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Infliximab for maintenance of medically-induced remission in Crohn's disease (Review)

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[Intervention Review]

Infliximab for maintenance of medically-induced remission in Crohn's disease

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ABSTRACT

Background

Infliximab is a monoclonal antibody that binds and neutralises tumour necrosis factor-alpha (TNF-α) which is present in high levels in the blood serum, mucosa and stool of patients with Crohn's disease.

Objectives

To determine the efficacy and safety of infliximab for maintaining remission in patients with Crohn's disease.

Search methods

On 31 August, 2021 and 23 June, 2023, we searched CENTRAL, Embase, MEDLINE, ClinicalTrials.gov, and WHO ICTRP.

Selection criteria

Randomised controlled trials (RCTs) in which infliximab was compared to placebo or another active comparator for maintenance, remission, or response in patients with Crohn's disease.

Data collection and analysis

Pairs of review authors independently selected studies and conducted data extraction and risk of bias assessment. We expressed outcomes as risk ratios and mean differences with 95% confidence intervals. We assessed the certainty of the evidence using GRADE.

Our primary outcome was clinical relapse. Secondary outcomes were loss of clinical response, endoscopic relapse, and withdrawal due to serious and adverse events.

Main results

Nine RCTs with 1257 participants were included. They were conducted between 1999 and 2022; seven RCTs included biologically-naive patients, and the remaining two included a mix of naive/not naive patients. Three studies included patients in clinical remission, five included patients with a mix of activity scores, and one study included biologic responders with active disease at baseline. All studies allowed some form of concomitant medication during their duration. One study exclusively included patients with fistulating disease. The age of the participants ranged from 18 to 69 years old.

All but one single-centre RCT were multicentre RCTs. Four studies were funded by pharmaceutical companies, two had a mix of commercial and public funding, and two had public funding.

Infliximab is probably superior to placebo in preventing clinical relapse in patients who have mixed levels of clinical disease activity at baseline, and are not naive to biologics (56% vs 75%, RR 0.73, 95% CI 0.63 to 0.84, NNTB = 5, moderate-certainty evidence). We cannot draw any conclusions on loss of clinical response (RR 0.59, 95% CI 0.37 to 0.96), withdrawals due to adverse events (RR 0.66, 95% CI 0.37 to 1.19), or serious adverse events (RR 0.60, 95% CI 0.36 to 1.00) because the evidence is very low certainty.

Infliximab combined with purine analogues is probably superior to purine analogues for clinical relapse (12% vs 59%, RR 0.20, 95% CI 0.10 to 0.42, NNTB = 2, moderate-certainty evidence), for patients in remission, and who are not naive to biologics. We cannot draw any conclusions on withdrawals due to adverse events (RR 0.47, 95% CI 0.15 to 1.49), and serious adverse events (RR 1.19, 95% CI 0.54 to 2.64) because the evidence is very low certainty.

We cannot draw any conclusions about the effects of infliximab on serious adverse events compared to purine analogues (RR 0.79, 95% CI 0.37 to 1.68) for a population in remission at baseline because the evidence is very low certainty. There was no evidence available for the outcomes of clinical relapse, loss of clinical response, and withdrawal due to adverse events.

Infliximab may be equivalent to biosimilar for clinical relapse (47% vs 40% RR 1.18, 95% CI 0.82 to 1.69), and it may be slightly less effective in averting loss of clinical response (49% vs 32%, RR 1.50, 95% CI 1.01 to 2.23, low-certainty evidence), for a population with mixed/low disease activity at baseline. Infliximab may be less effective than biosimilar in averting withdrawals due to adverse events (27% vs 0%, RR 20.73, 95% CI 2.86 to 150.33, low-certainty evidence). Infliximab may be equivalent to biosimilar for serious adverse events (10% vs 10%, RR 0.99, 95% CI 0.39 to 2.50, low-certainty evidence).

We cannot draw any conclusions on the effects of subcutaneous biosimilar compared with intravenous biosimilar on clinical relapse (RR 1.01, 95% CI 0.65 to 1.57), loss of clinical response (RR 0.94, 95% CI 0.70 to 1.25), and withdrawals due to adverse events (RR 0.77, 95% CI 0.30 to 1.97) for an active disease population with clinical response at baseline because the evidence is of very low certainty.

We cannot draw any conclusions on the effects of infliximab compared to adalimumab on loss of clinical response (RR 0.68, 95% CI 0.29 to 1.59), withdrawals due to adverse events (RR 0.10, 95% CI 0.01 to 0.72), serious adverse events (RR 0.09, 95% CI 0.01 to 1.54) for an active disease population with clinical response at baseline because the evidence is of very low certainty. There was no evidence available for the outcome of clinical relapse.

Authors' conclusions

Infliximab is probably more effective in preventing clinical relapse than placebo (moderate-certainty evidence). Infliximab in combination with purine analogues is probably more effective in preventing clinical and endoscopic relapse than purine analogues alone (moderate-certainty evidence). No conclusions can be drawn regarding prevention of loss of clinical response, occurrence of withdrawals due to adverse events, or total adverse events due to very low-certainty evidence for both of these comparisons.

There may be little or no difference in prevention of clinical relapse, withdrawal due to adverse events or total adverse events between infliximab and a biosimilar (low-certainty evidence). Infliximab may lead to more loss of clinical response than a biosimilar (low-certainty evidence).

We were unable to draw meaningful conclusions about other comparisons and outcomes related to missing data or very low-certainty evidence due to serious concerns about imprecision and risk of bias. Further research should focus on comparisons with other active therapies for maintaining remission, as well as ensuring adequate power calculations and reporting of methods.

PLAIN LANGUAGE SUMMARY

Infliximab for the maintenance of successful treatment in Crohn's Disease

Key messages

Infliximab is probably superior to placebo for preventing disease relapse for patients who have shown response to infliximab. It may also be superior to placebo for preventing loss of response in patients with fistulating disease. It may be similar to placebo in terms of total adverse events.

Infliximab combined with purine analogues is probably superior to purine analogues alone for preventing disease relapse, both clinically and endoscopically, for patients in remission, who have shown response to infliximab.

Infliximab may be similar to the biosimilar for preventing clinical relapse, and it may be slightly worse in preventing loss of clinical response, for patients with active disease who have shown response to infliximab. Infliximab may be worse than the biosimilar in terms of withdrawals due to adverse events. Infliximab may be similar to the biosimilar for serious and total adverse events.

What is Crohn's Disease?

Crohn's disease is a chronic (life-long) inflammatory disease that can affect any part of the gut. Common symptoms include bloody poo, diarrhoea, stomach ache, fever, weight loss, fatigue, and others. When someone is experiencing symptoms of Crohn's, they are said to

have 'active' disease and, when their symptoms are under control, they are considered 'in remission'. We don't know what exactly causes Crohn's, but it could be related to a combination of the genes, immune system malfunction, 'bad' gut bacteria, and environmental reasons. There is no known cure, but the symptoms are usually managed with drugs, such as steroids, immune system medications and, if necessary, surgery. At the turn of the century, a new type of drug called infliximab, which belongs to a drug category called biologics, became available and started being widely used for the treatment of Crohn's.

What did we want to find out?

We wanted to find out how infliximab compares to any other medical treatment, or dummy treatment (placebo), for maintaining remission or treatment response in Crohn's. We also wanted to find out how safe it is compared to other treatments.

What did we do?

We searched for randomised controlled trials (studies where participants are randomly assigned to one of two or more treatment groups, and can give us the highest standard of evidence) comparing infliximab with any other medical treatment for people with Crohn's Disease. We only included studies with adult patients. We had no restrictions in terms of sex, disease duration or previous medications used.

What did we find?

We found nine studies with 1257 participants that met our inclusion criteria.

Infliximab was compared to placebo, purine analogues (azathioprine and/or 6-mercaptopurine), a biosimilar (a drug designed to be very similar to infliximab), and a different biologic drug called adalimumab. Infliximab was also combined with purine analogues and compared to purine analogues alone, and two different forms of the biosimilar were compared to each other.

Three studies had participants who were in remission at the beginning of the study, while the other six had participants with various degrees of active disease who had responded to previous treatment with infliximab at the beginning of the study.

Infliximab is probably superior to placebo for preventing disease relapse for patients who have shown response to infliximab. It may also be superior to placebo for preventing loss of response in patients with fistulating disease. It may be similar to placebo in terms of total adverse events.

Infliximab combined with purine analogues is probably superior to purine analogues alone for preventing disease relapse, both clinically and endoscopically, for patients in remission, who have shown response to infliximab.

Infliximab may be similar to the biosimilar for preventing clinical relapse, and it may be slightly worse in preventing loss of clinical response, for patients with active disease who have shown response to infliximab. Infliximab may be worse than the biosimilar in terms of withdrawals due to adverse events. Infliximab may be similar to the biosimilar for serious and total adverse events.

We cannot draw any conclusions about any other comparisons or effects because of the very low quality of the evidence.

What are the limitations of the evidence?

A lot of the evidence is of low and very low quality. This is because of problems with the methodology, lack of planning, limited participant numbers, and problems with the reporting of the data in the included studies.

How up to date is this review?

This review is up to date to June 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Infliximab compared to placebo

Infliximab compared to placebo

Patient or population: patients with Crohn's disease (mixed disease activity population with clinical response at baseline)
Setting: hospitals in several countries
Intervention: infliximab
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with infliximab				
Clinical relapse (at 30-32 weeks, CDAI > 150)	Study population		RR 0.73 (0.63 to 0.84)	408 (2 studies)	⊕⊕⊕⊖ Moderate[a]	NNTB = 5
	753 per 1000	550 per 1000 (475 to 633)				
Loss of clinical response (at 32 weeks, less than 70 points in CDAI change)	Study population		RR 0.59 (0.37 to 0.96)	73 (1 study)	⊕⊖⊖⊖ Very low[b]	
	639 per 1000	377 per 1000 (236 to 613)				
Withdrawal due to adverse events (at 32-54 weeks)	Study population		RR 0.66 (0.37 to 1.19)	355 (2 studies)	⊕⊖⊖⊖ Very low[b]	
	133 per 1000	88 per 1000 (49 to 159)				
Serious adverse events (at 54 weeks)	Study population		RR 0.60 (0.36 to 1.00)	282 (1 study)	⊕⊖⊖⊖ Very low[b]	
	229 per 1000	137 per 1000 (82 to 229)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to concerns about risk for randomisation, selective reporting and other bias
[b]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk for blinding, and selective reporting

Summary of findings 2. Infliximab combined with purine analogues compared to purine analogues

Infliximab combined with purine analogues compared to purine analogues

Patient or population: Crohn's disease patients (in remission at baseline)
Setting: secondary care (multiple countries)
Intervention: infliximab combined with purine analogues
Comparison: purine analogues

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with purine analogues	Risk with infliximab combined with purine analogues				
Clinical relapse (at 48 weeks, CDAI of 150 or greater together with an increase in CDAI more than 70 points above baseline over 2 consecutive weeks or definitive clinical relapse requiring immediate intervention, as judged by the treating physician)	Study population		RR 0.20 (0.10 to 0.42)	115 (1 study)	⊕⊕⊕⊖ Moderate[a]	NNTB = 2
	589 per 1000	118 per 1000 (59 to 248)				
Loss of clinical response	-	-	-	-	-	
Withdrawal due to adverse events (at 48 weeks)	Study population		RR 0.47 (0.15 to 1.49)	115 (1 study)	⊕⊖⊖⊖ Very low[b]	
	142 per 1000	67 per 1000 (21 to 212)				
Serious adverse events (at 48 weeks to 2 years)	78 per 1000	94 per 1000 (42 to 206)	RR 1.19 (0.54 to 2.64)	257 (2 studies)	⊕⊖⊖⊖ Very low[b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to some concerns about bias from selective reporting
[b]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting

Summary of findings 3. Infliximab compared to purine analogues

Infliximab compared to purine analogues

Patient or population: Crohn's disease patients (in remission at baseline)
Setting: secondary care (multiple countries)
Intervention: infliximab
Comparison: purine analogues

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with purine analogues	Risk with infliximab				
Clinical relapse	-	-	-	-	-	
Loss of clinical response	-	-	-	-	-	
Withdrawal due to adverse events	-	-	-	-	-	
Serious adverse events (at 2 years)	183 per 1000	145 per 1000 (68 to 307)	RR 0.79 (0.37 to 1.68)	140 (1 study)	⊕⊖⊖⊖ Very low[a]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting

Summary of findings 4. Infliximab compared to biosimilar

Infliximab compared to biosimilar

Patient or population: patients with Crohn's disease (with mixed/low disease activity at baseline)
Setting: hospital in Norway
Intervention: infliximab
Comparison: biosimilar

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with biosimilar	Risk with infliximab				
Clinical relapse (at 52 weeks, HBI > 4)	Study population		RR 1.18 (0.82 to 1.69)	155 (1 study)	⊕⊕⊕⊖ Low[a]	
	403 per 1000	475 per 1000 (330 to 680)				
Loss of clinical response (at 52 weeks, HBI change from baseline of less than 4 points and a total score of less than 7 points)	Study population		RR 1.50 (1.01 to 2.23)	155 (1 study)	⊕⊕⊕⊖ Low[a]	
	325 per 1000	487 per 1000 (328 to 724)				
Withdrawal due to adverse events (at 52 weeks)	Study population		RR 20.73 (2.86 to 150.33)	155 (1 study)	⊕⊕⊕⊖ Low[a]	
	13 per 1000	269 per 1,000 (37 to 1000)				
Serious adverse events (at 52 weeks)	Study population		RR 0.99 (0.39 to 2.50)	155 (1 study)	⊕⊕⊕⊖ Low[a]	
	104 per 1000	103 per 1000 (41 to 260)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to serious imprecision from very low participant and event numbers

Summary of findings 5. Subcutaneous CT-P13 and purine analogues compared to intravenous CT-P13 and purine analogues

Subcutaneous CT-P13 and purine analogues compared to Intravenous CT-P13 and purine analogues

Patient or population: patients with Crohn's disease (active disease population with clinical response at baseline)
Setting: hospitals in several countries
Intervention: subcutaneous CT-P13 and purine analogues
Comparison: intravenous CT-P13 and purine analogues

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with intravenous CT-P13	Risk with subcutaneous CT-P13				
Clinical relapse (at 22 weeks, CDAI > 150)	Study population		RR 1.01 (0.65 to 1.57)	53 (1 study)	⊕⊖⊖⊖ Very low[a]	
	600 per 1000	606 per 1000 (390 to 942)				
Loss of clinical response (at 22 weeks, less than 100 points in CDAI change)	Study population		RR 0.94 (0.70 to 1.25)	53 (1 study)	⊕⊖⊖⊖ Very low[a]	
	800 per 1000	752 per 1000 (560 to 1000)				
Withdrawal due to adverse events (at 30 weeks)	Study population		RR 0.77 (0.30 to 1.97)	53 (1 study)	⊕⊖⊖⊖ Very low[a]	
	280 per 1000	216 per 1000 (84 to 552)				

Serious adverse events	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about several risk of bias fields

Summary of findings 6. Infliximab compared to adalimumab

Infliximab compared to adalimumab

Patient or population: patients with Crohn's disease (active disease population with clinical response at baseline)
Setting: hospital in Belgium
Intervention: infliximab
Comparison: adalimumab

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with adalimumab	Risk with infliximab				
Clinical relapse	-		-	-	-	
Loss of clinical response (at 56 weeks, less than 100 points in CDAI change)	Study population		RR 0.68 (0.29 to 1.59)	73 (1 study)	⊕⊖⊖⊖ Very low[a]	
	278 per 1000	189 per 1000 (81 to 442)				
Withdrawal due to adverse events (at 56 weeks)	Study population		RR 0.10 (0.01 to 0.72)	73 (1 study)	⊕⊖⊖⊖ Very low[a]	
	278 per 1000	28 per 1000 (3 to 200)				

Serious adverse events (at 56 weeks)	Study population		RR 0.09 (0.01 to 1.54)	73 (1 study)	⊕⊖⊖⊖ Very low[a]
	139 per 1000	13 per 1000 (1 to 214)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about several risk of bias fields

BACKGROUND

Description of the condition

Crohn's disease (CD) is an inflammatory bowel disease affecting the gastrointestinal tract (Baumgart 2012). Clinical manifestations vary greatly based on disease phenotype. Clinical manifestations include inflammatory disease (characterised by abdominal pain and diarrhoea), stricturing disease (typified by abdominal pain, cramping and bloating) and fistulising disease. Furthermore, musculoskeletal, dermatological, hepatobiliary and ocular extraintestinal manifestations are relatively common (Baumgart 2012). Ongoing transmural inflammation can cause structural complications, such as strictures and fistulae (Cosnes 2002). Surgery rates have improved from approximately 80% of CD patients requiring surgery during the course of their disease in the 90s (Munkholm 1995), but one in four people still require surgery after 10 years of diagnosis this decade (Tsai 2021).

The incidence of CD ranges from 0 to 20.2 per 100,000 person-years in North America and 0.3 to 12.7 per 100,000 person-years in Europe (Ananthakrishnan 2015). The prevalence of CD has been reported to be 319 per 100,000 persons and 322 per 100,000 persons in North America and Europe, respectively (Ananthakrishnan 2015; Molodecky 2012). The incidence of CD peaks in the second to fourth decade of life, with a potential second peak in the sixth to seventh decades of life (Ananthakrishnan 2015).

Description of the intervention

Infliximab, a chimeric anti-tumour necrosis factor-alpha (TNF-α) monoclonal antibody (Sandborn 1999), is an approved treatment for moderate-to-severe and fistulising CD (FDA 2011). TNF-α, a pro-inflammatory cytokine, plays a significant role in CD pathogenesis (Hanauer 2002). Macrophages and T lymphocytes produce TNF-α, which subsequently induces pro-inflammatory cytokines interleukin-1 (IL-1) and IL-6. These in turn enhance migration of leukocytes via endothelial cell and leukocyte adhesion molecule expression (Poggioli 2007), which subsequently activate leukocytes and induce metalloproteinases and acute-phase reactants. TNF-α serum, mucosal and faecal concentrations are elevated in patients with CD (Knight 1993; Poggioli 2007). Infliximab binds to and neutralises TNF-α and its activity (Hanauer 2002; Knight 1993; Poggioli 2007).

How the intervention might work

CD patients have significantly greater numbers of TNF-α producing cells in the lamina propria of the bowel (Poggioli 2007), resulting in greater chronic active inflammation. The mechanism of action of infliximab consists of neutralisation of both the soluble and transmembrane TNF-α components (Mitoma 2005Poggioli 2007) with subsequent reduction of TNF-α expressing cells (Baert 1999). Infliximab reduces adhesion molecule expression (ICAM-1 and LFA-1) (Baert 1999). Infliximab use in patients with CD has been demonstrated to induce and maintain endoscopic and histological healing (D'Haens 1999). These outcomes are consistently demonstrated to be the most reliable factor associated with improved outcomes, including hospitalisation and surgery (Khanna 2015; Shah 2016).

Why it is important to do this review

Prior to biologic medications, treatment options for CD patients were limited to enteric topical or systemic corticosteroids (e.g. budesonide, hydrocortisone or prednisone), aminosalicylates, and immunosuppressive medications (e.g. azathioprine, 6-mercaptopurine, methotrexate). However, systemic corticosteroids and oral 5-aminosalicylic acid as maintenance medication for CD do not reduce the risk of relapse (Akobeng 2016Steinhart 2003). Furthermore, only low-quality evidence demonstrated that azathioprine is superior to placebo for maintenance of remission in CD and its use is limited by adverse effects (Chande 2015). The ACCENT-I and ACCENT-II trials demonstrated that infliximab is effective for induction and maintenance of clinical remission in CD (Hanauer 2002; Sands 2004). Scheduled infliximab was more effective than sporadic treatment, as it increased the proportion of patients with mucosal healing and decreased hospital admissions (Baert 2010Rutgeerts 2006). In a 2008 Cochrane systematic review of four different anti-TNF-α agents, evidence from three randomised controlled trials demonstrated that maintenance of clinical remission, clinical response, corticosteroid-sparing, and fistula healing is achieved with administration of infliximab in CD patients who had previously responded to infliximab induction therapy (Behm 2008). However, a dedicated systematic review of infliximab for the maintenance of remission in CD does not exist. Furthermore, the advent of combination therapy with immunosuppressant agents and therapeutic drug monitoring has dramatically changed the use of infliximab for maintenance of remission in CD (Colombel 2010; Colombel 2012). Lastly, more studies have analysed this subject in the time that has elapsed since the aforementioned review (Behm 2008).

OBJECTIVES

To determine the efficacy and safety of infliximab for maintaining remission in patients with CD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were considered for inclusion. We excluded quasi-randomised trials (using no or non-appropriate randomisation).

Types of participants

Adult participants (> 18 years) with CD in remission or with response to treatment as defined by the authors (as per conventional clinical, radiological or endoscopic criteria) were considered for inclusion. No restrictions were applied for sex, disease duration, type of CD, or previous medication exposure.

Patients with surgically induced remission were not included in this review.

Studies including CD as a subset of a wider IBD population, were only included in the review if they offered separate data for their CD participants. Studies reporting on CD subsets (e.g. fistulating population) were included, and analysed separately from the general CD populations.

Types of interventions

Studies analysing infliximab, alone or in combination with another agent, compared to placebo or active medical therapies for maintenance of remission in CD were considered for inclusion.

For studies in which purine analogue use exceeded 50% amongst all participants, the purine analogues were considered part of the intervention.

Studies were eligible regardless of their dose, duration, or method of administration.

Types of outcome measures

Both dichotomous and continuous outcomes were included.

Primary outcomes

1) The primary outcome measure was the proportion of patients who experienced clinical relapse (as defined by the included studies).

Secondary outcomes

Secondary outcome measures included:

1) The proportion of patients who experienced clinical loss of response (as defined by the included studies);

2) The proportion of patients who experienced endoscopic relapse (as defined by the included studies);

3) Adverse events resulting in study withdrawal (we considered any patient without an explicit reason for withdrawal as a withdrawal due to adverse events);

4) Serious adverse events (patients experiencing at least one serious adverse event, defined by the included studies); and

5) Total adverse events (patients experiencing at least one adverse event, defined by the included studies).

Search methods for identification of studies

Electronic searches

On 31 August 2021 and 23 June 2023, Cochrane Gut Information Specialist searched the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library (Issue 6 of 12, June 2023);
- Embase via Ovid SP (1974 - 2023 Week 24);
- MEDLINE via Ovid SP (1946 - 22 June 2023);
- ClinicalTrials.gov;
- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP).

We did not apply any date, language, document type, or publication status limitations to this search (Aali 2021). The search strategies are described in Appendix 1.

Searching other resources

In addition to electronic database searching, we performed handsearches of conference proceedings between 2019 and 2023 from Digestive Disease Week, the European Crohn's and Colitis Organisation Congress, and the United European Gastroenterology Week, to identify studies published in abstract form only. To identify ongoing studies, we searched the clinicaltrials.gov database.

We also corresponded with authors to obtain relevant unpublished data.

Data collection and analysis

Selection of studies

Based on inclusion criteria above, eligibility of titles and abstracts identified by the literature search were screened by two authors (AS and VS) independently. Disagreements were resolved by discussion and consensus. A third author (MG) resolved cases in which consensus was not reached.

Data extraction and management

Information from selected studies was collected using a standardised data collection form. Two authors independently extracted data (AS and VS). Disagreement was resolved by discussion and consensus. A third author (MG) was consulted when consensus was not reached.

The following data were retrieved from the included studies:

1) General information (title, journal, year, publication type);

2) Study information (design, methods of randomisation, concealment of allocation and blinding, power calculation, a priori and post hoc analyses);

3) Intervention and control (type and dose of medication; placebo or active comparator);

4) Eligibility (total number of patients screened and randomised);

5) Baseline characteristics for each arm (age, sex, ethnicity, disease severity, concurrent medications, prior medications);

6) Follow-up (length of follow up, assessment of treatment compliance, withdrawals, number of patients lost to follow-up); and

7) Outcomes (primary and secondary outcomes).

Assessment of risk of bias in included studies

From each included study, independent evaluation by two authors assessed the risk of bias for each included study with the Cochrane risk of bias 1 tool (Higgins 2011). The following domains were assessed:

1) Sequence generation (i.e. was the allocation sequence adequately generated?);

2) Allocation sequence concealment (i.e. was allocation adequately concealed?);

3) Blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?);

4) Incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);

5) Selective outcome reporting (i.e. were reports of the study free of suggestion of selective outcome reporting?); and

6) Other potential sources of bias (i.e. was the study apparently free of other problems that could put it at high risk of bias?).

Studies were judged to be of high, low or unclear risk of bias. Disagreement was resolved by consensus via discussion. A third author (MG) resolved cases where consensus was not reached.

Measures of treatment effect

RevMan Web 2020 was used to analyse data.

For dichotomous outcomes, we expressed the treatment effect as risk ratios (RR) with corresponding 95% confidence intervals (CI). For continuous outcomes, we expressed the treatment effect as mean differences (MD) with 95% CIs.

When different scales were used to measure the same underlying construct, we calculated the standardised mean difference (SMD) and 95% CI.

Unit of analysis issues

The participant was the unit of analysis. For studies comparing more than two intervention groups, we made multiple pairwise comparisons between all possible pairs of intervention groups. To avoid double counts, we divided shared intervention groups evenly amongst the comparisons. For dichotomous outcomes, we divided both the number of events and the total number of participants. For continuous outcomes, we only divided the total number of participants, and left the means and standard deviations unchanged.

We included cross-over studies, but we only pooled their data if they were reported separately before and after cross-over, and we only used pre-cross-over data.

In the case of cluster-RCTs, we planned to use study data only if the authors used appropriate statistical methods in taking the clustering effect into account.

Dealing with missing data

We based our analysis based on the data made available by the authors. We contacted authors for missing data, or data that were not reported in sufficient detail, or were unclear.

For efficacy outcomes, we used the numbers randomised as denominators. As numerators, we used the numbers as reported by the authors. Patients with missing or unclear data were assumed to be treatment failures.

For safety outcomes, patients with missing or unclear withdrawal data were considered as withdrawals due to adverse events. The denominators used for these outcomes were as reported by the authors. For serious and total adverse events, we used the numbers of events per participant, as reported by the authors. Outcome data reported for mixes of randomised and non-randomised participants were discarded and not used for analysis.

Relapse and loss of response rates were rarely reported directly, while remission and response were reported more often. We accounted for that by inverting the reported remission and response rates to infer relapse and loss of response, for the studies where this was the case. Withdrawals have been added to the inverted rates, as all withdrawals have been counted as treatment failures.

The same methods were employed in our sensitivity analyses.

Assessment of heterogeneity

We scrutinised studies to ensure that they are clinically homogenous in terms of participants, interventions, comparators, and outcomes. To test for statistical heterogeneity, we used a Chi^2 test. A P value of less than 0.1 gave an indication of the presence of heterogeneity. Inconsistency was quantified and represented by the I^2 statistic. We interpreted the thresholds as follows (Higgins 2020):

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity;

50% to 90%; may represent substantial heterogeneity;

75% to 100%: considerable heterogeneity.

We examined possible explanations for heterogeneity when sufficient data were available, including factors such as participant characteristics (e.g. age, sex), condition severity, healthcare system, and country. We did not pool data in a meta-analysis when a considerable degree of statistical heterogeneity was detected (I^2 > 75%). In the case of considerable statistical heterogeneity, we investigated whether this could be explained on clinical grounds or risk of bias, in which case, we aimed to conduct sensitivity analyses. If we could not find reasons for the considerable statistical heterogeneity, we presented the results narratively, in detail.

Assessment of reporting biases

Our use of an inclusive search strategy minimised most reporting biases. We aimed to investigate publication bias using a funnel plot for outcomes with 10 or more studies and determined the magnitude of publication bias by visual inspection of the asymmetry of the funnel plot or other methods mentioned in the Cochrane Handbook (Higgins 2020). We would also test funnel plot asymmetry by performing a linear regression of the intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

We combined data from individual trials for meta-analysis when the interventions, patient groups and outcomes were sufficiently similar (as determined by consensus). For dichotomous outcomes, the pooled RR and 95% CI were calculated. For continuous outcomes, the pooled MD and corresponding 95% CI were calculated. A random-effects model was used to pool data. If a high degree of heterogeneity was detected ($I^2 \geq 75$), we did not pool data for meta-analysis.

Data that could not be meta-analysed were reported in narrative form.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were:

1) Different drug doses and dosing frequencies;

2) Concomitant immunosuppressant medication use; and

3) Different disease behaviours.

If heterogeneity was detected, we investigated possible causes, and addressed them using methods described in Higgins 2020.

Subgroups were compared using the formal test for subgroup differences in Revman.

Sensitivity analysis

Planned sensitivity analyses to examine the impact of the following variables on the pooled effect were:

1) Random-effects versus fixed-effect modelling;

2) Low risk of bias versus unclear or high risk of bias; and

3) Relevant loss to follow up (> 10%): best-case versus worst-case scenario;

4) Full text manuscript versus abstract or unpublished studies;

5) Removing cluster-randomised trials, if any were found, to assess their impact on the results.

Summary of findings and assessment of the certainty of the evidence

We have presented summary of findings tables for all comparisons, which include our primary outcome and the secondary outcomes of clinical loss of response, withdrawals due to adverse events, and serious adverse events. The same outcomes were presented in our abstract. The presented comparisons are infliximab vs placebo, infliximab combined with purine analogues vs purine analogues, infliximab vs purine analogues, infliximab vs biosimilar, subcutaneous CT-P13 and purine analogues vs intravenous CT-P13 and purine analogues, and infliximab vs adalimumab.

The overall certainty of evidence supporting the primary and secondary outcomes was assessed using the GRADE approach (Guyatt 2008; Schünemann 2011). Evidence retrieved from RCTs is usually regarded as high certainty. However, the certainty rating may be downgraded as a result of:

1) Risk of bias;

2) Indirect evidence;

3) Inconsistency (unexplained heterogeneity);

4) Imprecision; and

5) Publication bias.

GRADE Working Group grades of evidence

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

RESULTS

Description of studies

Results of the search

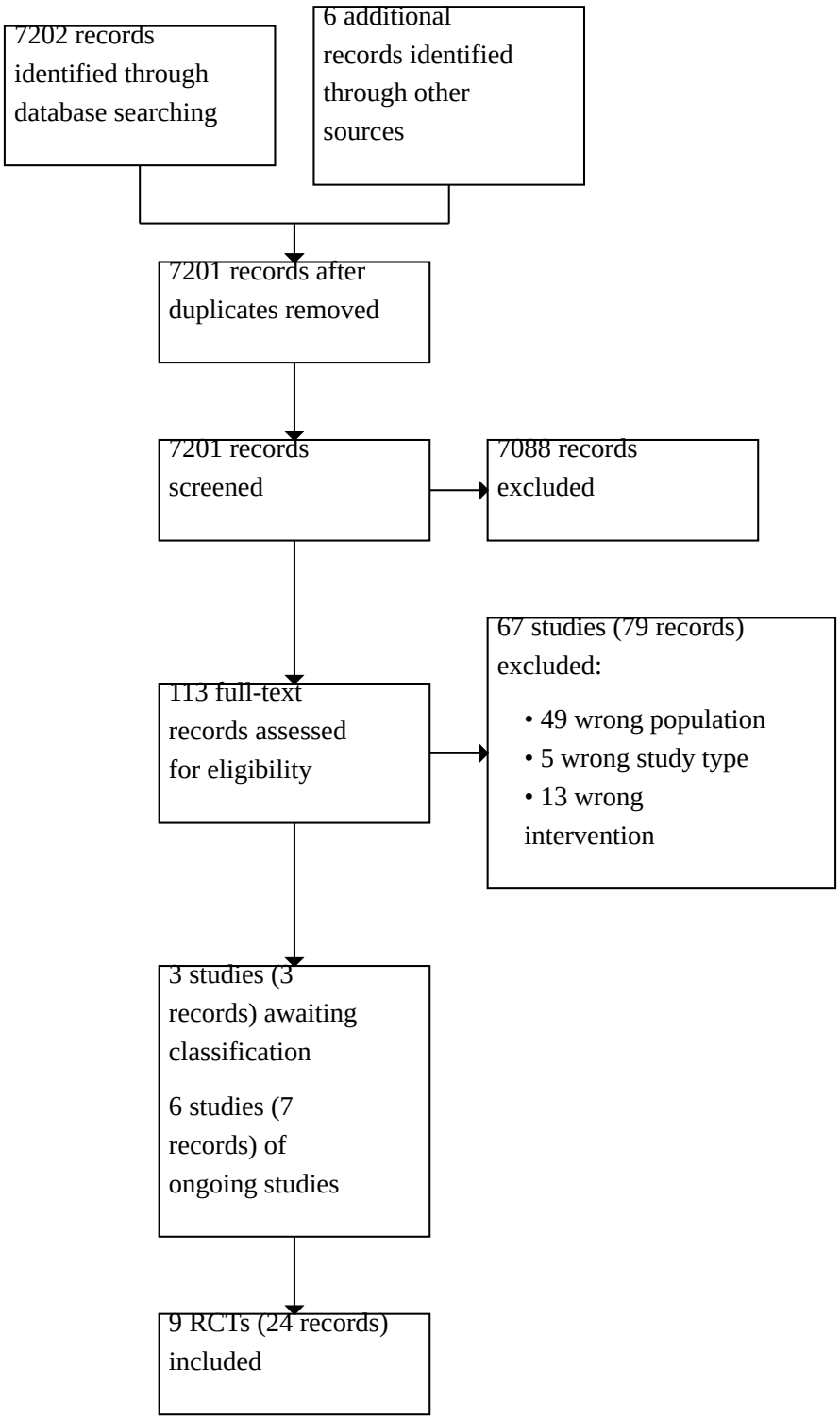
Our electronic search identified 7202 studies, in addition to six records identified through other sources. After removing duplicates, 7201 records underwent title and abstract screening to assess eligibility, of which 7088 were excluded. The remaining 113 records underwent full-text review, of which 67 full-text articles were excluded for the following reasons: 5 for wrong study type, 49 for wrong population type, and 13 for wrong study intervention.

Three studies were identified as awaiting classification: NTR1404; Chaparro 2023; Colombel 2023.

SIx ongoing studies were identified: ACTRN12621001498886 (SISS trial); ACTRN12622001458729; Chaparro 2019; EUCTR2019-001087-30; KCT0007470; NCT02994836.

The results of the search are presented in the study flow diagram (Figure 1).

Figure 1. Study flow diagram



Nine RCTs were included: (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Louis 2022 (SPARE); Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH); Volkers 2017 (SIMILAR)).

Included studies

A summary of key characteristics and interventions from the included studies is shown in Table 1 and Table 2.

Study design

The nine RCTs included a total of 1257 participants. Sixstudies were international studies conducted across multicentre hospitals in Europe, North America and Israel (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Louis 2022 (SPARE); Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021). Two studies were multicentre studies conducted in one country (Jorgensen 2017 (NORSWITCH); Volkers 2017 (SIMILAR)) and one study in a single centre in Belgium(VanAssche 2012 (SWITCH)).

Interventions

- Four studies compared Infliximab with placebo (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Rutgeerts 1999; Sands 2004 (ACCENT II)).
- One study compared CT-P13 to infliximab (Jorgensen 2017 (NORSWITCH)).
- One study compared anti-metabolites to infliximab or a combination of both (Louis 2022 (SPARE)).
- One study compared Intravenous CT-P13 with subcutaneous CT-P13 (Schreiber 2021).
- One study compared infliximab to adalimumab (VanAssche 2012 (SWITCH)).
- One study reported 'infliximab-biosimilar' as their comparison (Volkers 2017 (SIMILAR)).

Buhl 2022 (STOP IT) and Schreiber 2021 were the only studies with a purine analogue use > 50% amongst its participants (Table 1), and thus we considered that as part of their intervention for our analysis, per our methods.

Volkers 2017 (SIMILAR) was discontinued as an RCT and all available data comes from an abstract report. The data for this study have been published as part of a cohort study. The results of this study cannot be used in our review as it does not have randomised data.

Study arms

Seven studies had two arms (Buhl 2022 (STOP IT); Jorgensen 2017 (NORSWITCH); Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH); Volkers 2017 (SIMILAR)) whilst two studies had three arms (Hanauer 2002 (ACCENT I); Louis 2022 (SPARE)).

Concurrent therapies

- Buhl 2022 (STOP IT): allowed all immunosuppressants except for steroids.
- Hanauer 2002 (ACCENT I): allowed 5-ASA, antibiotics, corticosteroids including prednisolone, azathioprine and 6-mercaptopurine, and methotrexate.
- Jorgensen 2017 (NORSWITCH): did not allow any concurrent immunosuppressants or corticosteroids.
- Rutgeerts 1999: permitted concurrent use of 5-ASA, oral corticosteroids, azathioprine and 6-mercaptopurine.
- Sands 2004 (ACCENT II): permitted concurrent use of 5-ASA, oral corticosteroids, azathioprine and 6-mercaptopurine, methotrexate, antibiotics and mycophenolate.
- Schreiber 2021: permitted the use of azathioprine and 6-mercaptopurine, methotrexate and corticosteroids (including budesonide and prednisolone).
- VanAssche 2012 (SWITCH); reported permitting concurrent use of 'short (4 weeks) courses of steroids'.
- Louis 2022 (SPARE): allowed concomitant therapy with stable doses of immunosuppressants, but not steroids, other biologics, or thalidomide.
- Volkers 2017 (SIMILAR): did not mention the use of concurrent therapies in their studies.

Disease activity

Disease activity at the beginning of the study was reported in all studies, seven of which reported CDAI scores: (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Louis 2022 (SPARE); Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH); Rutgeerts 1999) whilst the other two reported HBI scores (Jorgensen 2017 (NORSWITCH); Volkers 2017 (SIMILAR)).

Three studies included patients in clinical remission (Buhl 2022 (STOP IT); Louis 2022 (SPARE); Volkers 2017 (SIMILAR)). Two studies included patients with a mix of activity scores (Jorgensen 2017 (NORSWITCH); VanAssche 2012 (SWITCH). Three studies preceded the maintenance RCT part of their studies with an induction phase and reported patients with active disease were included at the beginning of the induction phases (Hanauer 2002 (ACCENT I); Sands 2004 (ACCENT II); Schreiber 2021). One study (Rutgeerts 1999) included responders to infliximab or placebo treatment and reported patients with active disease at baseline.

One study included exclusively patients with fistulating disease (Sands 2004 (ACCENT II)).

Disease duration

Disease duration at baseline was reported in all studies except Volkers 2017 (SIMILAR). Mean disease duration ranged from five to 14 years and the overall range was from two months to 32.8 years.

Location of disease

Location of disease was described in seven studies (Buhl 2022 (STOP IT); Louis 2022 (SPARE); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Rutgeerts 1999; Sands 2004 (ACCENT II); VanAssche 2012 (SWITCH).

A total of 166 patients were reported to have ileal Crohn's, 273 colonic Crohn's, 478 ileocolonic Crohn's, 13 upper GI tract Crohn's, and 24 affecting gastroduodenum Crohn's.

Schreiber 2021 and Volkers 2017 (SIMILAR) did not report disease location.

Age

Mean or median participant age was reported in seven studies, and it ranged from 18 to 69 years: Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Louis 2022 (SPARE);

Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH).

One abstract report did not report on the age of participants (Volkers 2017 (SIMILAR)).

Conflicts of interest:

- Six studies reported conflicts of interest (Buhl 2022 (STOP IT); Louis 2022 (SPARE); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH)).
- One study did not report on presence or absence of conflict of interest (Rutgeerts 1999).
- One study reported to have no conflict of interest (Volkers 2017 (SIMILAR)).

Funding:

- Four studies reported commercial funding (Hanauer 2002 (ACCENT I); Rutgeerts 1999; Schreiber 2021; VanAssche 2012 (SWITCH)).
- Two studies reported public funding (Jorgensen 2017 (NORSWITCH); Louis 2022 (SPARE)).
- Two studies reported both public and commercial sources of funding (Buhl 2022 (STOP IT); Sands 2004 (ACCENT II)).
- One study did not report funding (Volkers 2017 (SIMILAR)).

Excluded studies

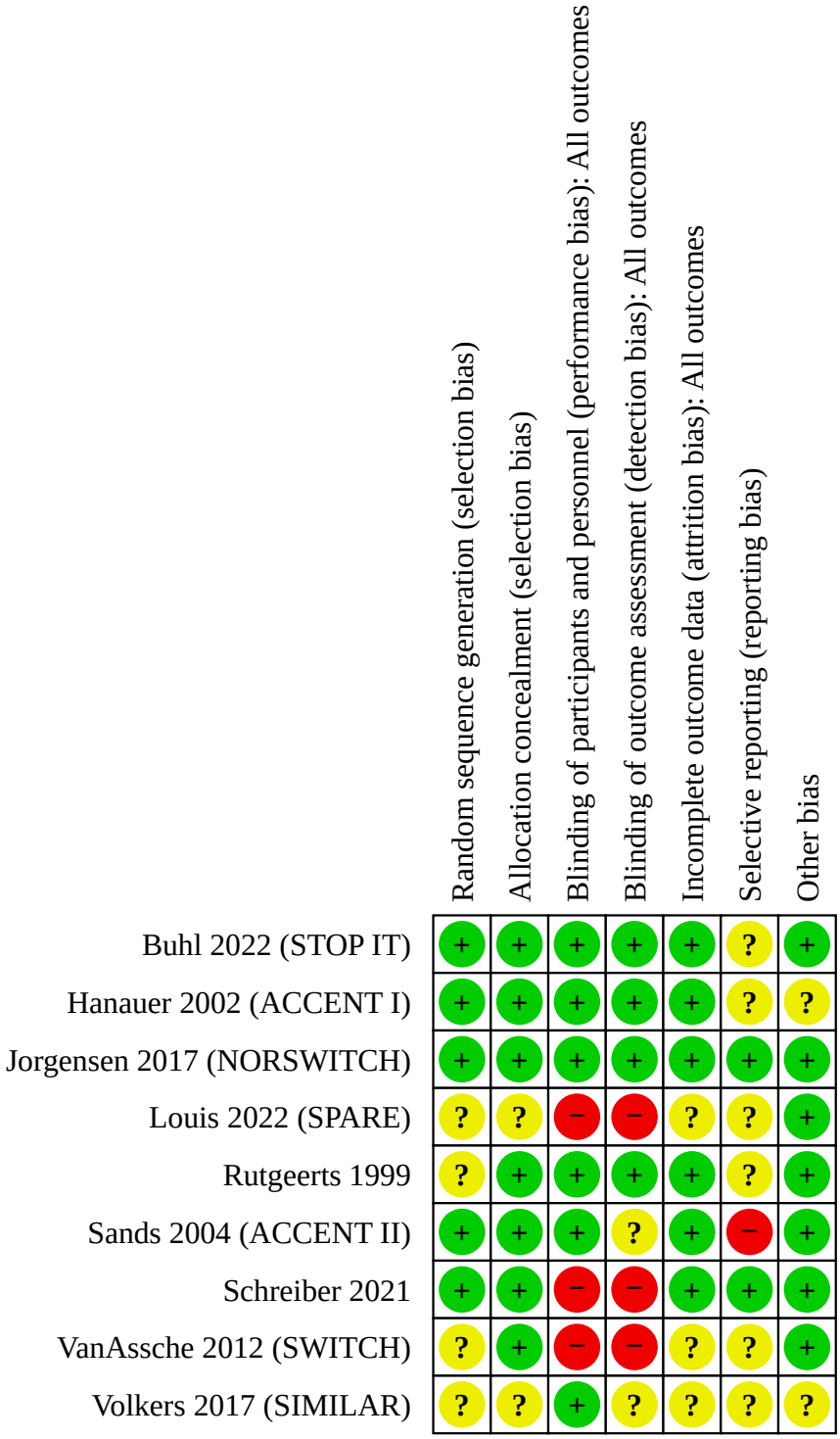
67 studies (79 records) were excluded:

- 49 wrong population: ACTRN12614000903684; Baldassano 2003; Bendix 2020; Colombel 2008; Colombel 2010; Cozijnsen 2016; D'Haens 2008; D'Haens 2018; EUCTR2004-002815-10-GB; EUCTR2008-006484-36-IT; EUCTR2011-003038-14-NL; Goll 2016; Goll 2017; Goll 2018; Goll 2019; Huang 2012;Hyams 2007; Hyams 2011; Keil 2016; Kim 2017; Kim 2017a; Kim 2017b; Lichtenstein 2011; Mantzaris 2004; NCT00094458; NCT00207662; NCT00269841; NCT00269854; NCT00688636; NCT00796250; NCT01442025; NCT01548014;NCT02096861; NCT02522169; NCT03393247; Present 1999; Regueiro 2009; Regueiro 2009a; Regueiro 2015; Regueiro 2016; Reinisch 2019; Ruemmele 2009; Sandborn 2009; Sandborn 2009a; Schreiber 2018;Tursi 2014; Wu 2016; Ye 2019; Ye 2020.
- 5 wrong study type: Balzola 2012; Endo 2011; Matsui 2008; Perks 2017; Roder 2018
- 13 wrong intervention: Casteele 2012; Casteele 2013; Matsuoka 2018; NCT00132899; NCT00752622;NCT02453776; NCT04835506; Steenholdt 2015; Strik 2019; Strik 2021;Van de Casteele 2012; Van de Casteele 2013; Van de Casteele 2015.

Risk of bias in included studies

The risk of bias in the included studies is displayed in Figure 2. We have contacted authors or study sponsors for clarifications on unclear judgements.

Figure 2. Risk of bias summary



Allocation

Five studies had sufficient information about randomisation to judge as being at low risk (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Sands 2004 (ACCENT II); Schreiber 2021). The remaining four studies were judged as being at unclear risk (Louis 2022 (SPARE); Rutgeerts 1999; VanAssche 2012 (SWITCH); Volkers 2017 (SIMILAR)).

Seven studies provided enough information on allocation concealment to be judged as being at low risk of bias (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH)). Two did not and were judged as being at unclear risk (Louis 2022 (SPARE); Volkers 2017 (SIMILAR)).

Blinding

Performance Bias:

- Six of the nine included studies were judged as being at low risk for performance bias (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Rutgeerts 1999; Sands 2004 (ACCENT II); Volkers 2017 (SIMILAR)).
- Three studies were judged to have a high risk of performance bias (Louis 2022 (SPARE); Schreiber 2021; VanAssche 2012 (SWITCH)).

Detection Bias:

- Four studies were judged to have low risk of bias: (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Rutgeerts 1999).
- Three studies were judged to have high risk of bias: (Louis 2022 (SPARE); Schreiber 2021; VanAssche 2012 (SWITCH)).
- Two of the studies were judged to have unclear risk of detection bias: (Sands 2004 (ACCENT II); Volkers 2017 (SIMILAR)).

Incomplete outcome data

Six studies were judged to have low risk of attrition bias (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Jorgensen 2017 (NORSWITCH); Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021).

The remaining studies were judged as being at unclear risk for attrition bias (Louis 2022 (SPARE); VanAssche 2012 (SWITCH); Volkers 2017 (SIMILAR)).

Selective reporting

Two studies were judged as being at low risk for selective reporting (Jorgensen 2017 (NORSWITCH); Schreiber 2021).

Six studied were judged as being at unclear risk (Buhl 2022 (STOP IT); Hanauer 2002 (ACCENT I); Louis 2022 (SPARE); Rutgeerts 1999; VanAssche 2012 (SWITCH); Volkers 2017 (SIMILAR)).

One study was judged as having high risk (Sands 2004 (ACCENT II)).

Other potential sources of bias

Seven studies were judged as being at unclear risk for other bias (Buhl 2022 (STOP IT); Jorgensen 2017 (NORSWITCH); Louis 2022 (SPARE); Rutgeerts 1999; Sands 2004 (ACCENT II); Schreiber 2021; VanAssche 2012 (SWITCH)).

Two were judged as having unclear risk (Hanauer 2002 (ACCENT I); Volkers 2017 (SIMILAR)).

Effects of interventions

See: **Summary of findings 1** Infliximab compared to placebo; **Summary of findings 2** Infliximab combined with purine analogues compared to purine analogues; **Summary of findings 3** Infliximab compared to purine analogues; **Summary of findings 4** Infliximab compared to biosimilar; **Summary of findings 5** Subcutaneous CT-P13 and purine analogues compared to intravenous CT-P13 and purine analogues; **Summary of findings 6** Infliximab compared to adalimumab

A summary of the reported outcome data can be found in Table 3.

Infliximab vs placebo

In total, three studies compared Infliximab to placebo (Hanauer 2002 (ACCENT I); Rutgeerts 1999; Sands 2004 (ACCENT II)). The studies included mixed disease activity patients, with clinical response to infliximab at baseline, which happened during induction phases that immediately preceded the maintenance trial, in all three studies.

Primary outcome: clinical relapse

Two of the studies provided data for a meta-analysis for this outcome (Hanauer 2002 (ACCENT I); Rutgeerts 1999). The data for the two different doses of infliximab in Hanauer 2002 (ACCENT I) have been combined for this analysis.

Infliximab (146/262) is probably superior to placebo (110/146) for maintenance therapy to prevent clinical relapse in patients who have mixed levels of clinical disease activity at baseline (RR 0.73, 95% CI 0.63 to 0.84, NNTB = 5; Analysis 1.1, Summary of findings 1).

The results are of moderate certainty, downgraded once due to concerns about the risk of bias.

Sands 2004 (ACCENT II) did not report clinical relapse.

Secondary outcome: loss of clinical response

Two studies reported data for loss of clinical response (Rutgeerts 1999; Sands 2004 (ACCENT II)).

Rutgeerts 1999 included patients with active disease that showed clinical response to infliximab at baseline, while Sands 2004 (ACCENT II) included an exclusively fistulating population with mixed disease activity that showed response to infliximab at baseline. Due to the difference in the included populations, the two studies could not be combined in a meta-analysis.

We cannot draw any conclusions on the effects of infliximab (14/37) on loss of clinical response compared to placebo (23/36) (RR 0.59, 95% CI 0.37 to 0.96, Analysis 1.2, Summary of findings 1).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to concerns about risk of bias.

Infliximab (54/96) may be superior compared to placebo (76/99) for loss of clinical response in an exclusively fistulating population (RR 0.73, 95% CI 0.60 to 0.90, Analysis 1.3).

The results are of low certainty, downgraded once due to imprecision and once due to concerns about the risk of bias.

Hanauer 2002 (ACCENT I) did not report this outcome.

Secondary outcome: endoscopic relapse

This was not reported in any of the studies.

Secondary outcome: withdrawal due to adverse events

Two studies reported data for this outcome (Rutgeerts 1999; Sands 2004 (ACCENT II)).

We cannot draw any conclusions on the effects of infliximab (15/175) on withdrawals due to adverse events compared to placebo (24/180) (RR 0.66, 95% CI 0.37 to 1.19, Analysis 1.4, Summary of findings 1).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to concerns about risk of bias.

Hanauer 2002 (ACCENT I) did not report this outcome.

Secondary outcome: serious adverse events

One study reported data for this outcome (Sands 2004 (ACCENT II)).

We cannot draw any conclusions on the effects of infliximab (33/144) on serious adverse events compared to placebo (19/138) (RR 0.60, 95% CI 0.36 to 1.00, Analysis 1.5, Summary of findings 1).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to concerns about risk of bias.

Hanauer 2002 (ACCENT I) and Rutgeerts 1999 did not report this outcome.

Secondary outcome: total adverse events

Two studies reported data for this outcome (Rutgeerts 1999; Sands 2004 (ACCENT II)).

Infliximab (158/175) may be similar to placebo (167/180) for total adverse events (RR 0.97, 95% CI 0.92 to 1.03, Analysis 1.6).

The results are of low certainty, downgraded once due to high imprecision and once due to concerns about risk of bias.

Hanauer 2002 (ACCENT I) did not report this outcome.

Infliximab combined with purine analogues vs purine analogues

Buhl 2022 (STOP IT) and Louis 2022 (SPARE) compared infliximab combined with purine analogies to purine analogues alone. Both studies had participants in remission at the beginning of each study, who were not biologically naive.

Primary outcome: clinical relapse

Buhl 2022 (STOP IT) reported data for this outcome that we could use for meta-analysis.

Infliximab combined with purine analogues (7/59) is probably superior for clinical relapse compared to purine analogues (33/56) (RR 0.20, 95% CI 0.10 to 0.42, NNTB = 2; Analysis 2.1, Summary of findings 2).

The results are of moderate certainty, downgraded once due to risk of bias.

Louis 2022 (SPARE) reported a total of 39 relapses out of a total of 211 participants randomised in the three groups of the study.

Secondary outcome: loss of clinical response

This was not reported in any of the studies.

Secondary outcome: endoscopic relapse

Buhl 2022 (STOP IT) reported data for this outcome that we could use for meta-analysis.

Infliximab combined with purine analogues (17/59) is probably superior for endoscopic relapse compared to purine analogues (42/56) (RR 0.38, 95% CI 0.25 to 0.59, NNTB = 2, Analysis 2.2).

The results are of moderate certainty, downgraded once due to risk of bias.

Louis 2022 (SPARE) did not report this outcome.

Secondary outcome: withdrawal due to adverse events

Buhl 2022 (STOP IT) reported data for this outcome that we could use for meta-analysis.

We cannot draw any conclusions on the effects of infliximab combined with purine analogues (4/59) on withdrawals due to adverse events compared to purine analogues (8/56) (RR 0.47, 95% CI 0.15 to 1.49, Analysis 2.3, Summary of findings 2).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Louis 2022 (SPARE) did not report this outcome.

Secondary outcome: serious adverse events

Both studies provided data for meta-analysis of this outcome.

We cannot draw any conclusions on the effects of infliximab combined with purine analogues (12/130) on serious adverse events compared to purine analogues (10/127) (RR 1.19, 95% CI 0.54 to 2.64, Analysis 2.4, Summary of findings 2).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: total adverse events

This was not reported in any of the studies.

Infliximab vs purine analogues

Louis 2022 (SPARE) compared infliximab to purine analogues for participants in remission at baseline, who were not biologically naive.

Primary outcome: clinical relapse

Louis 2022 (SPARE) reported a total of 39 relapses out of a total of 211 participants randomised in the three groups of the study.

No conclusions can be drawn about the effects of infliximab compared to purine analogues for clinical relapse. The results are of

very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: loss of clinical response

Not reported.

Secondary outcome: endoscopic relapse

Not reported.

Secondary outcome: withdrawal due to adverse events

Not reported.

Secondary outcome: serious adverse events

We cannot draw any conclusions on the effects of infliximab (10/69) on serious adverse events compared to purine analogues (13/71) (RR 0.79, 95% CI 0.37 to 1.68, Analysis 3.1, Summary of findings 3).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: total adverse events

Not reported.

Infliximab vs biosimilar

Two studies (Jorgensen 2017 (NORSWITCH); Volkers 2017 (SIMILAR)) compared infliximab to a biosimilar. Jorgensen 2017 (NORSWITCH) used the biosimilar CT-P13 and Volkers 2017 (SIMILAR) an unspecified biosimilar. Jorgensen 2017 (NORSWITCH) included participants both in active and inactive disease at the beginning of the study, who were a mix of biologically naive and not naive at recruitment.

Primary outcome: clinical relapse

Only Jorgensen 2017 (NORSWITCH) reported this outcome.

Infliximab (37/78) may be equivalent to CT-P13 (31/77) for clinical relapse (RR 1.18, 95% CI 0.82 to 1.69, Analysis 4.1, Summary of findings 4).

The results are of low certainty, downgraded twice due to very high imprecision.

Volkers 2017 (SIMILAR) did not report this outcome.

Secondary outcome: loss of clinical response

Only Jorgensen 2017 (NORSWITCH) reported this outcome.

Infliximab (38/78) may be slightly less effective than CT-P13 (25/77) in averting loss of clinical response (RR 1.50, 95% CI 1.01 to 2.23, Analysis 4.2, Summary of findings 4).

The results are of low certainty, downgraded twice due to very high imprecision.

Volkers 2017 (SIMILAR) did not report this outcome.

Secondary outcome: endoscopic relapse

This was not reported in any of the studies.

Secondary outcome: withdrawal due to adverse events

Only Jorgensen 2017 (NORSWITCH) reported this outcome.

Infliximab (21/78) may be less effective than CT-P13 (1/77) in averting withdrawals due to adverse events (RR 20.73, 95% CI 2.86 to 150.33, Analysis 4.3, Summary of findings 4).

The results are of low certainty, downgraded twice due to very high imprecision.

Volkers 2017 (SIMILAR) did not report this outcome.

Secondary outcome: serious adverse events

Only Jorgensen 2017 (NORSWITCH) reported this outcome.

Infliximab (8/78) may be equivalent to CT-P13 (8/77) for serious adverse events (RR 0.99, 95% CI 0.39 to 2.50, Analysis 4.4, Summary of findings 4).

The results are of low certainty, downgraded twice due to very high imprecision.

Volkers 2017 (SIMILAR) did not report this outcome.

Secondary outcome: total adverse events

Only Jorgensen 2017 (NORSWITCH) reported this outcome.

Infliximab (57/78) may be equivalent to CT-P13 (49/77) for total adverse events (RR 1.15, 95% CI 0.93 to 1.43, Analysis 4.5).

The results are of low certainty, downgraded twice due to very high imprecision.

Volkers 2017 (SIMILAR) did not report this outcome.

Subcutaneous biosimilar and purine analogues vs intravenous biosimilar and purine analogues

One study compared the use of SC CT-P13 biosimilar to IV CT-P13 biosimilar (Schreiber 2021). As more than 50% of the participants in this trial received concomitant purine analogues, these were considered part of the intervention.

Primary outcome: clinical relapse

We cannot draw any conclusions on the effects of SC CT-P13 (17/28) on clinical relapse compared with IV CT-P13 (15/25) (RR 1.01, 95% CI 0.65 to 1.57, Analysis 5.1, Summary of findings 5).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: loss of clinical response

We cannot draw any conclusions on the effects of SC CT-P13 (21/28) on loss of clinical response compared with IV CT-P13 (20/25) (RR 0.94, 95% CI 0.70 to 1.25, Analysis 5.2, Summary of findings 5).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: endoscopic relapse

We cannot draw any conclusions on the effects of SC CT-P13 (5/28) on endoscopic relapse compared with IV CT-P13 (1/25) (RR 4.46, 95% CI 0.56 to 35.67, Analysis 5.3).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: withdrawal due to adverse events

We cannot draw any conclusions on the effects of SC CT-P13 (6/28) on withdrawals due to adverse events compared with IV CT-P13 (7/25) (RR 0.77, 95% CI 0.30 to 1.97, Analysis 5.4, Summary of findings 5).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: serious adverse events

This outcome was reported for a combined population of CD and UC participants. Six out of 66 CD and UC participants experienced serious adverse events in the SC group compared with 10 out of 65 in the IV group.

We cannot draw any conclusions on the effects of SC CT-P13 on serious adverse events compared with IV CT-P13. The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: total adverse events

This outcome was reported for a combined population of CD and UC participants. Fifty out of 66 CD and UC participants experienced adverse events in the SC group compared with 27 out of 65 in the IV group.

We cannot draw any conclusions on the effects of SC CT-P13 on total adverse events compared with IV CT-P13. The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Infliximab vs adalimumab

One study compared infliximab with adalimumab (VanAssche 2012 (SWITCH)).

Primary outcome: clinical relapse

This outcome was not reported.

Secondary outcome: loss of clinical response

We cannot draw any conclusions on the effects of infliximab (7/37) on clinical response compared to adalimumab (10/36) (RR 0.68, 95% CI 0.29 to 1.59, Analysis 6.1, Summary of findings 6).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: endoscopic relapse

This outcome was not reported.

Secondary outcome: withdrawal due to adverse events

We cannot draw any conclusions on the effects of infliximab (1/37) on withdrawals due to adverse events compared to adalimumab (10/36) (RR 0.10, 95% CI 0.01 to 0.72, Analysis 6.2, Summary of findings 6).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: serious adverse events

We cannot draw any conclusions on the effects of infliximab (0/37) on serious adverse events compared to adalimumab (5/36) (RR 0.09, 95% CI 0.01 to 1.54, Analysis 6.3, Summary of findings 6).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

Secondary outcome: total adverse events

We cannot draw any conclusions on the effects of infliximab (27/37) on total adverse events compared to adalimumab (30/36) (RR 0.88, 95% CI 0.69 to 1.12, Analysis 6.4).

The results are of very low certainty, downgraded twice due to very high imprecision and once due to risk of bias.

DISCUSSION

Summary of main results

This review included nine RCTs included a total of 1257 participants. They were conducted between 1999 and 2022; seven of the nine RCTs were on biologically naive patients, and the remaining two on a mix of naive/not naive patients. Three studies included patients in clinical remission, five included patients with a mix of activity scores, and one study included biologic responders with active disease at baseline. All studies allowed some form of concomitant medication during their duration. One study exclusively included patients with fistulating disease.

Infliximab is probably superior to placebo for preventing clinical relapse in patients who have mixed levels of clinical disease activity at baseline. The results are of moderate certainty. We cannot draw any conclusions about loss of clinical response. The results are of very low certainty. Infliximab may be superior compared to placebo for loss of clinical response in an exclusively fistulating population. The results are of low certainty. We cannot draw any conclusions on the effects of infliximab compared to placebo on withdrawal due to adverse events and serious adverse events. The results are of very low certainty. Infliximab may be similar to placebo for total adverse events. The results are of low certainty.

Infliximab combined with purine analogues is probably superior compared to purine analogues alone for clinical and endoscopic relapse, for a population in remission at baseline. The results are of moderate certainty. We cannot draw any conclusions about withdrawal due to adverse events and serious adverse events. The results are of very low certainty. We cannot draw any conclusions on the effects of infliximab on serious adverse events compared to purine analogues, for a population in remission at baseline. The results are of very low certainty.

Infliximab may be equivalent to a biosimilar for clinical relapse, and it may be slightly less effective in averting loss of clinical response, for a population with mixed/low disease activity at baseline. The results are of low certainty. Infliximab may lead to more withdrawals due to adverse events than a biosimilar. The results are of low certainty. Infliximab may be equivalent to a biosimilar for serious and total adverse events. The results are of low certainty. We cannot draw any conclusions on the effects of a subcutaneous biosimilar compared with an intravenous biosimilar on clinical relapse, loss of clinical response, endoscopic relapse, and withdrawal due to adverse events, for an active disease

population with clinical response at baseline. The results are of very low certainty.

We cannot draw any conclusions on the effects of infliximab compared to adalimumab on clinical response, withdrawal due to adverse events, serious adverse events, and total adverse events, for an active disease population with clinical response at baseline. The results are of very low certainty.

Overall completeness and applicability of evidence

The evidence is incomplete in a number of ways. Given that the studies span 23 years between the first included study (Rutgeerts 1999) and the last study (Louis 2022 (SPARE)), there have been changes in practice that in turn impact the applicability of research. These are particularly related to how relapse or loss of response is defined and assessed, as well as the use of certain concomitant therapies, that all limit the applicability of the evidence synthesised.

The majority of studies included in this review used a clinical assessment of remission state for recruitment, which is considered the standard tool in Crohn's disease research. However, other measures of disease activity and, in turn, endpoints for studies, such as endoscopic and histological measures, were limited in reporting.

Moreover, in some contexts within Crohn's disease maintenance studies, homogeneity of patients at entry is perhaps implicit, such as maintenance treatment after surgery (Gjuladin-Hellon 2019a; Gjuladin-Hellon 2019b; Iheozor-Ejiofor 2019). The studies included in this review all involved patients with different pre-recruitment experience of induction therapy, as well as length of remission. This in turn limits the generalisability of conclusions.

The reporting of adverse events is another area of concern. After induction of remission, an often long and difficult process for people with IBD, balancing maintaining that remission with side effects from medications to support this is of great interest to all stakeholders. For common effects, randomised trial data can be sufficient to consider safety (Gordon 2021), but this is not the case for rarer and possibly more devastating outcomes where long-term safety data are not addressed by this synthesis.

Finally, for many outcomes, there were issues with precision in most GRADE analyses, probably due to the low number of participants. This is a pervasive issue within the field (Iheozor-Ejiofor 2021), but directly impacts the applicability of the outcomes of the review.

Quality of the evidence

We assessed studies for risk of bias and our outcomes of interest using GRADE to establish our certainty in the findings.

Of particular note were pervasive issues with unclear bias across multiple studies in many areas of assessment, despite attempts to access clarifying data from study authors. Additionally, several studies were open-label. There were just two studies with low risk of bias in all areas.

The certainty of outcomes on GRADE analysis ranged from moderate to very low, with not just the impact of risk of bias, but also imprecision, the most pervasive criteria that impacted the certainty of the evidence produced.

Potential biases in the review process

The review authors chose to contact the study authors as there were such significant issues with unclear risk of bias. The team aim to include any further data that may become available in future updates, but this could represent a source of bias in the review. Conversely, the use of such unpublished data can also be seen as a source of bias.

We are aware of the possibility of commercial funding impacting the validity of the results. Funding from manufacturing companies or any conflicts of interests from both primary studies and the review team have been reported.

Agreements and disagreements with other studies or reviews

The results broadly support current international guidelines in the UK (Lamb 2019), Europe (Torres 2020) and North America (Feuerstein 2021). However, the GRADE certainty ratings in these guidelines are higher than the judgements in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Infliximab is probably more effective in preventing clinical relapse than placebo (moderate-certainty evidence). Infliximab in combination with purine analogues is probably more effective in preventing clinical and endoscopic relapse than purine analogues alone (moderate-certainty evidence). No conclusions can be drawn regarding prevention of loss of clinical response, occurrence of withdrawal due to adverse events or total adverse events, due to very low-certainty evidence for both of these comparisons.

We were unable to draw meaningful conclusions on whether there is a difference between infliximab and purine analogues, infliximab compared to adalimumab or subcutaneous CT-P13 with purines compared with intravenous CT-P13 with purines. This is due to missing data or very low-certainty evidence for these outcomes due to serious concerns about imprecision and risk of bias.

There may be little or no difference in prevention of clinical relapse, withdrawal due to adverse events or total adverse events between infliximab and a biosimilar (low-certainty evidence). Infliximab may lead to more loss of clinical response than a biosimilar (low-certainty evidence).

Implications for research

There does not appear to be a role for further studies compared with placebo. Whilst the certainty of such outcomes is low, this is not a clinically meaningful comparison in research or practice. Rather, further targeted and appropriately designed randomised controlled trials may be needed to address the gaps in the evidence base in relation to active comparators drawn from the range of potential therapies that are currently used in practice. It is important that concurrent therapies, the method of induction of remission and the length of remission are well reported, if not key factors considered in recruitment and design of such studies.

Future research should comprehensively report the effects of infliximab on endoscopic and histological relapse, as these outcomes are rarely reported.

Appropriate power and design of these studies based on appropriate minimum clinical difference data (Gordon 2021b) is needed to solve the issue with imprecision in outcomes and add more certainty to the evolving evidence base.

Safety will always be a real priority but may need other design types and, in turn, other designs of synthesis, such as those using large cohort observational studies and designing longer studies.

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Editorial and peer-reviewer contributions

Cochrane Gut supported the authors in the development of this review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Grigoris Leontiadis, Co-ordinating Editor of the Cochrane Gut Group;
- Managing Editor (provided editorial guidance to authors, edited the article): Helen Wakeford, Central Editoral Service;
- Information Scientist: Dr Farhad Shokraneh (Systematic Review Consultants LTD) ran the searches in August 2021 and updated them in June 2023.
- Editorial Assistant (selected peer reviewers, collated comments, conducted editorial policy checks and supported editorial team): Sara Hales-Brittain, Central Editorial Service;
- Copy Editor (copy editing and production): Anne Lethaby, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Mark A. Ainsworth, Department of Medical Gastroenterology, Odense University Hospital (clinical/content review), Eugenia Shmidt, MD, University of Minnesota (clinical/content review), George Lillington, Consumer Reviewer, Cochrane (consumer review), Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review), Steve McDonald, Cochrane Australia (search review)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Buhl 2022 (STOP IT)

Study characteristics	
Methods	**Study design:** Double-blind, randomised, placebo-controlled **Single-centre or multicentre?** Multicentre (13 sites) **Countries:** Denmark, Finland, Norway, and Sweden **Study chronology:** January 2013 to May 2020 **Setting:** Secondary care
Participants	**Inactive disease at beginning of study:** Inactive disease **Inclusion criteria:** Adult patients (age ≥ 18 years) with luminal Crohn's disease defined by standardised diagnostic criteria in sustained complete remission on IFX maintenance therapy (infusions every 6–10 weeks, 5–10 mg/kg) with a treatment length of a minimum 12 months are eligible. Complete remission is defined as a CDAI score < 150, no signs of inflammation on biochemical parameters (normal CRP, leucocytes, haemoglobin (Hb) and albumin), and no other marks of disease activity, either from endoscopic examination (Simple Endoscopic Score for Crohn's Disease (SES-CD) score 0–2) and/or by MRI (defined by no signs of disease activity when evaluated by a trained radiologist). Sustained remission is defined as a clinical judgement of the disease to be stable at two consecutive treatment visits (corresponding to two scheduled IFX infusions) and no use of oral steroids within 3 months prior to inclusion. Concomitant therapy with immune suppressants, except steroids, is allowed. The dosage and frequency must have been stable 3 months prior to inclusion, and must remain stable throughout the study period. **Exclusion criteria:** Exclusion criteria include the initial indication for IFX being predominantly fistulising perianal disease, ongoing fistulising disease, and pregnancy or lactation. Further, in case of any contraindications for continuing IFX treatment, including prior acute or delayed infusion reaction to a TNF-inhibiting agent, former malignancy, moderate-to-severe heart disease, any active infection requiring parenteral or oral antibiotic treatment, known infection with tuberculosis, HIV or hepatitis virus, the patient cannot be included.

Buhl 2022 (STOP IT) *(Continued)*

Baseline disease characteristics

- Fistulating disease: IG 4/59 CG: 2/56
- Location of disease:
  - Ileal: IG 8/59 CG 4/56
  - Colonic: IG 17/59 CG 24/56
  - Ileocolonic: IG 34/59 CG 28/56
  - Isolated upper disease: IG 0/59 CG 0/56
- Duration or length of disease since diagnosis: years, mean (IQR) IG 6(3-12) CG 5(1-15)

How was remission achieved? This double-blind, randomised, PBO-controlled multicentre trial enroled patients with luminal CD who had been treated with standard IFX maintenance therapy for at least 1 year, in complete remission at the time of inclusion, defined as CD Activity Index (CDAI) < 150, normal biochemical parameters (CRP, WBC, Hgb, albumin), and no signs of inflammatory activity as assessed by ileo-colonoscopy, MRI, and/or capsule endoscopy.

How long have they been on remission: Patients were required to be in stable clinical remission at the two infliximab infusion visits before the inclusion visit (about 8 weeks).

Current remission activity score if reported: CDAI mean (IQR) IG 46 (16–71) CG 35 (14–65)

Endoscopic disease scoring: SES-CD mean (IQR) IG 0 (0–0) CG 0 (0–0)

Other baseline characteristics

Age at beginning of study per IG/CG: years, mean (IQR) IG 36 (26–50) CG 32 (25–50)

Sex (f/m) per IG/CG: IG 26/33 CG 28/28

Smoking per IG/CG: IG 13/59 CG 11/56

Number randomised per IG/CG: IG 59/115 CG 56/115

Number reaching end of study per IG/CG: IG 54/59 CG 47/56

Interventions	**IG:** Continued infliximab therapy at an unchanged dose for a duration of 48 weeks **CG:** Matching placebo for a duration of 48 weeks **Duration of study**: 48 weeks **Measurement time points during study:** weeks 4, 8, 16, 24, 32, 40, 48 **Any follow-up measurements after study end? If yes, what time-points?** No follow-up measurements
Outcomes	**Primary outcomes as defined by study authors (from the protocol):** Proportion of patients who maintain remission, i.e. CDAI < 150 **Secondary outcomes as defined by study authors (from the protocol):** Secondary end points assessed at the end of the trial after 48 weeks include: ‣ Proportion of patients who maintain complete remission (def. CDAI score < 150, no signs of inflammation in biochemical parameters and mucosal healing) ‣ Median time to relapse after discontinuation of IFX ‣ Proportion of patients experiencing relapse. Relapse, defined as a CDAI score > 150 and a greater than 70-point increase from inclusion over two consecutive weeks ‣ Change from baseline in disease activity (i.e. CDAI score, biochemical parameter including faecal calprotectin, SES-CD)

Buhl 2022 (STOP IT) *(Continued)*

- Economical expenses for treatment of Crohn's disease in the two groups

Notes	**Funding source:** This study is supported by Nordforsk, Herlev Hospital Research Council, Danish Colitis-Crohn Society, and A.P. Møller and Chastine Mc-Kinney Møller's Foundation for General Purposes. **Conflicts of interest:** CS has served as a speaker for MSD and Abbvie and as a consultant for MSD and Takeda Pharmaceutical Company. JB has served as an advisory board member for Abbvie. OØT has served as a speaker and consultant for UCB and Zealand Pharma, speaker for MSA, and primary investigator for Amgen, Biogen, Novo-Nordisk and Pfizer. KB has served as a speaker for Pfizer, Roche, Novo-Nordisk, Bristol-Meyers Squibb and Biomonitor and owns stocks in Novo-Nordisk and Biomonitor. Author was contacted on 11/3/2022 and no response was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally at Herlev University Hospital, Denmark, by non-blinded laboratory personnel who did not have contact with the patients or physicians, and used opaque, sealed envelopes.
Allocation concealment (selection bias)	Low risk	A non-blinded nurse, who was not involved in the treatment of the patients, received the allocation results and subsequently prepared and labelled infliximab or placebo medication accordingly.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching infliximab and placebo infusions, participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The treating physicians who performed the assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was balanced and explained in both groups. Not likely to have influenced outcomes
Selective reporting (reporting bias)	Unclear risk	The trial has been registered and a protocol was published in 2014. The primary and secondary outcomes were swapped, before blinding was broken, and this was justified as "using the originally proposed primary endpoint would not have incorporated all data collected, given that patients discontinuing treatment for reasons other than relapse would not have been included in the analysis, thus decreasing the power". Authors stated that analyses of key secondary endpoints were performed only if the primary efficacy analysis yielded statistically significant results.
Other bias	Low risk	Baseline characteristics were balanced. No other concerns

Hanauer 2002 (ACCENT I)

Study characteristics

Methods	**Study design:** RCT **Single-centre or multicentre:** Multicentre (55 sites)

Hanauer 2002 (ACCENT I) *(Continued)*

	Countries: North America (40 sites), Europe (13 sites), and Israel (2 sites) **Study chronology:** February 26, 1999 to March 15, 2001 **Setting:** Secondary care and educational institutions
Participants	**Active or inactive disease at beginning of study?:** Mixed activity CDAI scores for the cohort of responders and non-responders given, no group-specific baseline characteristics available **Inclusion criteria:** Eligible patients had Crohn's disease of at least 3 months' duration with a score on the CDAI between 220 and 400. Patients receiving the following treatments were eligible: 5-aminosalicylates or antibiotics (if the dose remained constant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks). Patients not receiving medical therapy had to have discontinued treatment for at least 4 weeks before screening. **Exclusion criteria:** Patients were excluded from the study if they had received previous treatment with infliximab or any other agent targeted at TNF. **Baseline Disease characteristics** • **Fistulating disease:** Not reported • **Location of disease**: Not reported per treatment group, but for the whole cohort. For week-2 responders – Ileum 74/331 (22%). Colon 74/331 (22%). Ileum and colon 183/331 (55%). Gastroduodenum 24/335 (7%) • **Duration or length (years) of disease since diagnosis**: For week-2 responders – 7.5 (3.7, 14.2) - mean and IQR • **How was remission achieved?** Before randomisation at week 0, all eligible patients received a 5 mg/kg intravenous infusion of infliximab. At week 2 (point of randomisation), patients were assessed for a response to treatment as defined by a decrease in CDAI score of 70 points or more from the baseline value and at least a 25% reduction in the total score. • **Current remission activity score if reported:** This is not a trial of maintenance of remission, but a trial of maintenance response (CDAI reduction of 70 points or more). CDAI scores per treatment group not given. Week-2 responders median CDAI 299 (264-342) • **How long have they been on remission:** Not reported • **Endoscoping disease scoring:** Not reported **Age (years) at beginning of study per IG/CG:** Not reported per IG/CG. For week-2 responders – 35 (27, 46) **Sex (m/f) per IG/CG:** Not reported per IG/CG. For week-2 responders – male 130 (39%) female 205 (61%) **Smoking per IG/CG:** Not reported **Number randomised per IG/CG:** **CG** – 110 (32.84%). **IG1** – 113 (33.73%). **IG2** – 112 (33.43%). **Number reaching end of study per IG/CG:** Unclear for the randomised responder groups
Interventions	**IG1:** Infliximab infusion (route intravenous), each infusion 5 mg/kg. Infusions at week 2 (start point of maintenance study), week 6, and every 8 weeks thereafter until week 46 **IG2:** Infliximab infusion, 5 mg/kg infusions at week 2 (start point of maintenance study) and week 6. 10 mg/kg every 8 weeks thereafter until week 46 **CG:** Placebo - identical in appearance to Infliximab infusion. Agent and route (IV or SC). Infusions at week 2 (start point of maintenance study), week 6, and every 8 weeks thereafter until week 46

Hanauer 2002 (ACCENT I) *(Continued)*

	Duration of study: 52 weeks (week 2 to week 54; first two weeks are non-randomised induction period) **Measurement time points during study:** Patients were assessed at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 54. **Any follow-up measurements after study end? If yes, what time-points?** Not reported
Outcomes	**Primary outcomes as defined by study authors:** The prespecified co-primary efficacy endpoints were the proportion of week-2 responders in clinical remission at week 30, and the time to loss of response up to week 54 amongst week-2 responders. The findings presented here address the primary objective of this study, which was to assess the benefit of infliximab maintenance treatment in patients with an initial early (within 2 weeks) response to a single infliximab infusion. Later, in an amendment made to the original protocol, the proportion of week-2 responders who were in remission at week 30, as defined by a CDAI score of less than 150 points, was added as a co-primary efficacy endpoint to provide an earlier assessment of the efficacy of maintenance infliximab infusions. **Secondary outcomes as defined by study authors:** Secondary objectives included the assessment of infliximab's corticosteroid-sparing effects and safety.
Notes	**Funding source:** Role of the funding source - This study was designed by a committee composed of Centocor staff members and the ACCENT Steering Committee members. Centocor staff collected data from all clinical sites to create the clinical database. Centocor staff members and members of the ACCENT Steering Committee analysed and interpreted the data, wrote the paper, and agreed to submit it for publication. The principal investigators approved the content of the paper before submission. **Conflicts of interest:** S. B. Hanauer has acted as a consultant for, received honoraria from, provided paid expert testimony for, and received travel grants from Centocor. B. G. Feagan has received honoraria from Centocor. G. R. Lichtenstein has acted as a consultant for, received honoraria from, and received travel grants from Centocor. L. F. Mayer has acted as a consultant for and received honoraria from Centocor. D. C. Wolf has acted as a consultant for, received honoraria from, and received travel grants from Centocor. A. Olson and W. Bao are employees of Centocor. P. Rutgeerts has provided paid expert testimony for Centocor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors mentioned random assignment via adaptive randomisation voice response system.
Allocation concealment (selection bias)	Low risk	"Allocation of patients to a treatment group was done with an adaptive stratified design" and "allocate patients centrally to treatment based on the current balance of treatment groups within each stratum".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patients nor study investigators were aware of the treatment assignment" and "pharmacist prepared the infusion (infliximab [Remicade] or an identically appearing placebo)".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the patients nor study investigators were aware of the treatment assignment" and "pharmacist prepared the infusion (infliximab [Remicade] or an identically appearing placebo)".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety data were presented for the entire cohort throughout the end of the study. No concerns that attrition might have affected the results
Selective reporting (reporting bias)	Unclear risk	Outcomes reported as per the methods section. The trial registration provided little information so we can't be sure if the prespecified plan was followed.

Hanauer 2002 (ACCENT I) *(Continued)*

Other bias	Unclear risk	Baseline characteristics were not provided per treatment group for the week-2 responders.

Jorgensen 2017 (NORSWITCH)

Study characteristics

Methods	**Study design:** randomised, double-blind, parallel-group, multicentre, non-inferiority comparative phase 4 study, in a hospital setting **Single-centre or multicentre?: Multicentre;** 25 Norwegian hospitals recruited patients to the study. 19 gastroenterology departments, 16 rheumatology departments, and five dermatology departments **Countries:** Norway **Study chronology:** Oct 24, 2014 to July 8, 2015 **Setting:** Hospital
Participants	**Active or inactive disease at beginning of study?:** Mixed/low (both the general and the disease-specific measures suggested low disease activity at baseline, with no differences between groups) **Inclusion criteria:** 1. A clinical diagnosis of either rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease or chronic plaque psoriasis; 2. Male or non-pregnant, non-nursing female; 3. > 18 years of age at screening; 4. Stable treatment of innovator infliximab (Remicade®) during the last 6 months; 5. Subject capable of understanding and signing an informed consent form; 6. Provision of written informed consent. **Exclusion criteria:** 1. Major co-morbidities, such as severe malignancies, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases and/or other diseases including inflammatory conditions for which infliximab is contraindicated; 2. Change of major co-medication during the last 2 months prior to randomisation: initiation of systemic corticosteroids or an immunosuppressant or other medication which, according to the investigator, would interfere with the stability of the disease; 3. Inadequate birth control, pregnancy, and/or breastfeeding. Adequate contraception includes oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or system, vasectomised partner or sexual abstinence; 4. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which make adherence to the study protocol impossible; 5. Change in treatment with innovator infliximab (Remicade®) during the last 6 months due to disease related factors, not including dose/frequency adjustments due to drug concentration measurements; 6. For patients with UC and CD: functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ. **Baseline characteristics, per IG/CG** • **Fistulating disease per IG/CG:** IG: 8/77, CG: 8/78 • **Location of disease (ileal, colonic, etc.) per IG/CG:** ileum (L1) IG - 13 (17%) CG- 13 (17%), colonic (l2) IG - 23 (30%) CG - 25 (32%), ileocolonic (L3) IG - 38 (49%) CG - 39 (50%), upper GI tract (L4) IG - 6 (9%) CG - 7 (10%) • **Duration or length (months/years) of disease since diagnosis per IG/CG:** IG - 14.3 (8.5) CG - 12.8 (9.0) • **How was remission achieved (specific medications, specific demographics if offered) per IG/CG?:** Inclusion criteria mention that only patients who have been on at least 6 months of Infliximab were included. Duration of ongoing treatment in years IG - 5.2 (3.3) CG - 5.7 (3.5) • **Current remission activity score if reported per IG/CG:** Harvey-Bradshaw Index 2 (1–4) in CG and 2 (0–4) in IG • **How long have participants been on remission per IG/CG:** Inclusion criteria require at least 6 months of infliximab treatment for participation in study. • **Endoscoping disease scoring per IG/CG:** not reported

Jorgensen 2017 (NORSWITCH) *(Continued)*

	Age at beginning of study per IG/CG: mean(SD) years IG: 39.5 (14.2), CG: 38.0 (13.4) **Sex per IG/CG:** Females IG - 30 (39%) CG - 33 (42%). Males IG - 47 (61%) CG - 45 (58%) **Smoking per IG/CG:** NR **Number randomised per IG/CG:** 78 in CG and 77 in IG **Number reaching end of study per IG/CG:** CG - 71 IG - 71
Interventions	**IG:** Patients were switched to biosimilar CT-P13 infusions at the same dose and intervals as their pre-randomisation infliximab regimen. **CG:** The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation. **Duration of study:** 52 weeks, extension study 78 weeks **Measurement time points during study:** Data were collected at infusion visits. The number of visits differed according to treatment regimen, ranging from 14 visits for patients with treatment every 4 weeks to five visits for patients with treatment every 12 weeks. **Any follow-up measurements after study end? If yes, what time points?:** The patients who completed the main study period (week 0 to week 52) were recruited to the open, 26-week follow-up extension trial (week 52 to week 78).
Outcomes	**Primary outcomes as defined by study authors:** disease-worsening during follow-up according to worsening in disease-specific composite measures or a consensus about disease-worsening between investigator and patient leading to major change in treatment. Disease-worsening according to disease-specific composite measures was defined as change from baseline in Harvey-Bradshaw Index of 4 points or more and a total score of 7 points or greater points for Crohn's disease. **Secondary outcomes as defined by study authors:** Secondary endpoints included time to disease-worsening, study drug discontinuation, overall remission status based on the main composite measures, changes (follow-up minus baseline) in investigator and patient global assessments, and changes in erythrocyte sedimentation rate and C-reactive protein (full details of secondary endpoints are provided in the appendix pp. 4, 20). Prespecified secondary endpoints for Crohn's disease and ulcerative colitis were change and remission status of Harvey-Bradshaw Index and Partial Mayo Score, as well as changes in faecal calprotectin levels
Notes	**Funding source:** This trial was supported by a direct grant from the Norwegian Government, by the Ministry of Health and Care Services. **Conflicts of interest:** KKJ reports personal fees from Tillott, Intercept, and Celltrion. ICO reports grants from Norwegian Ministry of Health and Care Services during the conduct of the study. GLG reports personal fees from Orion Pharma, Pfizer, Novartis, and AbbVie. ML reports personal fees from Novartis. NB reports personal fees received from Orion Pharma (advisory board), Napp Pharmaceuticals (lecture), Pfizer (advisory board), and Takeda (lecture, booklet co-authorship). EAH reports grants from AbbVie, Pfizer, UCB, Roche, and MSD. KEAL reports grants from MSD, and personal fees from Takeda, Orion, AbbVie, Pfizer, and MSD. CM reports personal fees from Novartis Norge AS, LEO Pharma AS, ACO Hud Norge AS, Cellgene AS, Abbvie, and Galderma Nordic AB. JJ has served as a speaker, consultant or advisory board member for MSD, AbbVie, Celltrion, Orion Pharma, Takeda, Napp Pharm, AstroPharma, Hikma, and Pfizer. TKK reports grants from the Norwegian Ministry of Health and Care Services during the conduct of the study and personal fees from AbbVie, Biogen, BMS, Boehringer Ingelheim, Celltrion, Eli Lilly, Epirus, Janssen, Merck-Serono, MSD, Mundipharma, Novartis, Oktal, Orion Pharma, Hospira/Pfizer, Roche, Sandoz, and UCB Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jorgensen 2017 (NORSWITCH) *(Continued)*

Random sequence generation (selection bias)	Low risk	This was computer-generated randomised as stated by the authors.
Allocation concealment (selection bias)	Low risk	Author stated "computer-generated randomised allocation sequence was imported into the electronic case report form (eCRF) system (Viedoc; version 3.20) and made available exclusively to the study nurse authorised by the local principal investigator to prepare infusions". The author has confirmed the nurse was unrelated to the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Author stated "site person authorised for infusion preparation logged into the eCRF system to reveal the allocation, prepared allocated treatment in identical infusion bags, and applied labels with patient number and dose" and specified that the "following personnel were not masked to treatment allocation: the statistician preparing the randomised allocation sequence; the data manager importing the allocation sequence into the eCRF system and providing access to the allocation sequence; and site personnel authorised to prepare study treatment". Author further stated "All individuals providing patient care were masked to treatment allocation, including investigators, nurses giving infusions, and personnel assessing outcomes. Monitors and patients were also masked to treatment allocation".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Author stated: "All individuals providing patient care were masked to treatment allocation, including investigators, nurses giving infusions, and personnel assessing outcomes. Monitors and patients were also masked to treatment allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition in both groups balanced and all numbers were accounted for with clear reasons provided.
Selective reporting (reporting bias)	Low risk	The author reported according to their method section on Harvey Bradshaw Index (HBI) for Crohn's Disease.
Other bias	Low risk	Baseline characteristics for each group reported and balanced. No other apparent sources of bias

Louis 2022 (SPARE)

Study characteristics	
Methods	**Study design:** RCT **Single-centre or multicentre:** multicentre (64 centres) **Countries:** France, United Kingdom, Belgium, Sweden, Australia, Germany and The Netherlands **Study chronology:** NR **Setting:** hospitals
Participants	**Active or inactive disease at beginning of study?** Inactive **Inclusion criteria:** CD patients treated with a combination therapy of infliximab (IFX) and anti-metabolite > 8 months and in sustained steroid-free remission > 6 months **Exclusion criteria:** NR **Baseline disease characteristics**

Louis 2022 (SPARE) *(Continued)*

- **Fistulating disease:** NR
- **Location of disease**: NR
- **Duration or length (years) of disease since diagnosis**: median(IQR) Group 1: 6.4(3.2-12.7), group 2: 6.7(3.3-10.7), group 3: 6.8(2.8-12.7)
- **How was remission achieved?** Combination therapy of infliximab (IFX) and anti-metabolite
- **Current remission activity score if reported:** NR
- **How long have they been on remission:** > 6 months
- **Endoscoping disease scoring:** CDEIS median (IQR): Group 1: 0(0-0), group 2: 0(0-0), group 3: 0 (0-0)

Age (years) at beginning of study per IG/CG: median (IQR): Group 1: 36(27-45.5), group 2: 32(25-42.5), group 3: 31(26-44)

Sex (m/f) per IG/CG: Group 1: 41/30, group 2: 43/28, group 3: 38/31

Smoking per IG/CG: NR

Number randomised per IG/CG: Group 1: 71, group 2: 71, group 3: 69

Number reaching end of study per IG/CG: Group 1: 48, group 2: 52, group 3: 45

Interventions

Group 1: Continuing combination therapy (infliximab + anti-metabolite). If the patient relapses, inflixmab therapy was intensified to 10mg/kg/8 weeks.

Group 2: Continuing anti-metabolite (discontinuing infliximab). If patients relapsed, they were given infliximab 5 mg/kg infusion. If no remission at 4 weeks, reinfusion at 10 mg/kg and then back to 5 mg/kg. If further relapse, same as group 1

Group 3: Continuing infliximab (discontinuing anti-metabolite). If the patient relapsed, inflixmab therapy was intensified to 10 mg/kg/8 weeks, same as group 1. If no remission, anti-metabolite was restarted.

Duration of study: 2 years

Measurement time points during study: 2 years

Any follow-up measurements after study end? If yes, what time points? No

Outcomes

Primary outcomes as defined by study authors:

1. Relapse rate over 2 years: CDAI >= 250 at any visit or between 150-250 with an increase of > 70 points over two consecutive visits one year apart, with a CRP > 5 mg/L and faecal calprotectin > 250 µg/g
2. Mean survival time spent in remission over 2 years

Secondary outcomes as defined by study authors:

A major secondary endpoint was treatment failure (complications or not recapturing remission).

Notes

Funding source: EU Horizon 2020 Grant, GETAID

Conflicts of interest: NR

The author was contacted on 21 March 2022 and no response was received.

The primary reference for this study was identified during the update search and the pre-publication abstract has been used for the data extraction. The additional information will be included in future updates of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement

Louis 2022 (SPARE) *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported in the abstract. This will be updated with the full-text information when this review is updated.
Allocation concealment (selection bias)	Unclear risk	Not reported in the abstract. This will be updated with the full-text information when this review is updated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Equal attrition between groups, however, the reasons are unclear. This will be updated with the full-text information when this review is updated.
Selective reporting (reporting bias)	Unclear risk	The outcome results have not been clearly presented per the trial registration or abstract. This will be updated with the full-text information when this review is updated.
Other bias	Low risk	The presented baseline characteristics were similar between groups. This will be updated with the full-text information when this review is updated.

Rutgeerts 1999

Study characteristics	
Methods	**Study design:** randomised, double-blind, placebo-controlled, parallel-group clinical trial **Single-centre or multicentre?:** Multicentre (17 centres) **Countries:** North America and Europe **Study chronology:** NR **Setting:** Hospital
Participants	**Active or inactive disease at beginning of study?:** active, CDAI between 220 and 400 **Inclusion criteria:** Before enrolment in the initial trial, patients were required to have had Crohn's disease for at least 6 months, with a CDAI between 220 and 400. Acceptable regimens for inclusion in the study were as follows: mesalamine, ≥ 8 weeks' duration and at a stable dosage for 4 weeks before screening; oral corticosteroids, ≥ 8 weeks' duration at a stable dosage for 2 weeks, with a maximum dosage of 40 mg/day; and 6-mercaptopurine or azathioprine, ≥ 6 months' duration at a stable dosage for 8 weeks. In addition, patients who had not responded to aminosalicylates, 6-mercaptopurine, azathioprine, methotrexate, or cyclosporine were eligible for the study. **Exclusion criteria:** Patients treated with methotrexate, cyclosporine, or experimental agents were excluded from the study. Exclusion criteria included symptomatic stenosis or ileal strictures; proctocolectomy, total colectomy, or stoma; a history of allergy to murine proteins; prior administration of murine, chimeric, or humanised monoclonal antibodies; or treatment with parenteral corticosteroids or adrenocorticotrophic hormone within 4 weeks before screening. **Baseline characteristics**

Rutgeerts 1999 *(Continued)*

	· **Fistulating disease per IG/CG:** NR · **Location of disease (ileal, colonic, etc.) per IG/CG:** CG (n = 36), ileum and colon 17 (47.2%), colon only 14 (38.9%), ileum 5 (13.9%). IG (n = 37), ileum and colon 17 (47.2%), colon only 14 (38.9%), ileum 5 (13.9%) · **Duration or length (months/years) of disease since diagnosis per IG/CG:** CG (n = 36) 12.1 years (0.3-32.8 range) CG (10 mg/kg) retreatment (n = 37) 9.4 years (1.1-30.8) ·**How was remission achieved (specific medications, specific demographics if offered) per IG/CG?:** IG - 5, 10 or 20 mg/kg infliximab, CG - placebo · **Current remission activity score if reported per IG/CG:** NR · **How long have participants been on remission per IG/CG:** NR ·**Endoscoping disease scoring per IG/CG:** NR **Age at beginning of study per IG/CG:** CG median - 39 y.o., range (20–65) IG median 34 y.o, range (20–64) **Sex per IG/CG:** CG (n = 36) female 13 (36.1%) male 23 (63.9%) IG (n = 37) female 22 (59.5%) male 15 (40.5%) **Smoking per IG/CG:** Not reported **Number randomised per IG/CG:** 73 total. CG - 36, IG - 37 **Number reaching end of study per IG/CG:** IG - 35, CG - 35
Interventions	**IG :** Infliximab (10 mg/kg) 4 intravenous infusions at weeks 12, 20, 28, and 36 **CG:** Placebo 4 intravenous infusions at weeks 12, 20, 28, and 36 **Duration of study:** 48 weeks **Measurement time points during study:** CDAI, IBDQ, CRP, measurements 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 weeks Serum infliximab, HACA measurements 0, 4, 8, 12, 20, 28, 36, 40, 44, 48 weeks **Any follow-up measurements after study end? If yes, what time points:** NR
Outcomes	**Primary outcomes as defined by study authors:** Efficacy evaluations included the number of patients maintaining a clinical response (defined as a ≥ 70-point decrease in the CDAI) at each 4-week evaluation, clinical remission (defined as a CDAI, 150) at each 4-week evaluation, and the proportion of patients who discontinued because of lack of efficacy. **Secondary outcomes as defined by study authors:** NR
Notes	**Funding source:** Centocor **Conflicts of interest:** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned in a 1:1 ratio to retreatment with 10 mg/kg infliximab or placebo at week 12 by an independent organization".

Rutgeerts 1999 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Randomly assigned in a 1:1 ratio to retreatment with 10 mg/kg infliximab or placebo at week 12 by an independent organization".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Investigators, all other study personnel, and patients were kept blinded at the time patients were determined to be eligible for the retreatment extension".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators, all other study personnel, and patients were kept blinded at the time patients were determined to be eligible for the retreatment extension".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition were explained. There was a small imbalance between groups but this did not affect outcomes.
Selective reporting (reporting bias)	Unclear risk	No prespecified plan or trial registration
Other bias	Low risk	Baseline characteristics were reported for each treatment group and balanced. No other apparent source of bias

Sands 2004 (ACCENT II)

Study characteristics	
Methods	**Study design:** multicentre, double-blind, randomised, placebo-controlled trial **Single-centre or multicentre?:** Multicentre, 45 sites **Countries:** 34 centres in North America, 9 in Europe, and 2 in Israel **Study chronology:** January 21, 2000-October 17, 2001 **Setting:** Hospital
Participants	**Active or inactive disease at beginning of study?:** Mixed disease activity **Inclusion criteria:** included men and women (patients 18 years of age or older) with Crohn's disease who had single or multiple draining fistulas, including perianal fistulas and enterocutaneous fistulas, for at least three months. Women with rectovaginal fistulas were included if they had at least one other enterocutaneous draining fistula. Setons were permitted at screening but were required to be removed by week 2. Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate, and antibiotics, were permitted. **Exclusion criteria:** excluded from the study if they had a stricture or abscess for which surgery might be indicated or if they had previously been treated with infliximab **Baseline characteristics:** • **Fistulating disease per IG/CG:** Numbers with 1 fistula: CG - 42 IG - 38; Numbers with > 1 fistulas: CG - 57 IG - 58 • **Location of disease per IG/CG:** CG – ileum 16 (16%), colon 30 (30%), ileum and colon 53 (54%). IG - Ileum 18 (19%), colon 34 (35%), ileum and colon 44 (46%) • **Duration or length:** CG- 12.3 years (0.5–31.6) range. IG- 10.5 years (0.2–32.2) range

Sands 2004 (ACCENT II) *(Continued)*

	·**How was remission achieved:** 306 patients enroled and given 5 mg of infliximab/kg at weeks 0, 2, and 6 ·**Current remission activity score per IG/CG:** CG - CDAI score ≥ 150 57 (59%); CDAI score ≥ 220 31 (32%). IG- CDAI score ≥ 150 57 (59%); CDAI score ≥ 220 33 (34%) · **How long have participants been on remission per IG/CG:** not reported · **Endoscoping disease scoring per IG/CG:** not reported **Age at beginning of study per IG/CG:** median (IQR) yearsCG 36 (29–46), IG 37 (28–47) **Sex per IG/CG:** CG - male 48 (49%) IG -male 53 (55%) **Smoking per IG/CG:** CG – nonsmoker 41 (41%), former smoker 20 (20%), current smoker 38 (38%). IG - non-smoker 34 (35%), former smoker 19 (20%), current smoker 43 (45%) **Number randomised per IG/CG:** CG 96 IG 99 **Number reaching end of study per IG/CG:** Unclear. AEs leading to discontinuation: CG 12, IG 5
Interventions	**IG** IG1 - responder + infliximab (5 mg/kg) maintenance - 96 IG2 - nonresponder + infliximab (5 mg/kg) maintenance - 43 **CG** CG1 - responder + placebo - 99 CG2 - nonresponder + placebo - 44 **Duration of study:** 54 weeks **Measurement time points during study:** Patients were assessed at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 54. Fistula examinations were conducted at each visit. The Crohn's Disease Activity Index was determined at weeks 0, 14, 30, and 54. **Any follow-up measurements after study end? If yes, what time points?:** not reported
Outcomes	**Primary outcomes as defined by study authors:** The primary analysis was the time to the loss of response amongst patients who had a response at week 14 and underwent randomisation. **Secondary outcomes as defined by study authors:** Patients without a response were also randomly assigned to a maintenance regimen of either placebo or infliximab to permit a secondary analysis of the proportion of patients who had a response to continued treatment after having had no response to the initial treatment.
Notes	**Funding source:** Presented in part at the American Gastroenterological Association Digestive Disease Week in San Francisco, May 19–22, 2002, and in Orlando, Fla., May 17–22, 2003, and at the United European Gastroenterology Week in Geneva, October 19–23, 2002. Supported by Centocor. Dr. Sands was supported in part by a grant (K23 DK002850) from the National Institutes of Health. Dr. Sands reports having served as a paid consultant on advisory boards to Centocor, Elan/Biogen, Protein Design Labs, Celltech, Otsuka America Pharmaceutical, and Berlex and having received lecture fees from Centocor and AstraZeneca and grant support from Centocor, Abbott, and Elan. Dr. Anderson reports having received consulting fees from Bristol-Myers Squibb, Hoffmann–LaRoche, Agouron, and Axcan Pharma and lecture fees from Schering Canada, Hoffmann–LaRoche, and Glaxo-Welcome. Dr. Bernstein reports having received consulting fees from Elan, Abbott, and Novartis Canada, owning stock in Pfizer, and having received grant support from Ferring Canada. Dr. Feagan reports having received consulting and lecture fees from Centocor and Schering-Plough. Dr. Fedorak reports having received consulting fees from Abbott, Celltech, and Serono and grant support from Centocor, Abbott, Serono, Millennium Pharmaceuticals, and Wyeth. Dr. Korzenik reports having received consulting fees from Amgen, Isis Pharmaceuticals, Berlex, and Incara, lecture fees from Centocor, Procter & Gamble, and Berlex, and

Sands 2004 (ACCENT II) *(Continued)*

grant support from Rhodia. Dr. Lashner reports having received lecture fees from AstraZeneca, Procter & Gamble, and Prometheus Laboratories. Dr. Onken reports owning stock in Schering-Plough. Dr. Rutgeerts reports having received consulting and lecture fees from Centocor, Schering-Plough, Celltech, Serono, and Elan/Biogen and grant support from Centocor and Schering-Plough. Dr. Wild reports having received consulting and lecture fees from Schering Canada. Dr. Wolf reports having received consulting fees from Centocor, AstraZeneca, Janssen, and Otsuka America Pharmaceutical. Dr. van Deventer reports having received consulting fees from Centocor, Schering-Plough, Merix Bioscience, Elan, Biogen, and Serono, owning stock in Merix Biosciences and Amsterdam Molecular Therapeutics, having received lecture fees from Centocor, Schering-Plough, AstraZeneca, and Elan, and having received grant support from Centocor, Protein Design Labs, Serono, and Genzyme. Mr. Marsters, Dr. Travers, and Dr. Blank are employees of Centocor and own Johnson & Johnson stock options.

Conflicts of interest: As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated adaptive randomisation scheme was used, which included the study site, the number of draining fistulas at baseline (one vs. more than one), and the presence or absence of active bowel disease at baseline (active bowel disease was considered to be present if the Crohn's Disease Activity Index was at least 150) as stratification factors.
Allocation concealment (selection bias)	Low risk	A pharmacist prepared each infusion of infliximab or an identical placebo. Neither the patients nor the study investigators were aware of the treatment assignment. Cross-overs were masked so that patients and physicians remained unaware of the treatment assignment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A pharmacist prepared each infusion of infliximab or an identical placebo. Neither the patients nor the study investigators were aware of the treatment assignment. Cross-overs were masked so that patients and physicians remained unaware of the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether the clinicians conducting the assessments and examinations at study visits were blinded to treatment assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and balanced attrition with no influence on outcomes
Selective reporting (reporting bias)	High risk	The reported outcomes have shifted from those published in the trial registration (NCT00207766).
Other bias	Low risk	Baseline characteristics are balanced across the study arms. No other concerns

Schreiber 2021

Study characteristics

Methods	**Study design:** randomised, multicentre, open-label, parallel-group, phase I study **Single-centre or multicentre?:** Multicentre **Countries:** 62 hospitals and clinical study centres in 16 countries

Schreiber 2021 *(Continued)*

	Study chronology: Patients screened 27th March, 2018-8th August, 2018 Study visits 7th May, 2018; 2nd October, 2019 Follow-up for all patients: 17th January, 2020 **Setting:** Hospital
Participants	**Active or inactive disease at beginning of trial:** Mixed disease activity **Inclusion criteria:** 1. Patient had CD with a score on the CDAI of 220–450 points. 2. Patient had met ≥ 1 of the following at screening: 1. C-reactive protein (CRP) concentration > 0.5 mg/dL 2. Faecal calprotectin (FC) > 100 µg/g 3. Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) of ≥ 6 points for ileal-colonic CD or ≥ 4 points including ulcer score from ≥ 1 segment for ileal CD or colonic CD 4. Patients had CD of ≥ 3 months' disease duration prior to first administration of study drug (Day 0). 5. Patient had been treated for active CD but had not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant, or was intolerant to or had medical contraindications for such therapies. 6. Patient was either on stable doses or currently not receiving (during specified time frame) the following CD medication: · AZA or 6-MP for ≥ 8 weeks prior to day 0 · Methotrexate for ≥ 6 weeks prior to day 0 · Oral corticosteroids at the equivalent dose of ≤ 20 mg/day of prednisone for ≥ 2 weeks prior to day 0 · Oral budesonide at the dose of ≤ 6 mg/day for ≥ 4 weeks prior to day 0 · 5-ASA for ≥ 4 weeks prior to day 0 **Exclusion criteria:** 1. Patient had previously received a biologic agent for the treatment of UC or CD and/or a tumour necrosis factor-α inhibitor for the treatment of other diseases. 2. Patient had allergies to any of the excipients of infliximab or any other murine and/or human proteins, or patient with a hypersensitivity to immunoglobulin products. 3. Patient had a current or past history of the following infections: · A known infection with human immunodeficiency virus, hepatitis B, or hepatitis C (carriers of hepatitis B and hepatitis C were not permitted to enrol into the study, but patients with resolved past hepatitis B infection could be enroled) · Acute infection requiring oral antibiotics ≤ 2 weeks or parenteral injection of antibiotics ≤ 4 weeks prior to day 0 · Other serious infection ≤ 6 months prior to day 0 · Recurrent herpes zoster or other chronic or recurrent infection ≤ 6 weeks prior to day 0 · Past or current granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis). A patient who had a

Schreiber 2021 *(Continued)*

past diagnosis of those infections with sufficient documentation of complete resolution could be enroled.

4. Patient had received or planned to receive any of following prohibited medications or treatments:

· Any biological agents for the treatment of UC or CD

· Parenteral corticosteroids for the treatment of UC or CD ≤ 2 weeks prior to screening

· Antibiotics for the treatment of UC or CD ≤ 2 weeks prior to day 0

· Alkylating agents ≤ 12 months prior to day 0

· Thalidomide, tacrolimus, or cyclosporine ≤ 3 months prior to day 0

· Live or live-attenuated vaccine ≤ 4 weeks prior to day 0

· Abdominal surgery, including but not limited to, for active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection, or intra-abdominal or pancreatic abscess requiring surgical drainage ≤ 6 months prior to day 0

· Subtotal and total colectomy prior to day 0

· Use of parenteral nutrition ≤ 1 month prior to day 0

· Use of exclusive enteral nutrition for > 3 consecutive days within a month or any single day of exclusive enteral nutrition ≤ 2 weeks prior to day 0

5. Patient had a medical condition including ≥ 1 of the following:

· Diagnosed with obstruction by imaging or clinical symptoms (e.g. abdominal distension or vomiting) highly suggestive of small bowel obstruction

· Diagnosed with short bowel syndrome

· Stoma (e.g. ileostomy or colostomy) ≤ 6 months prior to day 0

· Classified as obese (body mass index ≥ 35 kg/m^2)

· Uncontrolled diabetes mellitus, even after insulin treatment

· Uncontrolled hypertension (as defined by systolic blood pressure (BP) ≥ 160 mmHg or diastolic BP ≥ 100 mmHg)

· History of any malignancy ≤ 5 years prior to day 0 except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma

· History of lymphoma or lymphoproliferative disease or bone marrow hyperplasia

· New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram abnormalities), or myocardial infarction ≤ 6 months prior to day 0

· History of organ transplantation, including corneal graft/transplantation

· Any uncontrolled, clinically significant respiratory disease (in the opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion

· Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain–Barré syndrome

6. Patient had a current or past history of drug or alcohol abuse.

Schreiber 2021 *(Continued)*

	7. Patient had had treatment with any other investigational device or medical product ≤ 4 weeks prior to day 0 or 5 half-lives, whichever was longer. 8. Female patient was pregnant, breastfeeding, or planned to become pregnant or breastfeed within 6 months of the last dose of study drug. 9. Patient who, in the opinion of his or her general practitioner or investigator, should not have participated in the study **Active CD exclusion criteria** 1. Patient had active entero-vesical, entero-retroperitoneal, entero-cutaneous, and entero-vaginal fistulae ≤ 6 months prior to day 0. Entero-enteral fistulae without clinically significant symptoms (per investigator's opinion) and anal fistulae without draining problems were allowed. 2. Patient had > 3 small bowel resection procedures prior to day 0. **Baseline characteristics** ·**Fistulating disease per IG/CG:** NR · **Location of disease (ileal, colonic, etc.) per IG/CG:** NR ·**Duration or length (months/years) of disease since diagnosis per IG/CG:** mean (SD) IG 5.70 (6.01) CG 5.85 (6.29) · **How was remission achieved:** Induction phase with intravenous CT-P13 · **Current remission activity score if reported per IG/CG:** CDAI IV - 296.38 (59.21) SC - 294.75 (59.90) ·**How long have participants been on remission per IG/CG:** not in remission · **Endoscoping disease scoring per IG/CG:** NR **Age at beginning of study per IG/CG:** CG - 34.0 (18–69) IG 35.0 (19–53) **Sex per (m/f) IG/CG:**: SC 16/12, IV 11/14 **Smoking per IG/CG:** NR **Number randomised per IG/CG:** SC 28 IV 25 **Number reaching end of study per IG/CG:** SC 28 IV 25
Interventions	**IG** CT-P13 SC was administered via prefilled syringe containing 120 mg CT-P13 SC (SC group) **CG:** CT-P13 IV (5 mg/kg) was administered as a 2-hour (+15 minutes) IV infusion (IV group) **Duration of study:** 54 weeks **Any follow-up measurements after study end? If yes, what time points?:** NR
Outcomes	**Primary outcomes as defined by study authors:** The primary endpoint was a pharmacokinetic endpoint. Specifically, it was defined as non-inferiority of observed predose concentration of CT-P13 at week 22 for CT-P13 SC vs CT-P13 IV. **Secondary outcomes as defined by study authors:** efficacy, pharmacokinetics, biomarker responses, and safety (including immunogenicity) of CT-P13 SC and CT-P13 IV over the first 30 weeks, and of CT-P13 SC (including switching results from the CT-P13 IV arm) up to W54.
Notes	**Funding source:** The study was funded by Celltrion, Inc. (Incheon, Republic of Korea). The sponsor contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; and the preparation, review, and approval/decision to submit the manuscript. All au-

Schreiber 2021 *(Continued)*

thors, including employees of the sponsor, provided intellectual contribution to the manuscript development.

Conflicts of interest: These authors disclose the following: Stefan Schreiber has received personal fees from AbbVie, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Inc., Falk, Fresenius, Gilead, IMAB, Janssen, MSD, Mylan, Pfizer, Protagonist, Provention Bio, Takeda, and Theravance outside the submitted work. Shomron Ben-Horin has received consultancy/advisory board fees from AbbVie, Celltrion, Falk, Ferring, GSK, Janssen, Pfizer, and Takeda, and research support from AbbVie, Celltrion, Janssen, Pfizer, and Takeda. Jaroslaw Leszczyszyn has received speaker's fees from Astra Zeneca, MSD, and Janssen. Robert Dudkowiak has received investigator fees from AbbVie, Ferring, GSK, Janssen, and Pfizer. Adi Lahat has received consultancy or advisory board fees from AbbVie, Celltrion, and Takeda. Beata GawdisWojnarska has received fees from Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Inc., Gilead, Harbor, Janssen, Pfizer, Shire, Takeda, and Theravance. Aldis Pukitis has served as a consultant for AbbVie, Johnson & Johnson, and Takeda. Katalin Farkas has received advisory board fees from Bayer. Jaroslaw Kierkus has received consultation fees, research grants, or honoraria from AbbVie, Egis, Janssen, Nestlé, Nutricia, and Takeda. Sang Joon Lee, Sung Hyun Kim, Jee Hye Suh, Mi Rim Kim, and Seul Gi Lee are employees of Celltrion, Inc. Byong Duk Ye has received a research grant from Celltrion and Pfizer Korea; consulting fees from AbbVie Korea, Celltrion, Chong Kun Dang Pharm., Daewoong Pharma., Ferring Korea, IQVIA, Janssen Korea, Kangstem Biotech, LG Chem, Medtronic Korea, Shire Korea, Takeda, and Takeda Korea; speaking fees from AbbVie Korea, Celltrion, Ferring Korea, IQVIA, Janssen Korea, Pfizer Korea, Shire Korea, and Takeda Korea. Walter Reinisch has served as a speaker for Abbott Laboratories, AbbVie, AESCA, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; as a consultant for 4SC, Abbott Laboratories, AbbVie, AESCA, Algernon, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, AstraZeneca, Avaxia, Roland Berger, Bioclinica, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Cellerix, ChemoCentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, DSM, Elan, Eli Lilly, Ernst & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, MEDahead, MedImmune, Millennium, Mitsubishi Tanabe Pharma, MSD, Nash Pharmaceuticals, Nestlé, Nippon Kayaku, Novartis, Ocera, OMass, Otsuka, PAREXEL, PDL, PERI Consulting, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Protagonist, Provention, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, SetPoint Medical, Sigmoid, Sublimity, Takeda, Therakos, Theravance, TiGenix, UCB, Vifor, Zealand, and Zyngenia; as an advisory board member for 4SC, Abbott Laboratories, AbbVie, AESCA, Amgen, AM Pharma, Astellas, AstraZeneca, Avaxia, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Cellerix, ChemoCentryx, Celgene, Centocor, Celltrion, Danone Austria, DSM, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millennium, Mitsubishi Tanabe Pharma, MSD, Nestlé, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, SetPoint Medical, Takeda, Therakos, TiGenix, UCB, Zealand, and Zyngenia; and has received research funding from Abbott Laboratories, AbbVie, AESCA, Centocor, Falk Pharma, Immundiagnostik, and MSD. The remaining authors disclosed no conflicts.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done using an interactive web response system, following a randomisation schedule generated by a biostatistician.
Allocation concealment (selection bias)	Low risk	Randomisation was done using an interactive web response system, following a randomisation schedule generated by a biostatistician.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not conducted because of the open-label study design.

Schreiber 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not conducted because of the open-label study design.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and balanced attrition. Reasons explained. No influence on outcomes
Selective reporting (reporting bias)	Low risk	Reported per the trial registration (NCT02883452)
Other bias	Low risk	Balanced baseline characteristics

VanAssche 2012 (SWITCH)

Study characteristics	
Methods	**Study design:** Open-label randomised trial. **Single-centre or multicentre?** Single-centre **Countries :** Belgium **Study chronology:** NR **Setting:** University Hospitals
Participants	**Active or inactive disease at beginning of study?** Mix, CDAI had to be < 200 **Inclusion criteria:** Men and women aged >= 18 years with luminal Crohn's disease treated with scheduled infliximab maintenance therapy started at least 6 months before without episodic use during that time period were eligible. A durable complete clinical response with stable infliximab dosing intervals of at least 6 weeks for the last 6 months was required. Complete response was defined by physician global assessment of signs and symptoms, but the CDAI at baseline had to be < 200. **Exclusion criteria:** Patients with a draining abdominal enterocutaneous fistula, with a medical condition or laboratory tests precluding further anti-TNF therapy, with previous exposure to ADA, receiving Infliximab doses > 5mg/kg intravenously and those with an imminent need for surgery **Baseline disease characteristics** • **Fistulating disease:** NR • **Location of disease** (ileal, colonic, etc.): **Ileal – CG-IFX** 7/37 (18.92%) **IG-ADA** 3/36 (8.33%). **Colonic – CG-IFX** 11/37 (29.73%) **IG-ADA** 7/36 (19.44%). **Ileocolonic – CG-IFX** 19/37 (51.35%) **IG-ADA** 26/36 (72.22%) • **Duration or length of disease (months) since diagnosis, median (IQR) CG-IFX** 146 (116-218). **IG-ADA** 167 (76-213) • **How was remission achieved:** CG- adalimumab 5 mg/kg intravenously at the same interval for 56 weeks; IG - inflixmab 5 mg/kg intravenously at the same interval for 56 weeks • **How long have they been on remission:** NR • **Current remission activity score: CDAI [median (IQR)]: CG-IFX** 58 (34-122) **IG-ADA** 48 (24-110) • **Endoscoping disease scoring**: NR **Age at beginning of study per IG/CG[median (IQR)]: CG-IFX** 37 (29-42) **IG-ADA** 38 (27-47) **Sex(m/f) per IG/CG:** IG: 17/37 CG:18/36 **Smoking per IG/CG:** Current smoker CG-IFX 11/37 (30%) IG-ADA 9/36 (25%)

VanAssche 2012 (SWITCH) *(Continued)*

	Number randomised per IG/CG: IG: 36, CG: 37 **Number reaching end of study:** IG: 26, CG: 36
Interventions	**IG-ADA** 80 mg subcutaneous adalimumab at inclusion and 40 mg subcutaneous adalimumab every other week for 54 weeks. Patients with disease flare were allowed dose intensification – step-up to 40 mg every week. If complete loss of response, patients were allowed to switch over to the alternative treatment. Short (4-week) courses of steroids were also allowed per protocol. **CG-IFX** Continue infliximab 5 mg/kg intravenously at 8-week intervals for 56 weeks. Patients with disease flare were allowed dose intensification – decrease of dosing interval with 2-week decrements. Short (4-week) courses of steroids were also allowed per protocol. **Duration of study**: 56 weeks **Measurement time points during study:** Weeks 8, 16, 24, 32, 40, 48, 46 **Any follow-up measurements after study end? If yes, what time-points?** NR
Outcomes	**Primary outcomes as defined by study authors:** The main endpoints of this trial were **(i)** the proportion of patients in the ADA group preferring ADA over IFX and **(ii)** the proportion of patients who needed rescue therapy with short courses of steroids or intensified anti-TNF dosing or who had to stop the assigned anti-TNF agent. **Secondary outcomes as defined by study authors: (i)** The proportion of patients with an injection- or infusion-related reaction AND **(ii)** the proportion of patients with an increase in the CDAI of > 100 above baseline
Notes	**Funding source:** The design and conduct of the trial, data analysis and manuscript writing was performed independently by the authors. All authors had access to the data and decided to jointly submit the manuscript. Adalimumab serum levels were analysed by Abbot GMBH, Ludwigshafen, Germany. Adalimumab was provided for the patients in this trial by Abbott Belgium. **Conflicts of interest:** SV: grants/research support (UCB), consultancy (Astra-Zeneca, Ferring, Pfizer), speakers bureau (Schering-Plough, Abbott, Ferring, UCB), advisory committee (Shire, Ferring). PR: research grants, lecture fees, consultant fees (Abbott, Centocor, Schering-Plough, UCB). GVA: speaker fee/research support (Centocor, Schering-Plough, Abbott, UCB). GD'H: speaker fee/research support (Centocor, Schering-Plough, Abbott, UCB). The other authors had no conflicts of interest. **Professor Van Assche was contacted on 9 November 2021 and no response was received.**

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated "Random allocation was based on a centrally stored randomly generated list that was not accessible to the investigators".
Allocation concealment (selection bias)	Low risk	Authors stated "Random allocation was based on a centrally stored randomly generated list that was not accessible to the investigators".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study

VanAssche 2012 (SWITCH) *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors reported higher attrition in the adalimumab group (10/36) versus infliximab (1/37). Respective reasons were provided. There is a chance this might have affected outcomes.
Selective reporting (reporting bias)	Unclear risk	Trial registered NCT01338740. The authors reported the proportion of patients with specific CDAI score changes, however, the reporting of remission rates is unclear.
Other bias	Low risk	Baseline characteristics were reported for and balanced in both groups. No other apparent sources of bias

Volkers 2017 (SIMILAR)

Study characteristics	
Methods	**Study design :** Randomised, double-blind clinical trial **Single-centre or multicentre?** Multicentre (6 sites) **Countries**: The Netherlands **Study chronology:** NR **Setting:** Secondary care
Participants	**Active or inactive disease at beginning of study?:** Inactive disease **Inclusion criteria:** Patients eligible for inclusion had to be in clinical remission (HBI < 5 and MAYO < 2) and have a faecal calprotectin < 250 mg/g. **Exclusion criteria:** NR **Baseline disease characteristics** • **Fistulating disease:** NR • **Location of disease (ileal, colonic, etc.):** NR • **Duration or length of disease since diagnosis:** NR • **How was remission achieved (specific medications? surgery? specific demographics if offered?)** with infliximab - no other details • **How long have they been on remission**: NR • **Current remission activity score if reported**: NR • **Endoscoping disease scoring**: NR **Age at beginning of study per IG/CG:** NR **Sex(m/f) per IG/CG (numbers of patients):** NR **Smoking per IG/CG:** NR **Number randomised per IG/CG (numbers of patients):** NR **Number reaching end of study per IG/CG (numbers of patients):** NR
Interventions	**IG:** Infliximab biosimilar - Patients switched from infliximab-biological and received 4 to 6 doses of 5 mg/kg to 10 mg/kg of infliximab-biosimilar during the 30-week study period. **CG:** Infliximab biological – Patients continued infliximab-biological and received 4 to 6 doses of 5 mg/kg to 10 mg/kg of infliximab-biosimilar during the 30-week study period.

Volkers 2017 (SIMILAR) *(Continued)*

	Duration of study: NR **Measurement time points during study:** 30 weeks **Any follow-up measurements after study end? If yes, what time-points?** NR
Outcomes	**Primary outcomes as defined by study authors:** The primary endpoint was number of patients in remission at week 30. **Secondary outcomes as defined by study authors:** NR
Notes	**Funding source:** NR **Conflicts of interest:** All authors have declared no conflicts of interest. One author contacted on 27 September 2022. To his knowledge, there is no full report of the randomised results of this trial. He informed us that the data from the RCT have been used in the publication of a cohort study paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors did not describe how they achieved randomisation.
Allocation concealment (selection bias)	Unclear risk	Authors did not describe how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as a double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors provided the overall numbers of patients withdrawing in the abstract but did not specify how many had CD and, from the limited information provided, it is not possible to work out how many patients from each study arm withdrew. Authors only gave information on the primary outcome in the abstract but did not specify if it applied to CD or UC patients.
Selective reporting (reporting bias)	Unclear risk	Preliminary results; not all outcome results clearly reported Trial registration NCT02452151
Other bias	Unclear risk	No baseline information

ADA: adalimumab; AE: Adverse Events; BP: blood pressure; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index Score; CG: control group; CRP: C-reactive protein; def.: defined; FC: faecal calprotectin; HACA: human antichimeric antibodies; Hb: Haemoglobin; HBI: Harvey Bradshaw Index; Hgb: Haemoglobin; HIV: human immunodeficiency viruses ; IBDQ: Inflammatory Bowel Disease Questionnaire; IFX: Infliximab; IG: intervention group; IQR: Interquartile Range; IV: intravenous; MAYO: Mayo Score; MRI: Magnetic resonance imaging; NR: Not reported ; NYHA: New York Heart Association; pp: pages; SC: subcutaneous; SD: standard deviation; PBO: placebo; SES-CD: Simple Endoscopic Score Crohn's Disease; TNF: tumour-necrosis factor; UC: ulcerative colitis; WBC: white blood cells

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12614000903684	Wrong population
Baldassano 2003	Wrong population
Balzola 2012	Wrong study type (letter)
Bendix 2020	Wrong population (active disease)
Casteele 2012	Wrong intervention
Casteele 2013	Wrong intervention
Colombel 2008	Wrong population
Colombel 2010	Wrong population (induction study)
Cozijnsen 2016	Wrong population
D'Haens 2008	Wrong population
D'Haens 2018	Wrong population
Endo 2011	Wrong study type (review article)
EUCTR2004-002815-10-GB	Wrong population
EUCTR2008-006484-36-IT	Wrong population
EUCTR2011-003038-14-NL	Wrong population
Goll 2016	Wrong population
Goll 2017	Wrong population
Goll 2018	Wrong population
Goll 2019	Wrong population
Huang 2012	Wrong population
Hyams 2007	Wrong population
Hyams 2011	Wrong population
Keil 2016	Wrong population
Kim 2017	Wrong population
Kim 2017a	Wrong population
Kim 2017b	Wrong population

Study	Reason for exclusion
Lichtenstein 2011	Wrong population
Mantzaris 2004	Wrong population (induction RCT)
Matsui 2008	Wrong study type
Matsuoka 2018	Wrong intervention
NCT00094458	Wrong population
NCT00132899	Wrong intervention
NCT00207662	Wrong population
NCT00269841	Wrong population
NCT00269854	Wrong population
NCT00688636	Wrong population
NCT00752622	Wrong intervention
NCT00796250	Wrong population
NCT01442025	Wrong population
NCT01548014	Wrong population
NCT02096861	Wrong population
NCT02453776	Wrong intervention
NCT02522169	Wrong population
NCT03393247	Wrong population
NCT04835506	Wrong intervention
Perks 2017	Wrong study type
Present 1999	Wrong population (induction study)
Regueiro 2009	Wrong population
Regueiro 2009a	Wrong population
Regueiro 2015	Wrong population
Regueiro 2016	Wrong population (post-surgical)
Reinisch 2019	Wrong population
Roder 2018	Wrong study type (mice study)
Ruemmele 2009	Wrong population

Study	Reason for exclusion
Sandborn 2009	Wrong population
Sandborn 2009a	Wrong population
Schreiber 2018	Wrong population
Steenholdt 2015	Wrong intervention
Strik 2019	Wrong intervention
Strik 2021	Wrong intervention
Tursi 2014	Wrong population
Van de Casteele 2012	Wrong intervention
Van de Casteele 2013	Wrong intervention
Van de Casteele 2015	Wrong intervention
Wu 2016	Wrong population
Ye 2019	Wrong population (induction RCT)
Ye 2020	Wrong population

RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Chaparro 2023

Methods	RCT
Participants	140 patients with ulcerative colitis (UC) or Crohn's disease (CD) in clinical remission for > 6 months
Interventions	Anti-TNF treatment [maintenance arm (MA)] or to withdraw it [withdrawal arm (WA)]. Patients who were on infliximab (IFX) received IFX 5 mg/kg or an intravenous placebo every 8 weeks, while patients on adalimumab (ADA) received subcutaneous ADA 40 mg or placebo every other week.
Outcomes	Patients were followed up until 12 months or up to the time of clinical relapse, whichever came first.
Notes	This study was identified during the update search and will be included in future updates of this review.

Colombel 2023

Methods	RCT
Participants	Patients that responded to induction phase were re-randomised for maintenance at week 10.

Colombel 2023 *(Continued)*

Interventions	CT-P13 SC 120 mg (CT-P13 SC) or placebo every 2 weeks up to week 54
Outcomes	Clinical remission and endoscopic response were assessed as co-primary endpoints. Clinical response, clinical remission (alternative definition) endoscopic remission, and corticosteroid-free remission were assessed at week 54 as key secondary endpoints. Safety was evaluated up to week 54.
Notes	This study was identified during the update search for this review and will be included in future updates.

NTR1404

Methods	RCT
Participants	130
Interventions	Infliximab monotherapy Azathioprine monotherapy
Outcomes	Primary Occurrence of relapse - defined as a disease activity with a CDAI score greater than 150 - during the 12 months follow-up period Secondary 1. Mucosal healing at 12 months 2. Number of treatment failures after 12 months 3. Time to relapse 4. HRQOL at 12 months, measured by IBDQ
Notes	Open for patient inclusion Dr. E.J. Eshuis was contacted at e.j.eshuis@amc.nl.

ADA: adalimumab; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; CG: control group; FC: faecal calprotectin; HRQOL: Health-related quality of life; IBDQ: Inflammatory Bowel Disease Questionnaire; IFX: infliximab; IG: intervention group; IV: intravenous; MA: maintenance arm; RCT: randomised control trial; SC: subcutaneous; TNF: tumour-necrosis factor; UC: ulcerative colitis; WA: withdrawal arm

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12621001498886 (SISS trial)

Study name	Comparison between switching from intravenous to subcutaneous infliximab on the maintenance of clinical and biochemical remission in patients with inflammatory bowel disease
Methods	RCT
Participants	CD and UC patients
Interventions	IV vs SC infliximab
Outcomes	Composite primary outcome: Comparing the proportion of patients who remain in clinical remission [defined as partial Mayo score < 2 (for ulcerative colitis in SISS trial 1) or Harvey Bradshaw Index < 5 (for Crohn's disease in SISS trial 2) and biochemical remission [defined as C-reactive protein

ACTRN12621001498886 (SISS trial) *(Continued)*

	< 5 mg/L and/or faecal calprotectin < 150 µg/mL] in the intravenous (IV) infliximab group versus the subcutaneous (SC) infliximab group at week 48, AND having not met any of the following treatment endpoints: o Need for corticosteroids o Adding immunomodulator(s) o Need for dose-escalation of infliximab o Switching to another biological agent o Need for IBD surgery 11 secondary outcomes listed on the trial registration page
Starting date	Unclear (retrospectively registered)
Contact information	rupertleong@hotmail.com
Notes	

ACTRN12622001458729

Study name	DISCUS-IBD
Methods	RCT
Participants	Adult luminal CD or UC patients on maintenance escalated IV infliximab in clinical steroid-free remission for at least 6 months and biochemical remission at study entry
Interventions	IV infliximab vs subcutaneous infliximab
Outcomes	The primary outcome is rate of relapse between the two groups at week 48. Relapse is defined as composite clinical and objective activity OR need for corticosteroids, immunomodulator or switch in therapy OR need for IBD-related hospitalisation/surgery. Secondary endpoints will include changes in infliximab drug levels, anti-infliximab antibodies, economic impact, patient satisfaction and the change in clinical and biochemical markers of disease activity throughout the study.
Starting date	15 February 2023
Contact information	r.little@alfred.org.au; j.mckenzie@alfred.org.au
Notes	

Chaparro 2019

Study name	Anti-tumour necrosis factor discontinuation in inflammatory bowel disease patients in remission: study protocol of a prospective, multicentre, randomised clinical trial
Methods	RCT
Participants	194 patients (97 patients in each group)
Interventions	Patients in group 1 continue their current anti-TNF treatment (infliximab or adalimumab) while patients in group 2 are given a placebo matched to the drug they were previously receiving. That is, patients who were on infliximab receive an intravenous placebo, while patients who were receiv-

Chaparro 2019 *(Continued)*

	ing adalimumab receive a placebo administered subcutaneously. The placebo for infliximab is provided in the same pharmaceutical form and route of administration as the active drug, while the syringes for adalimumab and its placebo are masked, so they cannot be seen by the patient when the nurse is administering them. Infliximab (5 mg/kg) or infliximab placebo is administered every 8 weeks, while adalimumab (40 mg) or its placebo is administered every 2 weeks. Patients in both groups will continue to receive their usual immunosuppressant therapy (thiopurine or methotrexate).
Outcomes	The primary objective of this study is to compare the rates of clinical remission at 1 year in patients who discontinue treatment with an anti-TNF agent *versus* those who continue. Secondary endpoints being compared between the two groups include: the duration of relapse-free time; mucosal healing; quality of life (QoL) and work productivity; safety; and the identification of predictive factors for relapse.
Starting date	22 June, 2016
Contact information	javier.p.gisbert@gmail.com
Notes	The study was expected to finish in 2020 but is still ongoing.

EUCTR2019-001087-30

Study name	A randomised, placebo-controlled, double-blind, phase 3 study to evaluate the efficacy and safety of the subcutaneous injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active Crohn's disease
Methods	RCT
Participants	600
Interventions	CT-P13 versus placebo
Outcomes	Primary objective To demonstrate superiority of CT-P13 SC over placebo SC based on clinical remission and endoscopic response at week 54 Secondary objectives To evaluate additional efficacy, PK, pharmacodynamics (PD) and overall safety, including immunogenicity
Starting date	26 July, 2019
Contact information	Contact: sunghyun.kim@celltrion.com
Notes	-

KCT0007470

Study name	CHAMELEON Study
Methods	RCT

KCT0007470 *(Continued)*

Participants	Patients with Crohn's disease will be given IV (intravenous) infliximab 5 mg/kg at week 0 and 2. Then, they will be treated with SC (subcutaneous) infliximab every other week. At week 30, patients will be allocated to one of 3 arms according to their response to SC infliximab.
Interventions	[Arm 1] - Responders at week 30 will be randomly (1:1) allocated to one of the following two arms: [Arm 2] Switched to infliximab IV 5 mg/kg every 8 weeks or [Arm 3] Continued infliximab SC 120 mg every other week. CONDITION: Diseases of the digestive system
Outcomes	PRIMARY OUTCOME: Non-inferiority of arm 3 compared with arm 2 in terms of deep remission rate SECONDARY OUTCOMES: Corticosteroid-free clinical biochemical remission rate of each arm Corticosteroid-free clinical remission rate of each arm Corticosteroid-free clinical response rate of each arm Corticosteroid-free complete mucosal healing rate of each arm Corticosteroid-free endoscopic remission rate of each arm Non-inferiority of arm 3 compared with arm 1 in terms of deep remission rate Rate of anti-drug antibody positivity Safety evaluation (adverse events, vital signs, and laboratory results)
Starting date	30 September, 2022
Contact information	eunja.soul@gmail.com; bdye@amc.seoul.kr
Notes	

NCT02994836

Study name	
Methods	RCT
Participants	194
Interventions	Infliximab (infusion 5 mg/kg milligram(s)/kilogram-intravenous use) or adalimumab (subcutaneous 40 mg milligram(s)-subcutaneous) Physiological saline solution (infusion-intravenous use) or physiological saline solution (injection-subcutaneous use)
Outcomes	Primary: Sustained clinical remission after one year of follow-up Secondary: Clinical activity assessment Endoscopic activity assessment Radiologic activity assessment Quality of life assessment Work productivity and activity assessment Clinical activity assessment

NCT02994836 *(Continued)*	
	Endoscopic activity assessment
Starting date	
Contact information	
Notes	Active, not recruiting Javier MD Perez Gisbert, PhD, was contacted at javier.p.gisbert@gmail.com.

ADA: adalimumab; CD: Crohn's Disease; CG: control group; FC: faecal calprotectin; IBD: Inflammatory Bowel Disease; IFX: Infliximab; IG: intervention group; IV: intravenous; PD: pharmacodynamics; QoL: Quality of Life; SC: subcutaneous; SISS: SISS trial; TNF: tumour-necrosis factor; UC: ulcerative colitis

DATA AND ANALYSES

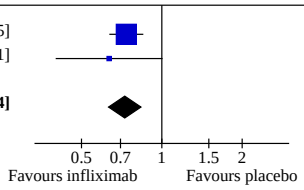
Comparison 1. Infliximab vs placebo (mixed disease activity population with clinical response at baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Clinical relapse	2	408	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.63, 0.84]
1.2 Loss of clinical response	1	73	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.96]
1.3 Loss of clinical response in patients with exclusively fistulating disease	1	195	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.60, 0.90]
1.4 Withdrawal due to adverse events	2	355	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.37, 1.19]
1.5 Serious adverse events	1	282	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 1.00]
1.6 Total adverse events	2	355	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.92, 1.03]

Analysis 1.1. Comparison 1: Infliximab vs placebo (mixed disease activity population with clinical response at baseline), Outcome 1: Clinical relapse

Study or Subgroup	Infliximab Events	Infliximab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hanauer 2002 (ACCENT I)	131	225	87	110	90.8%	0.74 [0.64 , 0.85]
Rutgeerts 1999	15	37	23	36	9.2%	0.63 [0.40 , 1.01]
Total (95% CI)		**262**		**146**	**100.0%**	**0.73 [0.63 , 0.84]**
Total events:	146		110			

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 4.49 (P < 0.00001)
Test for subgroup differences: Not applicable

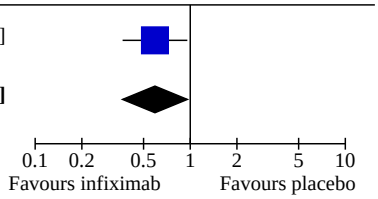


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Infliximab vs placebo (mixed disease activity population with clinical response at baseline), Outcome 2: Loss of clinical response

Study or Subgroup	Infliximab Events	Infliximab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Rutgeerts 1999	14	37	23	36	100.0%	0.59 [0.37 , 0.96]
Total (95% CI)		**37**		**36**	**100.0%**	**0.59 [0.37 , 0.96]**
Total events:	14		23			

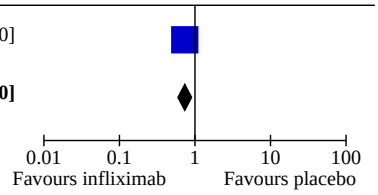
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Infliximab vs placebo (mixed disease activity population with clinical response at baseline), Outcome 3: Loss of clinical response in patients with exclusively fistulating disease

Study or Subgroup	Infliximab Events	Infliximab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Sands 2004 (ACCENT II)	54	96	76	99	100.0%	0.73 [0.60 , 0.90]
Total (95% CI)		**96**		**99**	**100.0%**	**0.73 [0.60 , 0.90]**
Total events:	54		76			

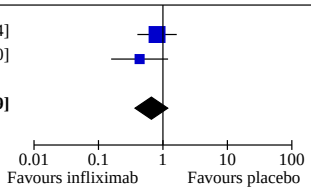
Heterogeneity: Not applicable
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Infliximab vs placebo (mixed disease activity population with clinical response at baseline), Outcome 4: Withdrawal due to adverse events

Study or Subgroup	Infliximab Events	Infliximab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Rutgeerts 1999	10	37	12	36	67.4%	0.81 [0.40 , 1.64]	? + + + + ? +
Sands 2004 (ACCENT II)	5	138	12	144	32.6%	0.43 [0.16 , 1.20]	+ + + ? + − +
Total (95% CI)		**175**		**180**	**100.0%**	**0.66 [0.37 , 1.19]**	
Total events:	15		24				

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%
Test for overall effect: Z = 1.39 (P = 0.17)
Test for subgroup differences: Not applicable

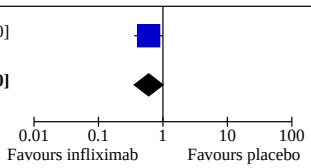


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Infliximab vs placebo (mixed disease activity population with clinical response at baseline), Outcome 5: Serious adverse events

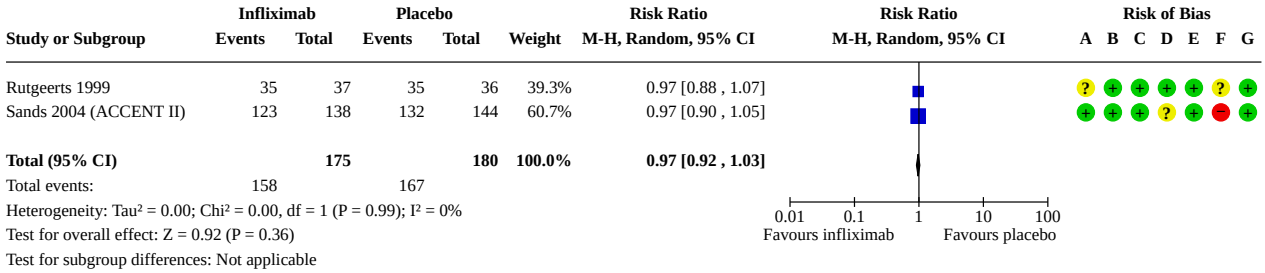
Study or Subgroup	Infliximab Events	Infliximab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Sands 2004 (ACCENT II)	19	138	33	144	100.0%	0.60 [0.36 , 1.00]	+ + + ? + − +
Total (95% CI)		**138**		**144**	**100.0%**	**0.60 [0.36 , 1.00]**	
Total events:	19		33				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Infliximab vs placebo (mixed disease activity population with clinical response at baseline), Outcome 6: Total adverse events

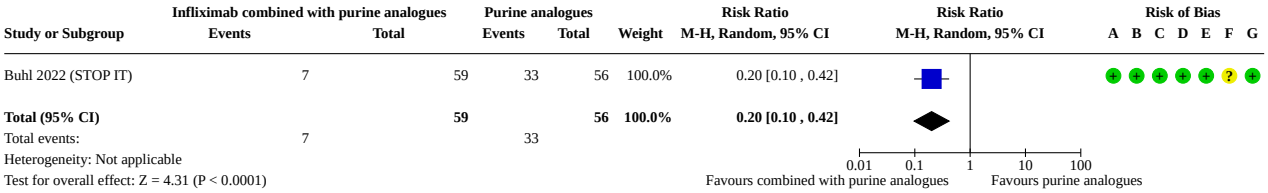


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Infliximab combined with purine analogues vs purine analogues (remission at baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Clinical relapse	1	115	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.10, 0.42]
2.2 Endoscopic relapse	1	115	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.25, 0.59]
2.3 Withdrawal due to adverse events	1	115	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.15, 1.49]
2.4 Serious adverse events	2	257	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.54, 2.64]

Analysis 2.1. Comparison 2: Infliximab combined with purine analogues vs purine analogues (remission at baseline), Outcome 1: Clinical relapse

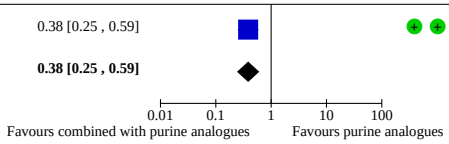


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Infliximab combined with purine analogues vs purine analogues (remission at baseline), Outcome 2: Endoscopic relapse

Study or Subgroup	Infliximab combined with purine analogues Events	Total	Purine analogues Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Buhl 2022 (STOP IT)	17	59	42	56	100.0%	0.38 [0.25 , 0.59]
Total (95% CI)		**59**		**56**	**100.0%**	**0.38 [0.25 , 0.59]**
Total events:	17		42			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.37 (P < 0.0001)
Test for subgroup differences: Not applicable

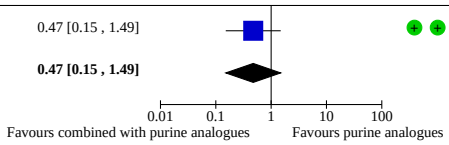


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Infliximab combined with purine analogues vs purine analogues (remission at baseline), Outcome 3: Withdrawal due to adverse events

Study or Subgroup	Infliximab combined with purine analogues Events	Total	Purine analogues Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Buhl 2022 (STOP IT)	4	59	8	56	100.0%	0.47 [0.15 , 1.49]
Total (95% CI)		**59**		**56**	**100.0%**	**0.47 [0.15 , 1.49]**
Total events:	4		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable

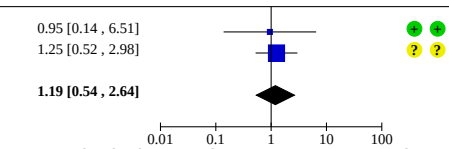


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Infliximab combined with purine analogues vs purine analogues (remission at baseline), Outcome 4: Serious adverse events

Study or Subgroup	Infliximab combined with purine analogues Events	Total	Purine analogues Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Buhl 2022 (STOP IT)	2	59	2	56	16.9%	0.95 [0.14 , 6.51]
Louis 2022 (SPARE)	10	71	8	71	83.1%	1.25 [0.52 , 2.98]
Total (95% CI)		**130**		**127**	**100.0%**	**1.19 [0.54 , 2.64]**
Total events:	12		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable

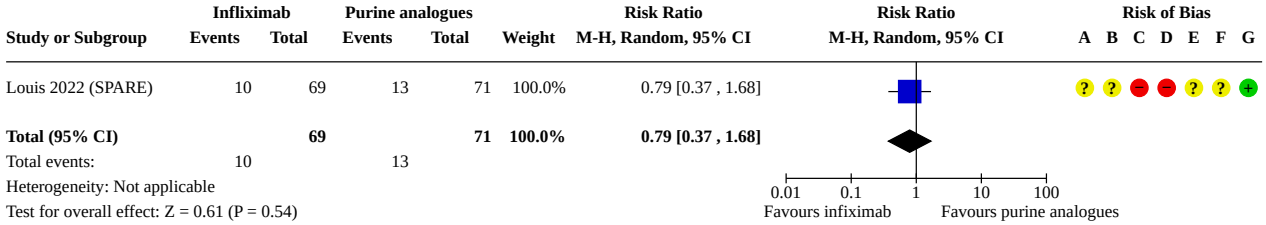


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Infliximab vs purine analogues (remission at baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Serious adverse events	1	140	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.37, 1.68]

Analysis 3.1. Comparison 3: Infliximab vs purine analogues (remission at baseline), Outcome 1: Serious adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

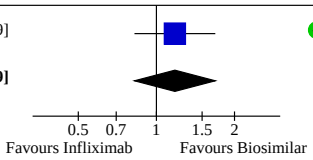
Comparison 4. Infliximab vs biosimilar (mixed/low disease activity at baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Clinical relapse	1	155	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.82, 1.69]
4.2 Loss of clinical response	1	155	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.01, 2.23]
4.3 Withdrawal due to adverse events	1	155	Risk Ratio (M-H, Random, 95% CI)	20.73 [2.86, 150.33]
4.4 Serious adverse events	1	155	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.39, 2.50]
4.5 Total adverse events	1	155	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.43]

Analysis 4.1. Comparison 4: Infliximab vs biosimilar (mixed/low disease activity at baseline), Outcome 1: Clinical relapse

Study or Subgroup	Infliximab Events	Infliximab Total	Biosimilar Events	Biosimilar Total	Weight	Risk Ratio M-H, Random, 95% CI
Jorgensen 2017 (NORSWITCH)	37	78	31	77	100.0%	1.18 [0.82 , 1.69]
Total (95% CI)		**78**		**77**	**100.0%**	**1.18 [0.82 , 1.69]**
Total events:	37		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable

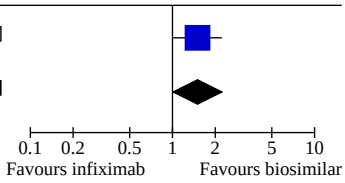


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Infliximab vs biosimilar (mixed/low disease activity at baseline), Outcome 2: Loss of clinical response

Study or Subgroup	Infliximab Events	Infliximab Total	Biosimilar Events	Biosimilar Total	Weight	Risk Ratio M-H, Random, 95% CI
Jorgensen 2017 (NORSWITCH)	38	78	25	77	100.0%	1.50 [1.01 , 2.23]
Total (95% CI)		**78**		**77**	**100.0%**	**1.50 [1.01 , 2.23]**
Total events:	38		25			

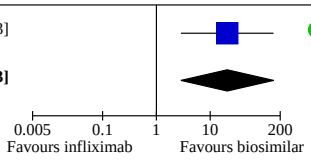
Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable

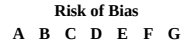


Analysis 4.3. Comparison 4: Infliximab vs biosimilar (mixed/low disease activity at baseline), Outcome 3: Withdrawal due to adverse events

Study or Subgroup	Infliximab Events	Infliximab Total	Biosimilar Events	Biosimilar Total	Weight	Risk Ratio M-H, Random, 95% CI
Jorgensen 2017 (NORSWITCH)	21	78	1	77	100.0%	20.73 [2.86 , 150.33]
Total (95% CI)		**78**		**77**	**100.0%**	**20.73 [2.86 , 150.33]**
Total events:	21		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable



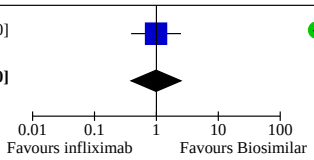


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: Infliximab vs biosimilar (mixed/ low disease activity at baseline), Outcome 4: Serious adverse events

Study or Subgroup	Infliximab Events	Infliximab Total	Biosimilar Events	Biosimilar Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Jorgensen 2017 (NORSWITCH)	8	78	8	77	100.0%	0.99 [0.39 , 2.50]	+ + + + + + +
Total (95% CI)		**78**		**77**	**100.0%**	**0.99 [0.39 , 2.50]**	
Total events:	8		8				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

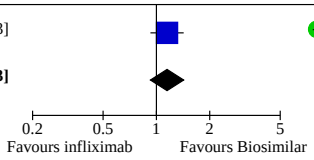


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.5. Comparison 4: Infliximab vs biosimilar (mixed/ low disease activity at baseline), Outcome 5: Total adverse events

Study or Subgroup	Infliximab Events	Infliximab Total	Biosimilar Events	Biosimilar Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Jorgensen 2017 (NORSWITCH)	57	78	49	77	100.0%	1.15 [0.93 , 1.43]	+ + + + + + +
Total (95% CI)		**78**		**77**	**100.0%**	**1.15 [0.93 , 1.43]**	
Total events:	57		49				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

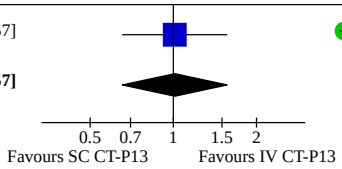
Comparison 5. Subcutaneous CT-P13 and purine analogues vs intravenous CT-P13 and purine analogues (active disease population with clinical response at baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Clinical relapse	1	53	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.65, 1.57]
5.2 Loss of clinical response	1	53	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.25]
5.3 Endoscopic relapse	1	53	Risk Ratio (M-H, Random, 95% CI)	4.46 [0.56, 35.67]
5.4 Withdrawal due to adverse events	1	53	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.30, 1.97]

Analysis 5.1. Comparison 5: Subcutaneous CT-P13 and purine analogues vs intravenous CT-P13 and purine analogues (active disease population with clinical response at baseline), Outcome 1: Clinical relapse

Study or Subgroup	SC CT-P13 Events	SC CT-P13 Total	IV CT-P13 Events	IV CT-P13 Total	Weight	Risk Ratio M-H, Random, 95% CI
Schreiber 2021	17	28	15	25	100.0%	1.01 [0.65 , 1.57]
Total (95% CI)		**28**		**25**	**100.0%**	**1.01 [0.65 , 1.57]**
Total events:	17		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable

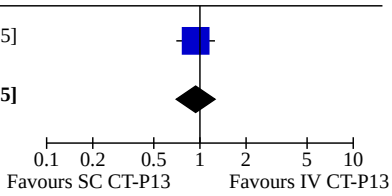


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: Subcutaneous CT-P13 and purine analogues vs intravenous CT-P13 and purine analogues (active disease population with clinical response at baseline), Outcome 2: Loss of clinical response

Study or Subgroup	SC CT-P13 Events	SC CT-P13 Total	IV CT-P13 Events	IV CT-P13 Total	Weight	Risk Ratio M-H, Random, 95% CI
Schreiber 2021	21	28	20	25	100.0%	0.94 [0.70 , 1.25]
Total (95% CI)		**28**		**25**	**100.0%**	**0.94 [0.70 , 1.25]**
Total events:	21		20			

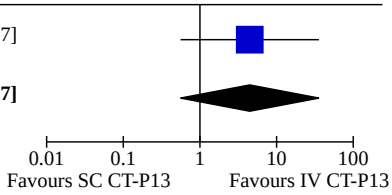
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Subcutaneous CT-P13 and purine analogues vs intravenous CT-P13 and purine analogues (active disease population with clinical response at baseline), Outcome 3: Endoscopic relapse

Study or Subgroup	SC CT-P13 Events	SC CT-P13 Total	IV CT-P13 Events	IV CT-P13 Total	Weight	Risk Ratio M-H, Random, 95% CI
Schreiber 2021	5	28	1	25	100.0%	4.46 [0.56 , 35.67]
Total (95% CI)		**28**		**25**	**100.0%**	**4.46 [0.56 , 35.67]**
Total events:	5		1			

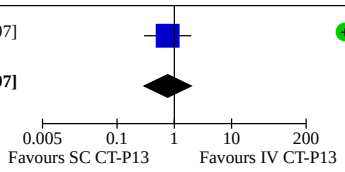
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Subcutaneous CT-P13 and purine analogues vs intravenous CT-P13 and purine analogues (active disease population with clinical response at baseline), Outcome 4: Withdrawal due to adverse events

Study or Subgroup	SC CT-P13 Events	SC CT-P13 Total	IV CT-P13 Events	IV CT-P13 Total	Weight	Risk Ratio M-H, Random, 95% CI
Schreiber 2021	6	28	7	25	100.0%	0.77 [0.30 , 1.97]
Total (95% CI)		**28**		**25**	**100.0%**	**0.77 [0.30 , 1.97]**
Total events:	6		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

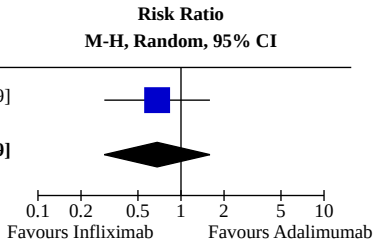
Comparison 6. Infliximab vs adalimumab (active disease population with clinical response at baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Loss of clinical response	1	73	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.29, 1.59]
6.2 Withdrawal due to adverse events	1	73	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.72]
6.3 Serious adverse events	1	73	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.54]
6.4 Total adverse events	1	73	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.12]

Analysis 6.1. Comparison 6: Infliximab vs adalimumab (active disease population with clinical response at baseline), Outcome 1: Loss of clinical response

Study or Subgroup	Infliximab Events	Infliximab Total	Adalimumab Events	Adalimumab Total	Weight	Risk Ratio M-H, Random, 95% CI
VanAssche 2012 (SWITCH)	7	37	10	36	100.0%	0.68 [0.29 , 1.59]
Total (95% CI)		**37**		**36**	**100.0%**	**0.68 [0.29 , 1.59]**
Total events:	7		10			

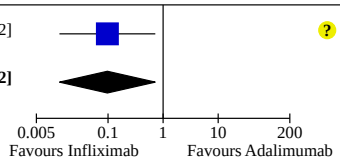
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Infliximab vs adalimumab (active disease population with clinical response at baseline), Outcome 2: Withdrawal due to adverse events

Study or Subgroup	Infliximab Events	Infliximab Total	Adalimumab Events	Adalimumab Total	Weight	Risk Ratio M-H, Random, 95% CI
VanAssche 2012 (SWITCH)	1	37	10	36	100.0%	0.10 [0.01 , 0.72]
Total (95% CI)		**37**		**36**	**100.0%**	**0.10 [0.01 , 0.72]**
Total events:	1		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable

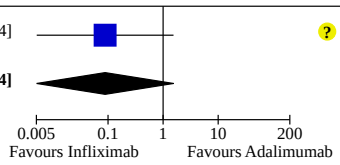


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.3. Comparison 6: Infliximab vs adalimumab (active disease population with clinical response at baseline), Outcome 3: Serious adverse events

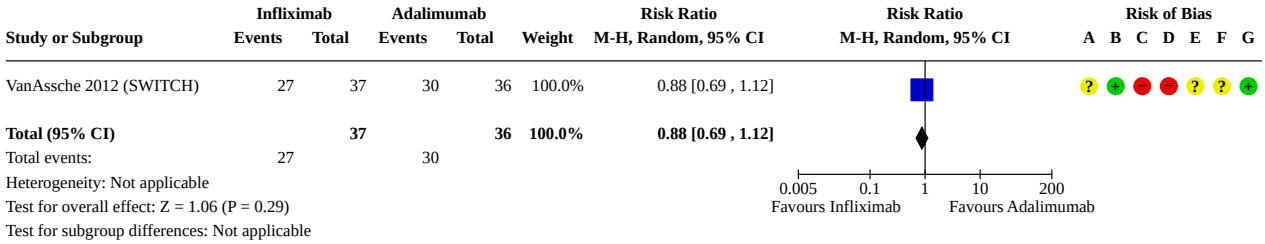
Study or Subgroup	Infliximab Events	Infliximab Total	Adalimumab Events	Adalimumab Total	Weight	Risk Ratio M-H, Random, 95% CI
VanAssche 2012 (SWITCH)	0	37	5	36	100.0%	0.09 [0.01 , 1.54]
Total (95% CI)		**37**		**36**	**100.0%**	**0.09 [0.01 , 1.54]**
Total events:	0		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.4. Comparison 6: Infliximab vs adalimumab (active disease population with clinical response at baseline), Outcome 4: Total adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Additional characteristics

Study ID	Numbers randomised, per IG/CG:	Purine analogues use	Biologic naive or not	Mixed disease state or remission only
Buhl 2022 (STOP IT)	**CG (placebo)** 56 **IG (IFX)** 59	Thiopurines 55% of all patients	Not	Remission
Hanauer 2002 (ACCENT I)	**CG (placebo)** – 110 **IG1 (IFX 5 mg)** – 113 **IG2 (IFX 10 mg)** – 112	6-MP and AZA – 81/335 (24%)	Not (the study included naive patients but had an induction phase with the biologic)	Active, CDAI 299 (264-342)
Jorgensen 2017 (NORSWITCH)	**CG (IFX):** 78 **IG (CT-P13):** 77	Use of immunosuppressives CG: 30/78 (38.5%) IG: 36/77 (46.8%)	Mix (60/77 and 61/78 naive)	Mixed/low activity HBI CG: 2 (1–4) IG: 2 (0–4)
Louis 2022 (SPARE)	**Group 1 (comb):** 71 **Group 2 (anti-metabolite):** 71 **Group 3 (IFX):** 69	Anti-metabolite and IFX combination for a year	Not	Remission
Rutgeerts 1999	**CG (placebo)**: 36 **IG (IFX)**: 37	6-MP or AZA > 6 months' duration at a stable dosage for 8 weeks was acceptable	Not (the study included patients that had responded to an initial infusion of infliximab or placebo)	Active, CDAI between 220 and 400

Table 1. Additional characteristics *(Continued)*

Sands 2004 (ACCENT II)	**CG (placebo):** 99 **IG (IFX):** 96	6-MP or AZA CG 35/99 (35%) IG 29/96 (30%)	Not (the study included naive patients but had an induction phase with the biologic)	Mixed > 150 CDAI CG: 57 IG: 57 > 220 CDAI CG: 31 IG: 33
Schreiber 2021	**CG (IV CT-P13)** 25 **IG (SC CT-P13)** 28	AZA/6-MP/methotrexate use IG: 14/28 (50%) CG: 13/25 (52%)	Not (the study included naive patients but had an induction phase with the biosimilar)	Active mean (SD) CDAI score CG: 296.38 (59.21) IG: 294.75 (59.90)
VanAssche 2012 (SWITCH)	**CG (IFX)** 37 **IG (ADA)** 36	AZA IG: 6/36 (16.7%) CG: 0/37 (0%)	Previous exposure to ADA, and receiving IFX doses > 5 mg/kg intravenously were excluded	Mix, CDAI baseline, median (IQR) 48 (24-110) and 58 (34-122) per group
Volkers 2017 (SIMILAR)	**IG (biosimilar)** NR **CG (IFX)** NR (total 47 participants)	NR	Not	Remission

6-MP: 6-mercaptopurine; ADA: adalimumab; AZA: Azathioprine; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; CG: control group; FC: faecal calprotectin; HBI: Harvey-Bradshaw Index; IFX: Infliximab; IG: intervention group; IV: intravenous; IQR: interquartile range; SC: subcutaneous; NR: not reported; SD: standard deviation; TNF: tumour-necrosis factor; UC: ulcerative colitis

Table 2. Intervention details

Study ID	Intervention medications IG (dosage, regimen, route)	Intervention medications CG (dosage, regimen, route)	Medications up to study beginning, per IG/CG	Medications that had to be discontinued prior to starting study
Buhl 2022 (STOP IT)	Continue infliximab therapy at an unchanged dose for a duration of 48 weeks	Matching placebo for a duration of 48 weeks	Concomitant therapy with immune suppressants, except steroids, was allowed. The dosage and frequency must have been stable 3 months prior to inclusion, and must remain stable throughout the study period. Continued concomitant therapy with stable doses of immunomodulators (thiopurines, methotrexate) was allowed (55% of patients).	No use of oral steroids within 3 months prior to inclusion
Hanauer 2002 (ACCENT I)	**IG1** – Infliximab infusion, each infusion 5 mg/kg. Infusions at week 2, week	Placebo - identical in appearance to Infliximab infu-	'Patients receiving the following treatments were eligible: 5-aminosalicylates or antibiotics (if the dose remained con-	'Patients not receiving medical therapy had

Table 2. Intervention details *(Continued)*

	6, and every 8 weeks thereafter until week 46 **IG2 –** Infliximab infusion, 5 mg/kg infusions at week 2 and week 6. 10 mg/kg every 8 weeks thereafter until week 46	sion. Infusions at week 2 (start point of maintenance study), week 6, and every 8 weeks thereafter until week 46	stant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks).' NOT REPORTED per IG/CG, the following data were based on responders as a whole. 5-aminosalicylates – 159/335 (47%) 6-mercaptopurine and azathioprine – 81/335 (24%) Methotrexate – 10/335 (3%) Corticosteroids of which (i) Any – 175/335 (52%) (ii) > 20mg per day – 61/335 (18%)	to have discontinued treatment for at least 4 weeks before screening'.
Jorgensen 2017 (NORSWITCH)	Patients were switched to biosimilar CT-P13 infusions on the same dose and intervals as their pre-randomisation infliximab regimen.	The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation.	Immunosuppressive therapy: IG: 36/77 CG: 30/78 Prednisolone: IG: 0/77 CG: 2/78 Pre-infusion steroids IV: IG: 6/77 CG: 8/78	Initiation of systemic corticosteroids or an immunosuppressant or other medication which according to the investigator would interfere with the stability of the disease was not allowed.
Louis 2022 (SPARE)	**Group 2:** Continuing anti-metabolite (discontinuing infliximab). If patient relapsed they were given infliximab 5 mg/kg. infusion. If no remission at 4 weeks, reinfusion at 10 mg/kg and then back to 5 mg/kg. If further relapse, same as Group 1. **Group 3:** Continuing infliximab (discontinuing anti-metabolite). If the patient relapsed, infliximab therapy was intensified to 10 mg/kg/8 weeks, same as Group 1. If no remission, anti-metabolite was restarted.	**Group 1:** Continuing combination therapy (infliximab + anti-metabolite). If the patient relapsed, infliximab therapy was intensified to 10 mg/kg/8 weeks.	"Patients were eligible provided that immunosuppressant therapy doses were stable for the past 3 months or more at least 1 mg/kg for mercaptopurine or 2 mg/kg for azathioprine, or the highest tolerated dose if intolerance to these standard doses; lower doses were also allowed if 6-thioguanine nucleotides (6-TGN) were higher than 235 pmol per 8×10^8 red blood cells. The minimum dose of methotrexate for eligibility was 15 mg per week subcutaneously" "Use of contraceptives during the whole study for female patients with childbearing potential" was compulsory for inclusion".	"Steroid use within 6 months before screening, and ongoing treatment with steroids, immunosuppressive drugs (other than thiopurines or methotrexate), biologics (other than infliximab), or thalidomide"
Rutgeerts 1999	IV 5, 10, or 20 mg/kg infliximab	IV infusion placebo	For patients undergoing concomitant therapy for Crohn's disease, acceptable	NR

Table 2. Intervention details *(Continued)*

			regimens for inclusion in the study were as follows: mesalamine 8 weeks' duration and at a stable dosage for 4 weeks before screening; oral corticosteroids, 8 weeks duration at a stable dosage for 2 weeks, with a maximum dosage of 40 mg/day; and 6-mercaptopurine or azathioprine, 6 months duration at a stable dosage for 8 weeks	
Sands 2004 (ACCENT II)	Infliximab 5 mg/kg at weeks 14, 22, 30, 38, and 46. Beginning at week 22, patients who had a loss of response (defined by recrudescence of draining fistulas, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy) were eligible to cross over to maintenance treatment with Infliximab 10 mg/kg.	Placebo at weeks 14, 22, 30, 38, and 46. Beginning at week 22, patients who had a loss of response (defined by recrudescence of draining fistulas, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy) were eligible to cross over to maintenance treatment with infliximab 5 mg/kg.	Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate, and antibiotics, were permitted. (i) 5-aminosalicylates (oral or rectal) [n (%)] – CG 49/99 (49%). IG 41/96 (43%) (ii) Mercaptopurine or azathioprine [n (%)] – CG 35/99 (35%). IG 29/96 (30%) (iii) Methotrexate [n (%)] – CG 2/99 (2%). IG 1/96 (1%) (iv) Antibiotics [n (%)] – CG 26/99 (26%). IG 28/96 (29%) (v) Corticosteroids. (va) Any [n (%)] – CG 30/99 (30%). IG 25/96 (26%). (vb) > 20 mg per day [n (%)] – CG 8/99 (8%). IG 8/96 (8%)	NR
Schreiber 2021	CT-P13 SC was administered via prefilled syringe containing 120 mg CT-P13 SC - SC Group.	CT-P13 IV (5 mg/kg) was administered as a 2-hour IV infusion - IV Group.	Patient was either on stable doses or currently not receiving (during specified time frame) the following CD medication: · AZA or 6-MP for ≥ 8 weeks prior to day 0 · Methotrexate for ≥ 6 weeks prior to day 0 · Oral corticosteroids at the equivalent dose of ≤ 20 mg/day of prednisone for ≥ 2 weeks prior to day 0 · Oral budesonide at the dose of ≤ 6 mg/day for ≥ 4 weeks prior to day 0 · 5-ASA for ≥ 4 weeks prior to day 0	Patient was ineligible if they had received or planned to receive any of following prohibited medications or treatments: · Any biological agents for the treatment of UC or CD · Parenteral corticosteroids for the treatment of UC or CD ≤ 2 weeks prior to screening · Antibiotics for the treatment of UC or CD ≤ 2

Table 2. Intervention details *(Continued)*

				weeks prior to day 0 · Alkylating agents ≤ 12 months prior to day 0 · Thalidomide, tacrolimus, or cyclosporine ≤ 3 months prior to day 0 · Live or live-attenuated vaccine ≤ 4 weeks prior to day 0
VanAssche 2012 (SWITCH)	**IG-ADA** 80 mg subcutaneous adalimumab at inclusion and 40 mg subcutaneous adalimumab every other week for 54 weeks. Patients with disease flare were allowed dose intensification – step-up to 40 mg every week. If complete loss of response, patients were allowed to switch over to the alternative treatment. Short (4-week) courses of steroids were also allowed per protocol.	**CG-IFX** Continue infliximab 5 mg/kg intravenously at 8-week intervals for 56 weeks. Patients with disease flare were allowed dose intensification – decrease of dosing interval with 2-week decrements. Short (4-week) courses of steroids were also allowed per protocol.	Azathioprine – CG-IFX 0/37, IG-ADA 6/36 Methotrexate – CG-IFX 2/37, IG-ADA 0/36	IFX doses > 5 mg/kg intravenously were excluded.
Volkers 2017 (SIMILAR)	Infliximab biosimilar - Patients switched from infliximab-biological and received 4 to 6 doses of 5 mg/kg to 10 mg/kg of infliximab-biosimilar during the 30-week study period.	Infliximab biological – Patients continued infliximab-biological and received 4 to 6 doses of 5 mg/kg to 10 mg/kg of infliximab-biosimilar during the 30-week study period.	NR	NR

6-MP: 6-mercaptopurine; ADA: adalimumab; AZA: Azathioprine; CD: Crohn's Disease; CG: control group; FC: faecal calprotectin; IFX: Infliximab; IG: intervention group; IV: intravenous; NR: not reported; SC: subcutaneous; TNF: tumour-necrosis factor; UC: ulcerative colitis

Table 3. Primary and secondary outcome data

Study ID	Clinical relapse, per IG/CG	Clinical loss of response, per IG/CG	Endoscopic relapse, per IG/CG	Withdrawal due to adverse events	Patients with serious adverse events	Total numbers of patients with adverse events

Table 3. Primary and secondary outcome data *(Continued)*

Buhl 2022 (STOP IT)	Week 48 (reported + withdrawals counted as treatment failures) CG 31/56 IG 7/59	NR	CG 42/56 IG 17/59	CG 8/56 IG 4/59	CG 2/56 IG 2/59	NR
Hanauer 2002 (ACCENT I)	Week 30: **CG (Placebo)** 87/110 **IG1 (IFX 5 mg)** 69/113 **IG2 (IFX 5-10 mg)** 62/112	NR	NR	NR	NR	NR
Jorgensen 2017 (NORSWITCH)	**Harvey-Bradshaw Index remission** (score less than or equal to 4)**:** **CG (IFX)** 37/78 **IG1 (CT-P13)** 31/77	Disease worsening was defined by worsening in Harvey-Bradshaw Index (HBI) for CD (a change from baseline of 4 points or more and a total score of 7 points or greater). **CG (IFX)** 38/78 **IG1 (CT-P13)** 25/77	NR	**CG (IFX)** 2/78 **IG1 (CT-P13)** 1/77	**CG (IFX)** 8/78 **IG1 (CT-P13)** 8/77	**CG (IFX)** 57/78 **IG1 (CT-P13)** 49/77
Louis 2022 (SPARE)	39 in total before retreatment but NR per group (2/23/3 patients were retreated)	NR	NR	NR	Group 1: 10 Group 2: 8 Group 3: 13	NR
Rutgeerts 1999	Week 44 (randomisation at week 12) CG (placebo): 23/36 IG (infliximab): 15/37	Week 44 (randomisation at week 12) CG (placebo): 23/36 IG (IFX): 14/37	NR	CG (PLB) 12/36 IG (IFX) 10/37	NR	CG (PLB) 35/36 IG (IFX) 35/37
Sands 2004 (ACCENT II)	NR	A response was defined as a reduction of at least 50 percent from baseline (week 0) in the number of draining fistulas at consecutive visits four or more weeks apart. A complete response was defined by – the absence of draining fistulas. **Loss of response [n (%)]** **Week 54**	NR	We couldn't separate the data for responders and non-responders. **Adverse events leading to discontinuation of study agent (combined data for both**	We couldn't separate the data for responders and non-responders. **Serious adverse events (combined data for both the responders and non-responders)**	We couldn't separate the data for responders and non-responders. **Adverse events (combined data for both the responders and non-respon-**

Table 3. Primary and secondary outcome data *(Continued)*

		CG: 76/99 IG: 54/96 (patients who discontinued were added in the totals).		**the responders and non-responders) [n (%)] – CG** 12/144 (8%). **IG** 5/138 (4%)	**[n (%)] – CG** 33/144 (23%). **IG** 19/138 (14%)	**ders) [n (%)] – CG** 132/144 (92%). **IG** 123/138 (89%)
Schreiber 2021	Week 22 CDAI < 150 SC: 17/28 IV: 15/25	Week 22 CDAI reduction >= 100 SC: 21/28 IV: 20/25	Week 22 SES-CD score =< 2 points SC: 5/28 IV: 1/25	SC - 6/28 IV - 7/25	SC - 6/66 IV - 10/65 (CD and UC combined)	SC - 50/66 IV - 27/65 (CD and UC combined)
VanAssche 2012 (SWITCH)	NR	**Patients without CDAI-100 response** **Week 54** (randomisation occurred at week 0)**:** **CG (ADA)** 10/36 **IG (IFX)** 7/37	NR	**CG (ADA)** 10/36 **IG (IFX)** 1/37	**CG (ADA)** 5/36 **IG (IFX)** 0/37	**CG (ADA)** 30/36 **IG (IFX)** 27/37
Volkers 2017 (SIMILAR)	NR	NR	NR	NR	NR	NR

ADA: adalimumab; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; CG: control group; FC: faecal calprotectin; HBI: Harvey Bradshaw Index; IFX: Infliximab; IG: intervention group; IV: intravenous; NR: not reported; PLB: Placebo; SC: subcutaneous; SES-CD: Simple Endoscopic Score; TNF: tumour-necrosis factor; UC: ulcerative colitis

APPENDICES

Appendix 1. Search strategy

CENTRAL

#1 ([mh "Crohn Disease"] OR [mh ^"Inflammatory Bowel Diseases"] OR Crohn* OR Inflammatory Bowel Disease* OR IBD) AND ([mh Infliximab] OR Infliximab OR "ABP 710" OR ABP710 OR Avakine OR Avsola OR cA2 OR Flixabi OR "GP 1111" OR GP1111 OR IFX OR Inflectra OR Ixifi OR "PF 06438179" OR "PF 6438179" OR PF06438179 OR PF6438179 OR Remicade OR Remsima OR Renflexis OR Revellex OR "TA 650" OR TA650 OR Zessly)

in Trials 924

Embase via Ovid SP

Database: Embase <1974 to 2023 Week 24>

1 exp Crohn Disease/ or Inflammatory Bowel Disease/ or (Crohn* or Inflammatory Bowel Disease* or IBD).mp. (204546)

2 Infliximab/ or (Infliximab or "ABP 710" or ABP710 or Avakine or Avsola or cA2 or Flixabi or "GP 1111" or GP1111 or IFX or Inflectra or Ixifi or "PF 06438179" or "PF 6438179" or PF06438179 or PF6438179 or Remicade or Remsima or Renflexis or Revellex or "TA 650" or TA650 or Zessly).mp. (169318)

3 Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention $1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (6335080)

4 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9485)

5 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or (randomi?ed controlled or control group$1).ti,ab.) (350346)

6 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (21660)

7 (Systematic review not (trial or study)).ti. (263055)

8 (nonrandom$ not random$).ti,ab. (18985)

9 ("Random field$" or (random cluster adj3 sampl$)).ti,ab. (4511)

10 (review.ab. and review.pt.) not trial.ti. (1123686)

11 "we searched".ab. and (review.ti. or review.pt.) (49996)

12 ("update review" or (databases adj4 searched)).ab. (63082)

13 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1229787)

14 Animal experiment/ not (human experiment/ or human/) (2583504)

15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (4348940)

16 3 not 15 (5590377)

17 1 and 2 and 16 (5252)

18 limit 17 to embase (2412)

MEDLINE via Ovid SP

Database: Ovid MEDLINE(R) ALL <1946 to June 22, 2023>

1 Crohn Disease/ or Inflammatory Bowel Diseases/ or (Crohn* or Inflammatory Bowel Disease* or IBD).mp. (111569)

2 Infliximab/ or (Infliximab or "ABP 710" or ABP710 or Avakine or Avsola or cA2 or Flixabi or "GP 1111" or GP1111 or IFX or Inflectra or Ixifi or "PF 06438179" or "PF 6438179" or PF06438179 or PF6438179 or Remicade or Remsima or Renflexis or Revellex or "TA 650" or TA650 or Zessly).mp. (181102)

3 ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.) (4982130)

4 1 and 2 and 3 (5181)

ClinicalTrials.gov

Advanced Search (Classic)

Condition or disease: Crohn Disease OR Inflammatory Bowel Diseases

Study type: Interventional Studies (Clinical Trials)

Intervention/treatment: Infliximab

132 Studies found

WHO ICTRP

Advanced Search

Crohn Disease OR Inflammatory Bowel Diseases *in the Condition*

Infliximab *in the Intervention*

Recruitment Status is ALL

78 records for 76 trials found

HISTORY

Protocol first published: Issue 3, 2017

CONTRIBUTIONS OF AUTHORS

Morris Gordon: secured funding, designed and developed, screened, extracted, resolved conflicts, assessed certainty, contributed to writing and editing, advised on, approved the final version prior to submission, and is a guarantor of the review.

Vassiliki Sinopoulou: assessed certainty, contributed to writing and editing, advised on, and approved the final version prior to submission.

Arni Sarian: screened, extracted, assessed certainty, contributed to writing and editing, and approved the final version prior to submission.

Anthony K Akobeng: advised on, and approved the final version prior to submission.

Gordon William Moran: screened, extracted, assessed certainty, contributed to writing and editing, and approved the final version prior to submission.

DECLARATIONS OF INTEREST

Morris Gordon: Nothing to declare

Vassiliki Sinopoulou: Nothing to declare

Arni Sarian: Nothing to declare

Anthony K Akobeng: Nothing to declare

Gordon William Moran: AbbVie (Independent Contractor - Consultant), Janssen Biotech (Grant / Contract), AstraZeneca AB (Grant / Contract)

AA and MG are Cochrane editors. They were not involved in the editorial process.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A protocol for this review was published in 2017 by a different author team (Battat 2017). We have updated the methods based on more recent Cochrane guidance, and we have amended the outcomes and planned analyses, before commencement of the review. We have also updated the background section.

Any planned analyses which are reported in the methods section but not in the results, could not be performed due to lack of sufficient data.

We changed the title of the review to 'Infliximab for maintenance of medically-induced remission in Crohn's disease' from the protocol title 'Infliximab for maintenance of remission in Crohn's disease' to clarify that surgical interventions were not considered for this review.