized Register from inception to 26 July 2018 (and from inception to 31 July 2019). In addition, we searched reference lists of all included studies and relevant reviews, conference proceedings and trials registers.

Selection criteria: Randomised controlled trials (RCTs) with a duration of at least three months that enrolled adults and children with surgically-induced remission of CD and compared AZA or 6-MP to no treatment, placebo or any other active intervention were considered for inclusion.

Data collection and analysis: Two authors independently assessed trial eligibility, extracted data, assessed the risk of bias and assessed the certainty of the evidence using GRADE. The primary outcome was clinical relapse. Secondary outcomes included endoscopic relapse, radiologic and surgical relapse, adverse events (AEs), serious adverse events (SAEs), withdrawal due to AEs and health-related quality of life.

Main results: Ten RCTs with a total of 928 participants were included. Study participants were adults recruited from university clinics and gastroenterology hospitals who received interventions post-surgery for a duration between 12 to 36 months. Most study participants were recruited less than three months after surgery in all except one study where participants were recruited between 6 to 24 months post-surgery. One study was rated as low risk of bias, six studies were rated high risk of bias and three were rated unclear risk of bias. There was moderate certainty evidence that purine analogues are more efficient for preventing clinical relapse than placebo. At 12 to 36 months, 51% (109/215) of AZA/6-MP participants relapsed compared to 64% (124/193) of placebo participants (RR 0.79; 95% CI 0.67 to 0.92; 408 participants; 3 studies; IR = 0%; moderate certainty evidence). The certainty of the evidence regarding the efficacy of AZA or 6-MP for maintaining postoperative clinical remission compared to 5-ASA compounds was low. At 12 to 24 months, 64% (113/177) of purine analogue participants relapsed compared to 59% (101/170) of 5-ASA participants (RR 1.05; 95% CI 0.89 to 1.24; 347 participants; 4 studies; IR = 8%; low certainty evidence). The certainty of evidence that purine analogues are inferior for preventing postsurgical clinical relapse compared to tumour necrosis factor alpha agents (anti-TNF-α) was very low. At 12 to 24 months, 43% (29/67) of AZA participants relapsed compared to 14% (10/72) of anti-TNF-α participants (RR 2.89; 95% CI 1.50 to 5.57; 139 participants; 3 studies; IR = 0%; very low certainty evidence).

The effect of purine analogues compounds on AEs compared to placebo or any active treatment was uncertain, as the quality of evidence ranged from very low to low. After 12 to 24 months, 14% (12/87) of purine analogue participants experienced an AE compared to 10%(8/81) of placebo participants (RR 1.36; 95% CI 0.57 to 3.27; 168 participants; 2 studies; IR = 0%; low certainty evidence).
The effect of purine analogues on AEs compared to 5-ASA agents was uncertain. At 12 to 24 months, 41% (73/176) of purine analogue participants had an AE compared to 47% (81/171) of 5-ASA participants (RR 0.89; 95% CI 0.74 to 1.07; 346 participants; 4 studies; IR = 15%; low certainty evidence). The effect of purine analogues on AEs in comparison to anti TNF-α agents was uncertain. At 12 to 24 months, 57% (32/56) of AZA participants had an AE compared to 51% (31/61) of anti-TNF-α participants (RR 1.13; 95% CI 0.83 to 1.53; 117 participants; 2 studies; IR = 0%; low certainty evidence). Purine analogue participants were more likely than 5-ASA participants to have a SAE (RR 3.39, 95% CI 1.26 to 9.13; 311 participants; 3 studies; IR = 9%; very low certainty evidence), or to withdraw due to an AE (RR 2.21, 95% CI 1.28 to 3.81; 425 participants; 5 studies; IR = 0%; low certainty evidence). Commonly reported AEs across all studies included leucopenia, arthralgia, abdominal pain or severe epigastric intolerance, elevated liver enzymes, nausea and vomiting, pancreatitis, anaemia, nasopharyngitis and flatulence. Authors’ conclusions: Moderate certainty evidence suggests that AZA and 6-MP may be superior to placebo for maintenance of surgically-induced remission in participants with CD. There was no clear difference in the number of clinical relapses when purine analogues were compared with 5-ASA agents, however this is based on low certainty evidence. There was very low certainty evidence that AZA and 6-MP are more likely to result in more serious adverse events (SAEs) and withdrawals due to an AE (low certainty) when compared to 5-ASA agents. Very low certainty evidence suggests that purine analogues may be inferior to anti-TNF-α agents, however, no firm conclusions can be drawn. Further research investigating the efficacy and safety of AZA and 6-MP in comparison to other active medications in surgically-induced remission of CD is warranted.

Database: Medline

18. Efficacy and safety of infliximab in pediatric Crohn disease: A systematic review and meta-analysis.

Author(s): Li S., Reynaert C., Su A.L., Sawh S.

Source: Canadian Journal of Hospital Pharmacy. 72 (3) (pp 227-238), 2019. Date of Publication: 2019.

Background: Crohn disease is an inflammatory bowel disease with intermittent symptoms relating to damage to the gastrointestinal tract. Compared with adult-onset Crohn disease, the childhood-onset form is more likely to be severe. Infliximab has shown efficacy in adult patients. Objective(s): To examine the efficacy and safety of infliximab in pediatric Crohn disease, by means of a systematic review. Data Sources: Three databases (MEDLINE, Embase, and Cochrane Central Register of Controlled Trials) and regulatory documents were searched from inception to December 2017. Clinical trial registries, conference abstracts, and reference lists were searched to March 2018. Study Selection and Data Extraction: Randomized controlled trials (RCTs) and prospective cohort studies that compared infliximab with active control were included in the analysis. Two reviewers independently performed screening, extracted data, and assessed risk of bias. The primary outcomes were induction and maintenance of endoscopic remission and severe adverse effects. Data Synthesis: Three eligible RCTs comparing different dose regimens, 16 prospective cohort studies comparing infliximab with other therapies (adalimumab, exclusive enteral nutrition, or standard of care), and 3 prospective cohort studies comparing different infliximab regimens were identified.
Meta-analysis of the RCTs showed no significant difference between infliximab every 8 weeks compared with longer intervals for maintenance of clinical remission (risk ratio [RR] 1.76, 95% confidence interval [CI] 0.98-3.19). Meta-analyses of the prospective cohort studies showed no significant differences between infliximab and adalimumab for maintenance of endoscopic remission (RR 1.07,95% CI 0.60-1.92), between infliximab and exclusive enteral nutrition for induction of clinical remission (RR 1.09, 95% CI 0.82-1.45), or between infliximab and standard of care for maintenance of clinical remission at 6 and 12 months (RR 1.12, 95% CI 0.58-2.17, and RR 1.24, 95% CI 0.84-1.84, respectively). Conclusion(s): Current evidence suggested comparable efficacy for infliximab and other therapies; however, the available literature was limited by risk of bias and small sample size. Further prospective studies are needed to confirm the efficacy and safety of this drug in pediatric Crohn disease. Copyright © 2019 Canadian Society of Hospital Pharmacists. All rights reserved.


Author(s): Kolar M., Duricova D., Bortlik M., Pudilova K., Hruba V., Machkova N., Mitrova K., Malickova K., Vasatko M., Vanickova R., Lukas M.


Background: Vedolizumab (VDZ) and ustekinumab (UST) have become available for the treatment of Crohn's disease (CD), however, due to limited clinical experience, the optimal treatment strategy after a failure of anti-tumor necrosis factor (anti-TNF) has yet to be elucidated. In our study, we aim to evaluate the efficiency and safety of VDZ and UST as second-line classes of biological therapy in a head-to-head manner in comparable populations of CD patients. Method(s): Consecutive patients with CD who have previously been treated with anti-TNF therapy were included. Patients were followed at regular intervals coincident with drug applications and clinical activity (HBI - Harvey-Bradshaw Index), inflammatory markers (C-reactive protein, fecal calprotectin) and adverse events were recorded. The primary outcome was the proportion of patients in clinical remission in weeks 30-32 (HBI <= 4), the clinical response in terms of HBI decrease, and the withdrawal rate. Result(s): Forty-five patients with VDZ and 50 with UST were included. Both groups were comparable in all the evaluated parameters with the exception of the male-to-female ratio and the proportion of patients with penetrating disease phenotype. The proportion of patients in clinical remission increased from 44.4% at baseline to 58.1% in weeks 30-32 in the VDZ group and from 55.1% to 63.2% in the UST group; however, the increase was not statistically significant. The mean paired HBI difference between weeks 30-32 and baseline reached -1.94 +/- 5.14 (p = 0.05) in the VDZ cohort and -2.94 +/- 5.91 (p = 0.01) in the UST cohort. The proportion of patients in steroid-free clinical remission increased from 38.8% to 62.5% in the UST cohort (p = 0.04), and from 33.3% to 45.2% in the VDZ (p = 0.67). Six patients on VDZ and none on UST discontinued the treatment. Conclusion(s): Our study demonstrated a comparable efficacy of VDZ and UST with respect to the rate of clinical remission and biomarker response; however, the steroid-sparing effect of UST was more prominent. There is a need for prospective randomized head-to-head trials to assess the optimal position of new biological agents in the treatment of patients with CD. Copyright © 2019 Galen s.r.o.. All rights reserved.

Database: Embase
20. Reliability evaluation of four different assays for therapeutic drug monitoring of infliximab levels.

**Author(s):** Perez I., Fernandez L., Sanchez-Ramon S., Alba C., Zatarain A., Canas M., Lopez O.N., Olivares D., Rey E., Taxonera C.

**Source:** Therapeutic Advances in Gastroenterology. 11 (no pagination), 2018. Date of Publication: 01 Jan 2018.

Background: The aim of this study was to evaluate reliability of four different assays for measuring infliximab trough levels and antibodies to infliximab (ATI). Method(s): In this non-interventional, cross-sectional study including IBD patients, infliximab levels and ATI were measured using four different assays: Lisa-Tracker, Promonitor, Q-Inflixi and Sanquin. Reliability and agreement for infliximab levels was assessed using the intraclass correlation coefficient (ICC) and Bland-Altman plots. Qualitative agreement for infliximab (based on a pre-established target window of trough levels between 3 micro g/ml and 7 micro g/ml) and for ATI were estimated by Cohen's kappa. Result(s): Serum samples of 84 IBD patients were evaluated for infliximab using the four assays. Reliability was 'substantial' between Lisa-Tracker versus Promonitor and 'almost perfect' between the remaining assay pairs, with ICCs [95% confidence interval (CI)] ranging from 0.93 (0.70-0.97) for Lisa-Tracker versus Promonitor to 0.97 (0.95-0.98) for Q-Inflixi versus Sanquin. Bland-Altman plots showed significant bias between assays except Promonitor versus Q-Inflixi, which had excellent agreement. The greatest differences in mean infliximab were found between Promonitor versus Lisa-Tracker (-0.91 micro g/ml) and Lisa-Tracker versus Q-Inflixi (0.69 micro g/ml). Qualitative agreement for infliximab was 'almost perfect' for Promonitor versus Q-Inflixi (kappa 0.84) and Q-Inflixi versus Sanquin (kappa 0.81), and 'substantial' for the remaining pairs. More than 10% of patients who had infliximab levels within the target interval by Lisa-Tracker had suboptimal concentrations (<3 micro g/ml) with Promonitor and Q-Inflixi. Furthermore, 11% of patients within the target interval by Q-Inflixi had supra-optimal levels (>7 micro g/ml) by Lisa-Tracker. In the remaining paired comparisons, fewer than 5% of patients were placed in different subgroups. Qualitative agreement for ATI fluctuated between 'moderate' and 'almost perfect'. Conclusion(s): All four assays seem suitable for therapeutic drug monitoring of infliximab. Promonitor and Q-Inflixi had the best agreement, making those assays fully interchangeable. Systematic biases between Lisa-Tracker with Promonitor and Q-Inflixi suggest that these assays should not be interchanged during the follow up of an individual patient. Copyright © The Author(s), 2018.

**Database:** Embase


**Author(s):** Kotze P.G., Ma C., Almutairdi A., Panaccione R.


The introduction of anti-tumor necrosis factor (TNF) therapy marked an important milestone in the management of moderate-to-severe Crohn's disease (CD). However, there remains a pressing demand for alternative therapeutic options for patients with primary nonresponse, secondary loss of
response, or intolerable side effects to conventional treatment and TNF antagonists. Ustekinumab (UST) is a fully human IgG1kappa monoclonal antibody that inhibits the p40 subunit shared by the proinflammatory cytokines, the interleukin (IL)-12 and -23. This blockade leads to dampening of the inflammatory cascade and differentiation of inflammatory T cells. The clinical development program for UST in CD includes dose finding Phase II (Crohn's Evaluation of Response to Ustekinumab Anti-Interleukin-12/23 for Induction [CERTIFI]) and the pivotal Phase III (UNITI) trials that demonstrated both the clinical efficacy and safety in anti-TNF-naive and anti-TNF-exposed patients. Real-world evidence has further defined the role of UST in CD management. In this review, we discuss the mechanism of action of UST, describe the results of the randomized controlled trials with this agent, and review the real-world efficacy and safety data from observational cohorts. Finally, we identify areas of future research in the IL-12/23 inflammatory pathway and discuss the positioning of this novel therapeutic option in CD treatment algorithms. Copyright © 2018 Kotze et al.

Database: Embase

22. Comparison of Safety and Efficacy of Tacrolimus versus Infliximab for Active Ulcerative Colitis.
Author(s): Takeuchi, Ken; Shimoyama, Takahiro; Yamamoto, Takayuki
Source: Digestive diseases (Basel, Switzerland); 2018; vol. 36 (no. 2); p. 106-112
Publication Date: 2018
Publication Type(s): Comparative Study Journal Article Review
PubMedID: 29050007
Abstract:BACKGROUNDThis narrative review was to determine which medication, tacrolimus (TAC) or infliximab (IFX), is safer and more effective in the management of active UC. Our literature search identified 5 studies directly comparing the outcomes of TAC versus IFX for active UC. A review of the 5 studies was undertaken.SUMMARYThe incidence of serious adverse events was not significantly different between the TAC and IFX groups. The short-term clinical remission and response rates and the colectomy-free rates were similar between the groups. TAC was usually withdrawn at week 12 and, therefore, the long-term efficacy of TAC could not be properly evaluated. The majority of patients in the IFX group maintained clinical remission in the long-term. The efficacy of IFX as second-line salvage therapy after failure of TAC appeared to be favourable, but the efficacy of TAC after failure of IFX was questionable. Key Messages: Both TAC and IFX appeared to be equally safe and effective in the short-term for patients with active UC. For the moment, treatment choice, TAC or IFX, should be guided by physician and centre experience. Randomised controlled trials are urgently warranted to rigorously compare the efficacy of TAC versus IFX for active UC.
Database: Medline

Author(s): Paschos, Paschalis; Katsoula, Anastasia; Salanti, Georgia; Giouleme, Olga; Athanasiadou, Eleni; Tsapas, Apostolos
Source: Alimentary pharmacology & therapeutics; Dec 2018; vol. 48 (no. 11-12); p. 1174-1185
Publication Date: Dec 2018
Publication Type(s): Journal Article Systematic Review
BACKGROUND Patient-reported outcomes are important in the assessment of efficacy of intervention for ulcerative colitis (UC). AIMS To compare the impact of interventions for moderate-to-severe UC on health-related quality of life (HRQL). METHODS We searched Medline, Embase, CENTRAL and grey literature sources through October 2017. We included randomised controlled trials (RCTs) that compared infliximab, adalimumab, golimumab, vedolizumab or tofacitinib to each other or placebo. Outcomes included the change in quality of life scores and the proportion of patients with improvement in quality of life. We performed random-effect pairwise and network meta-analysis. We assessed confidence in estimates using the CINeMA (Confidence in Network Meta-Analysis) framework. RESULTS Fourteen RCTs assessed HRQL using the Inflammatory Bowel Disease Questionnaire (IBDQ) (14 trials), the Short Form questionnaire-36 (SF-36) (seven trials) or the European Quality of Life-5 Dimensions questionnaire (EQ-5D) (three trials). At induction (13 trials), low to very low confidence evidence suggested that all agents significantly improved both generic and disease-specific HRQL scores compared to placebo. However, only infliximab (MD 18.58; 95% CI 13.19-23.97) and vedolizumab (MD 18.00; 95% CI 11.08-24.92) showed clinically meaningful improvement in IBDQ score. Differences among individual interventions were imprecise. For maintenance (four trials), very low confidence evidence suggested that vedolizumab, tofacitinib and adalimumab maintained improvement in HRQL. CONCLUSIONS Induction treatment with infliximab, adalimumab, golimumab, vedolizumab or tofacitinib improves quality of life compared to placebo. Evidence on maintenance therapy is sparse and uncertain. Head-to-head comparisons could enhance confidence in conclusions about differences between drugs in terms of HRQL.

Database: Medline

24. Higher Infliximab Trough Levels Are Associated With Better Outcome in Paediatric Patients With Inflammatory Bowel Disease.

Author(s): van Hoeve, Karen; Dreesen, Erwin; Hoffman, Ilse; Van Assche, Gert; Ferrante, Marc; Gils, Ann; Vermeire, Séverine

Source: Journal of Crohn’s & colitis; Nov 2018; vol. 12 (no. 11); p. 1316-1325

Publication Date: Nov 2018

Publication Type(s): Journal Article

PubMedID: 30239644

Abstract: The role of therapeutic drug monitoring for infliximab [IFX] therapy in children with inflammatory bowel disease [IBD] is poorly investigated. We determined if IFX exposure correlates with long-term remission in children. Methods In this retrospective study, all children with Crohn’s disease [CD] and ulcerative colitis [UC], receiving maintenance IFX at our centre, were included. Serum trough levels and cumulative drug exposure were correlated with clinical, biological, and endoscopic remission. All children received proactive drug monitoring and dose adaptation aiming to target a therapeutic window of 3-7 µg/mL. All data are presented as median [interquartile range]. Results A total of 686 serum levels during IFX maintenance in 52 paediatric patients [33 CD and 19 UC] were included (median 9 [4-18] per patient). With a median of 17 [8-36] months under IFX therapy, 39/52 [75%] patients were in clinical remission and 29/40 [73%] patients were in endoscopic remission. Median IFX trough levels were significantly higher when children achieved clinical remission (5.4 [3.8-8.0] µg/mL versus 4.2 [2.6-6.7] µg/mL), biological remission (5.2 [3.7-7.7] µg/mL versus 4.2 [2.6-6.5] µg/mL), combined clinical and biological remission (5.7 [4.0-8.2] µg/mL versus 4.4 [2.7-6.8] µg/mL) and endoscopic remission (6.5 [4.2-9.5] µg/mL versus 3.2 [2.3-5.6] µg/mL) compared with not meeting these criteria [all p ≤ 0.001]. Conclusions In this large paediatric
cohort, children with clinical and/or endoscopic remission had significantly higher IFX exposure during maintenance therapy. We showed excellent outcome data using serial and systematic measurements of drug levels. This could provide a rationale for the use of proactive drug monitoring in children in order to improve long-term outcomes.

**Database**: Medline

**25. Clinical Outcomes With Therapeutic Drug Monitoring in Inflammatory Bowel Disease: A Systematic Review With Meta-Analysis.**

**Author(s)**: Ricciuto, Amanda; Dhaliwal, Jasbir; Walters, Thomas D; Griffiths, Anne M; Church, Peter C

**Source**: Journal of Crohn's & colitis; Nov 2018; vol. 12 (no. 11); p. 1302-1315

**Publication Date**: Nov 2018

**Publication Type(s)**: Meta-analysis Journal Article Systematic Review

**PubMedID**: 30107416

**Abstract**: Background and Aims We undertook a systematic review and meta-analysis examining the effectiveness of therapeutic drug monitoring [TDM] to improve clinical outcomes in inflammatory bowel disease patients treated with anti-tumour necrosis factor alpha [anti-TNF] drugs.

Methods We searched MEDLINE, Epub Ahead of Print, EMBASE and Cochrane up to October 2017 for randomized trials [RCTs] and cohort studies comparing proactive or reactive TDM to each other or empiric care. Outcomes included clinical remission [primary], clinical relapse, endoscopic remission, anti-TNF response durability, cost and adverse events [secondary]. Pooled odds ratios and mean differences were calculated.

Results The search identified nine studies [three RCTs, six observational], focused on infliximab maintenance therapy in adults. Neither proactive nor reactive TDM was associated with superior clinical remission rates compared to empiric dose optimization. However, evidence of a cost benefit, particularly for reactive TDM vs empiric care, was identified. In several studies, TDM, particularly proactive TDM, was associated with favourable outcomes related to durability of anti-TNF response, such as lower drug discontinuation rates compared to empiric care and reactive TDM, and lower relapse rates compared to empiric care. No consistent benefit was found for endoscopic or surgical outcomes.

Conclusions The existing limited evidence does not support an association between any TDM strategy and superior clinical remission rates but does support a cost savings benefit [particularly for reactive TDM] and suggests a potential benefit for anti-TNF durability [particularly proactive TDM]. Additional, longer-term studies are needed, particularly to further investigate proactive TDM, and to generate data on other anti-TNF agents, the induction period and paediatric populations.

**Database**: Medline

**26. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease.**

**Author(s)**: Rutgeerts, Paul; Gasink, Christopher; Chan, Daphne; Lang, Yinhua; Pollack, Paul; Colombel, Jean-Frederic; Wolff, Douglas C; Jacobstein, Douglas; Johanss, Jewel; Szapary, Philippe; Adedokun, Omoniyi J; Feagan, Brian G; Sandborn, William J

**Source**: Gastroenterology; Oct 2018; vol. 155 (no. 4); p. 1045-1058

**Publication Date**: Oct 2018

**Publication Type(s)**: Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article Clinical Trial, Phase Iii

**PubMedID**: 29909019

Available at Gastroenterology - from Unpaywall
Abstract: BACKGROUND &AIMS: We evaluated the ability of ustekinumab, a monoclonal antibody against the p40 subunit of interleukins 12 and 23, to induce endoscopic healing in patients with moderate to severe Crohn's disease (CD). METHODS: We performed an endoscopy substudy of 334 patients with moderate to severe CD participating in 3 randomized controlled phase 3 studies to determine the safety and efficacy of ustekinumab induction and maintenance therapy. All patients underwent colonoscopy at baseline and week 8 of the induction studies and at week 44 of the maintenance study; all colonoscopies were assessed by a blinded central reader. During the induction studies, patients were randomly assigned to groups given intravenous ustekinumab (130 mg or 6 mg/kg) or placebo. At the baseline time point of the maintenance study (week 8 of the induction studies), patients with a clinical response to ustekinumab were randomly assigned to groups given subcutaneous ustekinumab (90 mg every 12 weeks or 8 weeks) or placebo. Additional maintenance analysis populations were patients who did not respond to ustekinumab or placebo during the induction studies, and patients who responded to placebo during the induction studies; we performed a post-hoc pooled analysis of randomly assigned and non-randomly assigned patients of the maintenance study. We analyzed data from patients with an ulcer in at least 1 segment at baseline of the induction studies. The primary end point was change in the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), from baseline, at week 8. We also assessed the efficacy of maintenance therapy. RESULTS: Patients given ustekinumab had a greater reduction in SES-CD from the induction baseline time point until week 8 than placebo (reduction of 2.8 in patients given ustekinumab vs a reduction of 0.7 points in patients given placebo; P = .012). Results were similar among patients in different induction studies and patients given different doses of ustekinumab. At week 44, reductions in the SES-CD from the induction baseline were greater in patients given ustekinumab (for combined groups, a reduction of 2.5; P = .176 and for every 8 weeks, a reduction of 3.1; P = .107) than patients given placebo (reduction of 1.9 points). Maintenance results were similar for the larger pooled post-hoc analysis. CONCLUSIONS: In an analysis of data from 3 trials of patients with moderate to severe CD, ustekinumab (intravenous induction and subcutaneous maintenance) reduces SES-CD compared with placebo. We observed significant reductions in endoscopic disease activity at week 8 of induction therapy with ustekinumab. (ClinicalTrials.gov numbers, NCT01369329, NCT01369342, and NCT01369355).

Database: Medline


Author(s): Singh, S; Fumery, M; Sandborn, W J; Murad, M H

Source: Alimentary pharmacology & therapeutics; Aug 2018; vol. 48 (no. 4); p. 394-409

Publication Date: Aug 2018

Publication Type(s): Research Support, Non-u.s. Gov't Meta-analysis Journal Article Systematic Review

PubMedID: 29920733

Available at Alimentary pharmacology & therapeutics - from Wiley Online Library Free Content - NHS

Available at Alimentary pharmacology & therapeutics - from Unpaywall

Abstract: BACKGROUND: There are limited data to inform positioning of agents for treating moderate-severe Crohn's disease (CD). AIM: We assessed comparative efficacy and safety of first-line (biologic-naive) and second-line (prior exposure to anti-tumour necrosis factor [TNF-α] agents) biologic therapy for moderate-severe CD, through a systematic review and network meta-analysis, and appraised quality of evidence (QoE) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. METHODS: We identified randomised controlled
trials (RCTs) in adults with moderate-severe CD treated with approved anti-TNF agents, anti-integrin agents and anti-IL12/23 agents, first-line or second-line, and compared with placebo or another active agent. Efficacy outcomes were induction and maintenance of clinical remission; safety outcomes were serious adverse events and infections. Network meta-analyses were performed, and ranking was assessed using surface under the cumulative ranking (SUCRA) probabilities.

RESULTS
No head-to-head trials were identified. In biologic-naïve patients, infliximab (SUCRA, 0.93) and adalimumab (SUCRA, 0.75) were ranked highest for induction of clinical remission (moderate QoE). In patients with prior anti-TNF exposure, adalimumab (SUCRA, 0.91; low QoE, in patients with prior response or intolerance to anti-TNF agents) and ustekinumab (SUCRA, 0.71) were ranked highest for induction of clinical remission. In patients with response to induction therapy, adalimumab (SUCRA, 0.97) and infliximab (SUCRA, 0.68) were ranked highest for maintenance of remission. Ustekinumab had lowest risk of serious adverse events (SUCRA, 0.72) and infection (SUCRA, 0.71; along with infliximab, SUCRA, 0.83) in maintenance trials.

CONCLUSION
Indirect comparisons suggest that infliximab or adalimumab may be preferred first-line agents, and ustekinumab a preferred second-line agent, for induction of remission in patients with moderate-severe CD. Head-to-head trials are warranted.

Database: Medline


Author(s): Nelson, Seana Ml; Nguyen, Tran M; McDonald, John Wd; MacDonald, John K

Source: The Cochrane database of systematic reviews; Aug 2018; vol. 8; p. CD006097

Publication Date: Aug 2018

Publication Type(s): Meta-analysis Journal Article Systematic Review

PubMedID: 30068022

Available at The Cochrane database of systematic reviews - from Cochrane Collaboration (Wiley)

Abstract: BACKGROUND This systematic review update summarizes the current evidence on the use of natalizumab for induction of remission in Crohn's disease (CD). OBJECTIVE To determine the efficacy and safety of natalizumab for induction of remission in CD. SEARCH METHODS We searched MEDLINE, Embase, CENTRAL, the Cochrane IBD Group Specialized Trials Register, and clinicaltrials.gov from inception to 10 May 2018. SELECTION CRITERIA We included randomized controlled trials (RCTs) comparing natalizumab to a placebo or control therapy for induction of remission in CD. DATA COLLECTION AND ANALYSIS Two authors independently screened studies, extracted data and assessed methodological quality using the Cochrane risk of bias tool. The primary outcome was failure to enter clinical remission. Secondary outcomes included clinical response, mean change in Crohn's Disease Activity Index (CDAI), adverse events (AEs), withdrawal due to AEs and serious AEs. For dichotomous outcomes, we calculated the risk ratio (RR) and 95% confidence interval (95% CI). For continuous outcomes we calculated the mean difference (MD) and 95% CI. Data were pooled for meta-analysis when the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). We used GRADE to assess the overall quality of the evidence. MAIN RESULTS A total of five RCTs (1771 participants) were included. Four studies (1692 participants) compared one, two or three infusions of natalizumab (300 mg or 3 mg/kg or 6mg/kg) to placebo. One study (79 participants) compared three infusions of natalizumab (300 mg) and infliximab (5 mg/kg) to infliximab and placebo. Four studies were rated as low risk of bias. One study was rated as unclear risk of bias for selective reporting. One, two and three infusions of natalizumab were superior to placebo for induction of remission and clinical response. Infusions were administered at weeks zero, four and eight. After one infusion, 76% (849/1117) of natalizumab participants failed to enter remission at 4 weeks compared to 83% (411/494) of placebo participants (RR 0.91, 95% CI 0.86 to 0.96, 3 studies, GRADE high quality). At 4 weeks, the RR for clinical response
was 0.78 (95% CI 0.66 to 0.92, 3 studies, 1611 participants, GRADE moderate quality). After two infusions, after 8 weeks, 66% (693/1049) of natalizumab participants failed to enter remission compared to 77% (382/494) of placebo participants (RR 0.85, 95% CI 0.76 to 0.95; 3 studies, GRADE high quality). After three infusions, at 12 weeks, 61% (596/983) of natalizumab participants failed to enter remission compared to 73% (313/431) of placebo participants (RR 0.85, 95% CI 0.78 to 0.92, 2 studies, GRADE high quality). One study (507 participants) reported on change in CDAI from baseline. Natalizumab participants had a larger drop in mean CDAI scores than placebo participants at 4, 8 and 12 weeks. The rates of AEs, withdrawals due to AEs and serious AEs were similar across groups at 4, 8 and 12 weeks. After one infusion, 74% (50/68) of natalizumab participants experienced an AE compared to 81% (51/63) of placebo participants (RR 0.91, 95% CI 0.75 to 1.09, GRADE moderate quality). Withdrawal due to an AE occurred in 1% (1/68) of natalizumab participants and 3% of placebo participants (RR 0.46, 95% CI 0.04 to 4.98, GRADE low quality). SAEs occurred in 10% (7/68) of natalizumab participants compared to 11% (7/63) of placebo participants (RR 0.93, 95% CI 0.34 to 2.49, GRADE low quality). After two infusions, 86% (57/66) of natalizumab participants experienced an AE compared to 81% (51/63) of placebo participants (RR 1.07, 95% CI 0.92 to 1.24, GRADE moderate quality). Withdrawal due to an AE occurred in 3% (2/66) natalizumab participants compared to 3% (2/63) placebo participants (RR 0.95, 95% CI 0.14 to 6.57, GRADE low quality). SAEs occurred in 9% (6/66) of natalizumab participants and 11% (7/63) of placebo participants (RR 0.82, 95% CI 0.29 to 2.30, GRADE low quality). After three infusions, 86% (848/984) of natalizumab participants experienced an AE compared to 83% (359/431) placebo participants (RR 1.03, 95% CI 0.98 to 1.08, GRADE high quality). Withdrawals due to AEs occurred in 8% (82/984) of natalizumab participants compared to 10% (45/431) of placebo participants (RR 0.86, 95% CI 0.59 to 1.26, GRADE moderate quality). SAEs occurred in 7% (65/983) of natalizumab participants and 8% (36/431) of placebo participants (RR 0.76, 95% CI 0.37 to 1.56, GRADE low quality). Adverse events included headache, nausea, nasopharyngitis, abdominal pain, fatigue, vomiting, and exacerbation of CD. The study comparing combination therapy with natalizumab and infliximab to infliximab and placebo demonstrated similar remission rates at 10 weeks. Sixty-four per cent (33/52) of participants assigned to natalizumab and infliximab failed to achieve remission compared to 70% (19/27) assigned to placebo and infliximab (RR 0.90, 95% CI 0.65 to 1.24, GRADE moderate quality). The rates of AEs (moderate quality evidence), withdrawals due to AEs (low quality evidence) and serious AEs (low quality evidence) were similar across groups at 10 weeks. Adverse events included headache, exacerbation of CD, nausea, and nasopharyngitis. Natalizumab is associated with the development of progressive multifocal leukoencephalopathy (PML) resulting in some patient deaths. There are currently no tests which can reliably predict those at risk of developing PML. AUTHORS’ CONCLUSIONS: High quality data suggest that natalizumab is effective for induction of clinical remission and response in some patients with moderately to severely active CD. However, none of the included studies had the power to detect rare but serious adverse events such as PML. Due to the association with PML, and the availability of alternative agents that are not associated with PML, natalizumab is not likely to be used in patients who fail currently available medical therapy. The use of natalizumab in select patients (e.g. patients allergic to different biologics) needs to be carefully considered against the potential risk of developing PML. Further studies of natalizumab are not likely to be done.

Database: Medline

29. Cost-Effectiveness Analysis of Crohn’s Disease Treatment with Vedolizumab and Ustekinumab After Failure of Tumor Necrosis Factor-α Antagonist.

Author(s): Holko, Przemysław; Kawalec, Paweł; Pilc, Andrzej
OBJECTIVE The aim was to evaluate the cost-effectiveness of Crohn's disease (CD) treatment with vedolizumab and ustekinumab after failure of therapy with tumor necrosis factor-α antagonists (anti-TNFs).

METHODS The Markov model incorporated the lifetime horizon, synthesis-based estimates of biologics' efficacy in relation to anti-TNF exposure, and administration of biologics reflecting clinical practice (e.g., sequence of biologics, retreatment, 12-month treatment). The utilities, non-medical costs, and indirect costs were derived from a study of 200 adult patients with CD, while the healthcare costs were from a study of 1393 adults with CD who used biologics in Poland. The quality-adjusted life years (QALYs) and costs (the societal perspective) were discounted with the annual rates of 3.5 and 5%, respectively.

RESULTS The addition of vedolizumab (ustekinumab) to the sequence of available anti-TNFs (after first-line infliximab or after second-line adalimumab) led to a gain of 0.364 (0.349) QALYs at an additional cost of €5600.24 (€6593.82). The incremental cost-effectiveness ratios (ICERs) were €15,369 [95% confidence interval (CI) 7496-61,354] and €18,878 (95% CI 9213-85,045) per QALY gained with vedolizumab and ustekinumab, respectively. Sensitivity analyses revealed a high impact on the ICERs of the relapse rate after discontinuation of biologic treatment. The highest value of vedolizumab/ustekinumab was estimated after the failure of therapies with both anti-TNFs.

CONCLUSIONS CD treatment with ustekinumab or vedolizumab after failure of anti-TNF therapy appears to be cost-effective at a threshold of €31,500. The replacement of the second-line anti-TNF with ustekinumab/vedolizumab and the course of the disease after discontinuation of biologics are influential drivers of the cost-effectiveness.

Database: Medline

30. Genetic Markers Predict Primary Nonresponse and Durable Response to Anti-Tumor Necrosis Factor Therapy in Ulcerative Colitis.

Author(s): Burke, Kristin E; Khalili, Hamed; Garber, John J; Haritunians, Talin; McGovern, Dermot P B; Xavier, Ramnik J; Ananthakrishnan, Ashwin N

Source: Inflammatory bowel diseases; Jul 2018; vol. 24 (no. 8); p. 1840-1848

Publication Date: Jul 2018

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article

PubMedID: 29718226

Available at Inflammatory bowel diseases - from Unpaywall

Abstract: Background Despite a high nonresponse rate, predictors of response to anti-tumor necrosis factor (anti-TNF) therapy in ulcerative colitis (UC) remain limited. We aim to determine clinical and genetic predictors of primary nonresponse (PNR) and durable response (DR) to anti-TNF therapy in a large prospective UC cohort. Methods Using the Illumina Immunochip, candidate polymorphisms associated with clinical outcomes of PNR and DR were separately evaluated and combined into weighted genetic risk scores. Combined genetic and clinical multivariable models for PNR and DR were compared with clinical predictive models using area under the receiver operating characteristic (AUROC) curves. Models were internally (DR) or externally (PNR) validated. Multivariable logistic regression was utilized to assess the association of genetic risk scores with infliximab levels and
antibodies. Results of 231 patients, 28 (12%) experienced PNR and 120 (52%) experienced DR. There was no significant difference in clinical features between primary nonresponders and responders. Eight alleles were associated with PNR. A combined clinical-genetic model (AUROC, 0.87) more accurately predicted PNR compared with a clinical-only model (AUROC, 0.57; P < 0.0001). In an external cohort of 131 patients, increasing tertiles of PNR genetic risk score correlated with increased risk of PNR (P = 0.052). Twelve candidate loci were associated with DR. Genetic risk score quartiles for DR demonstrated a strong dose-response relationship in predicting treatment duration. Genetic risk scores for PNR and DR were not associated with infliximab levels or antibody formation. Conclusion Genetic polymorphisms enhance prediction of PNR and DR to anti-TNF therapy in patients with UC.

Database: Medline

31. Clinical Benefit of Long-Term Adalimumab Treatment in Patients With Crohn's Disease Following Loss of Response or Intolerance to Infliximab: 96-Week Efficacy Data From GAIN/ADHERE Trials.

Author(s): Panaccione, Remo; Sandborn, William J; D'Haens, Geert; Wolf, Douglas C; Berg, Sofie; Maa, Jen-Fue; Petersson, Joel; Robinson, Anne M

Source: Journal of Crohn's & colitis; Jul 2018; vol. 12 (no. 8); p. 930-938

Publication Date: Jul 2018

Publication Type(s): Multicenter Study Journal Article

PubMedID: 29697818

Available at Journal of Crohn's & colitis - from Unpaywall

Abstract: Background and Aims: In the 4-week GAIN clinical trial, adalimumab was efficacious in inducing remission in patients with moderate-to-severe Crohn's disease [CD] who had prior loss of response/intolerance to infliximab. The efficacy and safety of adalimumab in these patients are reported here for up to 96 weeks or for 3 years, respectively, in the ADHERE open-label extension study. Methods Patients who completed GAIN could enroll in ADHERE and receive open-label adalimumab 40 mg every other week. Efficacy variables included clinical response (Crohn's Disease Activity Index [CDAI] decrease from baseline ≥70/≥100 points [CR-70/CR-100]) and remission [CDAI<150], steroid discontinuation and fistula remission [absence of drainage]. Data were reported using hybrid non-responder imputation [hNRI], last observation carried forward and as-observed analysis. Subgroup analyses were performed by randomized group in GAIN and by Week 4 efficacy in GAIN. Safety was also assessed. Results A total of 310 patients from GAIN enrolled in ADHERE. CR-70, CR-100 and remission rates at Week 96 were 39.0%, 35.5%, and 26.5% [hNRI], respectively. Of the patients with CR-70 response or remission at Week 4 of GAIN, 45.5% and 44.4% [hNRI], respectively, maintained the effect at Week 96. Steroid discontinuation and steroid-free remission rates increased from Week 12 to 96 in patients using corticosteroids at GAIN baseline. Conclusions Long-term adalimumab maintenance therapy led to sustained clinical remission and response, and steroid discontinuation in a considerable proportion of patients with CD previously treated with infliximab. No new safety signals were observed in this patient population.

Database: Medline

32. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis.
Background and Aims
We sought to analyze whether response to a second-line biologic varies depending on the reason for discontinuation of the primary anti-TNF agent (primary non-response [PNR], secondary loss of response [LOR] after initial response, or intolerance), through a systematic review and meta-analysis.

Methods
Through a systematic search through May 31, 2017, we identified eight randomized controlled trials [RCTs] of biologics in patients with IBD with prior exposure to anti-TNF agents, that stratified response to second-line therapy by reason for discontinuing primary anti-TNF therapy [PNR vs. LOR vs. intolerance]. We estimated relative risk [RR] (and 95% confidence interval [CI]) of achieving clinical remission in patients with PNR as compared with patients with LOR, and intolerance, through random effects meta-analysis.

Results
As compared with patients who discontinued prior anti-TNF due to intolerance, patients with prior PNR were 24% less likely to achieve remission with second-line biologics (RR, 0.76 [0.61-0.96]). As compared with patients who discontinued prior anti-TNF due to LOR, patients with prior PNR were 27% less likely to achieve remission with induction therapy with second-line biologics (RR, 0.73 [0.56-0.97]), particularly to ustekinumab (RR, 0.64 [0.52-0.80]). There was no difference in response to vedolizumab in patients with prior PNR or LOR to anti-TNF agents (RR, 1.16 [0.85-1.58]).

Conclusion
Patients with PNR to anti-TNF agents are less likely to respond to second-line non-TNF biologics, as compared with patients who discontinued therapy due to secondary LOR or intolerance. This may be attributed to underlying pharmacokinetics and pharmacodynamics of anti-TNF agents in patients with PNR.

Database: Medline
trials, comparing ustekinumab with placebo in two sub-populations (conventional care failure and anti-TNFα failure patients) of adults with moderate-to-severe CD. Three trials assessed treatment induction over 8 weeks, while the fourth recruited successfully induced patients into a maintenance trial for 1 year. These trials showed ustekinumab to be more effective than placebo in terms of its ability to induce and maintain clinical response and remission. In the absence of any direct head-to-head data, the Company conducted a network meta-analysis (NMA), which synthesised induction trial data on ustekinumab and relevant comparators (vedolizumab, adalimumab and infliximab) using placebo data as a common comparator. This analysis found ustekinumab to be of comparable efficacy to previously approved biologics in treatment induction. A 'treatment sequence analysis' compared long-term treatment efficacy, finding ustekinumab to be comparable in maintaining treatment response and remission to the three other biologic therapies. However, the ERG had identified many limitations and potential bias in this analysis, and urged caution when interpreting the results. The Company's economic model estimated ustekinumab to be dominant in both sub-populations compared with conventional care; however, the ERG's preferred base-case estimated an incremental cost-effectiveness ratio of £109,279 in the conventional care failure sub-population, and £110,967 in the anti-TNFα failure sub-population when compared with conventional care. However, the ERG identified significant failings in both the model structure and data inputs, which could not be addressed without complete restructuring. The ERG considered that the economic analysis presented by the Company failed to adequately address the decision problem specified in NICE's scope. The NICE Appraisal Committee recommended ustekinumab within its market authorisation, on the grounds of sufficiently similar efficacy and costs to previously recommended biologic therapies. However, the ERG's analyses demonstrated that all currently recommended biologics are unlikely to be cost effective relative to conventional care, raising broader questions regarding the appropriateness of cost-comparison exercises for decision making.

**Database:** Medline

34. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn’s Disease.

**Author(s):** D’Haens, Geert; Vermeire, Severine; Lambrecht, Guy; Baert, Filip; Bossuyt, Peter; Pariente, Benjamin; Buisson, Anthony; Bouhnik, Yoram; Filippi, Jérôme; Vander Woude, Janneke; Van Hooftegem, Philippe; Moreau, Jacques; Louis, Edouard; Franchimont, Denis; De Vos, Martine; Mana, Fazia; Peyrin-Biroulet, Laurent; Brixi, Hedia; Allez, Matthieu; Caenepeel, Philip; Aubourg, Alexandre; Oldenburg, Bas; Pierik, Marieke; Gils, Ann; Chevret, Sylvie; Laharie, David; GETAID

**Source:** Gastroenterology; Apr 2018; vol. 154 (no. 5); p. 1343

**Publication Date:** Apr 2018

**Publication Type(s):** Research Support, Non-u.s. Gov’t Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 29317275

**Abstract:** BACKGROUND & AIM: A combination of infliximab and immunomodulators is the most efficacious treatment for Crohn’s disease (CD). Patients have the best outcomes when their serum concentrations of these drugs are above a determined therapeutic threshold. We performed a prospective, randomized trial to determine whether therapeutic drug monitoring (TDM) to maintain serum levels of infliximab above 3 μg/mL produced higher rates of clinical and endoscopic remission than adapting dose based only on symptoms. METHODS: We performed a double-blind trial in which 122 biologic-naïve adult patients with active CD (71 female, median age 29.8 years) received induction treatment with infliximab in combination with an immunosuppressant, from July 2012 through September 2015 at 27 centers in Europe. At week 14 of treatment, patients were randomly
assigned (1:1:1) to 3 infliximab maintenance groups: dose increases (2 maximum) in steps of 2.5 mg/kg based on clinical symptoms and biomarker analysis and/or serum infliximab concentrations (dose intensification strategy [DIS1 group]; dose increase from 5 to 10 mg/kg based on the same criteria [DIS2 group]; dose increase to 10 mg/kg based on clinical symptoms alone [controls]). Patients’ CD activity index scores, levels of C-reactive protein, fecal levels of calprotectin, and serum concentrations of infliximab were determined at baseline and at weeks 2, 4, 6, 12, and 14 of treatment, and then every 4 weeks thereafter until week 54. The primary endpoint was sustained corticosteroid-free clinical remission (CD activity index <150) from weeks 22 through 54 with no ulcers at week 54.

RESULTSThe primary endpoint was reached by 15 (33%) of 45 patients in the DIS1 group, 10 (27%) of 37 patients in the DIS2 group, and 16 (40%) of 40 patients in the control group (P = .50).

CONCLUSIONSIn a prospective randomized exploratory trial of patients with active CD, we found increasing dose of infliximab based on a combination of symptoms, biomarkers, and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone.

EUDRACT NUMBER2011-003038-14.

Database: Medline

35. Long-term Outcomes After Switching to CT-P13 in Pediatric-Onset Inflammatory Bowel Disease: A Single-Center Prospective Observational Study.

Author(s): Kang, Ben; Lee, Yoon; Lee, Kiwuk; Choi, Young Ok; Choe, Yon Ho

Source: Inflammatory bowel diseases; Feb 2018; vol. 24 (no. 3); p. 607-616

Publication Date: Feb 2018

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article Observational Study

PubMedID: 29390113

Available at Inflammatory bowel diseases - from Unpaywall

Abstract:BackgroundThe relatively high cost and patent expiry of infliximab, an anti-tumor necrosis factor monoclonal antibody used in inflammatory bowel disease (IBD), has led to the development of biosimilar versions of the reference product (RP). This study investigated the long-term efficacy, safety, pharmacokinetics, and immunogenicity of CT-P13 after switching from infliximab RP in pediatric-onset IBD patients. MethodsIn this prospective observational study, patients with pediatric-onset IBD receiving maintenance infliximab RP were followed for 1 year after continuing infliximab RP (RP maintenance group) or switching to CT-P13 (CT-P13 switch group). Primary end points were the proportion of patients continuously receiving infliximab and the proportion achieving persistent remission-corticosteroid-free sustained clinical remission without dose intensification-at 1 year. ResultsThirty-six patients were recruited to the RP maintenance group and 38 to the CT-P13 switch group. At 1 year in the RP maintenance group and CT-P13 switch group, 86.1% (31/36) and 92.1% (35/38) patients had continuously received infliximab (P = 0.649), and 77.8% (28/36) and 78.9% (30/38) patients experienced persistent remission (P = 1.000), respectively. There were no statistically significant differences in any measures of disease activity, pharmacokinetics, or immunogenicity between the time of switch and 1-year postswitch in the CT-P13 switch group. Twenty-seven adverse events occurred in the maintenance group and 30 in the switch group. ConclusionsSwitching from maintenance infliximab RP to CT-P13 did not result in any significant differences in efficacy, pharmacokinetics, or immunogenicity in patients with pediatric-onset IBD, and no unexpected safety issues occurred, supporting findings from randomized controlled trials.

Database: Medline
36. An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients.

**Author(s):** Kawalec, Paweł; Moćko, Paweł

**Source:** Journal of comparative effectiveness research; Feb 2018; vol. 7 (no. 2); p. 101-111

**Publication Date:** Feb 2018

**Publication Type(s):** Meta-analysis Comparative Study Journal Article Systematic Review

**PubMedID:** 29115855

**Abstract:** AIM An indirect comparison of ustekinumab versus vedolizumab in patients with active moderate-to-severe Crohn's disease who were nonresponsive or intolerant to previous TNF-antagonist therapy. METHODSA systematic review was performed in Medline via PubMed, Embase, Cochrane Library, until 30 April 2017. Inclusion criteria were: randomized controlled trials, patients treated for Crohn's disease, ustekinumab or vedolizumab therapy. Included trials were critically appraised and afterward indirect comparison by Bucher was conducted; the manuscript was prepared in accordance to the PRISMA requirements. RESULTS Five randomized controlled trials were included and assessed for homogeneity; they occurred eligible for indirect comparison referring to induction or maintenance phase of TNF-antagonist failure population treatment; no statistically significant differences in clinical response (relative benefit [RB]: 1.14; 95% CI: 0.65-1.99; \( p = 0.64 \)) as well as in clinical remission (RB: 1.16; 95% CI: 0.54-2.48; \( p = 0.71 \)) in induction phase of therapy were revealed; no significant disparity was presented in a maintenance phase in clinical remission (RB: 0.72; 95% CI: 0.30-1.68; \( p = 0.44 \)). No significant differences were also revealed in primary and secondary nonresponders subpopulations in clinical response. Indirect comparison of the safety profile presented no statistically significant difference between the biologics (relative risk [RR]: 0.93; 95% CI: 0.81-1.08; \( p = 0.35 \)). CONCLUSION No significant differences between vedolizumab and ustekinumab in clinical response and clinical remission for induction and remission in maintenance phase of TNF refractory patients therapy were revealed. In addition, no significant disparities in the risk of adverse events suggest a similar safety profile.

**Database:** Medline

37. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab.

**Author(s):** Laharie, D; Bourreille, A; Branche, J; Allez, M; Bouhnik, Y; Filippi, J; Zerbib, F; Savoye, G; Vuitton, L; Moreau, J; Amiot, A; Cosnes, J; Ricart, E; Dewit, O; Lopez-Sanroman, A; Fumery, M; Carbonnel, F; Bommelaer, G; Coffin, B; Roblin, X; van Assche, G; Esteve, M; Farkkila, M; Gisbert, J P; Marteau, P; Nahon, S; de Vos, M; Lambert, J; Mary, J Y; Louis, E; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives

**Source:** Gut; Feb 2018; vol. 67 (no. 2); p. 237-243

**Publication Date:** Feb 2018

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 28053054

**Abstract:** OBJECTIVE Ciclosporin and infliximab have demonstrated short-term similar efficacy as second-line therapies in patients with acute severe UC (ASUC) refractory to intravenous steroids. The aim of this study was to assess long-term outcome of patients included in a randomised trial.
comparing ciclosporin and infliximab. DESIGN Between 2007 and 2010, 115 patients with steroid-refractory ASUC were randomised in 29 European centres to receive ciclosporin or infliximab in association with azathioprine. Patients were followed until death or last news up to January 2015. Colectomy-free survival rates at 1 and 5 years and changes in therapy were estimated through Kaplan-Meier method and compared between initial treatment groups through log-rank test. RESULTS After a median follow-up of 5.4 years, colectomy-free survival rates (95% CI) at 1 and 5 years were, respectively, 70.9% (59.2% to 82.6%) and 61.5% (48.7% to 74.2%) in patients who received ciclosporin and 69.1% (56.9% to 81.3%) and 65.1% (52.4% to 77.8%) in those who received infliximab (p=0.97). Cumulative incidence of first infliximab use at 1 and 5 years in patients initially treated with ciclosporin was, respectively, 45.7% (32.6% to 57.9%) and 57.1% (43.0% to 69.0%). Only four patients from the infliximab group were subsequently switched to ciclosporin. Three patients died during the follow-up, none directly related to UC or its treatment. CONCLUSIONS In this cohort of patients with steroid-refractory ASUC initially treated by ciclosporin or infliximab, long-term colectomy-free survival was independent from initial treatment. These long-term results further confirm a similar efficacy and good safety profiles of both drugs and do not favour one drug over the other. TRIAL REGISTRATION NUMBER EudraCT: 2006-005299-42; ClinicalTrials.gov number: NCT00542152; post-results.

Database: Medline

38. Optimizing Selection of Biologics in Inflammatory Bowel Disease: Development of an Online Patient Decision Aid Using Conjoint Analysis.

Author(s): Almario, Christopher V; Keller, Michelle S; Chen, Michelle; Lasch, Karen; Ursos, Lyann; Shklovskaya, Julia; Melmed, Gil Y; Spiegel, Brennan M R

Source: The American journal of gastroenterology; Jan 2018; vol. 113 (no. 1); p. 58-71

Publication Date: Jan 2018

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article

PubMedID: 29206816

Available at The American journal of gastroenterology - from ProQuest (Health Research Premium) - NHS Version

Abstract: OBJECTIVES Recent drug approvals have increased the availability of biologic therapies for inflammatory bowel disease (IBD), making it difficult for patients with ulcerative colitis (UC) and Crohn's disease (CD) to navigate treatment options. Here we developed a conjoint analysis to examine patient decision-making surrounding biologic medicines for IBD. We used the results to create an online patient decision aid that generates a unique "preferences report" for each patient to assist with shared decision-making with their provider. METHODS We administered an adaptive choice-based conjoint survey to IBD patients that quantifies the relative importance of biologic attributes (e.g., efficacy, side effect profile, mode of administration, and mechanism of action) in decision making. The conjoint software determined individual patient preferences by calculating part-worth utilities for each attribute. We conducted regression analyses to determine if demographic and disease characteristics (e.g., type of IBD and severity) predicted how patients made decisions. RESULTS 640 patients completed the survey (UC=304; CD=336). In regression analyses, demographics and IBD characteristics did not predict individual patient preferences; the main exception was IBD type. When compared to UC, CD patients were more likely to report side effect profile as most important (odds ratio (OR) 1.63, 95% confidence interval (CI) 1.16-2.30). Conversely, those with UC were more likely to value therapeutic efficacy (OR 1.41, 95% CI 1.01-2.00). CONCLUSIONS Biologic decision-making is highly personalized; demographic and disease characteristics poorly predict individual preferences, indicating that IBD patients are unique and
difficult to statistically categorize. The online decision tool resulting from this study (www.ibdandme.org) may be used by patients to support shared decision-making and optimize personalized biologic selection with their provider.

**Database:** Medline

39. **Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis.**

**Author(s):** Singh, S; Fumery, M; Sandborn, W J; Murad, M H

**Source:** Alimentary pharmacology & therapeutics; Jan 2018; vol. 47 (no. 2); p. 162-175

**Publication Date:** Jan 2018

**Publication Type(s):** Meta-analysis Journal Article Review

**PubMedID:** 29205406

Available at Alimentary pharmacology & therapeutics - from Wiley Online Library Free Content - NHS

Available at Alimentary pharmacology & therapeutics - from Unpaywall

**Abstract:** BACKGROUND There are limited data to inform positioning of agents for treating moderate-severe ulcerative colitis (UC). AIM To assess comparative efficacy and safety of different therapies as first-line (biologic-naïve) and second-line (prior exposure to anti-tumour necrosis factor(TNF)-α) agents for moderate-severe UC, through a systematic review and network meta-analysis, and appraise quality of evidence (QoE) using grading of recommendations, assessment, development and evaluation (GRADE) approach. METHODS We identified randomised controlled trials (RCTs) in adults with moderate-severe UC treated with anti-TNF agents, anti-integrin agents and janus kinase (JAK) inhibitors, as first-line or second-line agents, and compared with placebo or another active agent. Efficacy outcomes were induction/maintenance of remission and mucosal healing; and safety outcomes were serious adverse events and infections. Network meta-analyses were performed, and ranking was assessed using surface under the cumulative ranking (SUCRA) probabilities. RESULTS In biologic-naïve patients (12 trials, no head-to-head comparisons), infliximab and vedolizumab were ranked highest for induction of clinical remission (infliximab: odds ratio [OR], 4.10 [95% confidence intervals [CI], 2.58-6.52]; SUCRA, 0.85; vedolizumab:SUCRA, 0.82) and mucosal healing (infliximab:SUCRA, 0.91; vedolizumab:SUCRA, 0.81) (moderate QoE). In patients with prior anti-TNF exposure (4 trials, no head-to-head comparisons), tofacitinib was ranked highest for induction of clinical remission (OR, 11.88 [2.32-60.89]; SUCRA, 0.96) and mucosal healing (moderate QoE). Differences in trial design limited comparability of trials of maintenance therapy for efficacy. Vedolizumab was ranked safest in terms of serious adverse events (SUCRA, 0.91), and infection (SUCRA, 0.75) in maintenance trials. CONCLUSIONS Infliximab and vedolizumab are ranked highest as first-line agents, and tofacitinib is ranked highest as second-line agent, for induction of remission and mucosal healing in patients with moderate-severe UC, based on indirect comparisons. Head-to-head trials are warranted to inform clinical decision-making with greater confidence.

**Database:** Medline

40. **Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease.**

**Author(s):** Atreya R., Neurath M.F.

**Source:** The Lancet Gastroenterology and Hepatology. 3 (11) (pp 790-802), 2018. Date of Publication: November 2018.
Biological therapy has led to marked improvements in treatment of patients with inflammatory bowel disease, and an increasing number of drugs has been approved for treatment. However, only a subgroup of patients responds to therapy, highlighting the need to identify biomarkers for therapeutic response to allow personalised medicine in inflammatory bowel disease. Potential markers of response to biological therapy have been identified; however, studies also suggest that changes in the composition of immune cell infiltrates in response to therapeutic pressure lead to molecular resistance to these drugs. For instance, the cytokine interleukin 23 has been identified as a driver of evasion of apoptosis in response to anti-tumour necrosis factor drugs in patients with Crohn's disease, leading to expansion of apoptosis-resistant T cells and drug resistance. In this Review, we examine the concept of molecular resistance to biological therapy and discuss implications for future therapy. Copyright © 2018 Elsevier Ltd

**Database:** Embase

41. Comparative effectiveness of the biosimilar CT-P13.

**Author(s):** Yoo DH.


**Abstract:** The first biosimilar infliximab, CT-P13 (infliximab-dyyb) has been used for the treatment of inflammatory diseases for 4 years. CT-P13 has highly similar efficacy and safety profiles with a lower price than the originator infliximab and has been approved in 81 countries. Despite approval for clinical use, some knowledge gaps still limit the widespread and pertinent use of biosimilar CT-P13. One of the most important factors for proper utilization of CT-P13 for the treatment of immune-mediated inflammatory diseases is confidence in CT-P13, which could be enhanced by scientific evidence supporting the biosimilarity of CT-P13. Overall, five randomized controlled studies have been performed. For the other extrapolated indications, many observational induction and switching studies also support the utility of CT-P13 in the treatment of inflammatory diseases. Here, we review profiles of CT-P13 including physicochemical properties, clinical efficacy and safety data in all indications and current status.

**Database:** PubMed

42. Infliximab Biosimilars in the Treatment of Inflammatory Bowel Diseases: A Systematic Review.

**Author(s):** Radin M, Sciascia S, Roccatello D, Cuadrado MJ


**Abstract:** BACKGROUND: Biological therapies represent a fundamental innovation for the management of inflammatory bowel diseases (IBD). However, many biological originators have reached, or are about to reach, patent expiry and long-term therapy costs have become progressively unsustainable. CT-P13, a biosimilar of the anti-tumor necrosis factor (anti-TNF) monoclonal antibody infliximab, might represent a significant alternative to its originator, with the potential to decrease medical care costs and, therefore, become available to a large number of patients. OBJECTIVES: In this systematic review, we analyzed the data from available clinical trials that recently investigated the validity of indication extrapolation of CT-P13 for the treatment of IBD.
in naïve patients and in patients who switched from its originator infliximab, focusing on clinical efficacy, safety and immunogenicity. 

**METHODS:** A detailed literature search was developed a priori to identify articles that investigated the validity of indication extrapolation of CT-P13 for the treatment of IBD in TNF inhibitor treatment-naïve patients and in patients who switched from the originator infliximab. This was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus for content from 2012 to September 2016. 

**RESULTS:** We based our review on the available data from 11 studies that included a total of 1007 IBD patients: 570 patients suffering from Crohn’s disease (294 switched and 276 naïve), 435 patients suffering from ulcerative colitis (127 switched and 308 naïve), and two IBD unclassified patients (switched). Overall, no significant difference in efficacy and safety between the originator infliximab and its biosimilar CT-P13 was observed. When assessing the safety of CT-P13, we found that 9.2% of patients experienced adverse effects (4.1% infusion-related reactions and 4.3% infections). 

**CONCLUSION:** The analyzed studies did not report a significant difference in terms of efficacy, safety and immunogenicity when comparing the clinical experience with CT-P13 with the available literature data on the originator treatment in IBD. However, some debate is ongoing regarding interchangeability and immunogenicity.

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### 43. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial.

**Author(s):** Ponsioen, Cyriel Y; de Groof, E Joline; Eshuis, Emma J; Gardenbroek, Tjibbe J; Bossuyt, Patrick M M; Hart, Ailsa; Warusavitarne, Janindra; Buskens, Christianne J; van Bodegraven, Ad A; Brink, Menno A; Consten, Esther C J; van Wagensveld, Bart A; Rijk, Marno C M; Crolla, Rogier M P H; Noomen, Casper G; Houdijk, Alexander P J; Mallant, Rosalie C; Boom, Maarten; Marsman, Willem A; Stockmann, Hein B; Mol, Bregje; de Groof, A Jeroen; Stokkers, Pieter C; D’Haens, Geert R; Bemelman, Willem A; LIR!C study group

**Source:** The lancet. Gastroenterology & hepatology; Nov 2017; vol. 2 (no. 11); p. 785-792

**Publication Date:** Nov 2017

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 28838644

**Abstract:** BACKGROUNDTreatment of patients with ileocaecal Crohn’s disease who have not responded to conventional therapy is commonly scaled up to biological agents, but surgery can also offer excellent short-term and long-term results. We compared laparoscopic ileocaecal resection with infliximab to assess how they affect health-related quality of life. METHODSIn this randomised controlled, open-label trial, in 29 teaching hospitals and tertiary care centres in the Netherlands and the UK, adults with non-stricturing, ileocaecal Crohn’s disease, in whom conventional therapy has failed were randomly allocated (1:1) by an internet randomisation module with biased-coin minimisation for participating centres and perianal fistula to receive laparoscopic ileocaecal resection or infliximab. Eligible patients were aged 18-80 years, had active Crohn’s disease of the terminal ileum, and had not responded to at least 3 months of conventional therapy with glucocorticosteroids, thiopurines, or methotrexate. Patients with diseased terminal ileum longer than 40 cm or abdominal abscesses were excluded. The primary outcome was quality of life on the Inflammatory Bowel Disease Questionnaire (IBDQ) at 12 months. Secondary outcomes were general quality of life, measured by the Short Form-36 (SF-36) health survey and its physical and mental component subscales, days unable to participate in social life, days on sick leave, morbidity (additional procedures and hospital admissions), and body image and cosmesis. Analyses of the
primary outcome were done in the intention-to-treat population, and safety analyses were done in the per-protocol population. This trial is registered at the Dutch Trial Registry (NTR1150).

**FINDINGS**

Between May 2, 2008, and October 14, 2015, 73 patients were allocated to have resection and 70 to receive infliximab. Corrected for baseline differences, the mean IBDQ score at 12 months was 178·1 (95% CI 171·1-185·0) in the resection group versus 172·0 (164·3-179·6) in the infliximab group (mean difference 6·1 points, 95% CI -4·2 to 16·4; p=0·25). At 12 months, the mean SF-36 total score was 112·1 (95% CI 108·0-116·2) in the resection group versus 106·5 (102·1-110·9) in the infliximab group (mean difference 5·6, 95% CI -0·4 to 11·6), the mean physical component score was 47·7 (45·7-49·7) versus 44·6 (42·5-46·8; mean difference 3·1, 95% CI 0·3 to 17·3), and the mean mental component score was 49·5 (47·0-52·1) versus 46·1 (43·3-48·9; mean difference 3·5, 95% CI 0·3 to 7·3). Mean numbers of days of sick leave were 3·4 days (SD 7·1) in the resection group versus 1·4 days (SD 4·7) in the infliximab group (p<0·0001), days not able to take part in social life were 1·8 days (SD 6·3) versus 1·1 days (SD 4·5; p=0·20), days of scheduled hospital admission were 6·5 days (IQR 3·8-16·8) at baseline versus 17·8 (17·1-18·4) at 12 months, and cosmetic scale mean scores were 17·6 (16·6-18·6) versus 18·6 (17·6-19·6). Surgical intervention-related complications classified as IIIa or worse on the Clavien-Dindo scale occurred in four patients in the infliximab group. During a median follow-up of 4 years (IQR 2-6), 26 (37%) of 70 patients in the infliximab group had resection, and 19 (26%) of 73 patients in the resection group received anti-TNF.

**INTERPRETATION**

Laparoscopic resection in patients with limited (diseased terminal ileum <40 cm), non-stricturing, ileocaecal Crohn’s disease in whom conventional therapy has failed could be considered a reasonable alternative to infliximab therapy.

**FUNDING**

Netherlands Organisation for Health Research and Development.

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44. Efficacy and safety of ustekinumab in the induction therapy of TNF-α-refractory Crohn’s disease patients: a systematic review and meta-analysis.

**Author(s)**: Kawalec, Paweł; Moćko, Paweł; Malinowska-Lipien, Iwona; Brzostek, Tomasz

**Source**: Journal of comparative effectiveness research; Oct 2017; vol. 6 (no. 7); p. 601-612

**Publication Date**: Oct 2017

**Publication Type(s)**: Meta-analysis Comparative Study Journal Article Systematic Review

**PubMedID**: 28660802

**Abstract**: AIM The aim of the systematic review and meta-analysis was to assess the efficacy and safety of ustekinumab in the induction therapy of anti-TNF-α failure patients with Crohn’s disease. METHODS A systematic literature search was conducted in Medline (PubMed), EMBASE, Cochrane Library until 30 December 2016. We included randomized controlled trials that compared efficacy (clinical response and remission) and safety profile of ustekinumab in TNF-α failure Crohn’s disease patients; primary and secondary TNF-α nonresponders or intolerant patients were also assessed. Included studies were critically appraised according to the PRISMA statement protocol; data aggregation with a RevMan® software was performed. RESULTS Three randomized controlled trials were revealed in the systematic review but only two of them (CERTIFI and UNITI-1) were homogenous to be included in the meta-analysis; aggregation of data only for induction phase of therapy was possible. Clinical response was significantly higher for patients who received ustekinumab compared with placebo patients in a group of TNF-α antagonist failure patients (relative benefit [RB] = 1.62; 95% CI: 1.28-2.04) and in the following subgroups: secondary nonresponders (RB = 1.98; 95% CI: 1.49-2.63), intolerant patients (RB = 1.47; 95% CI: 1.01-2.13) and
patients who failed at least two TNF-α antagonists (RB = 2.19; 95% CI: 1.53-3.14) but in case of primary nonresponders it occurred insignificant (RB = 1.22; 95% CI: 0.76-1.98). The clinical remission in TNF-α antagonist failure population was significantly higher for patients who received ustekinumab compared with placebo (RB = 1.72; 95% CI: 1.17-2.53). Pooled analysis revealed that risk of adverse events in induction phase of therapy was not significantly different (risk ratio = 0.96; 95% CI: 0.86-1.06) between ustekinumab and placebo groups.

**CONCLUSION** The clinical response was significantly higher for TNF-α antagonist failure patients who received ustekinumab as well as in subgroups of secondary nonresponders or intolerant patients but not in case of primary nonresponders. Ustekinumab occurred as safe as placebo in the induction as well as in a maintenance phase of therapy.

**Database:** Medline

45. A comparison of short-term therapeutic efficacy between infliximab and tacrolimus for moderate to severe ulcerative colitis.

**Author(s):** Yamagami, Hirokazu; Nishida, Yu; Nagami, Yasuaki; Hosomi, Shuhei; Yukawa, Tomomi; Otani, Koji; Tanaka, Fumio; Taira, Koichi; Kamata, Noriko; Tanigawa, Tetsuya; Shiba, Masatsugu; Watanabe, Toshio; Fujiwara, Yasuhiro

**Source:** Romanian journal of internal medicine = Revue roumaine de medecine interne; Sep 2017; vol. 55 (no. 3); p. 151-157

**Publication Date:** Sep 2017

**Publication Type(s):** Comparative Study Journal Article

**PubMedID:** 28222041

Available at Romanian journal of internal medicine = Revue roumaine de medecine interne - from Unpaywall

**Abstract:** INTRODUCTION Both infliximab (IFX) and tacrolimus (Tac) are effective for inducing clinical remission in patients with ulcerative colitis (UC). However, no randomized study has addressed the relative efficacies of IFX and Tac for patients with moderate to severe UC. This study aimed to conduct a retrospective study on the relative efficacy of IFX and Tac in patients with moderate to severe UC, using an inverse probability of treatment weighting (IPTW) technique to adjust background factors statistically.

**METHODS** Between July 2009 and March 2016, data obtained from 122 patients with moderate to severe UC who were treated with either IFX (n = 58) or Tac (n = 64) were analyzed retrospectively. We compared the short-term therapeutic efficacy between the IFX group and Tac group using IPTW technique.

**RESULT** The clinical remission rate at 14 weeks after treatment was 37.9% (22/58) in the IFX group and 50% (32/64) in the Tac group, respectively. The efficacy of IFX and Tac for clinical remission rate was not different according to univariate (Odds ratio [OR] 1.64, 95% confidence interval [CI] 0.80-3.37 P = 0.18) and multivariate analyses (OR 2.19, 95% CI 0.85-5.61, P = 0.10). After the background and confounders factors were adjusted by using IPTW based on propensity score, the efficacy of IFX and Tac for clinical remission rate was not differed statistically (OR, 1.483; 95% CI, 0.581-3.785; P = 0.409). Conclusion. IFX and Tac have equivalent short-term efficacies for induction in patients with moderate to severe UC.

**Database:** Medline

46. Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review.

**Author(s):** Strand, Vibeke; Balsa, Alejandro; Al-Saleh, Jamal; Barile-Fabris, Leonor; Horiuchi, Takahiko; Takeuchi, Tsutomu; Lula, Sadiq; Hawes, Charles; Kola, Blerina; Marshall, Lisa
OBJECTIVES A systematic review was conducted to explore the immunogenicity of biologic agents across inflammatory diseases and its potential impact on efficacy/safety.

METHODS Literature searches were conducted through November 2016 to identify controlled and observational studies of biologics/biosimilars administered for treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), psoriasis (Ps), Crohn's disease, and ulcerative colitis. RESULTS Of >21,000 screened publications, 443 were included. Anti-drug antibody (ADAb) rates varied widely among biologics across diseases (and are not directly comparable because of immunoassay heterogeneity); the highest overall rates were reported with infliximab (0-83%), adalimumab (0-54%), and infliximab biosimilar CT-P13 (21-52%), and the lowest with secukinumab (0-1%), ustekinumab (1-11%), etanercept (0-13%), and golimumab (0-19%). Most ADAbs were neutralizing, except those to abatacept and etanercept. ADAb+ versus ADAb- patients had lower rates of clinical response to adalimumab (RA, PsA, JIA, AS, Ps), golimumab (RA), infliximab (RA, PsA, AS, Ps), rituximab (RA), ustekinumab (Ps), and CT-P13 (RA, AS). Higher rates of infusion-related reactions were reported in infliximab- and CT-P13-treated ADAb+ patients. Background immunosuppressives/anti-proliferatives reduced biologic immunogenicity across diseases. CONCLUSIONS Based on reviewed reports, biologic/biosimilar immunogenicity differs among agents, with the highest rates observed with infliximab and adalimumab. As ADAb formation in biologic/biosimilar-treated patients may increase the risk of lost response, the immunogenicity of these agents is an important (albeit not the only) consideration in the treatment decision-making process.
consented to participate in a genetics registry and been treated with anti-TNF agents were evaluated retrospectively and categorized as primary nonresponders or secondary nonresponders. We evaluated clinical, serological, and genetic characteristics associated with primary nonresponse or time to loss of response to anti-TNF agents.

**RESULTS**

We included 314 CD (51 [16.2%] primary nonresponders and 179 [57.0%] secondary nonresponders) and 145 subjects with ulcerative colitis (43 [29.7%] primary nonresponders and 74 [51.0%] secondary nonresponders). Colonic involvement (P = 0.017; odds ratio = 8.0) and anti-TNF monotherapy (P = 0.017; odds ratio = 4.9) were associated in a multivariate analysis with primary nonresponse to anti-TNF agents in CD. In addition, higher anti-nuclear cytoplasmic antibody levels (P = 0.019; hazard ratio = 1.01) in CD, anti-nuclear cytoplasmic antibody positivity (P = 0.038; hazard ratio = 1.6) in ulcerative colitis, and a positive family history of IBD (P = 0.044; hazard ratio = 1.3) in all patients with IBD were associated with time to loss of response to anti-TNF agents. Furthermore, various known IBD susceptibility single-nucleotide polymorphisms and additional variants in immune-mediated genes were shown to be associated with primary nonresponse or time to loss of response.

**CONCLUSIONS**

Our results may help to optimize the use of anti-TNF agents in clinical practice and position these therapies appropriately as clinicians strive for a more personalized approach to managing IBD.

Database: Medline

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**48. Clinical performance of an infliximab rapid quantification assay.**


**Source:** Therapeutic Advances in Gastroenterology. 10 (9) (pp 651-660), 2017. Date of Publication: 01 Sep 2017.

Background: Therapeutic drug monitoring (TDM)-based algorithms can be used to guide infliximab (IFX) adjustments in inflammatory bowel disease (IBD) patients. This study aimed to explore a rapid IFX-quantification test from a clinical perspective.

Method(s): This manuscript describes a prospective cohort study involving 110 ulcerative colitis (UC) patients on the maintenance phase of IFX. IFX trough levels were quantified using a rapid quantification assay and a commonly-used reference kit.

Result(s): Irrespective of the assay used to measure IFX, its through levels were statistically different between patients with and without endoscopic remission (Mayo endoscopic score = 0), as well as between patients stratified by their faecal calprotectin (FC) levels. Despite the fact that the two methods correlated well with each other [Spearman’s rank correlation coefficient = 0.843, p < 0.001; intraclass correlation coefficients = 0.857, 95% confidence interval (CI): 0.791-0.903], there was a discernible systematic variation; values obtained with the reference kit were on average 2.62 units higher than those obtained with the rapid assay. Notwithstanding, 3 mug/ml was shown to be an acceptable cut-off to assess endoscopic status and inflammatory burden levels using both assays. The percentage of patients that had a positive outcome when the IFX concentration measured by the rapid assay ranked above 3 mug/ml was 88% both for a Mayo endoscopic score 1/2 1 and for an FC concentration <250 mug/g.

Conclusion(s): Based on this study, we concluded that using the rapid IFX assessment system with a 3 mug/ml threshold is a reliable alternative to the time-consuming enzyme-linked immunosorbent assays in patients on the maintenance phase of IFX.

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Database: Embase
49. Therapeutic drug monitoring of CT-P13: A comparison of four different immunoassays.

Author(s): Afonso J., De Sousa H.T., Rosa I., Carvalho J., Dias C.C., Magro F.

Source: Therapeutic Advances in Gastroenterology. 10 (9) (pp 661-671), 2017. Date of Publication: 01 Sep 2017.

Background: The commercialization of CT-P13, an infliximab (IFX) biosimilar, has the potential to decrease health-related costs and enhance access to biological therapies. This study aimed to address the accuracy and inter-assay agreement of the CT-P13 quantification using four different assays initially developed to assess IFX. Method(s): The four different methods, one in-house method and three commercially available kits, were used to quantify exogenously-spiked samples and the sera from 185 inflammatory bowel disease (IBD) patients on CT-P13 therapy. Result(s): The quantification of the spiked samples unveiled a consistent and accurate behaviour of three of the tested methods, with average percentage recoveries of 90%, 102% and 109%. Results from the clinical samples demonstrated that these three assays were also highly correlated, both concerning Spearman’s rank coefficients (range 0.890-0.947) and intraclass correlation coefficients (range 0.907-0.935). There were a few systematic deviations among them, but their impact in the clinical stratification of the patients using different cut-offs was minimal, particularly when these cut-offs were in the 3-4 mug/ml range, for which the strength of agreement (as assessed by the Kappa statistics that ranged from 0.732 to 0.902) was substantial to almost perfect. Conclusion(s): Our results indicate that three of the tested IFX quantification methods can be used to accurately quantify CT-P13 without any adjustments. Copyright © SAGE Publications.

50. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial.

Author(s): Jørgensen, Kristin K; Olsen, Inge C; Goll, Guro L; Lorentzen, Merete; Bolstad, Nils; Haavardsholm, Espen A; Lundin, Knut E A; Mørk, Cato; Jahnsen, Jørgen; Kvien, Tore K; NOR-SWITCH study group

Source: Lancet (London, England); Jun 2017; vol. 389 (no. 10086); p. 2304-2316

Publication Date: Jun 2017

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Clinical Trial, Phase Iv Journal Article

PubMedID: 28502609

Available at Lancet (London, England) - from ProQuest (Health Research Premium) - NHS Version

Abstract: BACKGROUND TNF inhibitors have improved treatment of Crohn’s disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, but are expensive therapies. The aim of NOR-SWITCH was to examine switching from originator infliximab to the less expensive biosimilar CT-P13 regarding efficacy, safety, and immunogenicity. METHODS The study is a randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up. Adult patients on stable treatment with infliximab originator treated in a hospital setting for at least 6 months were eligible for participation. Patients with informed consent were randomised in a 1:1 ratio to either continued infliximab originator or to switch to CT-P13 treatment, with unchanged...
dosing regimen. Data were collected at infusion visits in 40 Norwegian study centres. Patients, assessors, and patient care providers were masked to treatment allocation. The primary endpoint was disease worsening during 52-week follow-up. 394 patients in the primary per-protocol set were needed to show a non-inferiority margin of 15%, assuming 30% disease worsening in each group. This trial is registered with ClinicalTrials.gov, number NCT02148640.

**FINDINGS**

Between Oct 24, 2014, and July 8, 2015, 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group). 155 (32%) patients in the full analysis set had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference -4.4%, 95% CI -12.7 to 3.9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for infliximab originator vs 21 [9%] for CT-P13; for overall adverse events, 168 [70%] vs 164 [68%]; and for adverse events leading to discontinuation, nine [4%] vs eight [3%], respectively).

**INTERPRETATION**

The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. The study was not powered to show non-inferiority in individual diseases.

**FUNDING**

Norwegian Ministry of Health and Care Services.

**Database:** Medline

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51. Biological Therapy in Pediatric Inflammatory Bowel Disease: A Systematic Review.

**Author(s):** Corica, Domenico; Romano, Claudio

**Source:** Journal of clinical gastroenterology; Feb 2017; vol. 51 (no. 2); p. 100-110

**Publication Date:** Feb 2017

**Publication Type(s):** Journal Article Review Systematic Review

**PubMedID:** 27636407

**Abstract:** The incidence of inflammatory bowel disease (IBD) has increased steadily worldwide, both in adult and in children; approximately 25% of IBD patients are diagnosed before the age of 18. The natural history of IBD is usually more severe in children than in adults, and can be associated with linear growth impairment, delayed puberty onset, reduced bone mass index, malnutrition, and the need for surgery. Biological therapies, especially blocking tumor necrosis factor-α (TNFα), have radically modified the treatment strategies and disease course of IBD in children. In particular, drugs such as Infliximab and Adalimumab are routinely used in the treatment of pediatric IBD. The role of Infliximab and Adalimumab in the management of pediatric IBD has been recently updated in the Consensus guidelines of ECCO/ESPGHAN. Data regarding short-term and long-term efficacy and safety of these drugs in children, and the effects of "top-down" and "step-up" strategies, are lacking. In this paper, the authors will review current indications, efficacy, and safety of biological therapy in pediatric IBD patients, evaluating all articles published after ECCO/ESPGHAN guidelines publication. The authors carried out a systemic search through MEDLINE through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) Embase, CINAHL, Cochrane Library, and gray literature, from January 2013 to January 2016. Anti-TNFα has been shown to be effective and safe to maintain remission and to achieve mucosal healing. Multicenter trials based on large sample size cohorts are needed to better clarify long-term efficacy of anti-TNFα and the real incidence of treatment-related complications in pediatric IBD.

**Database:** Medline
52. Safety Profile of Biologic Drugs in the Treatment of Inflammatory Bowel Diseases: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials.

Author(s): Moćko P, Kawalc P, Pilc A.


Abstract: BACKGROUND AND OBJECTIVES: Biologic drugs are used in innovative therapies for the management of inflammatory bowel diseases (IBDs). The aim of this study was to compare the safety profile of biologic drugs in patients with IBD. METHODS: A systematic literature search was performed using PubMed, Embase, and CENTRAL databases, up to 22 August 2016. We included randomized, placebo-controlled, or head-to-head clinical trials that compared the safety of different biologics in patients with IBDs. Two reviewers independently conducted the search and selection of studies and rated each trial's risk of bias. The network meta-analysis (NMA) was conducted for a mid-term (20-30 weeks) and long-term (≥52 weeks) follow-up with a Bayesian hierarchical random effects model using the ADDIS® software. The PROSPERO registration number was CRD42015029884. RESULTS: Sixteen randomized controlled trials were included in the systematic review with NMA. In the case of the mid-term follow-up, it was possible to conduct the NMA for assessing the relative safety profile of certolizumab pegol and infliximab, and in the case of the long-term follow-up, of infliximab, adalimumab, golimumab, and vedolizumab. There were no significant differences in the rate of adverse events in patients treated with all analyzed biologic drugs for IBD. The analysis of probability for being the safest treatment showed that infliximab was the best option in most analyzed endpoints both in mid-term and in long-term follow-ups. CONCLUSIONS: We showed no significant differences in the relative safety profile of the analyzed biologic drugs. Further studies are needed to confirm our findings, including head-to-head comparisons between these drugs.

Database: PubMed

53. Safety Profile of Biologic Drugs in the Treatment of Inflammatory Bowel Diseases: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials.

Author(s): Moćko, Paweł; Kawalić, Paweł; Pilc, Andrzej

Source: Clinical drug investigation; Jan 2017; vol. 37 (no. 1); p. 25-37

Publication Date: Jan 2017

Publication Type(s): Journal Article Review Systematic Review

PubMedID: 27599485

Available at Clinical drug investigation - from ProQuest (Health Research Premium) - NHS Version

Abstract: BACKGROUND AND OBJECTIVES: Biologic drugs are used in innovative therapies for the management of inflammatory bowel diseases (IBDs). The aim of this study was to compare the safety profile of biologic drugs in patients with IBD. METHODS: A systematic literature search was performed using PubMed, Embase, and CENTRAL databases, up to 22 August 2016. We included randomized, placebo-controlled, or head-to-head clinical trials that compared the safety of different biologics in patients with IBDs. Two reviewers independently conducted the search and selection of studies and rated each trial's risk of bias. The network meta-analysis (NMA) was conducted for a mid-term (20-30 weeks) and long-term (≥52 weeks) follow-up with a Bayesian hierarchical random effects model using the ADDIS® software. The PROSPERO registration number was CRD42015029884. RESULTS: Sixteen randomized controlled trials were included in the systematic review with NMA. In the case of the mid-term follow-up, it was possible to conduct the NMA for assessing the relative safety profile of certolizumab pegol and infliximab, and in the case of the long-term follow-up, of infliximab, adalimumab, golimumab, and vedolizumab. There were no significant differences in the rate of adverse events in patients treated with all analyzed biologic drugs for IBD. The analysis of probability for being the safest treatment showed that infliximab was the best option in most analyzed endpoints both in mid-term and in long-term follow-ups. CONCLUSIONS: We showed no significant differences in the relative safety profile of the analyzed biologic drugs. Further studies are needed to confirm our findings, including head-to-head comparisons between these drugs.

Database: PubMed
review with NMA. In the case of the mid-term follow-up, it was possible to conduct the NMA for assessing the relative safety profile of certolizumab pegol and infliximab, and in the case of the long-term follow-up, of infliximab, adalimumab, golimumab, and vedolizumab. There were no significant differences in the rate of adverse events in patients treated with all analyzed biologic drugs for IBD. The analysis of probability for being the safest treatment showed that infliximab was the best option in most analyzed endpoints both in mid-term and in long-term follow-ups. CONCLUSIONS We showed no significant differences in the relative safety profile of the analyzed biologic drugs. Further studies are needed to confirm our findings, including head-to-head comparisons between these drugs.

Database: Medline

54. Genetic Markers Predict Primary Non-Response and Durable Response to Anti-TNF Biologic Therapies in Crohn's Disease.

Author(s): Barber G.E., Yajnik V., Khalili H., Giallourakis C., Garber J., Xavier R., Ananthakrishnan A.N.


Objectives: One-fifth of patients with Crohn's disease (CD) are primary non-responders to anti-tumor necrosis factor (anti-TNF) therapy, and an estimated 10-15% will fail therapy annually. Little is known about the genetics of response to anti-TNF therapy. The aim of our study was to identify genetic factors associated with primary non-response (PNR) and loss of response to anti-TNFs in CD.

Method(s): From a prospective registry, we characterized the response of 427 CD patients to their first anti-TNF therapy. Patients were designated as achieving primary response, durable response, and non-durable response based on clinical, endoscopic, and radiologic criteria. Genotyping was performed on the Illumina Immunochip. Separate genetic scores based on presence of predictive genetic alleles were calculated for PNR and durable response and performance of clinical and genetics models were compared.

Result(s): From 359 patients, 36 were adjudged to have PNR (10%), 200 had durable response, and 74 had non-durable response. PNRs had longer disease duration and were more likely to be smokers. Fifteen risk alleles were associated with PNR. Patients with PNR had a significantly higher genetic risk score (GRS) (P =8 x 10^-12). A combined clinical-genetic model more accurately predicted PNR when compared with a clinical only model (0.93 vs. 0.70, P <0.001). Sixteen distinct single nucleotide polymorphisms predicted durable response with a higher GRS (P =7 x 10^-13). The GRSs for PNR and durable response were not mutually correlated, suggesting distinct mechanisms.

Conclusion(s): Genetic risk alleles can predict primary non-response and durable response to anti-TNF therapy in CD. Copyright © 2016 by the American College of Gastroenterology.

Database: Embase


Author(s): Moćko P, Kawalec P, Pilc A.

Abstract: OBJECTIVES: We compared the safety profile of biologic drugs in patients with moderately to severely active ulcerative colitis (UC). METHODS: A systematic literature search was performed using Medline (PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases through February 9, 2016. We included randomized controlled trials (RCTs) that compared the safety of biologic drugs (infliximab, adalimumab, golimumab, and vedolizumab) with one another or with placebo in patients with UC. Two reviewers independently conducted the search and selection of studies and rated the risk of bias in each trial. The network meta-analysis (NMA) was conducted for an induction phase (6-8 weeks) and maintenance phase (52-54 weeks) with a Bayesian hierarchical random effects model in Aggregate Data Drug Information System (ADDIS) software. The PROSPERO registration number was CRD42016032607. RESULTS: Seven RCTs were included in the systematic review with NMA. In the case of the induction phase, the NMA could be conducted for the assessment of the relative safety profile of adalimumab, golimumab, and vedolizumab, and in the case of the maintenance phase of infliximab, adalimumab, golimumab, and vedolizumab. The methodological quality of the included RCTs was evaluated as low risk of bias, but high risk of bias in the case of attrition bias (incomplete outcome data) according to the Cochrane criteria. No significant differences were found in the rate of adverse events in patients treated with the reviewed biologics. Vedolizumab was most likely to have the most favorable safety profile in the induction phase as was infliximab for the maintenance phase. CONCLUSIONS: The assessment of the relative safety profile revealed no significant differences between the biologic drugs. Further studies are needed to confirm our findings including head-to-head comparisons between the analyzed biologics. © 2016 Pharmacotherapy Publications, Inc.

Database: PubMed

56. Comparative Effectiveness of Infliximab and Adalimumab in Crohn's Disease and Ulcerative Colitis.

Author(s): Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Savova G, Churchill S, Karlson EW, Kohane I, Liao KP, Murphy SN.


Abstract: BACKGROUND: The availability of monoclonal antibodies to tumor necrosis factor α has revolutionized management of Crohn's disease (CD) and ulcerative colitis. However, limited data exist regarding comparative effectiveness of these agents to inform clinical practice. METHODS: This study consisted of patients with CD or ulcerative colitis initiation either infliximab (IFX) or adalimumab (ADA) between 1998 and 2010. A validated likelihood of nonresponse classification score using frequency of narrative mentions of relevant symptoms in the electronic health record was applied to assess comparative effectiveness at 1 year. Inflammatory bowel disease-related surgery, hospitalization, and use of steroids were determined during this period. RESULTS: Our final cohort included 1060 new initiations of IFX (68% for CD) and 391 of ADA (79% for CD). In CD, the likelihood of nonresponse was higher in ADA than IFX (odds ratio, 1.62 and 95% CI, 1.21-2.17). Similar differences favoring efficacy of IFX were observed for the individual symptoms of diarrhea, pain, bleeding, and fatigue. However, there was no difference in inflammatory bowel disease-related surgery, hospitalizations, or prednisone use within 1 year after initiation of IFX or ADA in CD. There
was no difference in narrative or codified outcomes between the 2 agents in ulcerative colitis. **CONCLUSIONS:** We identified a modestly higher likelihood of symptomatic nonresponse at 1 year for ADA compared with IFX in patients with CD. However, there were no differences in inflammatory bowel disease-related surgery or hospitalizations, suggesting these treatments are broadly comparable in effectiveness in routine clinical practice. **Database:** PubMed

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57. **Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease.**


**Abstract:** **BACKGROUND:** Ustekinumab, a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23, was evaluated as an intravenous induction therapy in two populations with moderately to severely active Crohn's disease. Ustekinumab was also evaluated as subcutaneous maintenance therapy. **METHODS:** We randomly assigned patients to receive a single intravenous dose of ustekinumab (either 130 mg or approximately 6 mg per kilogram of body weight) or placebo in two induction trials. The UNITI-1 trial included 741 patients who met the criteria for primary or secondary nonresponse to tumor necrosis factor (TNF) antagonists or had unacceptable side effects. The UNITI-2 trial included 628 patients in whom conventional therapy failed or unacceptable side effects occurred. Patients who completed these induction trials then participated in IM-UNITI, in which the 397 patients who had a response to ustekinumab were randomly assigned to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 8 weeks or every 12 weeks) or placebo. The primary end point for the induction trials was a clinical response at week 6 (defined as a decrease from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150). The primary end point for the maintenance trial was remission at week 44 (CDAI score <150). **RESULTS:** The rates of response at week 6 among patients receiving intravenous ustekinumab at a dose of either 130 mg or approximately 6 mg per kilogram were significantly higher than the rates among patients receiving placebo (in UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, with P<0.003 for both comparisons with placebo; in UNITI-2, 51.7%, 55.5%, and 28.7%, respectively, with P<0.001 for both doses). In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, as compared with 35.9% of those receiving placebo (P=0.005 and P=0.04, respectively). Within each trial, adverse-event rates were similar among treatment groups. **CONCLUSIONS:** Among patients with moderately to severely active Crohn's disease, those receiving intravenous ustekinumab had a significantly higher rate of response than did those receiving placebo. Subcutaneous ustekinumab maintained remission in patients who had a clinical response to induction therapy. (Funded by Janssen Research and Development; ClinicalTrials.gov numbers, NCT01369329, NCT01369342, and NCT01369355.). **Database:** PubMed

58. **Cost-effectiveness of adalimumab, infliximab or vedolizumab as first-line biological therapy in moderate-to-severe ulcerative colitis.**
**Author(s):** Yokomizo L., Limketkai B., Park K.T.

**Source:** BMJ Open Gastroenterology. 3 (1) (no pagination), 2016. Article Number: e000093. Date of Publication: 31 Dec 2016.

**Background:** There are no head-to-head randomised controlled trials (RCTs) comparing the effectiveness of biologics in ulcerative colitis (UC). We aimed to assess the cost-effectiveness of adalimumab, infliximab and vedolizumab as first-line agents to induce clinical remission and mucosal healing (MH) in UC. **Method(s):** We constructed a decision tree based on a payer's perspective in the USA to estimate the first year costs of adalimumab, infliximab or vedolizumab to achieve clinical remission and MH in patients with moderate-to-severe UC. Transition probabilities were derived from ACT, ULTRA and GEMINI RCT data. Costs were derived from Medicare reimbursement rates and wholesale drug prices. **Result(s):** Assuming a biological-naïve cohort, infliximab 5 mg/kg every 8 weeks was more cost-effective ($99,171 per MH achieved) than adalimumab 40 mg every other week ($316,378 per MH achieved) and vedolizumab every 8 weeks ($301,969 per MH achieved) at 1 year. Non-drug administration cost of infliximab exceeding $1974 per infusion would make adalimumab more cost-effective. First-line UC therapy with vedolizumab would be cost-effective if the drug acquisition price was <$2537 for each 300 mg administration during the 1-year time horizon. **Conclusion(s):** If non-drug costs of infliximab administration are not excessive (<$2000), infliximab is the most cost-effective first-line biologic for moderate-to-severe UC. Exceeding this threshold infusion-related cost would make adalimumab the more cost-effective therapy. Considering its drug costs in the USA, vedolizumab appears to be appropriately used as a second-line biologic after antitumour necrosis factor failure. Copyright © 2016 by the BMJ Publishing Group Ltd & British Society of Gastroenterology. All rights reserved.

**Database:** Embase

59. Systematic review and meta-analysis of third-line salvage therapy with infliximab or cyclosporine in severe ulcerative colitis.

**Author(s):** Feuerstein J.D., Akbari M., Tapper E.B., Cheifetz A.S.

**Source:** Annals of Gastroenterology. 29 (3) (pp 341-347), 2016. Date of Publication: 2016.

**Background** In patients with ulcerative colitis who fail corticosteroids and are treated with rescue therapy (e.g. infliximab or cyclosporine) but fail to respond, salvage therapy with infliximab or cyclosporine can be considered. We sought to assess the efficacy and safety of this third-line salvage therapy. **Methods** We performed a meta-analysis of trials published in PubMed up to January 2015 relating to the use of third-line salvage therapy following failure of intravenous corticosteroids and infliximab or cyclosporine. Pooled outcome rates for each salvage strategy and pooled odds ratio comparing the two strategies were calculated using the random effects model. Heterogeneity was assessed by the Q and I² statistics. **Results** The search strategy yielded 40 articles of which 4 were eligible for inclusion. Four articles assessed patients who were treated with infliximab after failure of cyclosporine and 2 articles assessed the use of cyclosporine after failure of infliximab. There were 138 patients using infliximab as a third-line salvage therapy and 30 patients using cyclosporine. When comparing these two strategies, there was no significant difference in clinical response (RR
1.03, 95% CI 0.7-1.46 P=0.87), clinical remission (RR 0.69, 95% CI 0.30-1.57 P=0.37), or colectomy at 12 months (RR 1.14, 95% CI 0.79-1.67 P=0.48). Similarly, there was no significant difference in total (RR 1.91, 95% CI 0.38-9.64 p=0.43) or serious adverse events (RR 1.18, 95% CI 0.34-4.07 P=0.80).

Conclusion While third-line salvage therapy may be efficacious in achieving short-term clinical response/remission, there remains a significant risk of colectomy and adverse events. Copyright © 2016 Hellenic Society of Gastroenterology.

Database: Embase

60. Detection of anti-infliximab antibodies is impacted by antibody titer, infliximab level and IgG4 antibodies: A systematic comparison of three different assays.


Source: Therapeutic Advances in Gastroenterology. 9 (6) (pp 781-794), 2016. Date of Publication: 01 Nov 2016.

Background: There is scant information on the accuracy of different assays used to measure anti-infliximab antibodies (ADAs), especially in the presence of detectable infliximab (IFX). We thus aimed to evaluate and compare three different assays for the detection of IFX and ADAs and to clarify the impact of the presence of circulating IFX on the accuracy of the ADA assays. Method(s): Blood samples from 79 ulcerative colitis (UC) patients treated with infliximab were assessed for IFX levels and ADAs using three different assays: an in-house assay and two commercial kits, Immundiagnostik and Theradiag. Sera samples with ADAs and undetectable levels of IFX were spiked with exogenous IFX and analyzed for ADAs. Result(s): The three assays showed 81-96% agreement for the measured IFX level. However, the in-house assay and Immundiagnostik assays detected ADAs in 34 out of 79 samples, whereas Theradiag only detected ADAs in 24 samples. Samples negative for ADAs with Theradiag, but ADA-positive in both the in-house and Immundiagnostik assays, were positive for IFX or IgG4 ADAs. In spiking experiments, a low concentration of exogenous IFX (5 mug/ml) hampered ADA detection with Theradiag in sera samples with ADA levels of between 3 and 10 mug/ml. In the Immundiagnostik assay detection interference was only observed at concentrations of exogenous IFX higher than 30 mug/ml. However, in samples with high levels of ADAs (>25 mug/ml) interference was only observed at IFX concentrations higher than 100 mug/ml in all three assays. Binary (IFX/ADA) stratification of the results showed that IFX+/ADA- and IFX-/ADAs+ were less influenced by the assay results than the double-positive (IFX+/ADAs+) and double-negative (IFX-/ADAs-) combination. Conclusion(s): All three methodologies are equally suitable for measuring IFX levels. However, erroneous therapeutic decisions may occur when patients show double-negative (IFX-/ADAs-) or double-positive (IFX+/ADAs+) status, since agreement between assays is significantly lower in these circumstances. Copyright © The Author(s), 2016.

Database: Embase
61. An indirect comparison of infliximab versus adalimumab or golimumab for active ulcerative colitis.

Author(s): Kawalec P., Pilc A.

Source: Archives of Medical Science. 12 (5) (pp 1097-1109), 2016. Date of Publication: 2016.

Introduction: The aim of the study was to compare adalimumab or golimumab with infliximab in patients with moderately-to-severely active ulcerative colitis (UC). Material(s) and Method(s): This paper was prepared according to the PRISMA guidelines. The systematic literature search was performed in PubMed, Embase, and Cochrane Library. No direct head-to-head comparisons for infliximab vs. adalimumab or golimumab were available so an indirect comparison according to the Bucher method was performed after a homogeneity evaluation of the included studies. Result(s): Six RCTs were included in the systematic review. An indirect comparison was performed, which revealed that infliximab was more effective in inducing clinical response compared with both doses of adalimumab (160/80 mg or 80/40 mg; p < 0.05), and, in clinical remission, infliximab was more effective than adalimumab (only for a dosage regime of 80/40 mg; p < 0.05). No statistically significant differences in clinical response and clinical remission were observed between infliximab and golimumab in the induction phase. A significant (p < 0.05) advantage only of infliximab compared with adalimumab at doses of 80/40 mg and 80/160 mg was seen in terms of clinical response in the maintenance phase (up to 52-54 weeks). The indirect comparison revealed that serious adverse events were significantly more frequent among patients treated with a maintenance dose of 100 mg of golimumab compared with those treated with infliximab (p < 0.05). Conclusion(s): No significant differences in efficacy in the maintenance phase between infliximab and golimumab or adalimumab were revealed. Infliximab proved to be more effective than adalimumab but of similar efficacy to that of golimumab in the induction phase. Copyright © 2016 Termedia & Banach.

62. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease.

Author(s): Chande, Nilesh; Townsend, Cassandra M; Parker, Claire E; MacDonald, John K

Source: The Cochrane database of systematic reviews; Oct 2016; vol. 10 ; p. CD000545

Publication Date: Oct 2016

Publication Type(s): Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review Systematic Review

PubMedID: 27783843

Abstract: BACKGROUNDThe results from controlled clinical trials investigating the efficacy of azathioprine and 6-mercaptopurine for the treatment of active Crohn's disease have been conflicting and controversial. An updated meta-analysis was performed to assess the effectiveness of these drugs for the induction of remission in active Crohn's disease. OBJECTIVESThe primary objective was to determine the efficacy and safety of azathioprine and 6-mercaptopurine for induction of remission in active Crohn's disease. SEARCH METHODS We searched MEDLINE, EMBASE and the Cochrane Library from inception to 30 October 2015. Review articles and conference proceedings were also searched to identify additional studies. SELECTION CRITERIA Randomized controlled trials (RCTs) of oral azathioprine or 6-mercaptopurine compared to placebo or active therapy involving adult patients with active Crohn's disease were selected for inclusion. DATA COLLECTION AND ANALYSIS Data were extracted by two independent observers based on the intention-to-treat...
principle. Outcomes of interest included: clinical remission, clinical improvement, fistula improvement or healing, steroid sparing, adverse events, withdrawals due to adverse events and serious adverse events. We calculated the pooled relative risk (RR) and 95% confidence intervals (95% CI) for each outcome. The methodological quality of included studies was evaluated using the Cochrane risk of bias tool. The overall quality of the evidence supporting each outcome was assessed using the GRADE criteria.

**MAIN RESULTS**

Thirteen RCTs (n = 1211 patients) of azathioprine and 6-mercaptopurine therapy in adult patients were identified: nine included placebo comparators and six included active comparators. The majority of included studies were rated as low risk of bias. There was no statistically significant difference in clinical remission rates between azathioprine or 6-mercaptopurine and placebo. Forty-eight per cent (95/197) of patients receiving antimetabolites achieved remission compared to 37% (68/183) of placebo patients (5 studies, 380 patients; RR 1.23, 95% CI 0.97 to 1.55). There was no statistically significant difference in clinical improvement rates between azathioprine or 6-mercaptopurine and placebo. Forty-eight per cent (107/225) of patients receiving antimetabolites achieved clinical improvement or remission compared to 36% (75/209) of placebo patients (8 studies, 434 patients; RR 1.26, 95% CI 0.98 to 1.62). There was a statistically significant difference in steroid sparing (defined as prednisone dose < 10 mg/day while maintaining remission) between azathioprine and placebo. Sixty-four per cent (47/163) of azathioprine patients were able to reduce their prednisone dose to < 10 mg/day compared to 46% (32/70) of placebo patients (RR 1.34, 95% CI 1.02 to 1.77). GRADE analyses rated the overall quality of the evidence for the outcomes clinical remission, clinical improvement and steroid sparing as moderate due to sparse data. There was no statistically significant difference in withdrawals due to adverse events or serious adverse events between antimetabolites and placebo. Ten percent of patients in the antimetabolite group withdrew due to adverse events compared to 5% of placebo patients (8 studies, 510 patients; RR 1.70, 95% CI 0.94 to 3.08). Serious adverse events were reported in 14% of patients receiving azathioprine compared to 4% of placebo patients (2 studies, 216 patients; RR 2.57, 95% CI 0.92 to 7.13). Common adverse events reported in the placebo controlled studies included: allergic reactions, leukopenia, pancreatitis and nausea. Azathioprine was significantly inferior to infliximab for induction of steroid-free clinical remission. Thirty per cent (51/170) of azathioprine patients achieved steroid-free remission compared to 44% (75/169) of infliximab patients (1 study, 339 patients; RR 0.68, 95% CI 0.51 to 0.90). The combination of azathioprine and infliximab was significantly superior to infliximab alone for induction of steroid-free clinical remission. Sixty per cent (116/194) of patients in the combined azathioprine and infliximab group achieved steroid-free remission compared to 48% (91/189) of infliximab patients (2 studies, 383 patients; RR 1.23, 95% CI 1.02 to 1.47). Azathioprine or 6-mercaptopurine therapy was found to be no better at inducing steroid free clinical remission compared to methotrexate (RR 1.13, 95% CI 0.85 to 1.49) and 5-aminosalicylate or sulfasalazine (RR 1.24, 95% CI 0.80 to 1.91). There were no statistically significant differences in withdrawals due to adverse events between azathioprine or 6-mercaptopurine and methotrexate (RR 0.78, 95% CI 0.23 to 2.71); between azathioprine or 6-mercaptopurine and 5-aminosalicylate or sulfasalazine (RR 0.98, 95% CI 0.38 to 2.54); between azathioprine and infliximab (RR 1.47, 95% CI 0.96 to 2.23); or between the combination of azathioprine and infliximab and infliximab (RR 1.16, 95% CI 0.75 to 1.80). Common adverse events in the active comparator trials included nausea, abdominal pain, pyrexia and headache.

**AUTHORS’ CONCLUSIONS**

Azathioprine and 6-mercaptopurine offer no advantage over placebo for induction of remission or clinical improvement in active Crohn's disease. Antimetabolite therapy may allow patients to reduce steroid consumption. Adverse events were more common in patients receiving antimetabolites although differences with placebo were not statistically significant. Azathioprine therapy is inferior to infliximab for induction of steroid-free remission. However, the combination of azathioprine and infliximab was superior to infliximab alone for induction of steroid-free remission.

**Database:** Medline
Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial.

**Author(s):** Williams, John G; Alam, M Fasih; Alrubaiy, Laith; Arnott, Ian; Clement, Clare; Cohen, David; Gordon, John N; Hawthorne, A Barney; Hilton, Mike; Hutchings, Hayley A; Jawhari, Aida U; Longo, Mirella; Mansfield, John; Morgan, Jayne M; Rapport, Frances; Seagrove, Anne C; Sebastian, Shaji; Shaw, Ian; Travis, Simon P L; Watkins, Alan

**Source:** The Lancet. Gastroenterology & Hepatology; Sep 2016; vol. 1 (no. 1); p. 15-24

**Publication Date:** Sep 2016

**Publication Type(s):** Research Support, Non-U.S. Gov't Comparative Study Pragmatic Clinical Trial Multicenter Study Journal Article

**PubMedID:** 27595142

**Abstract:**
BACKGROUND: Infliximab and ciclosporin are of similar efficacy in treating acute severe ulcerative colitis, but there has been no comparative evaluation of their relative clinical effectiveness and cost-effectiveness.

METHODS: In this mixed methods, open-label, pragmatic randomised trial, we recruited consenting patients aged 18 years or older at 52 district general and teaching hospitals in England, Scotland, and Wales who had been admitted, unscheduled, with severe ulcerative colitis and failed to respond to intravenous hydrocortisone within about 5 days. Patients were randomly allocated (1:1) to receive either infliximab (5 mg/kg intravenous infusion given over 2 h at baseline, and again at 2 weeks and 6 weeks after the first infusion) or ciclosporin (2 mg/kg per day by continuous infusion for up to 7 days, followed by twice-daily tablets delivering 5-5 mg/kg per day for 12 weeks). Randomisation used a web-based password-protected site, with a dynamic algorithm to generate allocations on request, thus protecting against investigator preference or other subversion, while ensuring that each trial group was balanced by centre, which was the only stratification used. Local investigators and participants were aware of the treatment allocated, but the chief investigator and analysts were masked. Analysis was by treatment allocated. The primary outcome was quality-adjusted survival—ie, the area under the curve (AUC) of scores from the Crohn's and Ulcerative Colitis Questionnaire (CUCQ) completed by participants at baseline, 3 months, and 6 months, then every 6 months from 1 year to 3 years. This trial is registered with the ISRCTN Registry, number ISRCTN22663589.

FINDINGS: Between June 17, 2010, and Feb 26, 2013, 270 patients were recruited. 135 patients were allocated to the infliximab group and 135 to the ciclosporin group. 121 (90%) patients in each group were included in the analysis of the primary outcome. There was no significant difference between groups in quality-adjusted survival (mean AUC 564·0 [SD 241·9] in the infliximab group vs 587·0 [226·2] in the ciclosporin group; mean adjusted difference 7·9 [95% CI -22·0 to 37·8]; p=0·603). Likewise, there were no significant differences between groups in the secondary outcomes of CUCQ scores, EQ-5D, or SF-6D scores; frequency of colectomy (55 [41%] of 135 patients in the infliximab group vs 65 [48%] of 135 patients in the ciclosporin group; p=0·223); or mean time to colectomy (811 [95% CI 707-912] days in the infliximab group vs 744 [638-850] days in the ciclosporin group; p=0·251). There were no differences in serious adverse reactions (16 reactions in 14 participants receiving infliximab vs ten in nine patients receiving ciclosporin); serious adverse events (21 in 16 patients vs 25 in 17 patients); or deaths (three in the infliximab group vs none in the ciclosporin group).

INTERPRETATION: There was no significant difference between ciclosporin and infliximab in clinical effectiveness.

FUNDING: NIHR Health Technology Assessment programme.

**Database:** Medline

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64. **A Systematic Review on Infliximab and Adalimumab Drug Monitoring: Levels, Clinical Outcomes and Assays.**

**Author(s):** Silva-Ferreira, Filipa; Afonso, Joana; Pinto-Lopes, Pedro; Magro, Fernando
Abstract: BACKGROUND Immunogenicity to therapeutic proteins has been linked to loss of response by a large percentage of patients taking anti-tumor necrosis factor-alpha agents. Drug monitoring can be extremely useful, allowing physicians to adjust the therapeutic scheme individually. This article aims to systematically review the published data with respect to cutoff levels of infliximab (IFX) and adalimumab (ADA) and relate them to the methodology adopted for quantification of IFX and ADA levels and clinical outcomes. METHODS The PubMed database was searched to identify studies focusing on the association between IFX or ADA cutoff levels and clinical outcomes in patients with inflammatory bowel disease. RESULTS Of the 1654 articles initially selected by queries, 20 were included. A receiver operating characteristic curve analysis was performed to identify cutoff levels of IFX or ADA that correlated with a clinical outcome, but only 6 studies performed the same analysis for antidrug antibody levels. Cutoff levels were different between studies. The methodology chosen for level quantifications, clinical outcomes, and sample size and characteristics were also different. Nevertheless, measurement of drug levels should be performed during maintenance, and with loss of response, with persistent high levels of C-reactive protein, and when mucosal lesions are still present. In these scenarios, drug and antidrug levels were correlated with clinical outcomes. CONCLUSIONS Concerning drug levels monitoring any methodology is adequate. With respect to antidrug antibody levels, it will be necessary to define a gold standard method or to establish different cutoff levels for different methodologies.


Author(s): Moćko, Paweł; Kawalec, Paweł; Pilc, Andrzej

Abstract: OBJECTIVES We compared the safety profile of biologic drugs in patients with moderately to severely active ulcerative colitis (UC). METHODS A systematic literature search was performed using Medline (PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases through February 9, 2016. We included randomized controlled trials (RCTs) that compared the safety of biologic drugs (infliximab, adalimumab, golimumab, and vedolizumab) with one another or with placebo in patients with UC. Two reviewers independently conducted the search and selection of studies and rated the risk of bias in each trial. The network meta-analysis (NMA) was conducted for an induction phase (6-8 weeks) and maintenance phase (52-54 weeks) with a Bayesian hierarchical random effects model in Aggregate Data Drug Information System (ADDIS) software. The PROSPERO registration number was CRD42016032607. RESULTS Seven RCTs were included in the systematic review with NMA. In the case of the induction phase, the NMA could be conducted for the assessment of the relative safety profile of adalimumab, golimumab, and vedolizumab, and in the case of the maintenance phase of infliximab, adalimumab, golimumab, and vedolizumab. The methodological quality of the included RCTs was evaluated as low risk of bias, but high risk of bias in the case of attrition bias (incomplete outcome data) according to the Cochrane criteria. No
significant differences were found in the rate of adverse events in patients treated with the reviewed biologics. Vedolizumab was most likely to have the most favorable safety profile in the induction phase as was infliximab for the maintenance phase. CONCLUSION The assessment of the relative safety profile revealed no significant differences between the biologic drugs. Further studies are needed to confirm our findings including head-to-head comparisons between the analyzed biologics.

**Database:** Medline

66. **Comparison Of Infliximab and Ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT).**

**Author(s):** Williams, John G; Alam, M Fasihul; Alrubaiy, Laith; Clement, Clare; Cohen, David; Grey, Michelle; Hilton, Mike; Hutchings, Hayley A; Longo, Mirella; Morgan, Jayne M; Rapport, Frances L; Seagrove, Anne C; Watkins, Alan

**Source:** Health technology assessment (Winchester, England); Jun 2016; vol. 20 (no. 44); p. 1-320

**Publication Date:** Jun 2016

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 27329657

Available at Health technology assessment (Winchester, England) - from Unpaywall

**Abstract:** BACKGROUND The efficacy of infliximab and ciclosporin in treating severe ulcerative colitis (UC) is proven, but there has been no comparative evaluation of effectiveness. OBJECTIVE To compare the clinical effectiveness and cost-effectiveness of infliximab and ciclosporin in treating steroid-resistant acute severe UC. METHOD Between May 2010 and February 2013 we recruited 270 participants from 52 hospitals in England, Scotland and Wales to an open-label parallel-group, pragmatic randomised trial. Consent patients admitted with severe colitis completed baseline quality-of-life questionnaires before receiving intravenous hydrocortisone. If they failed to respond within about 5 days, and met other inclusion criteria, we invited them to participate and used a web-based adaptive randomisation algorithm to allocate them in equal proportions between 5 mg/kg of intravenous infliximab at 0, 2 and 6 weeks or 2 mg/kg/day of intravenous ciclosporin for 7 days followed by 5.5 mg/kg/day of oral ciclosporin until 12 weeks from randomisation. Further treatment was at the discretion of physicians responsible for clinical management. The primary outcome was quality-adjusted survival (QAS): the area under the curve (AUC) of scores derived from Crohn's and Ulcerative Colitis Questionnaires completed by participants at 3 and 6 months, and then 6-monthly over 1-3 years, more frequently after surgery. Secondary outcomes collected simultaneously included European Quality of Life-5 Dimensions (EQ-5D) scores and NHS resource use to estimate cost-effectiveness. Blinding was possible only for data analysts. We interviewed 20 trial participants and 23 participating professionals. Funded data collection finished in March 2014. Most participants consented to complete annual questionnaires and for us to analyse their routinely collected health data over 10 years. RESULTS The 135 participants in each group were well matched at baseline. In 121 participants analysed in each group, we found no significant difference between infliximab and ciclosporin in QAS [mean difference in AUC/day 0.0297 favouring ciclosporin, 95% confidence interval (CI) -0.0088 to 0.0682; p = 0.129]; EQ-5D scores (quality-adjusted life-year mean difference 0.021 favouring ciclosporin, 95% CI -0.032 to 0.096; p = 0.350); Short Form questionnaire-6 Dimensions scores (mean difference 0.0051 favouring ciclosporin, 95% CI -0.0250 to 0.0353; p = 0.737). There was no statistically significant difference in colectomy rates [odds ratio (OR) 1.350 favouring infliximab, 95% CI 0.832 to 2.188; p = 0.223]; numbers of serious adverse reactions [event ratio = 0.938 favouring ciclosporin, 95% CI 0.590 to 1.493; p = 0.788]; participants with serious adverse reactions (OR 0.660 favouring ciclosporin, 95% CI 0.282 to 1.546; p = 0.338); numbers of
serious adverse events (event ratio 1.075 favouring infliximab, 95% CI 0.603 to 1.917; p = 0.807); participants with serious adverse events (OR 0.999 favouring infliximab, 95% CI 0.473 to 2.114; p = 0.998); deaths (all three who died received infliximab; p = 0.247) or concomitant use of immunosuppressants. The lower cost of ciclosporin led to lower total NHS costs (mean difference -£5632, 95% CI -£8305 to -£2773; p < 0.001). Interviews highlighted the debilitating effect of UC; participants were more positive about infliximab than ciclosporin. Professionals reported advantages and disadvantages with both drugs, but nurses disliked the intravenous ciclosporin.

CONCLUSIONSTotal cost to the NHS was considerably higher for infliximab than ciclosporin. Nevertheless, there was no significant difference between the two drugs in clinical effectiveness, colectomy rates, incidence of SAEs or reactions, or mortality, when measured 1-3 years post treatment. To assess long-term outcome participants will be followed up for 10 years post randomisation, using questionnaires and routinely collected data. Further studies will be needed to evaluate the efficacy and effectiveness of new anti-tumour necrosis factor drugs and formulations of ciclosporin. TRIAL REGISTRATIONCurrent Controlled Trials ISRCTN22663589. FUNDINGThis project was funded by the NIHR Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 20, No. 44. See the NIHR Journals Library website for further project information.

Database: Medline

67. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn’s Disease After Ileocolonic Resection.

**Author(s):** Regueiro, Miguel; Feagan, Brian G; Zou, Bin; Johanss, Jewel; Blank, Marion A; Chevrier, Marc; Plevy, Scott; Popp, John; Cornillie, Freddy J; Lukas, Milan; Danese, Silvio; Gionchetti, Paolo; Hanauer, Stephen B; Reinsch, Walter; Sandborn, William J; Sorrentino, Dario; Rutgeerts, Paul; PREVENT Study Group

**Source:** Gastroenterology; Jun 2016; vol. 150 (no. 7); p. 1568-1578

**Publication Date:** Jun 2016

**Publication Type(s):** Randomized Controlled Trial Journal Article

**PubMedID:** 26946343

Available at Gastroenterology - from Unpaywall

**Abstract:**BACKGROUND & AIMSMost patients with Crohn’s disease (CD) eventually require an intestinal resection. However, CD frequently recurs after resection. We performed a randomized trial to compare the ability of infliximab vs placebo to prevent CD recurrence. METHODS We evaluated the efficacy of infliximab in preventing postoperative recurrence of CD in 297 patients at 104 sites worldwide from November 2010 through May 2012. All study patients had undergone ileocolonic resection within 45 days before randomization. Patients were randomly assigned (1:1) to groups given infliximab (5 mg/kg) or placebo every 8 weeks for 200 weeks. The primary end point was clinical recurrence, defined as a composite outcome consisting of a CD Activity Index score >200 and a ≥70-point increase from baseline, and endoscopic recurrence (Rutgeerts score ≥12, determined by a central reader) or development of a new or re-draining fistula or abscess, before or at week 76. Endoscopic recurrence was a major secondary end point. RESULTS A smaller proportion of patients in the infliximab group had a clinical recurrence before or at week 76 compared with the placebo group, but this difference was not statistically significant (12.9% vs 20.0%; absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval: -1.3% to 15.5%; P = .097). A significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared with the placebo group (30.6% vs 60.0%; ARR with infliximab, 29.4%; 95% confidence interval: 18.6% to 40.2%; P < .001). Additionally, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence based only on Rutgeerts scores ≥12 (22.4% vs 51.3%; ARR with infliximab,
28.9%; 95% confidence interval: 18.4% to 39.4%; P < .001). Patients previously treated with anti-tumor necrosis factor agents or those with more than 1 resection were at greater risk for clinical recurrence. The safety profile of infliximab was similar to that from previous reports.

**CONCLUSIONS**

Infliximab is not superior to placebo in preventing clinical recurrence after CD-related resection. However, infliximab does reduce endoscopic recurrence. ClinicalTrials.gov ID NCT01190839.

**Database:** Medline

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**68. Systematic Review and Meta-Analysis: Serum Infliximab Levels During Maintenance Therapy and Outcomes in Inflammatory Bowel Disease.**

**Author(s):** Moore, Clare; Corbett, Gillian; Moss, Alan C

**Source:** Journal of Crohn's & colitis; May 2016; vol. 10 (no. 5); p. 619-625

**Publication Date:** May 2016

**Publication Type(s):** Meta-analysis Journal Article Review Systematic Review

**PubMedID:** 26763722

Available at Journal of Crohn's & colitis - from Unpaywall

**Abstract:** BACKGROUND AND AIM: A number of observational studies have reported an association between serum levels of infliximab [IFX] at various thresholds, and clinical outcomes in inflammatory bowel disease [IBD]. This association has not previously been systematically analysed. METHODS: Systematic review of studies that reported serum infliximab levels according to outcomes in IBD. Primary outcome was clinical remission, and secondary outcomes included endoscopic remission, C-reactive protein [CRP] levels, and colectomy. Meta-analysis of raw data was performed where appropriate. A quality assessment was also undertaken. RESULTS: A total of 22 studies met the inclusion criteria, including 3483 patients; 12 studies reported IFX levels in a manner suitable for determining effect estimates. During maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients not in remission: 3.1 µg/ml versus 0.9 µg/ml. The standardised mean difference in serum IFX levels between groups was 0.6 µg/ml [95% confidence interval [CI] 0.4-0.9, p = 0.0002]. Patients with an IFX level > 2 µg/ml were more likely to be in clinical remission (risk ratio [RR] 2.9, 95% CI 1.8-4.7, p < 0.001), or achieve endoscopic remission [RR 3, 95% CI 1.4-6.5, p = 0.004] than patients with levels 2 µg/ml is associated with a greater probability of clinical remission and mucosal healing.

**Database:** Medline

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**69. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model.**

**Author(s):** Archer, Rachel; Tappenden, Paul; Ren, Shijie; Martyn-St James, Marrissa; Harvey, Rebecca; Basarir, Hasan; Stevens, John; Carroll, Christopher; Cantrell, Anna; Lobo, Alan; Hoque, Sami

**Source:** Health technology assessment (Winchester, England); May 2016; vol. 20 (no. 39); p. 1-326

**Publication Date:** May 2016

**Publication Type(s):** Journal Article Review Systematic Review

**PubMedID:** 27220829

Available at Health technology assessment (Winchester, England) - from Unpaywall
Abstract: Ulcerative colitis (UC) is the most common form of inflammatory bowel disease in the UK. UC can have a considerable impact on patients' quality of life. The burden for the NHS is substantial. OBJECTIVES: To evaluate the clinical effectiveness and safety of interventions, to evaluate the incremental cost-effectiveness of all interventions and comparators (including medical and surgical options), to estimate the expected net budget impact of each intervention, and to identify key research priorities. DATA SOURCES: Peer-reviewed publications, European Public Assessment Reports and manufacturers' submissions. The following databases were searched from inception to December 2013 for clinical effectiveness searches and from inception to January 2014 for cost-effectiveness searches for published and unpublished research evidence: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects, the Health Technology Assessment database and NHS Economic Evaluation Database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science and Bioscience Information Service Previews. The US Food and Drug Administration website and the European Medicines Agency website were also searched, as were research registers, conference proceedings and key journals. REVIEW METHODS: A systematic review [including network meta-analysis (NMA)] was conducted to evaluate the clinical effectiveness and safety of named interventions. The health economic analysis included a review of published economic evaluations and the development of a de novo model. RESULTS: Ten randomised controlled trials were included in the systematic review. The trials suggest that adult patients receiving infliximab (IFX) [Remicade®, Merck Sharp & Dohme Ltd (MSD)], adalimumab (ADA) (Humira®, AbbVie) or golimumab (GOL) (Simponi®, MSD) were more likely to achieve clinical response and remission than those receiving placebo (PBO). Hospitalisation data were limited, but suggested more favourable outcomes for ADA- and IFX-treated patients. Data on the use of surgical intervention were sparse, with a potential benefit for intervention-treated patients. Data were available from one trial to support the use of IFX in paediatric patients. Safety issues identified included serious infections, malignancies and administration site reactions. Based on the NMA, in the induction phase, all biological treatments were associated with statistically significant beneficial effects relative to PBO, with the greatest effect associated with IFX. For patients in response following induction, all treatments except ADA and GOL 100 mg at 32-52 weeks were associated with beneficial effects when compared with PBO, although these were not significant. The greatest effects at 8-32 and 32-52 weeks were associated with 100 mg of GOL and 5 mg/kg of IFX, respectively. For patients in remission following induction, all treatments except ADA at 8-32 weeks and GOL 50 mg at 32-52 weeks were associated with beneficial effects when compared with PBO, although only the effect of ADA at 32-52 weeks was significant. The greatest effects were associated with GOL (at 8-32 weeks) and ADA (at 32-52 weeks). The economic analysis suggests that colectomy is expected to dominate drug therapies, but for some patients, colectomy may not be considered acceptable. In circumstances in which only drug options are considered, IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness ratio for ADA versus conventional treatment is approximately £50,300 per QALY gained. LIMITATIONS: The health economic model is subject to several limitations: uncertainty associated with extrapolating trial data over a lifetime horizon, the model does not consider explicit sequential pathways of non-biological treatments, and evidence relating to complications of colectomy was identified through consideration of approaches used within previous models rather than a full systematic review. CONCLUSIONS: Adult patients receiving IFX, ADA or GOL were more likely to achieve clinical response and remission than those receiving PBO. Further data are required to conclusively demonstrate the effect of interventions on hospitalisation and surgical outcomes. The economic analysis indicates that colectomy is expected to dominate medical treatments for moderate to severe UC. STUDY REGISTRATION: This study is registered as PROSPERO CRD42013006883. FUNDING: The National Institute for Health Research Health Technology Assessment programme.
70. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids.

Author(s): Narula, Neeraj; Marshall, John K; Colombel, Jean-Frederic; Leontiadis, Grigorios I; Williams, John G; Muqtadir, Zack; Reinisch, Walter

Source: The American journal of gastroenterology; Apr 2016; vol. 111 (no. 4); p. 477-491

Publication Date: Apr 2016

Publication Type(s): Meta-analysis Journal Article Review Systematic Review

PubMedID: 26856754

Available at The American journal of gastroenterology - from ProQuest (Health Research Premium) - NHS Version

Abstract: OBJECTIVES Acute severe steroid-refractory ulcerative colitis (UC) carries a poor prognosis and requires optimal management. A systematic review and meta-analysis were conducted to assess cyclosporine and infliximab (IFX) as rescue agents in patients with steroid-refractory UC. METHODS A literature search identified studies that investigated IFX and cyclosporine in steroid-refractory UC patients. The primary outcome was short-term response to treatment. Secondary outcomes included the rates of colectomy at 3 months and 12 months, adverse drug reactions, post-operative complications in those who received rescue therapy but underwent colectomy subsequently, and mortality. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. RESULTS Overall, 16 studies with 1,473 participants were eligible for inclusion. Among three randomized controlled trials, no significant difference was seen with IFX compared with cyclosporine with regard to treatment response and 3- or 12-month colectomy. Among 13 non-randomized studies, IFX was associated with significantly higher rates of treatment response (OR 2.96 (95% CI 2.12-4.14, χ²=6.50, I²=0%)) and a lower 12-month colectomy rate (OR 0.42 (95% CI 0.22-0.83, χ²=30.94, I²=71%)), with no significant difference seen in the 3-month colectomy rate (OR 0.53 (95% CI 0.22-1.28, χ²=22.73, I²=69%)) compared with cyclosporine. There were no significant differences between IFX and cyclosporine in adverse drug-related events, post-operative complications, or mortality. CONCLUSIONS In the management of steroid-refractory severe UC, no definitive difference between IFX and cyclosporine is demonstrated by randomized trials, but non-randomized studies suggest that IFX is associated with better treatment response and lower risk of colectomy at 12 months. Prospective studies comparing dose-optimized IFX with cyclosporine are needed.

Database: Medline

71. Colectomy rates in patients with ulcerative colitis following treatment with infliximab or ciclosporin: a systematic literature review.

Author(s): Thorne, Kymberley; Alrubaiy, Laith; Akbari, Ashley; Samuel, David G; Morrison-Rees, Sian; Roberts, Stephen E

Source: European journal of gastroenterology & hepatology; Apr 2016; vol. 28 (no. 4); p. 369-382

Publication Date: Apr 2016

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article Review Systematic Review

PubMedID: 26825217

Abstract: This review aimed to compile all available published data on colectomy rates following treatment using infliximab or ciclosporin in adult ulcerative colitis patients and to analyse colectomy rates, timing to colectomy and postcolectomy mortality for each treatment. We systematically
reviewed the literature after 1990 reporting colectomy rates in ulcerative colitis patients treated with infliximab or ciclosporin, excluding articles on paediatric patients, patients with indeterminate colitis or Crohn's disease and bowel surgery not related to ulcerative colitis. We presented weighted mean colectomy rates and mortality rates. Cox's regression was used to assess time to colectomy adjusting for colitis severity, patient age and sex. We tabulated 78 studies reporting on ciclosporin and/or infliximab and colectomy rates or postcolectomy mortality rates. Not all studies reported data in a standardized manner. Infliximab had a significantly lower colectomy rate than ciclosporin at 36 months when analysing all studies, studies directly comparing infliximab and ciclosporin and studies using severe colitis patients, but not at 3, 12 or 24 months. Severity and age were key indicators in the likelihood of undergoing colectomy after treatment. Postcolectomy mortality rates were less than 1.5% for both drugs. This review indicates that long-term colectomy rates following infliximab are significantly lower than ciclosporin in the longer term, and that postcolectomy mortality following infliximab and ciclosporin is very low. However, many key data items were missing from research articles, reducing our ability to establish with more confidence the actual impact of these two drugs on colectomy rates and postcolectomy mortality rates.

Database: Medline

72. Effectiveness and risk associated with infliximab alone and in combination with immunosuppressors for crohn's disease: A systematic review and meta-analysis.


Date of Publication: 2015.

Objective: Infliximab (IFX) monotherapy and IFX combined with immunosuppressors have been used in the treatment of Crohn's disease. However, the differences between combination therapy and IFX alone remain controversial. The aim of this meta-analysis was to evaluate the effectiveness and risk associated with combination therapy and IFX monotherapy. Method(s): Systematic searches were performed for randomized controlled trials with PubMed, Web of Science, OVID, and the Cochrane Library. The analyzed contents included induction of remission, short-term maintenance of remission, long-term maintenance of remission, and risks. The final results were estimated using statistical data of odds ratio (OR), relevant 95% confidence interval (CI), and P value. Result(s): 6 out of 1041 citations met the selection criteria. There was no statistical difference in the effectiveness of induction and long-term maintenance of remission between two groups (P=0.07, 0.12). However, for short-term maintenance of remission, there was mild statistical difference between two groups (P=0.02, OR=1.66). For risks, apart from the difference in the aspect of reaction to infusion (OR=0.43, 95% CI=0.29-0.65, P<0.0001), there was no statistical difference. Conclusion(s): There was no significant difference in effectiveness and risks between the therapy groups. However, these outcomes should be interpreted with caution. Specific categories of combination therapy and periodic medication should be paid more attention in future studies. Copyright © 2015, E-Century Publishing Corporation. All rights reserved.

Database: Embase

73. Infliximab is superior to other biological agents for treatment of active ulcerative colitis: A meta-analysis.
Author(s): Mei WQ, Hu HZ, Liu Y, Li ZC, Wang WG.


Abstract: AIM: To compare the efficacy and safety of biological agents for the treatment of active ulcerative colitis (UC). METHODS: PubMed, MEDLINE, EMBASE and the Cochrane library were searched to screen relevant articles from January 1996 to August 2014. The mixed treatment comparison meta-analysis within a Bayesian framework was performed using WinBUGS14 software. The proportions of patients reaching clinical response, clinical remission and mucosal healing in induction and maintenance phases were analyzed as efficacy indicators. Serious adverse events in maintenance phase were analyzed as safety indicators. RESULTS: The meta-analysis results showed that biological agents achieved better clinical response, clinical remission and mucosal healing than placebo. Indirect comparison indicated that in induction phase, infliximab was more effective than adalimumab in inducing clinical response (OR = 0.41, 95%CI: 0.29-0.57), clinical remission (OR = 0.33, 95%CI: 0.19-0.56) and mucosal healing (OR = 0.33, 95%CI: 0.19-0.56), and golimumab in inducing clinical response (OR = 0.66, 95%CI: 0.39-2.33) and mucosal healing (OR = 2.15, 95%CI: 1.18-4.22). No significant difference was found between placebo and biological agents regarding their safety.

CONCLUSION: All biological agents were superior to placebo for UC treatment in both induction and maintenance phases with a similar safety profile, and infliximab had a better clinical effect than the other biological agents.

Database: PubMed

74. Indirect comparison for Anti-TNF drugs in moderate to severe ulcerative colitis.

Author(s): Galván-Banqueri M, Vega-Coca MD, Castillo-Muñoz MA, et al.


Abstract: OBJECTIVE: To compare the relative efficacy of infliximab, adalimumab and golimumab through adjusted indirect treatment comparisons (ITCs). METHODS: An exhaustive search was performed until October 2013. Databases consulted were MEDLINE, EMBASE, the Cochrane Library, the Centre for Reviews and Dissemination and the Web of Science. Randomized control trials (RCTs) comparing the efficacy of infliximab, adalimumab or golimumab versus placebo, in terms of clinical remission, clinical response and mucosal healing, were included. In the case that more than one RCT fulfilled the inclusion criteria for the same drug, a metanalysis was undertaken using a fixed effects model. ITCs were carried out using the method proposed by Bucher et al. RESULTS: 6 RCTs published in 5 papers were included: 2 for infliximab (ACT 1 and ACT 2), 2 for adalimumab (ULTRA 1 y ULTRA 2) and 2 for golimumab (PURSUIT-SC y PURSUIT-M). In these RCTs, each biological agent was superior in efficacy to placebo. The results of the adjusted ITC are the following. In relation to the clinical remission, in the induction and maintenance period, there are no statistically significant differences between the three anti-TNF drugs. In relation to the clinical response and mucosal healing, in the induction period, there are statistically significant differences between infliximab and adalimumab. CONCLUSION: In view of the results obtained, infliximab, adalimumab and golimumab appear to be similarly effective therapeutic alternatives. Therefore, other considerations such as
The introduction of anti-TNF monoclonal antibodies to the therapeutic arsenal has represented a major advance in the management of Crohn's disease (CD). Anti-TNF agents are able to induce and maintain remission of the disease over time. These treatments also have the ability to close fistulae, heal mucosal lesions, and reduce rates of hospitalizations and surgeries. Such properties have been demonstrated in randomized clinical trials and have been confirmed in patient cohorts. Anti-TNF monoclonal antibodies represent the most effective agents currently available for the treatment of CD. Three anti-TNF monoclonal antibodies have demonstrated efficacies for the treatment of this disease: infliximab, adalimumab and certolizumab pegol. They are classically administered following a step-up approach to patients with refractory disease who are unresponsive to conventional therapies or are steroid-dependent. They may be used earlier in the disease course to treat patients presenting with aggressive disease or features predictive of poor prognosis. Indeed, several studies have suggested that early intervention with combination therapy may modify the long-term course of CD. The higher efficacies of these therapies compared to those of classical treatments have incited clinicians to have more ambitious objectives, such as endoscopic healing. In this chapter, we describe the major randomized controlled trials that have demonstrated the efficacies of infliximab, adalimumab and certolizumab pegol in the treatment of luminal CD, and that, together with data on safety, have defined their drug labeling. We also summarize the current international guidelines and discuss their usage in clinical practice. Copyright © 2015 S. Karger AG, Basel.
used were: "infliximab," "adalimumab," "certolizumab," "golimumab," "natalizumab," "vedolizumab," "ustekinumab," "azathioprine," "methotrexate," "Crohn's disease," and "ulcerative colitis." Results: In Crohn's disease, studies supporting induction and maintenance therapies were documented for infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and ustekinumab. Infliximab, adalimumab, and certolizumab have evidences for fistulizing Crohn's disease and only infliximab and adalimumab have evidences for mucosal healing. In ulcerative colitis, studies supporting induction, maintenance, and mucosal healing were found with infliximab, adalimumab, golimumab, and vedolizumab. Only infliximab was associated with evidences for combination therapy with thiopurine and acute severe colitis in ulcerative colitis. Conclusion(s): Management with biologics in IBD patients is well validated by high-quality clinical trials. Copyright © 2015, © Author(s) 2015.

Database: Embase

77. The impact of biological interventions for ulcerative colitis on health-related quality of life.
Author(s): LeBlanc, Katie; Mosli, Mahmoud H; Parker, Claire E; MacDonald, John K
Source: The Cochrane database of systematic reviews; Sep 2015 (no. 9); p. CD008655
Publication Date: Sep 2015
Publication Type(s): Meta-analysis Journal Article Review Systematic Review
PubMedID: 26393522
Available at The Cochrane database of systematic reviews - from Cochrane Collaboration (Wiley)
Abstract:BACKGROUNDUlcerative colitis (UC) is a chronic inflammatory disorder of the colon that has a relapsing-remitting course. Health related quality of life (HRQL) is significantly lower in patients with UC than the general population due to the negative effects of the disease on physical, psychological and social well-being. Randomized controlled trials (RCTs) evaluating medical interventions for UC have traditionally used clinical disease activity indices that focus on symptoms to define primary outcomes such as clinical remission or improvement. However, this approach does not evaluate benefits that are highly relevant to patients such as HRQL OBJECTIVES: The primary objective was to assess the impact of biologic therapy on the HRQL of UC patients.SEARCH METHODSWe searched PubMed, MEDLINE, EMBASE and CENTRAL from inception to September, 2015. Conference abstracts and reference lists were also searched.SELECTION CRITERIARCTs that compared biologics to placebo in UC patients and reported on HRQL using the Inflammatory Bowel Disease Questionnaire (IBDQ), or the SF-36 or EQ-5D to measure HRQL were included.DATA COLLECTION AND ANALYSISITwo authors independently screened studies for inclusion, extracted data and assessed study quality using the Cochrane risk of bias tool. The primary outcome was improvement in HRQL. For dichotomous outcomes we calculated the risk ratio (RR) and 95% confidence interval (CI). For continuous outcomes we calculated the mean difference (MD) and 95% CI. The overall quality of the evidence supporting the primary outcome was assessed using GRADE.MAIN RESULTSNine RCTs (n = 4143) were included. Biologics included rituximab (one small study), interferon-ß-1a (one study), vedolizumab (one study), and the tumor necrosis factor-alpha (TNF-α) antagonists infliximab (two studies), adalimumab (three studies), and golimumab (one study). Risk of bias was low in eight studies. The rituximab study was judged to be at high risk of bias due to attrition bias. The studies comparing interferon-ß-1a and rituximab to placebo found no clear evidence of a difference in the proportion of patients who experienced an improvement in HRQL at 8 or 12 weeks respectively. The proportion of patients with a clinically meaningful improvement in HRQL at 6 or 52 weeks was significantly higher in vedolizumab patients compared to placebo. At 6
weeks 37% (83/225) of vedolizumab patients had an improvement in IBDQ score of at least 16 points from baseline compared to 23% (34/149) of placebo patients (RR 1.62, 95% CI 1.15 to 2.27; 1 study). At 52 weeks, 64% (157/247) of vedolizumab patients had an improvement in IBDQ score of at least 16 points from baseline compared to 38% (48/126) of placebo patients (RR 1.62, 95% CI 1.15 to 2.27; 1 study). A GRADE analysis indicated that the overall quality of the evidence supporting these outcomes was moderate due to sparse data (< 400 events). Patients who received maintenance vedolizumab every eight weeks had significantly higher mean SF-36 scores than placebo patients at 52 weeks (MD 3.40, 95% CI 1.56 to 5.24, 1 study 248 patients). This difference appears to be clinically meaningful as the lower boundary for a clinically meaningful change in SF-36 is three points. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (< 400 events). Adalimumab patients had significantly higher mean IBDQ scores than placebo patients at weeks 8 (MD 9.00, 95% CI 2.65 to 15.35; 1 study, 494 patients) and 52 (MD 8.00, 95% CI 0.68 to 15.32; 1 study, 494 patients). However, these differences may not be clinically meaningful as the lower boundary for a clinically meaningful change in IBDQ is 16 points. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (16 points from baseline compared to 50% of placebo patients (RR 1.39, 95% CI 1.21 to 1.60; 1 study). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was high. Similar results were found between infliximab and placebo when HRQL was measured using the SF-36 instrument. One small study (n = 43) found no difference in HRQL between infliximab and placebo when measured by the EQ-5D. Pooled analyses of TNF-α antagonists showed a benefit in HRQL favouring TNF-α over placebo.AUTORS’ CONCLUSIONSThese results suggest that biologics have the potential to improve HRQL in UC patients. High quality evidence suggests that infliximab provides a clinically meaningful improvement in HRQL in UC patients receiving induction therapy. Moderate quality evidence suggests that vedolizumab provides a clinically meaningful improvement in HRQL in UC patients receiving maintenance therapy. These findings are important since there is a paucity of effective drugs for the treatment of UC that have the potential to both decrease disease activity and improve HRQL. More research is needed to assess the long-term effect of biologic therapy on HRQL in patients with UC. More research is needed to assess the impact of golimumab and adalimumab on HRQL in UC patients. Trials involving direct head to head comparisons of biologics would help determine which biologics provide optimum benefit for HRQL.

Database: Medline

78. Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis.

Author(s): Jiang, Xue-Liang; Cui, Hui-Fei; Gao, Jing; Fan, Hua

Source: Journal of clinical gastroenterology; Aug 2015; vol. 49 (no. 7); p. 582-588

Publication Date: Aug 2015

Publication Type(s): Randomized Controlled Trial Journal Article

PubMedID: 25844841

Abstract: GOAL To evaluate the efficacy of low-dose (3.5 mg/kg) infliximab for induction and maintenance treatment in Chinese patients with ulcerative colitis. BACKGROUND Treatment with 4 to 5 mg/kg of infliximab also proved to be effective in treating moderate to severe ulcerative colitis. At present there is no relevant study on the effectiveness of infliximab doses lower than 4 mg/kg in patients with ulcerative colitis. STUDY A prospective, randomized, double-blind, placebo-controlled, and single-centered study was designed. A total of 123 patients (from 17 provinces of China) with moderate to severe active ulcerative colitis despite treatment with concurrent drugs received placebo or low-dose (3.5 mg/kg) or standard-dose (5 mg/kg) infliximab intravenously at weeks 0, 2,
and 6 and then every 8 weeks through week 22. Patients were followed up for 30 weeks.

**RESULTS**

Overall, 73% and 78% of patients who received low-dose (3.5 mg/kg) and standard-dose (5 mg/kg) infliximab, respectively, had clinical responses at week 8, as compared with 37% of patients who received placebo (P<0.01 for both comparisons with placebo). The number of patients who received low-dose (3.5 mg/kg) or standard-dose (5 mg/kg) infliximab with a clinical response at week 30 (63% and 66%, respectively) was more than the patients who received placebo (27%, P<0.01 for both comparisons).

**CONCLUSIONS**

Chinese patients with moderate to severe active ulcerative colitis treated with low-dose (3.5 mg/kg) or standard-dose (5 mg/kg) infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter were more likely to have a clinical response at weeks 8 and 30 than those who received placebo.

**Database:** Medline

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**79. Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease.**

**Author(s):** Kierkuś, Jarosław; Iwańczak, Barbara; Wegner, Agnieszka; Dadalski, Maciej; Grzybowska-Chlebowczyk, Urszula; Łazowska, Izabella; Maśłana, Jolanta; Toporowska-Kowalska, Ewa; Czaja-Bulsa, Grażyna; Mierzwa, Grażyna; Korczowski, Bartosz; Czkwianianc, Elżbieta; Żabka, Alicja; Szymańska, Edyta; Krzesiek, Elżbieta; Więcek, Sabina; Sładek, Małgorzata

**Source:** Journal of pediatric gastroenterology and nutrition; May 2015; vol. 60 (no. 5); p. 580-585

**Publication Date:** May 2015

**Publication Type(s):** Comparative Study Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID:** 25564804

Available at [Journal of pediatric gastroenterology and nutrition](https://www.ncbi.nlm.nih.gov/pubmed/25564804) - from Unpaywall

**Abstract:**

**OBJECTIVE**

The aim of the present study was to compare the efficacy and safety of 2 protocols of maintenance therapy with infliximab (IFX) and an immunomodulatory agent in pediatric patients with Crohn disease (CD): withdrawal of immunomodulators versus continuation of immunosuppressants.

**METHODS**

The present multicenter randomized open-label trial included 99 patients with CD (ages 14.5 ± 2.6 years) who were administered IFX (5 mg/kg body weight) along with an immunomodulatory agent (azathioprine 1.5-3 mg/kg body weight per day, methotrexate 10-25 mg/week). After 10 weeks of the induction therapy, 84 responders were centrally randomized into 1 of the following groups: group I (n = 45) in which IFX and an immunomodulatory agent were continued up to week 54 and group II (n = 39) in which the immunomodulatory agent was discontinued after 26 weeks.

**RESULTS**

The induction therapy was reflected by a significant decrease in Pediatric Crohn’s Disease Activity Index (PCDAI) and Simplified Endoscopic Activity Score for Crohn’s Disease (SES-CD) values. After the maintenance phase, the analyzed groups did not differ significantly in terms of the clinical response loss rates and final PCDAI and SES-CD scores. Furthermore, no significant intragroup differences were documented between mean PCDAI scores determined at the end of induction and maintenance phases. Intensification/modification of the treatment was required in 13 of 45 (29%) and 11 of 39 (28%) patients of groups I and II, respectively. A total of 9 serious adverse events were documented; none of the patients died during the trial.

**CONCLUSIONS**

Twenty-six weeks likely represent the safe duration of combined IFX/imunomodulatory therapy in our sample of pediatric patients with CD.

**Database:** Medline
80. Comparative efficacy of golimumab, infliximab, and adalimumab for moderately to severely active ulcerative colitis: a network meta-analysis accounting for differences in trial designs.

Author(s): Thorlund, Kristian; Druyts, Eric; Toor, Kabirraaj; Mills, Edward J

Source: Expert review of gastroenterology & hepatology; May 2015; vol. 9 (no. 5); p. 693-700

Publication Date: May 2015

Publication Type(s): Research Support, Non-u.s. Gov’t Meta-analysis Comparative Study Journal Article

PubMedID: 25763862

Abstract:
AIMTo conduct a network meta-analysis (NMA) to establish the comparative efficacy of infliximab, adalimumab and golimumab for the treatment of moderately to severely active ulcerative colitis (UC).

DESIGNA systematic literature search identified five randomized controlled trials for inclusion in the NMA. One trial assessed golimumab, two assessed infliximab and two assessed adalimumab. Outcomes included clinical response, clinical remission, mucosal healing, sustained clinical response and sustained clinical remission. Innovative methods were used to allow inclusion of the golimumab trial data given the alternative design of this trial (i.e., two-stage randomization).

RESULTSAfter induction, no statistically significant differences were found between golimumab and adalimumab or between golimumab and infliximab. Infliximab was statistically superior to adalimumab after induction for all outcomes and treatment ranking suggested infliximab as the superior treatment for induction. Golimumab and infliximab were associated with similar efficacy for achieving maintained clinical remission and sustained clinical remission, whereas adalimumab was not significantly better than placebo for sustained clinical remission. Golimumab and infliximab were also associated with similar efficacy for achieving maintained clinical response, sustained clinical response and mucosal healing. Finally, golimumab 50 and 100 mg was statistically superior to adalimumab for clinical response and sustained clinical response, and golimumab 100 mg was also statistically superior to adalimumab for mucosal healing.

CONCLUSIONThe results of our NMA suggest that infliximab was statistically superior to adalimumab after induction, and that golimumab was statistically superior to adalimumab for sustained outcomes. Golimumab and infliximab appeared comparable in efficacy.

Database: Medline

81. Combining genetic and nongenetic biomarkers to realize the promise of pharmacogenomics for inflammatory diseases.

Author(s): Maranville J.C., Di Rienzo A.

Source: Pharmacogenomics. 15 (15) (pp 1931-1940), 2014. Date of Publication: 01 Nov 2014.

Many drugs used to treat inflammatory diseases are ineffective in a substantial proportion of patients. Identifying patients that are likely to respond to specific therapies would facilitate personalized treatment strategies that could improve outcomes while reducing costs and risks of adverse events. Despite these clear benefits, there are limited examples of predictive biomarkers of drug efficacy currently implemented into clinical practice for inflammatory diseases. We review efforts to identify genetic and nongenetic biomarkers of drug response in these diseases and consider potential benefits from combining multiple sources of biological data into multifeature predictive models. Copyright © 2014 Future Medicine Ltd.

Database: Embase

Author(s): Stidham RW, Lee TC, Higgins PD, et al.

Abstract: BACKGROUND: Anti-tumour necrosis factor-alpha agents (anti-TNF) are effective therapies for the treatment of Crohn’s disease (CD), but their comparative efficacy is unknown.
AIM: To perform a network meta-analysis comparing the efficacy of anti-TNF therapies in CD.
METHODS: After screening 506 studies, reviewers extracted information on 10 studies. Traditional meta-analysis (TMA) was used to compare each anti-TNF agent to placebo. Bayesian network meta-analysis (NMA) was performed to compare the effects of anti-TNF agents to placebo. In addition, sample sizes for comparative efficacy trials were calculated. RESULTS: Compared to placebo, TMA revealed that anti-TNF agents result in a higher likelihood of induction of remission and response (RR: 1.66, 95% CI: 1.17-2.36 and RR: 1.43, 95% CI: 1.17-1.73, respectively) as well as maintenance of remission and response (RR: 1.78, 95% CI: 1.51-2.09 and RR: 1.68, 95% CI: 1.46-1.93, respectively). NMA found nonsignificant trends between infliximab and adalimumab or certolizumab pegol. Among subcutaneous therapies, NMA demonstrated superiority of adalimumab to certolizumab pegol for induction of remission (RR: 2.93, 95% CrI: 1.21-7.75). Sample size calculations suggest that adequately powered head-to-head comparative efficacy trials would require greater than 3000 patients. CONCLUSIONS: All anti-TNF agents are effective for induction and maintenance of response and remission in the treatment of CD. Although adalimumab is superior to certolizumab pegol for induction of remission, there is no evidence of clinical superiority among anti-TNF agents. Head-to-head trials among the anti-TNF agents are impractical in terms of size and cost. © 2014 John Wiley & Sons Ltd.

Database: PubMed


Author(s): Stidham RW, Lee TC, Higgins PD, et al.
Erratum in Corrigendum. [Aliment Pharmacol Ther. 2015]

Abstract: BACKGROUND: Antibodies against tumour necrosis factor-alpha (anti-TNF) are effective therapies in the treatment of ulcerative colitis (UC), but their comparative efficacy is unknown.
AIM: To perform a network meta-analysis comparing the efficacy of anti-TNF agents in UC.
METHODS: After screening 506 studies, reviewers extracted information on seven studies. Traditional meta-analysis (TMA) was used to compare each anti-TNF agent to placebo. Bayesian network meta-analysis (NMA) was performed to compare the effects of anti-TNF agents to placebo. In addition, sample sizes for comparative efficacy trials were calculated. RESULTS: Compared to placebo, TMA revealed that anti-TNF agents result in a higher likelihood of induction of remission and response (RR: 2.45, 95% CI: 1.72-3.47 and RR: 1.65, 95% CI: 1.37-1.99 respectively) as well as maintenance of remission and response (RR: 2.00, 95% CI: 1.52-2.62 and RR: 1.76, 95% CI: 1.46-2.14
respectively). Individually, infliximab, adalimumab and golimumab resulted in a higher likelihood of induction and maintenance for both remission and response. NMA found nonsignificant trends in comparisons of the individual agents. The required sample sizes for direct head-to-head trials between infliximab and adalimumab for induction and maintenance are 174 and 204 subjects respectively. **CONCLUSIONS:** This study demonstrates that, compared to placebo, infliximab, adalimumab and golimumab are all effective for the induction and maintenance of remission in ulcerative colitis. However, network meta-analysis demonstrates that no single agent is clinically superior to the others and therefore, other factors such as cost, safety, route of administration and patient preference should dictate our choice of anti-TNF agents. A randomised comparative efficacy trial between infliximab and adalimumab in UC is of practical size and should be performed. © 2014 John Wiley & Sons Ltd.

**Database:** PubMed

84. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn’s disease.

**Author(s):** Feagan BG, McDonald JW, Panaccione R, et al.

**Abstract:** **BACKGROUND & AIMS:** Methotrexate and infliximab are effective therapies for Crohn’s disease (CD). In the combination of maintenance methotrexate-infliximab trial, we evaluated the potential superiority of combination therapy over infliximab alone. **METHODS:** In a 50-week, double-blind, placebo-controlled trial, we compared methotrexate and infliximab with infliximab alone in 126 patients with CD who had initiated prednisone induction therapy (15-40 mg/day) within the preceding 6 weeks. Patients were assigned randomly to groups given methotrexate at an initial weekly dose of 10 mg, escalating to 25 mg/week (n = 63), or placebo (n = 63). Both groups received infliximab (5 mg/kg of body weight) at weeks 1, 3, 7, and 14, and every 8 weeks thereafter. Prednisone was tapered, beginning at week 1, and discontinued no later than week 14. The primary outcome was time to treatment failure, defined as a lack of prednisone-free remission (CD Activity Index, <150) at week 14 or failure to maintain remission through week 50. **RESULTS:** Patients’ baseline characteristics were similar between groups. By week 50, the actuarial rate of treatment failure was 30.6% in the combination therapy group compared with 29.8% in the infliximab monotherapy group (P = .63; hazard ratio, 1.16; 95% confidence interval, 0.62-2.17). Prespecified subgroup analyses failed to show a benefit in patients with short disease duration or an increased level of C-reactive protein. No clinically meaningful differences were observed in secondary outcomes. Combination therapy was well tolerated. **CONCLUSIONS:** The combination of infliximab and methotrexate, although safe, was no more effective than infliximab alone in patients with CD receiving treatment with prednisone. ClinicalTrials.gov number, NCT00132899.

85. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis.
OBJECTIVE To study the comparative efficacy of biologic therapy in the management of biologic-naïve patients with Crohn disease (CD).

PATIENTS AND METHODS We conducted a systematic review of randomized controlled trials published from January 1, 1985, through September 30, 2013, comparing biologic agents (infliximab [IFX], adalimumab [ADA], certolizumab pegol, natalizumab, vedolizumab, and ustekinumab) with each other or placebo for inducing and maintaining clinical remission in adults with moderate to severe CD. To increase comparability across trials, we focused on a subset of biologic-naïve patients for the induction end point and on responders to induction therapy for the maintenance end point. We followed a Bayesian network meta-analysis approach.

RESULTS We identified 17 randomized controlled trials of good methodological quality comparing 6 biologic agents with placebo, with no direct comparison of biologic agents. In network meta-analysis, we observed that IFX (relative risk [RR], 6.11; 95% credible interval [CrI], 2.49-18.29) and ADA (RR, 2.98; 95% CrI, 1.12-8.18), but not certolizumab pegol (RR, 1.48; 95% CrI, 0.76-2.93), natalizumab (RR, 1.36; 95% CrI, 0.69-2.86), vedolizumab (RR, 1.40; 95% CrI, 0.63-3.28), and ustekinumab (RR, 0.61; 95% CrI, 0.15-2.49), were more likely to induce remission than placebo. Similar results were observed for maintenance of remission. Infliximab had the highest probability of being ranked as the most efficacious agent for induction (86%) and ADA for maintenance of remission (48%).

CONCLUSION On the basis of network meta-analysis, IFX may be most efficacious agent for inducing remission in CD in biologic-naïve patients. In the absence of head-to-head treatment comparison, the confidence in these estimates is low. Future comparative efficacy studies are warranted.

Database: Medline
randomized to receive IFX or ADA for 1 year. Co-primary endpoints were endoscopic, histological and clinical recurrence after 12 months of therapy.

RESULTS Twenty consecutive CD patients (9 males and 11 females; median age 32.5 years, range 20-39 years) were enrolled after undergoing curative ileocolonic resection. Among the 10 patients treated with IFX, 2 (20%) had endoscopic recurrence compared to 1 (10%) in the group of 10 ADA patients (p = 1.0). Three out of 10 (30%) IFX patients and 2 out of 10 (20%) ADA patients had histological recurrence (p = 1.0). No significant clinical differences were found between the two groups. CONCLUSIONS IFX and ADA were similar in preventing histological, endoscopic and clinical recurrence after curative ileocolonic resection in high risk CD patients.

Database: Medline

87. Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naïve to anti-TNF therapy: an indirect treatment comparison meta-analysis.

Author(s): Thorlund, Kristian; Druyts, Eric; Mills, Edward J; Fedorak, Richard N; Marshall, John K

Source: Journal of Crohn's & colitis; Jul 2014; vol. 8 (no. 7); p. 571-581

Publication Date: Jul 2014

Publication Type(s): Research Support, Non-u.s. Gov't Meta-analysis Comparative Study Journal Article Review Systematic Review

PubMedID: 24491514

Available at Journal of Crohn's & colitis - from Unpaywall

Abstract: OBJECTIVE To compare the efficacy of adalimumab and infliximab for the treatment of moderate to severe ulcerative colitis using indirect treatment comparison meta-analysis. METHODSA systematic review and Bayesian indirect treatment comparison meta-analyses were performed for seven patient-important clinical outcomes at 8 weeks and 52 weeks. Odds ratio (OR) estimates and associated 95% credible intervals (CrIs) were produced. RESULTS Five eligible RCTs informed clinical remission, response, mucosal healing, quality of life, colectomy, serious adverse events, and discontinuation due to adverse events at 8 weeks and 52 weeks. At 8 weeks of induction therapy, clinical remission (OR=0.42, 95% CrI 0.17-0.97), clinical response (OR=0.45, 95% CrI 0.23-0.89) and mucosal healing (OR=0.46, 95% CrI 0.25-0.86) statistically favored infliximab. However, after 52 weeks of maintenance therapy OR estimates showed no significant difference between infliximab and adalimumab. For serious adverse events and discontinuations due to adverse events, adalimumab and infliximab were similar to placebo. Further, the indirect treatment comparison of adalimumab and infliximab yielded odds ratios close to 1.00 with wide credible intervals. CONCLUSION The findings of this indirect treatment comparison meta-analysis suggest that both infliximab and adalimumab are superior to placebo in the treatment of moderate to moderately severe ulcerative colitis. While infliximab is statistically more effective than adalimumab in the induction of remission, response and mucosal healing at 8 weeks, infliximab and adalimumab are comparable in efficacy at 52 weeks of maintenance treatment.

Database: Medline

88. Biologic therapies in inflammatory bowel disease.

Author(s): Cohen, Lawrence B; Nanau, Radu M; Delzor, Faustine; Neuman, Manuela G

Source: Translational research : the journal of laboratory and clinical medicine; Jun 2014; vol. 163 (no. 6); p. 533-556

Publication Date: Jun 2014
Inflammatory bowel disease, including its 2 entities ulcerative colitis and Crohn’s disease, is a chronic medical condition characterized by the destructive inflammation of the intestinal tract. Biologics represent a class of therapeutics with immune intervention potential. These agents block the proinflammatory cascade that triggers the activation and proliferation of T lymphocytes at the level of the intestine, therefore reestablishing the balance between the pro- and anti-inflammatory messages. All 7 biologics showing clinical benefits in inflammatory bowel disease are monoclonal antibodies. The following systematic review discusses the pharmacokinetics and efficacy of the tumor necrosis factor blockers infliximab, adalimumab, certolizumab pegol, and golimumab. In addition, we describe the α4 integrin inhibitors natalizumab and vedolizumab, which are directed against cell adhesion molecules, as well as the interleukin 12/23 blocker ustekinumab.

89. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis.

**Author(s):** Danese, Silvio; Fiorino, Gionata; Peyrin-Biroulet, Laurent; Lucenteforte, Ersilia; Virgili, Gianni; Moja, Lorenzo; Bonovas, Stefanos

**Source:** Annals of internal medicine; May 2014; vol. 160 (no. 10); p. 704-711

**Abstract:** Biological agents are emerging treatment options for the management of ulcerative colitis (UC). PURPOSE To assess the comparative efficacy and harm of biological agents in adult patients with moderately to severely active UC who are naive to biological agents. DATA SOURCES MedLINE, EMBASE, and Cochrane Library from inception through December 2013, without language restrictions, and ClinicalTrials.gov, European Medicines Agency, and U.S. Food and Drug Administration Web sites. STUDY SELECTION Randomized, placebo-controlled or head-to-head trials assessing biological agents as induction or maintenance therapy for moderately to severely active UC. DATA EXTRACTION Two reviewers independently abstracted study data and outcomes and rated each trial’s risk of bias. DATA SYNTHESIS There were no head-to-head trials. There were 7 double-blind, placebo-controlled trials that were rated as low risk of bias and showed that all biological agents (adalimumab, golimumab, infliximab, and vedolizumab) resulted in more clinical responses, clinical remissions, and mucosal healings than placebo for induction therapy. The results of network meta-analysis suggested that infliximab is more effective to induce clinical response (odds ratio, 2.36 [95% credible interval, 1.22 to 4.63]) and mucosal healing (odds ratio, 2.02 [95% credible interval, 1.13 to 3.59]) than adalimumab. No other indirect comparison reached statistical significance. For maintenance, 6 double-blind, placebo-controlled trials that were rated high risk of bias showed that all biological agents have greater clinical efficacy than placebo. The occurrence of adverse events was not different between biological agents and placebo. LIMITATION Few trials, no head-to-head comparisons, and inadequate follow-up in maintenance trials. CONCLUSION Biological agents are effective treatments for UC, but head-to-head trials are warranted to establish the best therapeutic option.

**Database:** Medline
90. Costs of adalimumab versus infliximab as first-line biological therapy for luminal Crohn's disease.

**Author(s):** Choi, Grace K H; Collins, Stephanie D E; Greer, Daniel P; Warren, Lisa; Dowson, Grace; Clark, Tanya; Hamlin, P John; Ford, Alexander C

**Source:** Journal of Crohn's & colitis; May 2014; vol. 8 (no. 5); p. 375-383

**Publication Date:** May 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Journal Article

**PubMedID:** 24129316

Available at [Journal of Crohn’s & colitis](https://www.jamm.com/journal-of-crohn-s-colitis) - from Unpaywall

**Abstract:**

BACKGROUND AND AIMS Randomised controlled trials demonstrate that the anti-tumour necrosis factor-α (anti-TNFα) therapies infliximab and adalimumab are effective in inducing remission and preventing relapse of Crohn's disease (CD). As few studies have compared costs and efficacy of these two drugs directly, we examined this issue.

**METHODS** Data were collected for patients receiving either drug as first-line anti-TNFα for CD. Patients were matched as closely as possible on age, gender, weight, height, and date of commencement of therapy. Response to induction therapy was assessed at 12 weeks, and sustained clinical benefit at last point of follow-up.

**Resource data were collected for all patients until study end, with National Health Services reference costs applied to calculate the total cost per patient with adalimumab compared with infliximab.**

**RESULTS** Thirty-six patients had been treated with adalimumab as first-line anti-TNFα since 2010. We matched an identical number of infliximab patients. Demographic data were similar between the two groups. Costs were significantly lower with adalimumab (£6692.95 less per patient (95% confidence interval £1816.61-£11569.29)), which was largely driven by the drug costs and drug administration costs associated with infliximab. Twenty-nine (80.6%) patients responded to induction therapy with both drugs, and 22 (61.1%) achieved glucocorticosteroid-free sustained clinical benefit with either drug at last point of follow-up.

**CONCLUSION** Costs of infliximab used as first-line anti-TNFα therapy are greater, which may have implications for selection. Clinical outcomes appeared comparable, although power to detect a statistically significant difference would be limited.

**Database:** Medline

91. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis.

**Author(s):** Panaccione, Remo; Ghosh, Subrata; Middleton, Stephen; Márquez, Juan R; Scott, Boyd B; Flint, Laurence; van Hoogstraten, Hubert J F; Chen, Annie C; Zheng, Hanzhe; Danese, Silvio; Rutgeerts, Paul

**Source:** Gastroenterology; Feb 2014; vol. 146 (no. 2); p. 392

**Publication Date:** Feb 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Journal Article

**PubMedID:** 24512909

**Abstract:**

**BACKGROUND & AIMS** The comparative efficacy and safety of infliximab and azathioprine therapy alone or in combination for ulcerative colitis (UC) have not been evaluated previously.

**METHODS** This randomized, double-blind trial evaluated the efficacy and safety of 16 weeks of treatment with infliximab monotherapy, azathioprine monotherapy, or the 2 drugs combined in tumor necrosis factor-α antagonist-naive adults with moderate to severe UC. Patients were assigned randomly to receive intravenous infusions of infliximab 5 mg/kg at weeks 0, 2, 6, and
14 plus daily oral placebo capsules; oral azathioprine 2.5 mg/kg daily plus placebo infusions on the infliximab schedule; or combination therapy with the 2 drugs. Corticosteroid-free clinical remission (primary end point, week 16) was evaluated at weeks 8 and 16. The study was terminated before the enrollment target was reached. RESULTS A total of 239 patients were included in efficacy analyses. Baseline characteristics were similar between treatment groups. Corticosteroid-free remission at week 16 was achieved by 39.7% (31 of 78) of patients receiving infliximab/azathioprine, compared with 22.1% (17 of 77) receiving infliximab alone (P = .017) and 23.7% (18 of 76) receiving azathioprine alone (P = .032). Mucosal healing at week 16 occurred in 62.8% (49 of 78) of patients receiving infliximab/azathioprine, compared with 54.6% (42 of 77) receiving infliximab (P = .295) and 36.8% (28 of 76) receiving azathioprine (P = .001). Serious infections occurred in 2 patients (1 patient receiving infliximab, and 1 patient receiving azathioprine). CONCLUSIONS Anti–tumor necrosis factor-alpha-naive patients with moderate to severe UC treated with infliximab plus azathioprine were more likely to achieve corticosteroid-free remission at 16 weeks than those receiving either monotherapy. Combination therapy led to significantly better mucosal healing than azathioprine monotherapy. ClinicalTrials.gov number, NCT00537316.

Database: Medline

92. Tumor necrosis factor-alpha antibodies (infliximab, adalimumab and certolizumab) in Crohn’s disease: Systematic review and meta-analysis.

Author(s): Kawalec P., Mikrut A., Wisniewska N., Pilc A.

Source: Archives of Medical Science. 9 (5) (pp 765-779), 2013. Date of Publication: October 2013.

Introduction: This meta-analysis compares the effectiveness and safety of tumor necrosis factor alpha (TNF-alpha) antibodies (infliximab, adalimumab and certolizumab) with either a placebo or each of them in the treatment of Crohn's disease (CD). Material(s) and Method(s): A systematic review of literature published up to November 2012 was performed and a meta-analysis of identified studies was carried out. We searched the following databases: PubMed, EMBASE, The Cochrane Library and others. Only randomized or clinical controlled trials were included. Result(s): Nineteen clinical trials fulfilled the established criteria (5 studies for infliximab vs. placebo, 6 for each adalimumab or certolizumab vs. placebo and 2 comparing infliximab with adalimumab). The results of meta-analysis showed that anti-TNF therapy in patients with CD is safe and statistically significantly more effective when compared with the placebo for induction of remission at week 4 (RB = 1.90, 95% CI: 1.55-2.33, p < 0.00001), maintenance of remission at weeks 20-30 (RB = 1.86, 95% CI: 1.61-2.15, p < 0.00001) and at weeks 48-56 (RB = 2.75, 95% CI: 2.13-3.54, p < 0.00001) in patients who responded to the induction therapy and patients randomized before the induction. Anti-TNF agents were also superior to the placebo in fistula healing (during short-term induction, as well as long-term maintenance) and inducing CR-70 but not CR-100 at week 4. Moreover, the anti-TNF therapy had a significant effect on achieving both CR-70 and CR-100 during long-term maintenance. Conclusion(s): Infliximab, adalimumab and certolizumab are effective as both induction and maintenance therapy in moderate to severe Crohn’s disease in adults, including patients with fistulas. The safety profile was acceptable. Copyright © 2013 Termedia & Banach.

Database: Embase
93. Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-α agents.

**Author(s):** Kestens C, van Oijen MG, Mulder CL, et al.


**Abstract:** **BACKGROUND & AIMS:** Infliximab (IFX) and adalimumab (ADA) are thought to have equal efficacy for the treatment of Crohn's disease (CD), although no direct comparison has been performed. We compared the effectiveness and safety of IFX and ADA in carefully matched cohorts.

**METHODS:** We performed a retrospective cohort study of 200 patients with CD (100 treated with IFX and 100 treated with ADA, starting in 2006 or later) who had not received anti-tumor necrosis factor α agents previously; the patients were identified from databases of 6 hospitals in The Netherlands. The groups were matched carefully for indication, duration of disease, age, and Montreal classification. The primary end point was the steroid-free clinical response, defined by a combination of multiple clinical parameters, after 1 year. **RESULTS:** Of the total patient population, 63.5% and 45% had a clinical response after 1 and 2 years, respectively. There were no significant differences between treatment groups: at 1 and 2 years, 62% and 41% of those receiving ADA vs 65% and 49% of those receiving IFX had responses, respectively. Kaplan-Meier curves showed identical decreases in response rates over time. Combining IFX or ADA with immunomodulator therapy was associated with a higher clinical response than monotherapy, although this was only significant among patients who received IFX (P = .03). There were no differences in numbers of side effects or opportunistic infections. **CONCLUSIONS:** The effectiveness of ADA or IFX treatment in anti-tumor necrosis factor α-naive patients with CD is comparable after 1 and 2 years of follow-up evaluation. The efficacies of IFX and ADA each seem to increase when given with immunomodulator therapy, although only significantly for IFX. Copyright © 2013 AGA Institute. Published by Elsevier Inc. All rights reserved.

**Database:** PubMed

94. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis.

**Author(s):** Garcés S, Demengeot J, Benito-Garcia E.


**Abstract:** **BACKGROUND:** Immunogenicity of aTNFs is one of the mechanisms behind treatment failure. **OBJECTIVE:** To assess the effect of anti-drug antibodies (ADA) on drug response to infliximab, adalimumab and etanercept, and the effect of immunosuppression on ADA detection, in patients with Rheumatoid Arthritis, Spondyloarthritis, Psoriasis and Inflammatory Bowel Diseases. **DATA SOURCES:** PubMed, EMBASE, Cochrane databases, article reference lists (through August 19 2012). **STUDY SELECTION:** Out of 2082 studies, 17 were used in the meta-analysis (1RCT; 16 observational studies). **DATA EXTRACTION:** Two reviewers extracted data. Risk ratios (RR), 95% CI, using random-effect models, sensitivity analysis, meta-regressions and Egger’s test were calculated.
DATA SYNTHESIS: Of 865 patients, ADA against infliximab or adalimumab reduced drug response rate by 68% (RR=0.68, 95% CI=0.12 to 0.36), an effect attenuated by concomitant methotrexate (MTX): <74% MTX+: RR=0.23, 95% CI=0.15 to 0.36; ≥74% MTX+: RR=0.32, 95% CI=0.22 to 0.48. Anti-etanercept antibodies were not detected. Of 936 patients, concomitant MTX or azathioprine/mercaptopurine reduced ADA frequency by 47% (RR=0.53, 95% CI=0.42 to 0.67), particularly when ADA were assessed by RIA (RR=0.36, 95% CI=0.23 to 0.55) compared with ELISA (RR=0.63, 95% CI=0.53 to 0.74). CONCLUSIONS: ADA reduces drug response, an effect that can be attenuated by concomitant immunosuppression, which reduces ADA frequency. Drug immunogenicity should be considered for the management of patients receiving biological therapies.

95. Development of psoriasis scalp with alopecia during treatment of Crohn's disease with infliximab and rapid response to both diseases to ustekinumab.
Author(s): Andrisani, G; Marzo, M; Celleno, L; Guidi, L; Papa, A; Gasbarrini, A; Armuzzi, A
Source: European review for medical and pharmacological sciences; Oct 2013; vol. 17 (no. 20); p. 2831-2836
Publication Date: Oct 2013
Publication Type(s): Case Reports Journal Article
PubMedID: 24174369
Abstract: Anti tumor necrosis factor antibodies are used to treat both psoriasis and inflammatory bowel disease. Several paradoxical cases of psoriatic skin lesions induced by tumor necrosis factor antagonist therapy have been described in IBD patients in the recent years. Ustekinumab, a fully human anti-interleukin-12/23 monoclonal antibody, is the first drug of a new class of biologic therapy approved for the treatment of moderate to severe plaque psoriasis. Data on the efficacy of ustekinumab in patients with moderate-to-severe Crohn's disease, especially in patients previously treated with infliximab, have been recently published. We report about the effectiveness of ustekinumab in the treatment of both severe scalp psoriasis lesions with alopecia and active Crohn's disease.
Database: Medline

96. Comparison of techniques for monitoring infliximab and antibodies against infliximab in Crohn's disease.
Author(s): Steenholdt, Casper; Ainsworth, Mark A; Tovey, Michael; Klausen, Tobias W; Thomsen, Ole O; Brynskov, Jørn; Bendtzen, Klaus
Source: Therapeutic drug monitoring; Aug 2013; vol. 35 (no. 4); p. 530-538
Publication Date: Aug 2013
Publication Type(s): Research Support, Non-u.s. Gov't Comparative Study Journal Article
PubMedID: 23765033
Abstract: BACKGROUND Several techniques are used to measure infliximab (IFX) and anti-IFX antibodies (Abs) in Crohn's disease. The aim of this study was to compare different assays for this purpose. METHODS Fluid-phase radioimmunoassay (RIA), solid-phase enzyme-linked immunosorbent assay (ELISA), reporter gene assay (RGA), and enzyme immunoassay (EIA; anti-IFX Ab only) were assessed. IFX was added to pooled serum from 13 patients with inactive Crohn's disease to yield
concentrations of 0, 1, 3, and 9 µg/mL. Anti-IFX Abs were assessed in 6 patients.RESULTSIFX assessments: RIA and RGA had lower limit of detection than ELISA (0.07 µg/mL and 0.13 versus 0.26). Maximal inaccuracies were 39%, 24%, and 23%. Imprecisions (coefficients of variation) were ≤20% within IFX concentrations between 1 and 9 µg/mL. All assays showed linear correlations (R = 0.97-0.99), but sample concentrations differed by up to 1.55 µg/mL for RIA and RGA, 1.41 µg/mL for ELISA and RIA, and 0.48 µg/mL for ELISA and RGA (P < 0.05). Anti-IFX Ab assessments: RGA gave highly reproducible results (coefficients of variation ≤ 7%) compared with all others (24%-26%). All assays had linear correlations (R = 0.71-0.93), except ELISA versus RGA and EIA. Assays disagreed on anti-IFX Ab titers with mean difference -420 (-1200 to 210) in RGA and EIA, and up to 4500 (-2700 to 11,800) in RIA and RGA. A contributing factor to these discrepancies was inability of ELISA to detect IgG4 anti-IFX Abs.CONCLUSIONSPerformances of assays for IFX and anti-IFX Abs are comparable. However, IFX concentrations and anti-IFX Ab titers show systematic differences, and in individual patients, only the same assay should be used. Problems may arise when different assays are used to manage therapies in the same patient.

Database: Medline

97. Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis.

Author(s): Chang, Kah Hoong; Burke, John P; Coffey, J Calvin

Source: International journal of colorectal disease; Mar 2013; vol. 28 (no. 3); p. 287-293

Publication Date: Mar 2013

Publication Type(s): Meta-analysis Comparative Study Journal Article Review Systematic Review

PubMedID: 23114475

Available at International journal of colorectal disease - from ProQuest (Health Research Premium) - NHS Version

Abstract: PURPOSE Acute severe colitis affects 25% of patients with ulcerative colitis (UC). Up to 30-40% of these patients are resistant to intensive steroid therapy and therefore require rescue therapy to prevent emergent colectomy. Data comparing rescue therapy using infliximab and cyclosporine are limited and equivocal. This study evaluates the outcomes of UC patients receiving infliximab or cyclosporine as rescue therapy in acute severe steroid-refractory exacerbations.

METHODS Electronic databases (PubMed, EMBASE, and Cochrane database) were searched for studies directly comparing infliximab and cyclosporine in UC, and references of included studies were screened. Two independent reviewers identified relevant studies and extracted data. Meta-analyses were performed using the random effect model. Outcome measures included 3- and 12-month colectomy rates, adverse drug reactions, and postoperative complications.

RESULTS Six retrospective cohort studies describing 321 patients met the inclusion criteria. The meta-analysis did not show significant differences between infliximab and cyclosporine in the 3-month colectomy rate (odds ratio (OR) = 0.86, 95% confidence interval (CI) = 0.31-2.41, p = 0.775), in the 12-month colectomy rate (OR = 0.60, 95% CI = 0.19-1.89, p = 0.381), in adverse drug reactions (OR = 0.76, 95% CI = 0.34-1.70, p = 0.508), and in postoperative complications (OR = 1.66, 95% CI = 0.26-10.50, p = 0.591). Funnel plot revealed no publication bias.

CONCLUSION Infliximab and cyclosporine are comparable when used as rescue therapy in acute severe steroid-refractory UC. Randomized trials are required to further evaluate these agents.

Database: Medline
98. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial.

Author(s): Laharie, David; Bourreille, Arnaud; Branche, Julien; Allez, Matthieu; Bouhnik, Yoram; Filippi, Jerome; Zerbib, Frank; Savoye, Guillaume; Nachury, Maria; Moreau, Jacques; Delchier, Jean-Charles; Cosnes, Jacques; Ricart, Elena; Dewit, Olivier; Lopez-Sanroman, Antonio; Dupas, Jean-Louis; Carbonnel, Franck; Bommelaer, Gilles; Coffin, Benoit; Robin, Xavier; Van Assche, Gert; Esteve, Maria; Färkkilä, Martti; Gisbert, Javier P; Marteau, Philippe; Nahon, Stephane; de Vos, Martine; Franchimont, Denis; Mary, Jean-Yves; Colombel, Jean-Frederic; Lémann, Marc; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives

Source: Lancet (London, England); Dec 2012; vol. 380 (no. 9857); p. 1909-1915

Publication Date: Dec 2012

Publication Type(s): Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Multicenter Study Journal Article

PubMedID: 23063316

Available at Lancet (London, England) - from ScienceDirect
Available at Lancet (London, England) - from ProQuest (Health Research Premium) - NHS Version

Abstract: BACKGROUND Ciclosporin and infliximab are potential rescue treatments to avoid colectomy in patients with acute severe ulcerative colitis refractory to intravenous corticosteroids. We compared the efficacy and safety of these drugs for this indication. METHODS In this parallel, open-label, randomised controlled trial, patients were aged at least 18 years, had an acute severe flare of ulcerative colitis defined by a Lichtiger score greater than 10 points, and had been given an unsuccessful course of high-dose intravenous steroids. None of the patients had previously received ciclosporin or infliximab. Between June 1, 2007, and Aug 31, 2010, patients at 27 European centres were randomly assigned (via computer-derived permutation tables; 1:1) to receive either intravenous ciclosporin (2 mg/kg per day for 1 week, followed by oral drug until day 98) or infliximab (5 mg/kg on days 0, 14, and 42). In both groups, azathioprine was started at day 7 in patients with a clinical response. Neither patients nor investigators were masked to study treatment. The primary efficacy outcome was treatment failure defined by absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, severe adverse events leading to treatment interruption, colectomy, or death. Analysis was by intention to treat. This trial is registered with EudraCT (2006-005299-42) and ClinicalTrials.gov (NCT00542152). FINDINGS 115 patients were randomly assigned; 58 patients were allocated to receive ciclosporin and 57 to receive infliximab. Treatment failure occurred in 35 (60%) patients given ciclosporin and 31 (54%) given infliximab (absolute risk difference 6%; 95% CI -7 to 19; p=0.52). Nine (16%) patients in the ciclosporin group and 14 (25%) in the infliximab group had severe adverse events. INTERPRETATION Ciclosporin was not more effective than infliximab in patients with acute severe ulcerative colitis refractory to intravenous steroids. In clinical practice, treatment choice should be guided by physician and centre experience. FUNDING Association François Aupetit, Société Nationale Française de Gastroentérologie, and the International Organization for the study of Inflammatory Bowel Disease.

Database: Medline


Author(s): Roberts, Rebecca L; Barclay, Murray L

Source: Journal of gastroenterology and hepatology; Oct 2012; vol. 27 (no. 10); p. 1546-1554
Abstract: No drug therapy is completely risk free, and the costs associated with non-response and adverse effects can exceed the cost of the therapy. The ultimate goal of pharmacogenetic research is to find robust genetic predictors of drug response that enable the development of prospective genetic tests to reliably identify patients at risk of non-response or of developing an adverse effect prior to the drug being prescribed. Currently, thiopurine S-methyltransferase (TPMT) deficiency is the only pharmacogenetic factor that is prospectively assessed before azathioprine or 6-mercaptopurine immunomodulation is commenced in patients with Crohn's disease (CD). As yet no other inherited determinant of drug response has made the transition from bench to bedside for the management of this disease. In this review we summarize what is known about TPMT deficiency and explore whether there is evidence to support a role of other genetic polymorphisms in predicting the response of CD patients to thiopurine drugs, methotrexate, and anti-tumor necrosis factor α (TNFα) therapy.

100. Ustekinumab induction and maintenance therapy in refractory Crohn's disease.


Abstract: BACKGROUND: In patients with Crohn's disease, the efficacy of ustekinumab, a human monoclonal antibody against interleukin-12 and interleukin-23, is unknown. METHODS: We evaluated ustekinumab in adults with moderate-to-severe Crohn's disease that was resistant to anti-tumor necrosis factor (TNF) treatment. During induction, 526 patients were randomly assigned to receive intravenous ustekinumab (at a dose of 1, 3, or 6 mg per kilogram of body weight) or placebo at week 0. During the maintenance phase, 145 patients who had a response to ustekinumab at 6 weeks underwent a second randomization to receive subcutaneous injections of ustekinumab (90 mg) or placebo at weeks 8 and 16. The primary end point was a clinical response at 6 weeks.

RESULTS: The proportions of patients who reached the primary end point were 36.6%, 34.1%, and 39.7% for 1, 3, and 6 mg of ustekinumab per kilogram, respectively, as compared with 23.5% for placebo (P=0.005 for the comparison with the 6-mg group). The rate of clinical remission with the 6-mg dose did not differ significantly from the rate with placebo at 6 weeks. Maintenance therapy with ustekinumab, as compared with placebo, resulted in significantly increased rates of clinical remission (41.7% vs. 27.4%, P=0.03) and response (69.4% vs. 42.5%, P<0.001) at 22 weeks. Serious infections occurred in 7 patients (6 receiving ustekinumab) during induction and 11 patients (4 receiving ustekinumab) during maintenance. Basal-cell carcinoma developed in 1 patient receiving ustekinumab. CONCLUSIONS: Patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists had an increased rate of response to induction with ustekinumab, as compared with placebo. Patients with an initial response to ustekinumab had significantly increased rates of response and remission with ustekinumab as maintenance therapy. (Funded by Janssen Research and Development; CERTIFI ClinicalTrials.gov number, NCT00771667.)
101. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis.


**Abstract:** **BACKGROUND & AIMS:** We evaluated the efficacy and safety of infliximab for inducing and maintaining benefit in children with moderately to severely active ulcerative colitis (UC).

**METHODS:** Patients (6-17 years old) who had active UC (Mayo scores of 6-12; endoscopic subscores ≥ 2) and had not responded to or tolerated conventional treatment were given 5 mg/kg infliximab at weeks 0, 2, and 6. The primary end point was response at week 8 (decreases in Mayo scores ≥ 30% and ≥ 3 points and decreases in rectal bleeding subscores of ≥ 1 or an absolute subscore of ≤ 1). At week 8, only responders were randomly assigned to groups given infliximab every 8 or 12 weeks (q8w or q12w) and followed through week 54. Maintenance end points included pediatric UC activity index scores <10 points, defined as remission. **RESULTS:** At week 8, infliximab induced a response in 73.3% of patients (44 of 60) (95% confidence interval, 62.1%-84.5%; a positive result was defined by 95% confidence interval lower limit >40%). Among responders, twice as many were in remission at week 54 after q8w (8 of 21, 38.1%) than q12w (4 of 22, 18.2%; P = .146) therapy. Assuming the q8w remission rate for responders, the overall remission rate at week 54 would be 28.6%. Serious adverse events and infusion reactions occurred in similar proportions in the q8w and q12w groups. No deaths, malignancies, opportunistic infections, tuberculosis, or delayed hypersensitivity reactions were reported. **CONCLUSIONS:** Infliximab was safe and effective, inducing a response at week 8 in 73.3% of pediatric patients with moderate to severely active UC who did not respond to conventional therapy. The overall remission rate at week 54 for all enrolled patients was 28.6%, assuming the more effective q8w remission rate.© 2012 AGA Institute. Published by Elsevier Inc. All rights reserved.

**Database:** PubMed


**Abstract:** **BACKGROUND:** The aim was to evaluate long-term efficacy, quality of life, and safety in ulcerative colitis patients who received infliximab during the ACT-1 and -2 extension studies.
METHODS: Adults with moderate-to-severely active ulcerative colitis in the 54-week ACT-1 and 30-week ACT-2 studies who achieved benefit from infliximab were eligible to participate in extension studies and receive up to 3 additional years of therapy. Patients received randomized study medication until all sites were unblinded; placebo-treated patients were discontinued. Patients receiving 5 or 10 mg/kg infliximab continued to receive open-label infliximab every 8 weeks. Patients receiving infliximab 10 mg/kg could decrease to 5 mg/kg; patients receiving infliximab 5 mg/kg could increase to 10 mg/kg if response was lost. RESULTS: A total of 229 of 484 infliximab-treated patients from the ACT-1 and ACT-2 main studies entered the long-term extensions. Overall, 70 (30.6%) patients discontinued infliximab infusions for adverse events (24 [10.5%]), lack of efficacy (11 [4.8%]), required a colectomy (1 [0.4%]), or for other reasons (34 [14.8%]). Proportions of patients whose Physician’s Global Assessment scores were indicative of no or mild disease (score = 0 or 1) were maintained during the extension studies; 76.5% at Extension week 0 and ranged between 90.0% and 94.3% through Extension week 152. Improvement in Inflammatory Bowel Disease Questionnaire scores observed in the main studies was maintained. During the long-term extension, the infliximab safety profile was consistent with that of the main studies; no new or unexpected safety signals were observed. CONCLUSIONS: Long-term treatment with infliximab for up to 3 additional years was effective and well tolerated.

Database: PubMed

103. Immunotherapy in inflammatory bowel disease.
Author(s): Ahluwalia, Jatinder P
Source: The Medical clinics of North America; May 2012; vol. 96 (no. 3); p. 525
Publication Date: May 2012
Publication Type(s): Journal Article Review
PubMedID: 22703854
Abstract: Inflammatory bowel disease affects an increasing number of patients worldwide and is associated with significant morbidity. The dysregulation of the immune system with increased expression of proinflammatory cytokines and increased mucosal expression of vascular adhesion molecules play an important role in its pathogenesis. Strategies targeting TNF-alpha and alpha4-integrin have led to the development of novel therapies for treatment of patients with IBD. This article discusses the efficacy of immunologic agents currently approved for treating Crohn disease and ulcerative colitis and reviews the risks and challenges associated with their use.

Database: Medline

104. A systematic review and meta-analysis of the efficacy and adverse events of infliximab in comparison to corticosteroids and placebo in active ulcerative colitis.
Author(s): Nikfar S., Ehteshami-Afshar S., Abdollahi M.
The proinflammatory cytokine tumor necrosis factor alpha (TNF-a) plays a major role in severity of Ulcerative Colitis (UC) and thus inhibition of TNF-a is used to control severe cases of UC. The present meta-analysis was performed to collect and review all the clinical trials that investigated the efficacy
and tolerability of infliximab in order to determine whether infliximab is more effective than placebo or corticosteroids in inducing response and remission in UC. All bibliographic databases such as PubMed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials were searched for studies investigated the efficacy of infliximab for the management of UC. Data were collected from 1966 to September 2010. Three trials represented 57 patients with UC who were randomized to receive infliximab or corticosteroids and 5 trials represented 827 patients with UC who were randomized to receive infliximab or placebo were included in the analysis. The summary Relative Risk (RR) for clinical remission in comparison of infliximab with placebo was 1.93 with a 95% Confidence Interval (CI) of 1.62-2.3 and a significant RR (p<0.0001). Summary RR for adverse events of infliximab comparing to placebo was 1.07 with a 95% CI of 0.99-1.14, a non-significant RR (p = 0.0725). The summary RR for serious adverse events of infliximab comparing to placebo was 0.83 with a 95% CI of 0.44-1.54 as a non-significant RR (p = 0.5472). The summary RR for clinical remission of infliximab comparing to corticosteroids was 1.07 with a 95% CI of 0.87-1.31 as a non-significant RR (p = 0.5353). Patients receiving infliximab were 1.93 and 1.07 times more likely to go to the remission as compared to those receiving placebo and corticosteroids, respectively. Meanwhile, the risk of adverse events in the patients receiving infliximab was 1.07 times more than placebo group. The risk of opportunistic infection was high in patients who have failed steroids and cyclosporine and were using infliximab. Although infliximab is more effective than corticosteroids in inducing clinical remission, we believe further trials are still needed to judge stronger in this respect. © 2011 Asian Network for Scientific Information.

Database: Embase

105. Colon salvage therapy for acute severe colitis: cyclosporine or infliximab?

Author(s): Burger DC, Travis S.


Abstract: PURPOSE OF REVIEW: Steroid-refractory acute severe colitis (ASC) poses a significant clinical challenge to both physicians and surgeons alike. This review highlights advances in management of these patients and the role of cyclosporine compared to infliximab. RECENT FINDINGS: ASC affects 25% of patients with ulcerative colitis and is associated with measurable morbidity and mortality. Simple clinical and laboratory measures predict steroid refractoriness (such as stool frequency 3-8/day and C-reactive protein > 45 mg/l on day 3) and salvage therapy is appropriate at this stage. Preliminary data from randomized controlled trials suggest that early (7 and 98 day) response to cyclosporine and infliximab are comparable. Serum trough infliximab concentrations may correlate with outcome. Sequential therapy cannot usually be recommended due to limited response (70% colectomy at 3 years) and high rate of serious adverse events. SUMMARY: Optimal salvage therapy will depend on detailed results of randomized controlled trials. Meanwhile, patients with ASC should receive either cyclosporine or infliximab before surgery as long as there is specialist expertise that allows early decision-making.

Database: PubMed
106. Genetic and genomic predictors of anti-TNF response.

Author(s): Prajapati R., Plant D., Barton A.


The introduction of anti-TNF therapy has dramatically improved the outlook for patients suffering from a number of inflammatory conditions including rheumatoid arthritis and inflammatory bowel disease. Despite this, a substantial proportion of patients (approximately 30-40%) fail to respond to these potentially toxic and expensive therapies. Treatment response is likely to be multifactorial; however, variation in genes or their expression may identify those most likely to respond. By targeted testing of variants within candidate genes, potential predictors of anti-TNF response have been reported; however, very few markers have replicated consistently between studies. Emerging genome-wide association studies suggest that there may be a number of genes with modest effects on treatment response rather than a few genes of large effect. Other potential serum biomarkers of response have also been explored including cytokines and autoantibodies, with antibodies developing to the anti-TNF drugs themselves being correlated with treatment failure. © 2011 Future Medicine Ltd.

Database: Embase


Author(s): Tamboli C.P., Doman D.B., Patel A.


Background: Crohn's disease (CD), a chronic inflammatory bowel disease (IBD), occurs in genetically susceptible individuals who develop aberrant immune responses to endoluminal bacteria. Recurrent inflammation increases the risk of several complications. Despite use of a traditional "step-up" therapy with corticosteroids and immunomodulators, most CD patients eventually require surgery at some time in their disease course. Newer biologic agents have been remarkably effective in controlling severe disease. Thus, "top-down," early aggressive therapy has been proposed to yield better outcomes, especially in complicated disease. However, safety and cost issues mandate the need for careful patient selection. Identification of high-risk candidates who may benefit from aggressive therapy is becoming increasingly relevant. Serologic and genetic markers of CD have great potential in this regard. The aim of this review is to highlight the clinical relevance of these markers for diagnostics and prognostication. Method(s): A current PubMed literature search identified articles regarding the role of biomarkers in IBD diagnosis, severity prediction, and stratification. Studies were also reviewed on the presence of IBD markers in non-IBD diseases. Result(s): Several IBD seromarkers and genetic markers appear to be associated with complex CD phenotypes. Qualitative and quantitative serum immune reactivity to microbial antigens may be predictive of disease progression and complications. Conclusion(s): The cumulative evidence provided by serologic and genetic testing has the potential to enhance clinical decision-making when formulating individualized IBD therapeutic plans. © 2011 Tamboli et al.

Database: Embase
108. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis.

Author(s): Ford, Alexander C; Sandborn, William J; Khan, Khurram J; Hanauer, Stephen B; Talley, Nicholas J; Moayyedi, Paul

Source: The American journal of gastroenterology; Apr 2011; vol. 106 (no. 4); p. 644

Publication Date: Apr 2011

Publication Type(s): Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review Systematic Review

PubMedID: 21407183

Available at The American journal of gastroenterology - from ProQuest (Health Research Premium) - NHS Version

Abstract:OBJECTIVESCrohn's disease (CD) and ulcerative colitis (UC) are inflammatory disorders of the gastrointestinal tract of unknown etiology. Evidence for treatment of the condition with biological therapies exists, but no systematic review and meta-analysis has examined this issue in its entirety.METHODSMEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through to December 2010). Trials recruiting adults with active or quiescent CD or UC and comparing biological therapies (anti-tumor necrosis factor-α (TNFα) antibodies or natalizumab) with placebo were eligible. Dichotomous symptom data were pooled to obtain relative risk (RR) of failure to achieve remission in active disease and RR of relapse of activity in quiescent disease once remission had occurred, with a 95% confidence interval (CI).RESULTSThe search strategy identified 3,061 citations, 27 of which were eligible. Anti-TNFα antibodies and natalizumab were both superior to placebo in inducing remission of luminal CD (RR of no remission=0.87; 95% CI 0.80-0.94 and RR=0.88; 95% CI 0.83-0.94, respectively). Anti-TNFα antibodies were also superior to placebo in preventing relapse of luminal CD (RR of relapse=0.71; 95% CI 0.65-0.76). Infliximab was superior to placebo in inducing remission of moderate to severely active UC (RR=0.72; 95% CI 0.57-0.91).CONCLUSIONSBiological therapies were superior to placebo in inducing remission of active CD and UC, and in preventing relapse of quiescent CD.

Database: Medline


Author(s): Hyams, Jeffrey; Walters, Thomas D; Crandall, Wallace; Kugathasan, Subra; Griffiths, Anne; Blank, Marion; Johanns, Jewel; Lang, Yinhua; Markowitz, James; Cohen, Stanley; Winter, Harland S; Veereman-Wauters, Gigi; Ferry, George; Baldassano, Robert

Source: Current medical research and opinion; Mar 2011; vol. 27 (no. 3); p. 651-662

Publication Date: Mar 2011

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

PubMedID: 21241207

Abstract:OBJECTIVEAssess long-term effects of maintenance infliximab therapy in children with moderately-to-severely active Crohn's disease.RESEARCH DESIGN AND METHODOOne hundred twelve patients with a Pediatric Crohn's Disease Activity Index (PCDAI) score >30 received infliximab 5 mg/kg at weeks 0, 2, and 6 in the REACH study. Patients considered responders at week 10 were randomized to infliximab 5 mg/kg every 8 (q8w) or 12 (q12w) weeks. Patients who completed
treatment through week 46, and who the investigator believed would benefit from continued treatment, could enter the open-label extension (OLE) and receive up to three additional years of infliximab. No hypothesis testing was performed.CLINICAL TRIAL REGISTRATIONww.clinicaltrials.gov, identifier: NCT00207677.RESULTSSixty children entered the OLE: 33, 12, and 15 patients were receiving infliximab 5 mg/kg q8w, 5 mg/kg q12w, and 10 mg/kg q8w, respectively, at extension entry. Patients receiving infliximab for up to 3 years during the OLE maintained clinical benefit, with approximately 80% of patients consistently having no to mild disease activity per the physician's global assessment and very good to fair health in the past 2 weeks per the patient and parent/guardian global assessments. Patients with ≥1-year delay in bone age at baseline trended toward improvement in height during the OLE. Respiratory system disorders, most commonly upper respiratory infections, were the most prevalent adverse events reported; six (10%) patients had serious infections.CONCLUSIONSAmong children with moderately-to-severely active Crohn's disease who received infliximab for 46 weeks in REACH and then for up to 3 additional years in the REACH OLE, infliximab was effective in maintaining clinical benefit and was generally well-tolerated.

Database: Medline

110. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease.

Author(s): Dretzke, J; Edlin, R; Round, J; Connock, M; Hulme, C; Czeczot, J; Fry-Smith, A; McCabe, C; Meads, C

Source: Health technology assessment (Winchester, England); Feb 2011; vol. 15 (no. 6); p. 1-244

Publication Date: Feb 2011

Publication Type(s): Journal Article Review Systematic Review

PubMedID: 21291629

Available at Health technology assessment (Winchester, England) - from Unpaywall

Abstract:BACKGROUNDCrohn's disease (CD) is a severe, lifelong disease characterised by inflammation of the gastrointestinal mucosa. The impact on patients and society is high as ill health can be lifelong and can negatively affect patients' quality of life. Costs to the NHS are high, particularly for patients needing hospitalisation. Conventional treatment pathways are complex. More recently, a group of drugs called tumour necrosis factor (TNF) inhibitors (anti-TNF-α agents) have been evaluated for their effectiveness in CD. One of these, infliximab, is currently recommended by the National Institute for Health and Clinical Excellence (NICE; 2002) for patients with severe, active CD where patients are refractory to or intolerant of conventional treatment.OBJECTIVESTo investigate whether there is evidence for greater clinical effectiveness or cost-effectiveness for either adalimumab or infliximab.DATASOURCESCochrane Library (Cochrane Central Register of Controlled Trials) 2007 Issue 2; MEDLINE (Ovid) 2000 to May/June 2007; MEDLINE In-Process & Other Non-Indexed Citations (Ovid) 4 June and 26 June 2007; EMBASE (Ovid) 2000 to May/June 2007. The European Medicines Agency, the US Food and Drug Administration and other relevant websites.REVIEW METHODSStandard systematic review methods were used for study identification and selection, data extraction and quality assessment. Only randomised controlled trials (RCTs) comparing adalimumab or infliximab with standard treatment (placebo), RCTs comparing adalimumab with infliximab, or RCTs comparing different dosing regimens of either adalimumab or infliximab in adults and children with moderate-to-severe active CD intolerant or resistant to conventional treatment were eligible for inclusion. A systematic review of published studies on the cost and cost-effectiveness of adalimumab and infliximab was undertaken. The economic models of cost-effectiveness submitted by the manufacturers of both drugs were critically appraised and, where appropriate, rerun using parameter inputs based on the evidence identified by
the authors of the technology assessment report. A de novo Markov state transition model was constructed to calculate the incremental cost-effectiveness ratio for adalimumab and infliximab therapy compared with standard care. RESULTS Based on 11 trials, there was evidence from both induction and maintenance trials that both adalimumab and infliximab therapy were beneficial compared with placebo (standard care) for adults with moderate-to-severe CD and, for infliximab, for adults with fistulising CD; results were statistically significant for some time points. Between 6% and 24% (adalimumab), and 21% and 44% (infliximab) more patients achieved remission with anti-TNF-α antibodies than with placebo in the induction trials. Between 24% and 29% (adalimumab), and 14% and 24% (infliximab) more patients achieved remission with anti-TNF-α antibodies in the two large maintenance trials at reported follow-up. In fistulising CD, between 29% and 42% (induction trial) and 23% (maintenance trial) more patients achieved a > 50% reduction in fistulas with infliximab than with placebo at reported follow-up. There was no direct evidence to show that ‘responders’ were more likely to benefit from treatment than ‘non-responders’ in the longer term. Few differences were found between treatment and standard care arms for selected adverse events, though high proportions of scheduled crossovers resulted in a lack of a true placebo group in most of the maintenance trials. No published studies on the cost-effectiveness of adalimumab were identified. The four independently funded studies identified for infliximab suggested high cost-effectiveness ratios [all above £50,000/quality-adjusted life-year (QALY) for non-fistulising disease and all above £100,000/QALY for fistulising disease]. A budget impact assessment suggested that total cost to the NHS in England and Wales for induction in severe disease only could range between £17M and £92M and for maintenance for 1 year between £140M and £200M. LIMITATIONS Regarding clinical effectiveness, there were concerns about the trial design and lack of clarity, which may have affected interpretation of results. None of the trials matched exactly the licence indications or NICE guidance, which specify the use of these drugs in patients with ‘severe’ disease. All trials were multicentre, and applicability to UK populations, particularly in terms of standard care being provided and in terms of patients having failed or having become intolerant to conventional treatment, was uncertain. The published economic models relied heavily on little information and data from small samples. CONCLUSIONS Anti-TNF therapy with adalimumab or infliximab may have a beneficial effect compared with standard care on outcome measures for induction and maintenance. The findings were that for induction, both adalimumab and infliximab are cost-effective (dominant relative to standard care) in the management of severe CD, and adalimumab (but not infliximab) is cost-effective for moderate CD, according to limits generally accepted by NICE. On the basis of the analysis presented here, neither drug is likely to be cost-effective as maintenance therapy for moderate or severe disease. Perhaps, most importantly, the analysis reflected the fact that a substantial number of patients would achieve remission under standard care and that the incidence of relapse among those in remission was such that maintenance therapy would have to show greater effectiveness than at present and/or be much less costly than it currently is in order to reach the levels of generally accepted cost-effectiveness. Any future trials need to be designed to meet the particular challenges of measuring and quantifying benefit in this patient group. FUNDING The research was funded by the HTA programme on behalf of NICE.

Database: Medline

111. Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single-centre cohort.

Author(s): Gies, N; Kroeker, K I; Wong, K; Fedorak, R N

Source: Alimentary pharmacology & therapeutics; Aug 2010; vol. 32 (no. 4); p. 522-528

Publication Date: Aug 2010

Publication Type(s): Journal Article
Abstract: Aliment Pharmacol Ther 2010; 32: 522-528 Summary Background Randomized, controlled trials have demonstrated that anti-TNF agents are efficacious in inducing remission in cases of Crohn’s disease and ulcerative colitis. However, response rates for anti-TNF agents in 'real life' clinical practice are less well-defined. Aims To examine the response rates and long-term outcomes of infliximab and adalimumab treatment for out-patients with ulcerative colitis and to study the variables associated with response rates. Methods In a prospective study, a single-centre out-patient cohort was treated and followed up according to a structured protocol of clinical care. Response to treatment was assessed using a physician’s global assessment that focused on normalization of bowel frequency, absence of blood with defecation and tapering of corticosteroids to zero. Results Fifty-three ulcerative colitis patients were included in the study. Responses to induction therapy were 96.4% (27/28) for infliximab and 80% (20/25) for adalimumab (P = 0.0889). Responses to maintenance therapy were similar: infliximab 77.8% (14/18) and adalimumab 70.0% (14/20) (P = 0.7190). Multivariate analyses of the induction and maintenance responses did not reveal confounding elements. No new safety signals were identified. Conclusions This long-term follow-up of a single-centre cohort of ulcerative colitis patients demonstrates that 'real-life' out-patient treatment with infliximab and adalimumab is effective in induction and maintenance of response.

Database: Medline

112. Infliximab for the treatment of acute exacerbations of ulcerative colitis.

Author(s): Bryan, S; Andronis, L; Hyde, C; Connock, M; Fry-Smith, A; Wang, D

Source: Health technology assessment (Winchester, England); May 2010; vol. 14

Publication Date: May 2010

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article Review

PubMedID: 20507798

Abstract: This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis, in accordance with the licensed indication, based upon the manufacturer’s submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence included four randomised controlled trials (RCTs), two comparing infliximab with placebo in patients not responsive to initial treatment with intravenous corticosteroids and one comparing ciclosporin with placebo. A fourth RCT compared ciclosporin with intravenous corticosteroids as the initial treatment after hospitalisation. The manufacturer’s submission concluded that infliximab provides clinical benefit to patients with acute severe, steroid-refractory ulcerative colitis and is well tolerated; it also provides additional clinical benefits over ciclosporin, particularly avoidance of colectomy. A decision tree model was built to compare infliximab with strategies involving ciclosporin, standard care and surgery. After correcting a small number of errors in the model, the revised base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with standard care was 20,000 pounds. However, sensitivity analyses revealed considerable uncertainty emanating from the weight of the patient, the timeframe considered and, most importantly, the colectomy rates used. When a more appropriate mix of trials were included in the estimation of colectomy rates, the ICER for infliximab rose to 48,000 pounds. The guidance issued by NICE on 31 October 2008 states that infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis.
colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient; for people who do not meet this criterion, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

**Database**: Medline

### 113. Infliximab, azathioprine, or combination therapy for Crohn's disease.

**Author(s)**: Colombel, Jean Frédéric; Sandborn, William J; Reinisch, Walter; Mantzaris, Gerassimos J; Kornbluth, Asher; Rachmilewitz, Daniel; Lichtiger, Simon; D'Haens, Geert; Diamond, Robert H; Broussard, Delma L; Tang, Kezhen L; van der Woude, C Janneke; Rutgeerts, Paul; SONIC Study Group

**Source**: The New England journal of medicine; Apr 2010; vol. 362 (no. 15); p. 1383-1395

**Publication Date**: Apr 2010

**Publication Type(s)**: Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID**: 20393175

Available at The New England journal of medicine - from ProQuest (Health Research Premium) - NHS Version

Available at The New England journal of medicine - from Exeter Health Library print Local Print Collection [location]: Exeter Health Library - PRINT COPY ONLY.

Available at The New England journal of medicine - from Unpaywall

**Abstract**: BACKGROUND The comparative efficacy and safety of infliximab and azathioprine therapy alone or in combination for Crohn's disease are unknown. METHODS In this randomized, double-blind trial, we evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe Crohn's disease who had not undergone previous immunosuppressive or biologic therapy. Patients were randomly assigned to receive an intravenous infusion of 5 mg of infliximab per kilogram of body weight at weeks 0, 2, and 6 and then every 8 weeks plus daily oral placebo capsules; 2.5 mg of oral azathioprine per kilogram daily plus a placebo infusion on the standard schedule; or combination therapy with the two drugs. Patients received study medication through week 30 and could continue in a blinded study extension through week 50. RESULTS OF the 169 patients receiving combination therapy, 96 (56.8%) were in corticosteroid-free clinical remission at week 26 (the primary end point), as compared with 75 of 169 patients (44.4%) receiving infliximab alone (P=0.02) and 51 of 170 patients (30.0%) receiving azathioprine alone (P<0.001 for the comparison with combination therapy and P=0.006 for the comparison with infliximab). Similar numerical trends were found at week 50. At week 26, mucosal healing had occurred in 47 of 107 patients (43.9%) receiving combination therapy, as compared with 28 of 93 patients (30.1%) receiving infliximab (P=0.06) and 18 of 109 patients (16.5%) receiving azathioprine (P<0.001 for the comparison with combination therapy and P=0.02 for the comparison with infliximab). Serious infections developed in 3.9% of patients in the combination-therapy group, 4.9% of those in the infliximab group, and 5.6% of those in the azathioprine group. CONCLUSIONS Patients with moderate-to-severe Crohn's disease who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine monotherapy. (ClinicalTrials.gov number, NCT00094458.)

**Database**: Medline
**Databases searched:** Cochrane, Embase, Medline, NICE Evidence

**Embase via Ovid 31st March 2020**

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