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CADTH RAPID RESPONSE REPORT:
PEER REVIEWED SUMMARY WITH CRITICAL APPRAISAL

Biologics versus Immunomodulators for the Treatment of Ulcerative Colitis: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 17, 2019
Report Length:	19 Pages

CADTH

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Cite As: Biologics versus immunomodulators for the treatment of ulcerative colitis: a review of comparative clinical effectiveness and cost-effectiveness. Ottawa: CADTH; 2019 Apr. (CADTH rapid response report: peer-reviewed summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Reviewers

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This document was externally reviewed by content experts and the following individuals granted permission to be cited.

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Abbreviations

AUC	area under the curve
AZA	azathioprine
CADTH	Canadian Agency for Drugs and Technologies in Health
CD	Crohn's disease
CI	confidence interval
CS	corticosteroid
CUCQ	Crohn's and Ulcerative Colitis Questionnaire
CySIF	Cyclosporine with Infliximab in steroid-refractory severe attacks of ulcerative colitis
EQ-5D	European Quality of Life-5 Dimensions
FCD	fistulizing Crohn's disease
HTA	health technology assessment
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IFX	infliximab
IgG	immunoglobulin
IL	interleukin
ISRCTN	International Standard Randomised Controlled Trial Number
MRSA	Methicillin-Resistent *Staphylococcus Aureus*
NHS	National Health Service
OR	odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
TNF	tumor necrosis factor
UC	ulcerative colitis
QAS	quality-adjusted survival
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SAR	serious adverse reaction
SF-36	36-item Short Form Health Survey
UC	ulcerative colitis

Context and Policy Issues

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a disease involving inflammation conditions located in colon and small intestines.[1] Ulcerative colitis (UC) and Crohn's disease (CD) are two primary types of IBD with different characteristics.[1] UC is a mucosal disease that often affects the rectum and all or part of the colon.[2] Sometimes it is difficult to distinguish UC and CD clinically.[2] The symptoms commonly seen in the patients with UC include diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain.[2] The inflammation may cause major consequences, particularly a fibrostenotic obstructing pattern or a penetrating fistulous pattern.[2] Depending on disease severity, the options of conventional treatment for IBD include 5-aminosalicylic acid agents, glucocorticoids, antibiotics, and immunomodulators.[3] Immunomodulators include azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine, and modify the activities of the immune system.[4] The use of immunomodulators are associated with minor or severe adverse events, such as headache, infection, and certain cancers.[4] Due to such risks, the use of immunomodulators needs to be closely monitored.[4]

Conventionally, a “step-up” treatment strategy usually include a sequential use of aminosalicylates, steroids, immunomodulators, and finally biologics.[5] Medications such as 5-aminosalicylic acids or prednisolone are tried first.[5] Biologics or pharmacological immunomodulators are particularly useful when patients are not responsive to steroids for induction or relapse prevention.[5]

Biologics

Recent advances in IBD treatment include biologics (also called biologic agents or biologic therapies), particularly for patients unresponsive to conventional therapy.[3] Biologics are protein-based molecules that can block inflammation in several immune-related diseases.[6,7] The first biologic approved for IBD is infliximab, a chimeric immunoglobulin (IgG)1 antibody against tumor necrosis factor (TNF)-α.[3] The usual dose of infliximab is to repeat infusion 5mg/kg every eight weeks.[3] Infliximab was approved by Health Canada to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis,[8] CD, fistulizing Crohn disease (FCD), and UC.[8] Currently, three types of biologics are approved for the treatment of one or both primary types of IBD: anti-TNF agents (infliximab, adalimumab, and golimumab), anti-integrin agents (vedolizumab) and anti-interleukin (IL) 12/23 IgG1 kappa agents (ustekinumab).[9,10]

Place in therapy

Health Canada has approved several biologics or biosimilars for the treatment of ulcerative colitis in patients without adequate response to conventional therapy, including infliximab[11] and vedolizumab.[12] Although, infliximab and other biologics are often reserved for patients unresponsive to conventional therapy,[7,8] some practitioners argue that early adoption of biologics or immunomodulators may be beneficial to patients with IBD.[13] The benefits of early adoption may include avoiding toxic effects of immunomodulators and fewer adverse effects related to conventional therapy.[5] It is uncertain whether early adoption of biologics or immunomodulators may be beneficial to patients with UC. This study aims to review the literature and understand the effectiveness and cost-effectiveness of biologics and immunomodulators among UC patients naïve to both types of drugs.

Research Questions

1. What is the comparative clinical effectiveness of biologics (with or without concomitant immunomodulators) compared with immunomodulators for ulcerative colitis?
2. What is the cost-effectiveness of biologics (with or without concomitant immunomodulators) compared with immunomodulators for ulcerative colitis?

Key Findings

One good-quality RCT and one poor-quality RCT were included. Intravenous infliximab was compared to oral ciclosporin, azathioprine, and the combination of azathioprine and infliximab among moderate-to-severe ulcerative colitis patients without adequate response to corticosteroid treatment. In a pragmatic trial, there was no significant difference in quality-adjusted survival, mortality, colectomy rates, time to colectomy, lengths of hospital stay after randomization, severe adverse reactions or severe adverse effects, and quality of life measures. However, ciclosporin was associated with longer log-transformed hospital stays than infliximab. In the same trial, the UK resource use was considered. It was

concluded that the total health service costs for ciclosporin were considerably lower than infliximab and ciclosporin was not less effective than infliximab.

In a good-quality RCT, the combination of intravenous infliximab and oral azathioprine was significantly more effective than infliximab or azathioprine alone in corticosteroid-free remission at week 16. However, infliximab alone was not significantly more effective than azathioprine alone for the same outcome. The combination was more effective than azathioprine alone in mucosal healing at week 16, but similarly effective as infliximab. Due to limited evidence identified, further research on the clinical effectiveness and cost-effectiveness of biologics compared to immunomodulators in patients without previous exposure to these two types of drugs may be needed.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline via OVID, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and February 25, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients with ulcerative colitis not previously treated with immunomodulators or biologics.
Intervention	Biologics: adalimumab, infliximab, vedolizumab, golimumab administered with or without immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate, cyclosporine), aminosalicylates or glucocorticoids
Comparator	Immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate, cyclosporine) May be combined with glucocorticoids and/or aminosalicylates May be lumped under the term “conventional therapy”
Outcomes	Q1: Commonly accepted disease activity scales such as the Mayo score, clinical response rate, primary non-response, secondary loss of response, clinical remission, steroid-free remission, endoscopic or histologic remission (mucosal healing), corticosteroid use, need for surgery, hospitalization, mortality, quality of life, safety outcomes (harms including infections and malignancies, adverse events and serious adverse events, discontinuation, complications due to being hospitalized e.g. hospital-acquired infections like C. difficile/MRSA), development of anti-drug antibodies Q2: Cost-effectiveness
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, or Economic Evaluations

HTA = health technology assessment, MRSA = Methicillin-Resistant *Staphylococcus Aureus*

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009.

Critical Appraisal of Individual Studies

The included randomized studies were critically appraised using the Cochrane Risk of Bias Tool.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 827 citations were identified in the literature search. Following screening of titles and abstracts, 645 citations were excluded and 182 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 180 publications were excluded for various reasons. Of the 180 articles exluded at full-text screening, 173 included patients exposed to biologics or immunomodulators which was not specified in the abstracts. Two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

Two multi-centre randomized controlled trials (RCTs) were identified.[15,16] Williams et al. conducted an open-label RCT.[15] Panaccione et al. implemented a double-blind, double-dummy RCT.[16]

Country of Origin

The RCT by Williams et al. was conducted in the UK[15] and the first author of Panaccione et al. was based in Canada.[16]

Patient Population

Williams et al. recruited 270 patients with steroid-resistant acute severe UC.[15] Panaccione et al. studied 239 patients with moderate-to-severe UC, who did not respond to corticosteroid treatment with or without mesalamine and were free from azathioprine for at least three months.[16] The proportions of previous exposure to azathioprine and the reasons to discontinue azathioprine were not reported.[16]

Interventions and Comparators

Both Williams et al. and Panaccione et al. adopted standard-dose 5 mg/kg infliximab at weeks 0, 2, 6.[15,16] Williams et al. compared intravenous infliximab to ciclosporin.[15] In Williams et al., ciclosporin was initially injected intravenously and then delivered orally in order to achieve trough ciclosporin concentration of 100 to 200 ng/ml.[15] Panaccione et al. compared intravenous infliximab with oral azathioprine and the combination of infliximab and azathioprine.[16]

Outcomes

Williams et al. studied the clinical effectiveness and resource use of infliximab.[15] The primary outcome was quality-adjusted survival measured with the area under the curve (AUC) of scores from Crohn's and Ulcerative Colitis Questionnaires (CUCQ) over one to three years.[15] The secondary outcome was the cost-effectiveness measured with European Quality of Life-5 Dimensions (EQ-5D) scores and UK National Health Service (NHS) resource use.[15]

The primary outcome assessed in Panaccione et al. was corticosteroid-free clinical remission at weeks 8 and 16.[16] Clinical remission was defined as a total Mayo score of 2 points or less, with no individual subscore exceeding 1 point, without the use of CSs at week 16.[16]

Summary of Critical Appraisal

Williams et al. adopted multiple criteria to select patients with severe UC from 52 hospitals in the UK and randomzed the participants into two groups.[15] In this open-label trial, only the chief investigator, trial methodologists, outcome specialists, health economists, and statisticians were blinded.[15] Patient attrition was reported and the statistical significance in the difference in the lost to follow-up between two groups was not reported.[15] Selective outcome reporting was not likely and a detailed list of resource use was listed.[15] The funding sources were declared.[15] However, intervention allocation was not concealed and both patients and outcome assessors were not blinded.[15]

Panaccione et al. recruited patients from 62 centres with moderate to severe UC and centrally randomized the subjects.[16] The representativeness of the patients was not reported.[16] Intervention allocation was concealed by double-dummy design.[16] Patients were given intravenous placebo if allocated to azathioprine and they were provided with oral placebo if allocated to infliximab.[16] Patients' previous exposure to azathioprine was not reported.[16] Participants and outcome assessors were blinded to allocation.[16] Patient attrition was reported and 26 patients in the azathioprine group received infliximab rescue therapy due to the lack of response to azathioprine.[16] Nonresponse was considered as treatment failure in the full analysis set.[16] Selective outcome reporting was not likely.[16]

Summary of Findings

Details of the individual study findings can be found in Appendix 4.

Clinical effectiveness

In Williams et al., there was no significant difference in quality-adjusted survival, mortality, colectomy rates, time to colectomy, lengths of hospital stay after randomization, severe adverse reactions or severe adverse effects, and quality of life measures including the AUC of the CUCQ scores, Short Form questionnaire-6 Dimensions scores, and EQ-5D scores between infliximab and ciclosporin.[15] Due to the skewed distribution, the lengths of hospital stays were also compared in geometrical mean.[15] Ciclosporin was associated with longer log-transformed hospital stays than infliximab.[15]

In Panaccione et al., the combination of intravenous infliximab and oral azathioprine was significantly more effective than infliximab or azathioprine alone in corticosteroid-free remission at week 16.[16] The combination was more effective than azathioprine in mucosal healing at week 16, but similarly effective as infliximab.[16]

Cost-effectiveness

In Williams et al., the UK NHS resource use was considered and the total health service costs for ciclosporin was significantly lower than infliximab and ciclosporin was not less effective than infliximab.[15]

Limitations

There were a limited number of primary studies and no systematic reviews included. The objective of this report was to review the clinical effectiveness in patients without previous exposure to immunomodulators or biologics. In major trials testing infliximab or biosimilars, investigators have usually recruited patients with inadequate responses to immunomodulators and other conventional therapy, consistent with the approved indications for these treatments.[17-28] Many articles were excluded for the enrollment of patients treated with biologics or immunomodulators. Williams et al. only included patients diagnosed with acute and severe UC, which may limit generalizability to patients with less severe UC.[15] The cost estimation, based on the resource use in the UK,[15] might differ from the estimates obtained in Canada. In Panaccione et al., patients became eligible if they were not exposed to azathioprine for at least three months.[16] The proportions of previous exposure to azathioprine were not reported, and it is unclear whether this would have affected the findings.[16]

Conclusions and Implications for Decision or Policy Making

One good-quality[16] and one poor-quality RCT[15] were included. Intravenous infliximab was compared to ciclosporin,[15] azathioprine, and the combination of azathioprine and infliximab.[16] In the pragmatic trial by Williams et al., there was no significant difference between ciclosporin an infliximab in quality-adjusted survival, mortality, colectomy rates, time to colectomy, lengths of hospital stay after randomization, severe adverse reactions or severe adverse effects, and quality of life measures.[15] However, ciclopsorin was associated with longer log-transformed hospital stays than infliximab.[15] In the same trial, the UK NHS resource use was considered and the total health service costs for ciclosporin was considerably lower than infliximab for the same level of effectiveness.[15]

In the good-quality RCT by Panaccione et al., the combination of intravenous infliximab and oral azathioprine was significantly more effective than infliximab or azathioprine alone in corticosteroid-free remission at week 16.[16] However, infliximab alone was not significantly more effective than azathioprine alone in corticosteroid-free remission at week 6.[16] The combination or infliximab alone were more effective than azathioprine in achieving mucosal healing at week 16.[16]

There were several limitations to this review. A limited number of primary studies were identified. One reason may be that studies of biologics are often conducted in UC patients without adequate responses to conventional therapy including immunomodulators and other biologics,[18,21,23,24,28] while this review meant to compare treatments in a naïve population and thus focused on patients who had not received previous immunomodulatory or biologic treatment.

In light of the scarce and inconsistent evidence found here, more trials may be needed to answer the policy question asking whether biologics or immunomodulators are preferable for patients with UC who are not adequately reponding to corticosteroids.

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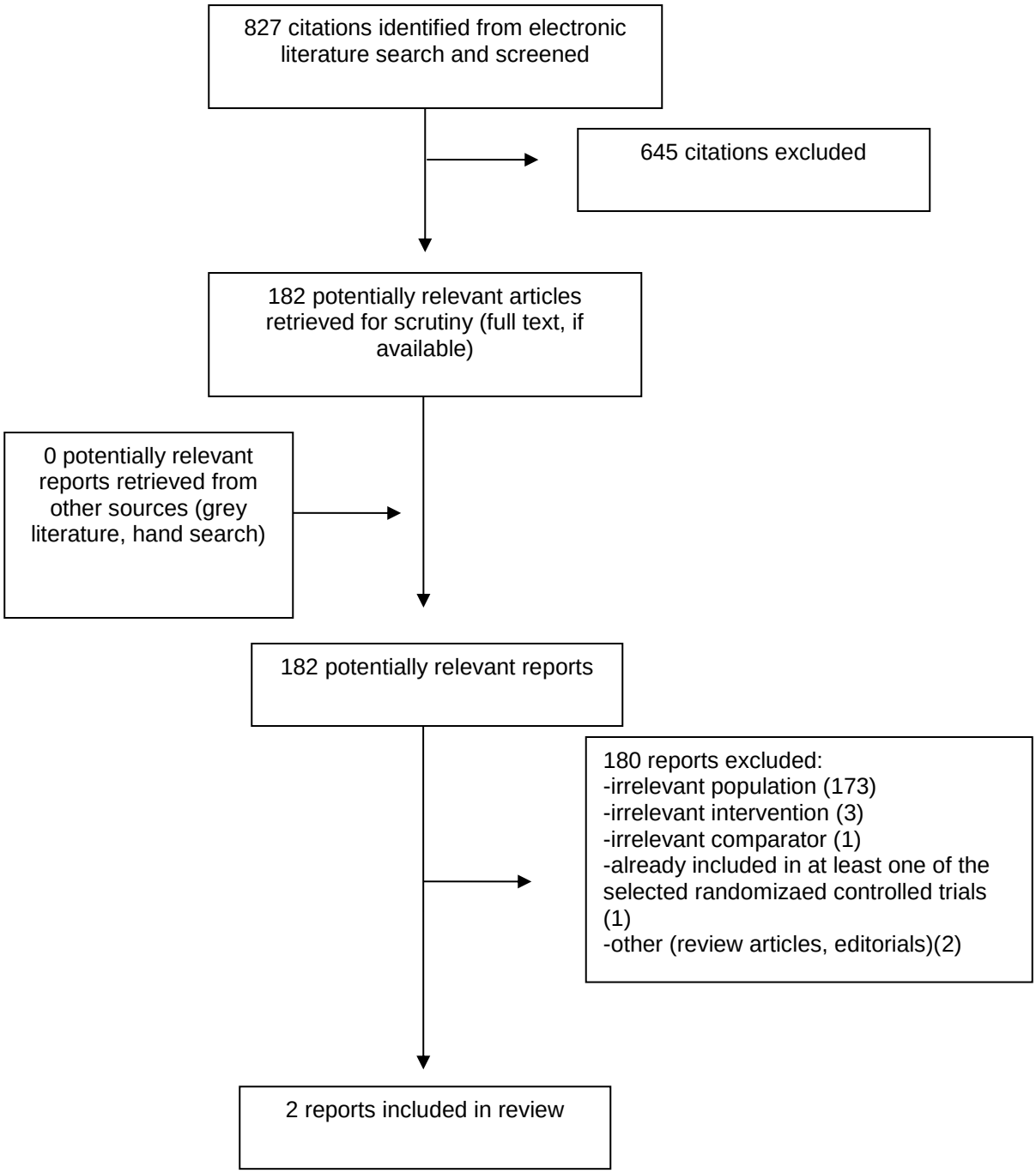
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
Williams et al. 2016,[15] **UK**	RCT, open-label parallel-group, pragmatic, multi-centre Registration: Current Controlled Trials ISRCTN22663589[15]	N = 270 patients with steroid-resistant acute severe UC Inclusion criteria: "*admitted unscheduled with colitis judged as severe (by the criteria of Truelove and Witts, a Mayo score of at least 2 on endoscopic finding, or clinical judgement); who then failed to respond to about 2–5 days of intravenous hydrocortisone; and also had a proven histological diagnosis of UC, indeterminate colitis where clinical judgement suggested a diagnosis of UC rather than Crohn's disease, or symptoms typical of UC awaiting histology.*" (p. xxiv)	**Infliximab versus ciclosporin** 5 mg/kg of intravenous infliximab at 0, 2 and 6 weeks versus 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	Clinical effectiveness and cost-effectiveness Primary outcome: quality-adjusted survival (QAS) measured with 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: cost-effectiveness measured with European Quality of Life-5 Dimensions (EQ-5D) scores and NHS resource use
Panaccione et al. 2014,[16] **Canada**	RCT, double-blind, double-dummy, multi-centre, "*terminated before the enrollment target was reached*" (p. 392) UC SUCCESS (NCT00537316, protocol number P04807)	N = 239 Inclusion criteria: at least 21 years of age, moderate to severe UC as defined by Mayo score at baseline (6 to 8 and 9 to 12, respectively), endoscopic evidence of UC within 14 days before baseline, inadequate response to a course of corticosteroid with or without mesalamine within the past 12 weeks, TNF-a	**Infliximab versus azathioprine versus the combination of infliximab and azathioprine** 1) Infliximab: 5 mg/kg at weeks 0, 2, 6, and 14 plus daily oral placebo capsules versus 2) oral azathioprine 2.5 mg/kg daily plus placebo infusions on the infliximab schedule	Primary outcome: Corticosteroid-free clinical remission at weeks 8 and 16 Clinical remission: a total Mayo score of 2 points or less, with no individual subscore exceeding 1 point, without the use of CSs at week 16 Follow-up time: 16 weeks

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		antagonist-naïve, either AZA-naive or free from AZA treatment for at least 3 months before enrollment Prohibited medications at study entry: methotrexate, calcineurin inhibitors (tacrolimus, cyclosporine), antibiotics, rectal therapy with CSs or mesalamine, and antimotility agents or laxatives.	3) combination therapy with the 2 drugs	

AUC = area under the curve, AZA = azathioprine, CS = corticosteroid, CADTH = Canadian Agency for Drugs and Technologies in Health; IV = intravenous, QAS = quality-adjusted survival, RCT = randomized controlled trial, TNF = tumour necrosis factor, UC = ulcerative colitis, UK = United Kingdom

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Randomized Controlled Trials using the Cochrane Risk of Bias Tool[14]

Strengths	Limitations
Williams et al. 2016[15]	
- Subjects randomized - Chief investigator, trial methodologist, outcomes specialist, health economists and statisticians blinded - Patient attrition reported - Selective outcome reporting not likely - Funding declared	- Allocation not concealed - Participants not blinded - Outcome assessors not blinded
Panaccione et al. 2014[16]	
- Subjects centrally randomized - Allocation concealed by double-dummy design - Participants blinded - Outcome assessors blinded - Patient attrition reported - Selective outcome reporting not likely - Conflict of interest declared	- None

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Williams et al. 2016[15]	
Primary outcome **Clinical effectiveness: QAS** - "*no significant difference in QAS between infliximab and ciclosporin; the mean adjusted difference in total area under the CUCQ curve was 7.9 favouring ciclosporin (95% CI –22.0 to 37.8; p = 0.603); and mean adjusted difference in AUC per day was 0.0297 favouring ciclosporin (95% CI –0.0088 to 0.0682; p = 0.129)*" (p.xxvi) **Secondary outcomes** **Quality of life measures** - " At no time point after randomisation was there any significant difference between groups in CUCQ scores (mean adjusted difference in AUC/day of survivors 0.0195 favouring ciclosporin, 95% CI –0.0191 to 0.0581; p = 0.319), Short Form questionnaire-6 Dimensions scores (mean adjusted difference 0.0051 favouring ciclosporin, 95% CI –0.0250 to 0.0353; p = 0.737); EQ-5D scores (QALY mean adjusted difference 0.021 favouring ciclosporin, 95% CI –0.032 to 0.096; p = 0.350)" (p. xxvii) **Mortality** - No significant difference - 3 who died had taken infliximab; ***P*** = 0.25 **Colectomy rates** - OR = 1.350 favouring infliximab (95% CI = 0.832 to 2.188; ***P*** = 0.223) **Time to colectomy** - Hazard ratio =1.234 favouring infliximab (95% CI = 0.862 to 1.768; ***P*** = 0.251) **Length of hospital stay after randomization** - Not significantly different between groups - Mean adjusted difference: 1.542 days more for ciclosporin, 95% CI = –1.297 to 4.381 days assuming normal distribution of residuals in general linear model; ***P*** = 0.286) - Distribution skewed and invalidating the assumption of normality **Geometrical mean of adjusted stays** - Ciclosporin with a factor of 1.527 times longer than that after infliximab (95%CI 1.278 to 1.817; ***P*** <0.001) **SARs or SAEs** - 14 infliximab participants with 16 SARs and 9 ciclosporin participants with 10 SARs (event ratio 0.938 favouring ciclosporin, 95% CI = 0.590 to 1.493; p = 0.788; OR 0.660 favouring ciclosporin, 95% CI = 0.282 to 1.546; p = 0.338) - 16 infliximab participants with 21 SAEs and 17 ciclosporin participants with 25 SAEs not related to disease progression or colectomy (event ratio 1.075 favouring infliximab, 95% CI = 0.603 to 1.917; p = 0.807; OR 0.999 favouring infliximab, 95% CI = 0.473 to 2.114; p = 0.998)	**Infliximab versus ciclosporin** - "*ciclosporin costs the NHS much less than infliximab but is clinically no less effective. Even so, 120 participants (45%) needed a colectomy. Our findings are consistent with those of the study Comparing Cyclosporine with Infliximab in steroid-refractory severe attacks of ulcerative colitis (CySIF), the only other randomised trial of these two drugs for acute severe UC*" (p.xxviii) - "*Our interviews highlighted the debilitating effect of UC; participants liked infliximab better than ciclosporin, but doctors were more equivocal, whereas nurses disliked the more resource-intensive infusion requirements of ciclosporin*" (p.xxviii)

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
- 2 malignancies on infliximab (basal cell carcinoma and colorectal cancer) and 1 on ciclosporin (endometrial cancer) **Cost-effectiveness at 30 months** - "*total health service costs for ciclosporin (£14,609) were significantly lower than for infliximab (£20,241) (mean adjusted difference –£5632, 95% CI –£8305 to –£2773; p < 0.001)*" (p.xxvii) **Qualitative results** - "*Interviews with participants revealed the substantial impact of UC on their QoL, and the potential benefits from these medical treatments and from surgery*" (p.xxvii) - "*Participants treated with infliximab generally spoke more positively about the treatment than those treated with ciclosporin*" (p.xxvii) . "*Interviews with nurses showed preference for infliximab, largely because of the resource-intensive infusion protocol for ciclosporin*" (p.xxvii) - "*Although some consultants favoured infliximab, most were indifferent, perceiving both drugs as effective, with a more predictable speed of benefit with ciclosporin balancing a perceived higher rate of side effects*" (p.xxvii)	
Panaccione et al. 2014[16]	
Corticosteroid-free remission at week 16 - "*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)*" (p. 392) - Insignificant difference between azathioprine and infliximab (***P*** = 0.813) **Mucosal healing at week 16** - "*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)*" (p. 392) - Significant better mucosal healing in the infliximab group than in the azathioprine group (***P*** = 0.28) **Change in total Mayo score** - At week 16, **"*the improvement in total Mayo scores was significantly greater for IFX/AZA combination therapy than AZA monotherapy (P < .001) or IFX monotherapy (P = .028). Improvement in Mayo scores was greater in patients receiving IFX monotherapy than AZA monotherapy (P = .013)***" (p.396) **Quality of life** - Measured by IBDQ and SF-36. - "***Improvements in both measures were generally greater in the IFX/AZA combination therapy group than in the AZA or IFX monotherapy groups***" (p.397) - Differences between the AZA and IFX groups insignificant. **Safety** - "***Adverse hepatobiliary events were reported by a significantly greater percentage of patients who received***	**Combination Therapy With Infliximab and Azathioprine versus Infliximab or Azathioprine alone** - "*Anti– tumor necrosis factor-a–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*" (p.392) - "*Combination therapy led to significantly better mucosal healing than azathioprine monotherapy*" (p.392)

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
AZA (16%; 95% CI, -4.40 to 9.21; P = .720) than IFX/AZA (6%; 95% CI, -20.0 to -0.46; P = .048) or IFX (4%; 95% CI, -21.8 to -3.39; P = .015)." (p.397) - Serious infections, infusion reactions, tuberculosis, opportunistic infections, malignancies, or lymphomas: no significant differences **Antibody status** - "***Only 38% of patients had evaluable antibody samples, and about 60% of these yielded inconclusive results regarding the presence of IFX antibodies***" (p.398)	

AUC = area under the curve, AZA = azathioprine, CI = confidence interval, CUCQ = Crohn's and Ulcerative Colitis, CySIF = Comparing Cyclosporine with Infliximab in steroid-refractory severe attacks of ulcerative colitis, EQ-5D = European Quality of Life-5 Dimensions, IBDQ = Inflammatory Bowel Disease Questionnaire, IFX = infliximab, OR = odds ratio, QAS = quality-adjusted survival, QoL = quality of life, SAE = severe adverse effect, SAR = severe adverse reaction, SF-36 =36-item Short Form Health Survey , UC = ulcerative colitis

Appendix 5: Additional References of Potential Interest

Reviews without systematic literature searches

Essat M, Tappenden P, Ren S, et al. Vedolizumab for the treatment of adults with moderate-to-severe active ulcerative colitis: an evidence review group perspective of a NICE single technology appraisal. *Pharmacoeconomics.* 2016;34(3):245-257.

Candadian Drug Expert Committee (CDEC) Recommendations

CADTH Canadian Drug Expert Committee (CDEC) final recommendation: infliximab (renflexis - Samsung Bioepis Co., Ltd., distributed by Merck Canada). Ottawa (ON): CADTH; 2018 Feb 20: https://www.cadth.ca/sites/default/files/cdr/complete/SE0532%20Renflexis%20-%20CDEC%20Final%20Recommendation%20February%2020%2C%202018%28redacted%29_for%20posting.pdf. Accessed 2019 Mar 26.

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