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Methotrexate for induction of remission in refractory Crohn's disease (Review)

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[Intervention Review]

Methotrexate for induction of remission in refractory Crohn's disease

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ABSTRACT

Background

Although corticosteroids are effective for induction of remission of Crohn's disease, many patients relapse when steroids are withdrawn or become steroid dependent. Furthermore, corticosteroids exhibit significant adverse effects. The success of methotrexate as a treatment for rheumatoid arthritis led to its evaluation in patients with refractory Crohn's disease. Methotrexate has been studied for induction of remission of refractory Crohn's disease and has become the principal alternative to azathioprine or 6-mercaptopurine therapy. This systematic review is an update of previously published Cochrane reviews.

Objectives

The primary objective was to assess the efficacy and safety of methotrexate for induction of remission in patients with active Crohn's disease in the presence or absence of concomitant steroid therapy.

Search methods

We searched MEDLINE, EMBASE, CENTRAL and the Cochrane IBD/FBD group specialized register from inception to June 9, 2014 for relevant studies. Conference proceedings and reference lists were also searched to identify additional studies.

Selection criteria

Randomized controlled trials of methotrexate compared to placebo or an active comparator for treatment of active refractory Crohn's disease in adult patients (> 17 years) were considered for inclusion.

Data collection and analysis

The primary outcome was failure to enter remission and withdraw from steroids. Secondary outcomes included adverse events, withdrawal due to adverse events, serious adverse events and quality of life. We calculated the relative risk (RR) and 95% confidence intervals (95% CI) for each outcome. Data were analyzed on an intention-to-treat basis. The Cochrane risk of bias tool was used to assess the methodological quality of included studies. The GRADE approach was used to assess the overall quality of evidence supporting the primary outcome.

Main results

Seven studies (495 patients) were included. Four studies were rated as low risk of bias. Three studies were rated as high risk of bias due to open label or single-blind designs. The seven studies differed with respect to participants, intervention, and outcomes to the extent that meta-analysis was considered to be inappropriate. GRADE analyses indicated that the quality of evidence was very low to low for most outcomes due to sparse data and inadequate blinding. Three small studies which employed low dose oral methotrexate showed no statistically significant difference in failure to induce remission between methotrexate and placebo or between methotrexate and 6-mercaptopurine. For the study using 15 mg/week of oral methotrexate 33% (5/15) of methotrexate patients failed to enter remission compared to 11% (2/18) of placebo patients (RR 3.00, 95% CI 0.68 to 13.31). For the study using 12.5 mg/week of oral methotrexate 62%

(16/26) of methotrexate patients failed to enter remission compared to 54% (14/26) of placebo patients (RR 1.14, 95% CI 0.72 to 1.82). This study also had an active comparator arm, 62% (16/26) of methotrexate patients failed to enter remission compared to 59% (19/32) of 6-mercaptopurine patients (RR 1.04, 95% CI 0.68 to 1.57). For the active comparator study using 15 mg/week oral methotrexate, 20% (3/15) of methotrexate patients failed to enter remission compared to 6% of 6-mercaptopurine patients (RR 3.20, 95% CI 0.37 to 27.49). This study also had a 5-ASA arm and found that methotrexate patients were significantly more likely to enter remission than 5-ASA patients. Twenty per cent (3/15) of methotrexate patients failed to enter remission compared to 86% (6/7) of 5-ASA patients (RR 0.23, 95% CI 0.08 to 0.67). One small study which used a higher dose of intravenous or oral methotrexate (25 mg/week) showed no statistically significant difference between methotrexate and azathioprine. Forty-four per cent (12/27) of methotrexate patients failed to enter remission compared to 37% of azathioprine patients (RR 1.20, 95% CI 0.63 to 2.29). Two studies found no statistically significant difference in failure to enter remission between the combination of infliximab and methotrexate and infliximab monotherapy. One small study utilized intravenous methotrexate (20 mg/week) for 5 weeks and then switched to oral (20 mg/week). Forty-five per cent (5/11) of patients in the combination group failed to enter remission compared to 62% of infliximab patients (RR 0.73, 95% CI 0.31 to 1.69). The other study assessing combination therapy utilized subcutaneous methotrexate (maximum dose 25 mg/week). Twenty-four per cent (15/63) of patients in the combination group failed to enter remission compared to 22% (14/63) of infliximab patients (RR 1.07, 95% CI 0.57 to 2.03). A large placebo-controlled study which employed a high dose of methotrexate intramuscularly showed a statistically significant benefit relative to placebo. Sixty-one per cent of methotrexate patients failed to enter remission compared to 81% of placebo patients (RR 0.75, 95% CI 0.61 to 0.93; number needed to treat, NNT=5). Withdrawals due to adverse events were significantly more common in methotrexate patients than placebo in this study. Seventeen per cent of methotrexate patients withdrew due to adverse events compared to 2% of placebo patients (RR 8.00, 95% CI 1.09 to 58.51). The incidence of adverse events was significantly more common in methotrexate patients (63%, 17/27) than azathioprine patients (26%, 7/27) in one small study (RR 2.42, 95% CI 1.21 to 4.89). No other statistically significant differences in adverse events, withdrawals due to adverse events or serious adverse events were reported in any of the other placebo-controlled or active comparator studies. Common adverse events included nausea and vomiting, abdominal pain, diarrhea, skin rash and headache.

Authors' conclusions

There is evidence from a single large randomized trial which suggests that intramuscular methotrexate (25 mg/week) provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory Crohn's disease. Lower dose oral methotrexate does not appear to provide any significant benefit relative to placebo or active comparator. However, these trials were small and further studies of oral methotrexate may be justified. Comparative studies of methotrexate to drugs such as azathioprine or 6-mercaptopurine would require the randomization of large numbers of patients. The addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infliximab monotherapy. However these studies were relatively small and further research is needed to determine the role of methotrexate when used in conjunction with infliximab or other biological therapies.

PLAIN LANGUAGE SUMMARY

Methotrexate for treatment of active treatment resistant Crohn's disease

Although corticosteroids are effective for induction of remission of Crohn's disease, many patients relapse when steroids are withdrawn or become steroid dependent. Furthermore, corticosteroids exhibit significant side effects. Methotrexate is an immunosuppressive drug that is used to treat active treatment resistant Crohn's disease. This review includes seven randomized trials with a total of 495 participants. There is evidence from one large study which suggests that methotrexate (25 mg/week) injected intramuscularly for 16 weeks among patients with active treatment resistant Crohn's disease may provide a benefit for induction of remission and complete withdrawal from steroids. This reduction in steroid use could reduce steroid-induced side effects for people with chronic Crohn's disease. Although side effects are more common with high dose methotrexate therapy, no serious side effects have been observed. Common side effects associated with methotrexate therapy include nausea and vomiting, abdominal pain, diarrhea, skin rash and headache. Studies comparing lower dose oral methotrexate (12.5 to 15 mg/week) to placebo (e.g. sugar pill) or other active drugs (e.g. azathioprine or 6-mercaptopurine) indicate that lower dose oral methotrexate does not appear to provide any benefit for treatment of active treatment resistant Crohn's disease. However, these trials were small in size and further studies of oral methotrexate may be justified. Two studies looked at the combination of methotrexate and infliximab (a biological drug) compared to infliximab therapy alone. These studies indicated that the addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infiximab. However these studies were relatively small and further research is needed to determine the role of methotrexate when used in conjunction with infliximab or other biological therapies.

Summary of findings for the main comparison. Methotrexate compared to placebo for induction of remission in refractory Crohn's disease

Methotrexate compared to placebo for induction of remission in refractory Crohn's disease

Patient or population: Adult patients with refractory Crohn's disease

Settings: Outpatient

Intervention: Methotrexate

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Methotrexate				
Failure to enter remission or possible remission at 16 weeks (Arora 1999)	**111 per 1000[1]**	**333 per 1000** (75 to 1477)	**RR 3.00** (0.68 to 13.31)	33 (1 study)	⊕⊕⊝⊝ **low[2]**	
Failure to enter remission or possible remission at 16 weeks (Oren 1997)	**538 per 1000[1]**	**613 per 1000** (387 to 979)	**RR 1.05** (0.79 to 1.39)	52 (1 study)	⊕⊕⊝⊝ **low[3,4]**	
Failure to enter remission or possible remission at 16 weeks (Feagan 1995)	**808 per 1000[1]**	**606 per 1000** (493 to 751)	**RR 0.75** (0.61 to 0.93)	141 (1study)	⊕⊕⊕⊝ **moderate[5]**	
Withdrawal due to adverse event (Feagan 1995)	**21 per 1000[1]**	**168 per 1000** (23 to 1229)	**RR 8.00** (1.09 to 58.51)	141 (1 study)	⊕⊕⊝⊝ **low[6]**	
Withdrawal due to adverse event (Oren 1997)	**0 per 1000[1]**	**38 per 1000** (2 to 903)	**RR 3.00** (0.13 to 70.42)	52 (1 study)	⊕⊕⊝⊝ **low[7]**	
Withdrawal due to adverse event (Arora 1999)	**0 per 1000[1]**	**24 per 1000** (11 to 3591)	**RR 8.31** (0.46 to 149.21)	33 (1 study)	⊕⊕⊝⊝ **low[8]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk Ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Control group risk comes from control arm of study
2. Rated down due to very sparse data (7 events)
3. Rated down due to very sparse data (30 events)
4. Unknown risk of bias for random sequence generation and allocation concealment
5. Rated down due to sparse data (95 events)
6. Rated down due to very sparse data (17 events)
7. Rated down due to very sparse data (1 events)
8. Rated down due to very sparse data (3 events)

Summary of findings 2. Methotrexate compared to 6-MP or azathioprine for induction of remission in refractory Crohn's disease

Methotrexate compared to 6-MP or azathioprine for induction of remission in refractory Crohn's disease

Patient or population: adult patients with refractory Crohn's disease

Settings: outpatient

Intervention: Methotrexate

Comparison: 6-MP or azathioprine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	6-MP or azathioprine	Methotrexate				
Failure to enter remission or possible remission at 24-36 weeks (Oren 1997)	**594 per 1000[1]**	**808 per 1000** (576 to 1140)	**RR 1.36** (0.97 to 1.92)	58 (1 study)	⊕⊕⊝⊝ **low[2,3]**	

Failure to enter remission or possible remission at 24-36 weeks (Maté-Jiménez 2000 **)**	63 per 1000[1]	202 (23 to 1732)	RR 3.20 (0.37 to 27.49)	31 (1 study)	⊕⊖⊖⊖ **very low[4,5]**
Failure to enter remission or possible remission at 24-36 weeks (Ardizzone 2003 **)**	370 per 1000[1]	444 (233 to 847)	RR 1.20 (0.63 to 2.29)	54 (1 study)	⊕⊖⊖⊖ **very low[6,7]**
Adverse events (Ardizzone 2003)	**259 per 1000[1]**	**629 per 1000** (313 to 1267)	**RR 2.43** (1.21 to 4.89)	54 (1 study)	⊕⊖⊖⊖ **very low[7,8]**
Withdrawal due to adverse event (Oren 1997)	**31 per 1000[1]**	**38per 1000** (2 to 581)	**RR 1.23** (0.08 to 18.74)	58 (1 study)	⊕⊖⊖⊖ **very low[9,10]**
Withdrawal due to adverse event (Maté-Jiménez 2000 **)**	63 per 1000[1]	134 per 1000 (14 to 1334)	RR 2.13 (0.22 to 21.17)	31 (1 study)	⊕⊖⊖⊖ **very low[5,11]**
Withdrawal due to adverse event (Ardizzone 2003 **)**	111 per 1000[1]	111 per 1000 (24 to 502)	RR 1.00 (0.22 to 4.52)	54 (1 study)	⊕⊖⊖⊖ **very low[7,12]**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk Ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Control group risk comes from control arm of each individual study
2. Rated down due to sparse data (35 events)
3. Unknown risk of bias for random sequence generation and allocation concealment
4. Rated down due to very sparse data (4 events)
5. High risk of bias due to no blinding
6. Rated down due to very sparse data (22 events)
7. High risk of bias due to investigator-only blinding
8. Rated down due to very sparse data (24 events)
9. Rated down due to very sparse data (2 events)
10. Unknown risk of bias for random sequence generation and allocation concealment
11. Rated down due to very sparse data (2 events)
12. Rated down due to very sparse data (6 events)

Summary of findings 3. Methotrexate compared to 5-ASA for induction of remission in refractory Crohn's disease

Methotrexate compared to 5-ASA for induction of remission in refractory Crohn's disease

Patient or population: Adult patients with refractory Crohn's disease

Settings: Outpatient

Intervention: Methotrexate

Comparison: 5-ASA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5-ASA	Methotrexate				
Failure to enter remission or possible remission at 30 weeks (Maté-Jiménez 2000)	**857 per 1000**[1]	**197 per 1000** (69 to 574)	**RR 0.23** (0.08 to 0.67)	22 (1 study)	⊕⊝⊝⊝ **very low**[2,3]	
Withdrawal due to adverse event (Maté-Jiménez 2000)	**0 per 1000**[1]	**133 per 1000** (7 to 2454)	**RR 2.5** (0.14 to 46.14)	22 (1 study)	⊕⊝⊝⊝ **very low**[3,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Control group risk comes from control arm of each individual study
2. Rated down due to very sparse data (9 events)
3. High risk of bias due to no blinding
4. Rated down due to very sparse data (2 events)

Summary of findings 4. Methotrexate + infliximab compared to infliximab alone for induction of remission in refractory Crohn's disease

Methotrexate compared with Infliximab for refractory Crohn's disease

Patient or population: adult patients with refractory Crohn's disease

Settings: Outpatient

Intervention: Methotrexate + infliximab

Comparison: Infliximab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Infliximab	Methotrexate + infliximab				
Failure to enter remission at 14 weeks or 24 weeks (Feagan 2014)	**222 per 1000[1]**	**238 per 1000** (127 to 451)	**RR 1.07** (0.57 to 2.03)	126 (1 study)	⊕⊕⊖⊖ **low[2]**	
Failure to enter remission at 14 weeks or 24 weeks (Schröder 2006)	**625 per 1000[1]**	**456 per 1000** (194 to 1056)	**RR 0.73** (0.31 to 1.69)	19 (1 study)	⊕⊖⊖⊖ **very low[3,4]**	
Adverse events (Schröder 2006)	**625 per 1000[1]**	**638 per 1000** (324 to 1281)	**RR 1.02** (0.51 to 2.05)	19 (1 study)	⊕⊖⊖⊖ **very low[4,5]**	
Serious adverse events (Schröder 2006)	**125 per 1000[1]**	**0per 1000** (1 to 681)	**RR 0.25** (0.01 to 5.45)	19 (1 study)	⊕⊖⊖⊖ **very low[4,6]**	
Withdrawals due to adverse event (Feagan 2014)	**16 per 1000[1]**	**32 per 1000** (3 to 344)	**RR 2.00** (0.19 to 21.50)	126 (1 study)	⊕⊕⊖⊖ **low[7]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1.Control group risk comes from control arm of study
2.Rated down due to very sparse data (29 events)
3.Rated down due to very sparse data (10 events)
4.High risk of bias due to no blinding
5.Rated down due to very sparse data (12 events)
6.Rated down due to very sparse data (1 event)
7.Rated down due to very sparse data (3 events)

BACKGROUND

Although corticosteroids are effective for induction of remission of Crohn's disease, approximately 20% of patients who respond relapse when steroids are withdrawn and become steroid dependent (Binder 1985). Furthermore, corticosteroids exhibit significant adverse effects. Other immunosuppressive agents have been used to try to induce remission of Crohn's disease or reduce the dose of corticosteroid required in corticosteroid dependent patients. A recently updated Cochrane review indicates that purine antimetabolites (i.e. azathioprine or 6-mercaptopurine) are not effective for induction of remission in Crohn's disease but may have steroid sparing effects in patients with refractory Crohn's disease (Chande 2013). The use of these agents varies widely among practitioners, perhaps because of concern about adverse effects and efficacy. Cyclosporine has been found to be ineffective for treatment of Crohn's disease and is a nephrotoxic drug (McDonald 2005). The success of methotrexate as a treatment for rheumatoid arthritis led to its evaluation in patients with refractory Crohn's disease (Baron 1993; Houben 1994). Methotrexate has been studied for induction of remission of refractory Crohn's disease and has become the principal alternative to azathioprine or 6-mercaptopurine therapy. The objective of this systematic review was to assess the efficacy and safety of methotrexate for the treatment of active refractory Crohn's disease. This systematic review is an update of previously published Cochrane reviews (Alfadhli 2004; McDonald 2012).

OBJECTIVES

The primary objective was to assess the efficacy and safety of methotrexate used for the treatment of active refractory Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing oral or parenteral methotrexate with a placebo or a control medication were considered for inclusion.

Types of participants

Patients greater than 17 years of age with refractory Crohn's disease defined by conventional clinical, radiological and endoscopic criteria, which was categorized as being active (Crohn's disease activity index 'CDAI' > 150) in the presence or in the absence of concomitant steroid therapy were considered for inclusion.

Types of interventions

Trials where at least one arm of the study received oral or parenteral methotrexate were considered for inclusion.

Types of outcome measures

In most clinical trials in Crohn's disease, disease activity is assessed using a validated clinical index, the Crohn's disease activity index (CDAI) or the Harvey Bradshaw score (HBS). These indices share specific variables and values and are interchangeable (Harvey 1980). In some clinical trials a validated disease specific quality of life score (IBDQ) was also employed.

Primary outcomes

The primary outcome was the proportion of patients who failed to enter clinical remission and withdraw from steroids.

Secondary outcomes

Secondary outcomes included:

- Adverse events;
- Withdrawal due to adverse events;
- Serious adverse events; and
- Quality of life (IBDQ) score.

Search methods for identification of studies

A computer assisted search of the Cochrane IBD/FBD Review Group Specialized Trials Register and the on-line databases MEDLINE,EMBASE, and CENTRAL was performed to identify relevant publications from inception to 9 June 2014. Manual searches of reference lists from potentially relevant papers were performed in order to identify additional studies that may have been missed using the computer assisted search strategy. Review articles and conference proceedings were also searched to identify additional studies. The search strategies are reported in Appendix 1.

Data collection and analysis

Study selection: The publications were assessed independently by two authors (YW and JKM), and relevant studies were selected according to the inclusion criteria. Any disagreement among authors was resolved by consensus.

Data extraction: Two authors (YW and JKM) independently extracted data. The outcome data of interest were the number of patients randomized into each treatment group and the number of patients in each group who failed to enter remission. The numbers lost to follow-up and the duration of follow-up were also recorded. Treatment and control modalities were summarized, as were the demographics of the study population. In cases where the necessary data were not available from the published report, the authors were contacted and asked to supply missing data. However, no further information has been supplied to date.

The methodological quality of the included studies was evaluated using the Cochrane risk of bias tool (Higgins 2011). This tool involves rating trials as high, low or unclear risk for each of the following criteria:

1. Randomization sequence generation;
2. Allocation concealment;
3. Blinding;
4. Missing data and attrition;
5. Outcome reporting; and
6. Other sources of bias.

The overall quality of the evidence was evaluated using the GRADE approach (Guyatt 2008; Schünemann 2011). Outcome data were rated as high, moderate, low or very low quality evidence. Data from randomized controlled trials begin as high quality but can be downgraded based on the following criteria:

1. Risk of bias in the included trials;

2. Indirect evidence;
3. Inconsistent findings (including unexplained heterogeneity);
4. Imprecision (i.e. sparse data or wide confidence intervals); and
5. Reporting bias.

The different quality ratings are interpreted as the likelihood that future research would affect the estimate of effect. An estimate of effect based on high quality evidence is unlikely to change with further research. If the overall evidence is of moderate quality further research may have an impact on our confidence in the estimate and may change the estimate. Low quality evidence is likely to have an impact on the effect estimate. Very low quality research means that we are very uncertain about the finding (Guyatt 2008; Schünemann 2011).

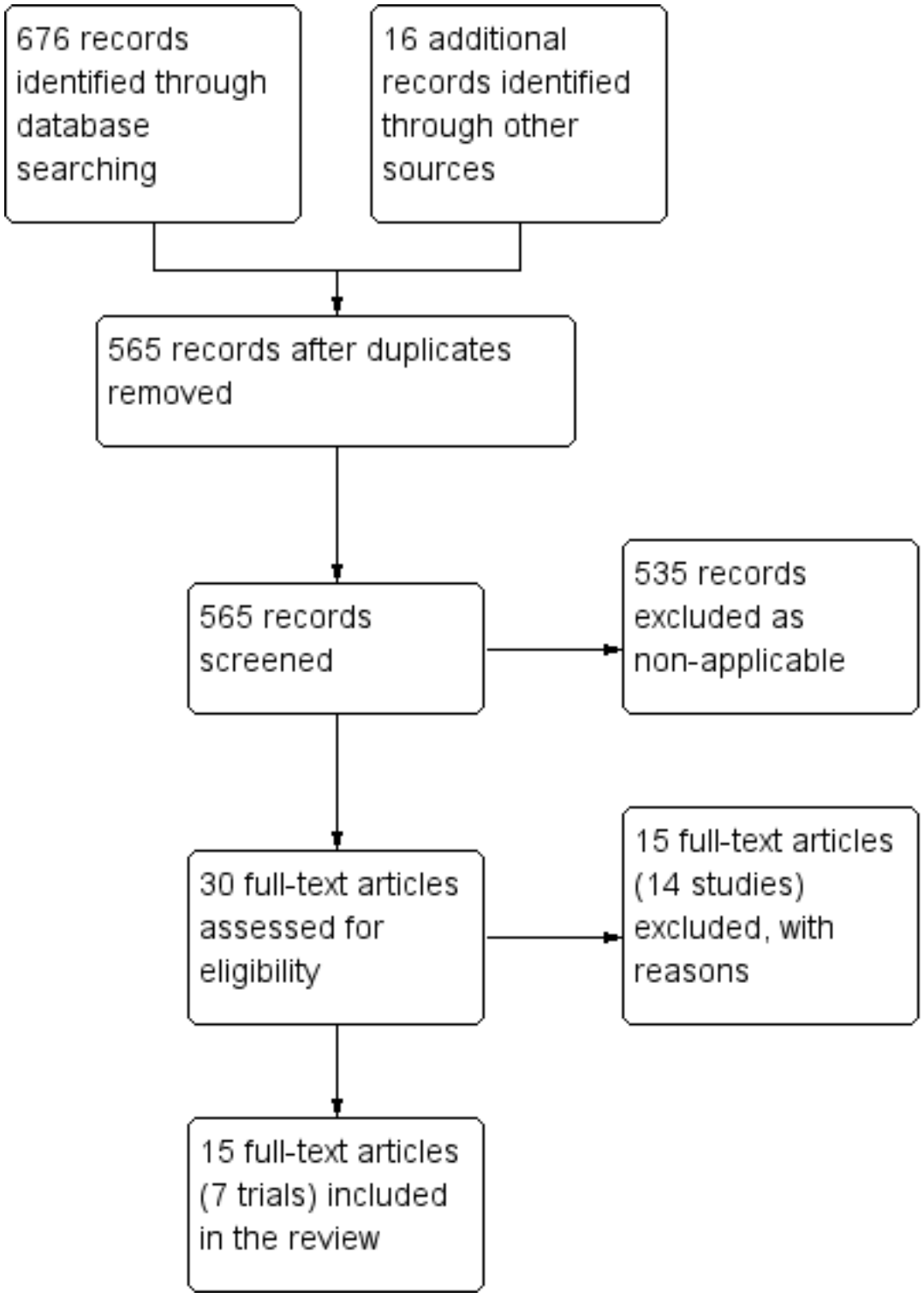
Statistical Analysis: Data were analysed using Review Manager (RevMan 5.3). We calculated the risk ratio and corresponding 95% confidence interval (95% CI) for dichotomous outcomes. Trials were first reviewed to assess the clinical comparability of the trial protocols and study populations. If the trials were apparently comparable it was planned to next examine the homogeneity of the outcomes from the various trials to assess the statistical validity of combining the results of the various trials. This would be carried out using the Chi^2 test.

RESULTS

Description of studies

A literature search conducted on June 9, 2014 identified 692 records. After duplicates were removed, a total of 565 records remained for review of titles and abstracts. Two authors (YW and JKM) independently reviewed the titles and abstracts of these trials and 30 records were selected for full text review (see Figure 1). Fifteen reports of 14 studies were excluded (See: Characteristics of excluded studies). Fifeteen reports of seven trials (total of 495 patients) met the pre-defined inclusion criteria and were included in the review (Ardizzone 2003; Arora 1999; Feagan 1995; Feagan 2014; Maté-Jiménez 2000; Oren 1997; Schröder 2006). No new studies were identified for this update.

Figure 1. Study flow diagram.



Ardizzone 2003 conducted a randomized, single center, investigator blinded comparison of intravenous and oral methotrexate versus oral azathioprine for the treatment of chronic active Crohn's disease (N = 54). The aim of the study was to evaluate the efficacy and safety of methotrexate in comparison to azathioprine and to establish whether methotrexate has a shorter onset of action. Chronicity was defined as the need for steroid therapy of ≥ 10 mg/day for at least four months during the preceding 12 months with at least one attempt to discontinue treatment and a CDAI ≥ 200. Patients in the methotrexate group (n = 27) received 25 mg/week intravenously for three months and then were switched to oral administration at the same dosage for the next three months.

Patients in the azathioprine group (n = 27) received 2 mg/kg/day for six months. The primary outcome was the proportion of patients entering first remission after three and six months of treatment. Clinical remission was defined as complete withdrawal from corticosteroid therapy and CDAI ≤ 150. Secondary outcomes included decrease in steroid requirements, decrease in mean CDAI scores, decrease in mean CRP and ESR and fistula closure. At the end of three months 44% (12/27) of methotrexate treated patients were in remission compared to 33% (9/27) who received azathioprine (P = 0.28). The respective figures at six months were 56% and 63% (P = 0.39). There were no statistically significant differences in the proportion of patients who withdrew due to adverse events. However, drug related adverse events occurred more frequently in the methotrexate group (P < 0.001). Although Ardizzone 2003 concluded that the results did not support a more rapid treatment effect of methotrexate it should be noted that the number of patients studied in the trial was inadequate to address this question. In fact, the 11% absolute difference in favour of methotrexate is consistent with a clinically meaningful difference in the three month remission rates (95% CI for the 11% difference; -36.9 to 15%).

Arora 1999 randomized 33 patients who had Crohn's disease that was prednisone-dependent for at least six months with CDAI > 150 on 10 mg/day of prednisone or < 150 on prednisone dose of ≥ 15 mg/day. Patients received either placebo or methotrexate 15 mg/week orally with dose escalation to a maximum of 22.5 mg/week according to clinical response. Outcome was assessed by reduction in prednisone dosage, CDAI, hospital admission and laboratory parameters. Treatment failure was defined as no improvement in the CDAI at 3 months with any reduction in steroid dose or the development of severe clinical illness. Four patients were dropped from the study for non-compliance and one because of intercurrent illness, and 28 patients could be evaluated. There was no statistically significant difference (P = 0.142) in exacerbations of Crohn's disease between methotrexate-treated patients (6/13) and placebo-treated patients (12/15). There was no statistically significant difference (P = 0.175) in the number of adverse effects in methotrexate-treated patients (3/13) as compared to the placebo-treated patients (0/15).

Feagan 1995 conducted a randomized, multicenter, double blind placebo-controlled trial of intramuscular methotrexate in patients with chronic steroid-dependent Crohn's disease (N = 141). Eligible patients had chronically active Crohn's disease with at least three months of symptoms despite a daily dose of at least 12.5 mg of prednisone with at least one attempt to discontinue treatment. A total of 141 patients were randomly assigned in a 2:1 ratio to receive either 25 mg/wk methotrexate (n = 94 patients) or placebo (n = 47 patients). Remission was defined as discontinuation of prednisone therapy and CDAI score of < 150 point at the end of 16 weeks. After 16 weeks, 37 patients (39.4 percent) were in clinical remission in the methotrexate group compared to 9 patients (19.1 percent) in the placebo group (P = 0.025). Patients in the methotrexate group received less prednisone overall than those in the placebo group (P = 0.026). The mean score on the Crohn's Disease Activity Index after 16 weeks of treatment was significantly lower in the methotrexate group (162 +/- 12) than in the placebo group (204 +/- 17, P = 0.002). In the methotrexate group, 16 patients (17 percent) withdrew from treatment because of adverse events as compared with 1 patient (2 percent) in the placebo group (P = 0.012).

Feagan 2014 conducted a randomized, double-blind, multicenter trial comparing the combination of methotrexate and infliximab to infliximab monotherapy in patients with active Crohn's disease. One-hundred and twenty-six patients were randomized to infliximab or placebo (monotherapy, n = 63) or infliximab and methotrexate (combination therapy, n = 63) for 50 weeks of treatment. All patients received prednisone during the study with tapering of doses beginning after week 1. Infliximab was given intravenously at 5 mg/kg at weeks 1, 3, 7, 14, 22, 30, 38, and 46. Methotrexate doses were given subcutaneously and gradually increased to 25 mg/week by week 25. Remission was defined as CDAI < 150. The primary outcomes were failure to achieve remission by week 14 and failure to maintain remission by week 50. Those not in remission by week 14 were withdrawn from the maintenance phase. Other outcomes included number of patients who achieved and maintained remission, change in CDAI, SF-36 and c-reactive protein, serum infliximab levels, and antibodies to infliximab. At week 14, 15/63 and 14/63 patients receiving combination therapy and monotherapy respectively failed to enter remission.

Maté-Jiménez 2000 conducted a randomized single center comparison of oral methotrexate, oral 6-mercaptopurine and oral 5-ASA for the treatment of chronic steroid-dependent inflammatory bowel disease (N = 72). Steroid dependence was defined as those patients whose prednisone could not be lowered to 20 mg/day without presenting inflammatory activity determined by a CDAI score of ≥ 200 or having presented more than two episodes in the last six months or more than three in the last 12 months. None of the patients received methotrexate or 6-mercaptopurine prior to entry. Thirty-eight patients with Crohn's disease were randomized to 15 mg/week methotrexate (n = 15), 1.5 mg/kg/day 6-mercaptopurine (n = 16) or 3 g/day 5-ASA for 30 weeks of treatment. The primary outcome was clinical remission defined as stopping prednisone and a CDAI of < 150 and a normal serum orosomucoid concentration. No statistically significant differences in remission rates were found between the methotrexate (12/15, 80%) and 6-mercaptopurine groups (15/16, 94%). A statistically significant difference in remission rate was found between the methotrexate and 5-ASA (1/7, 14%, P < 0.01) groups and between the 6-mercaptopurine and 5-ASA groups (P < 0.001). There were no statistically significant differences in the proportion of patients who withdrew due to adverse events (methotrexate 2/15, 6-MP 1/15, 5-ASA 0/7).

Oren 1997 conducted a multicenter, randomized, double blind placebo-controlled trial assessing the efficacy of oral methotrexate in chronic steroid-dependent Crohn's disease. The study included patients with active Crohn's disease, who had received steroids or immunosuppressives or both for at least 4 months during the preceding 12 months and with current HBS of >7 (no immunosuppressive therapy 3 months prior to entry). Patients were randomized to one of three treatment arms: placebo, oral methotrexate 12.5 mg/week, or oral 6-mercaptopurine 50 mg daily for nine months in addition to steroids and 5-aminosalicylic acid as clinically indicated. The authors defined four outcomes without defining a primary outcome:
1) The proportion of patients entering first remission which was defined as HBS < 3 and the patients not receiving steroids;
2) Maintenance of remission in those patients entering remission;
3) Decrease in steroid requirement during the study; and
4) General well being at the beginning and throughout the study.

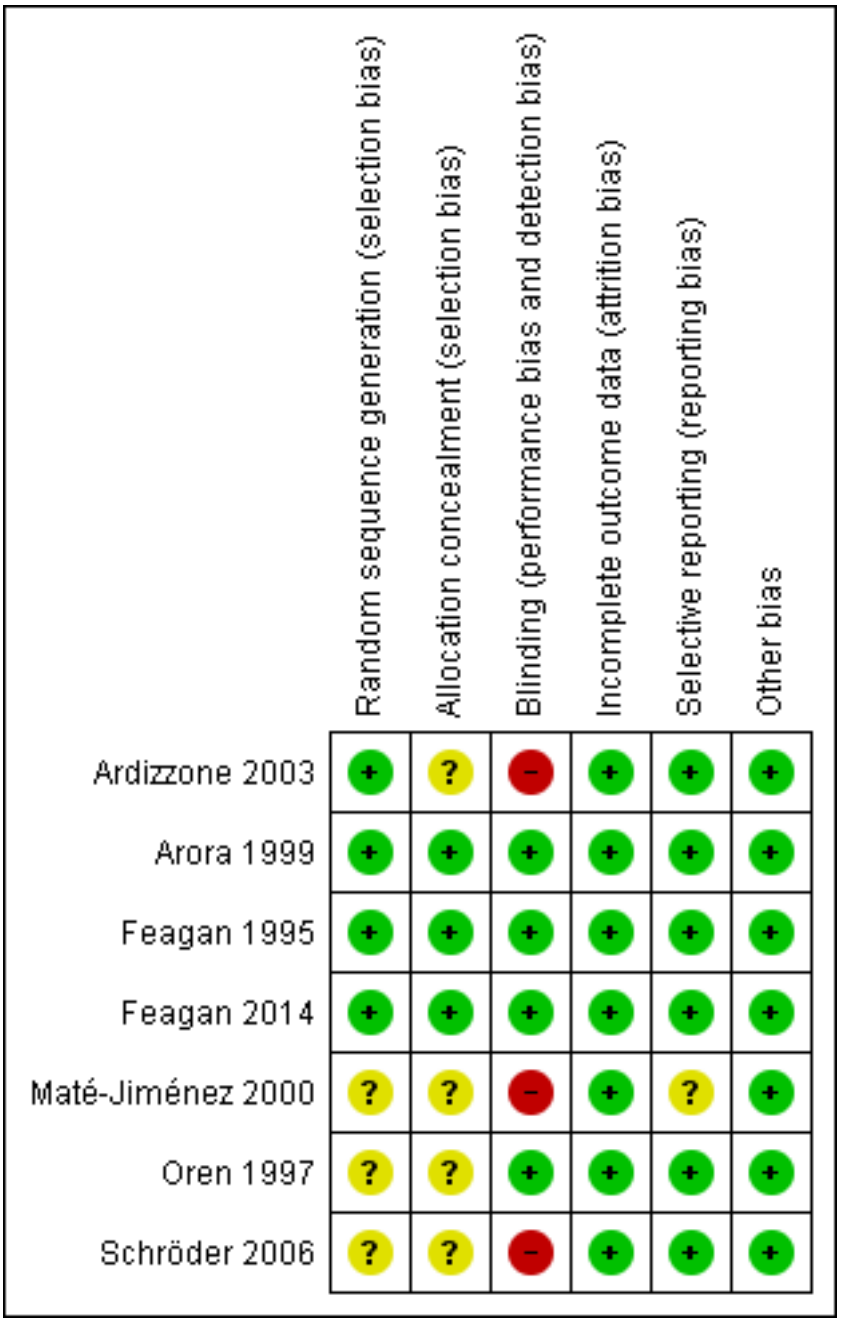
Eighty-four patients were included (methotrexate, 26 patients; 6-mercaptopurine, 32 patients; placebo, 26 patients). There was no statistically significant difference between the groups in the proportion of patients entering first remission or the proportion of patients relapsing after first remission. The Harvey-Bradshaw score and the mean monthly steroid doses were not different between the two groups.

Schröder 2006 recruited 19 patients with Crohn's disease to an open label study comparing infliximab monotherapy (n = 8) to infliximab and methotrexate (combination therapy, n = 11). Patients were eligible if they had chronically active Crohn's disease (steroid-dependent or steroid-refractory and resistant or intolerant to azathioprine therapy). Patients could not be taking more than 4 g/day of an 5-aminosalicylate or less than 40 mg/day of prednisolone. The trial lasted 48 weeks. All patients received two infusions of infliximab at 5 mg/kg at week zero and two. Patients randomized to methotrexate received six infusions of methotrexate (20 mg/week) on weeks zero to five, they then were administered oral methotrexate (20 mg/week) for the remainder of the study. Remission was defined as CDAI < 150. Secondary outcomes included time to clinical remission and steroid doses. Ten of 11 patients in the combination group and four of eight patients receiving monotherapy achieved remission at some point in the trial (P = 0.04). This outcome was also assessed at various weeks throughout the study. At 24 weeks, 6/11 and 3/8 patients in the combination and monotherapy groups respectively achieved remission (P = 0.65). Six of the 19 patients withdrew from the trial, primarily due to lack of efficacy.

Risk of bias in included studies

Figure 2 summarizes the risk of bias analysis for the included studies. Four studies described the methods used for random sequence generation and were rated as low risk of bias for that item (Ardizzone 2003; Arora 1999; Feagan 1995; Feagan 2014). Three studies reported adequate methods for allocation concealment and were rated as low risk for that item (Arora 1999; Feagan 1995; Feagan 2014). Four studies did not describe methods used for allocation concealment and were rated as unclear risk for this item (Ardizzone 2003; Maté-Jiménez 2000; Oren 1997; Schröder 2006). Three studies were rated as high risk of bias for blinding due to open label (Maté-Jiménez 2000; Schröder 2006) or investigator blind (Ardizzone 2003) designs. All of the included trials were rated as low risk of bias for incomplete outcome data (Ardizzone 2003; Arora 1999; Feagan 1995; Feagan 2014; Maté-Jiménez 2000; Oren 1997; Schröder 2006). Maté-Jiménez 2000 was rated as unclear risk of bias for selective reporting because of a post hoc outcome. No other issues were found with the trials and they were rated as low risk of bias for the other bias item (Ardizzone 2003; Arora 1999; Feagan 1995; Feagan 2014; Maté-Jiménez 2000; Oren 1997; Schröder 2006).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Methotrexate compared to placebo for induction of remission in refractory Crohn's disease; **Summary of findings 2** Methotrexate compared to 6-MP or azathioprine for induction of remission in refractory Crohn's disease; **Summary of findings 3** Methotrexate compared to 5-ASA for induction of remission in refractory Crohn's disease; **Summary of findings 4** Methotrexate + infliximab compared to infliximab alone for induction of remission in refractory Crohn's disease

The seven included studies differed with respect to participants, intervention, and outcomes to the extent that it was considered to be inappropriate to pool the data for meta-analysis. Although in three studies methotrexate was administered orally in low doses these studies were sufficiently heterogeneic in terms of methotrexate dose, treatment duration, disease duration and steroid use that it was not valid to combine the data. GRADE analyses were performed on individual studies instead of pooled data.

Two studies which employed low doses of oral methotrexate showed no statistically significant difference for induction of remission between methotrexate and placebo treated patients. The Arora 1999 study reported that 33% (5/15) of methotrexate patients and 11% (2/18) of placebo patients failed to enter remission (RR

3.00, 95% CI 0.68 to 13.31). A GRADE analysis indicated that the overall quality of the evidence supporting the primary outcome was low due to very sparse data (7 events, See Summary of findings for the main comparison). Oren 1997 reported that 62% (16/26) and 54% (14/26) of patients receiving methotrexate and placebo, respectively, failed to enter remission (RR 1.14, 95% CI 0.72 to 1.82). A GRADE analysis indicated that the overall quality of the evidence supporting the primary outcome was low due sparse data (30 events) and unknown risk of bias for random sequence generation and allocation concealment (See Summary of findings for the main comparison).

The Feagan 1995 study which employed a higher dose of intramuscularly administered methotrexate showed a statistically significant benefit relative to placebo. Sixty-one per cent (57/94) of methotrexate patients failed to achieve remission compared to 81% (38/47) of placebo patients (RR 0.75, 95% CI 0.61 to 0.93; number needed to treat, NNT=5). This study also demonstrated a statistically significant improvement in quality of life with methotrexate treatment (IBDQ: methotrexate 169 +/- 4, placebo 151+/- 6 , P < 0.002). A GRADE analysis indicated that the overall quality of the evidence supporting the primary outcome was moderate due to sparse data (95 events, see Summary of findings for the main comparison).

A number of studies compared methotrexate to other active comparators. Oren 1997 found no statistically significant difference for induction of remission between oral methotrexate and oral 6-mercaptopurine. Sixty-two per cent (16/26) of methotrexate patients failed to enter remission compared to 59% (19/32) of 6-mercaptopurine patients (RR 1.04, 95% CI 0.68 to 1.57). A GRADE analysis indicated that the overall quality of the evidence supporting the primary outcome was low due to sparse data (35 events) and unknown risk of bias for random sequence generation and allocation concealment (See Summary of findings 2). Maté-Jiménez 2000 also found no statistically significant difference for induction of remission, with 20% (3/15) and 6% (1/16) of patients receiving oral methotrexate and oral 6-mercaptopurine, respectively, failing to enter remission (RR 3.20, 95% CI 0.37 to 27.49). A GRADE analysis indicated that the quality of evidence supporting this outcome is very low due to sparse data and lack of blinding (4 events, See Summary of findings 2). However, Maté-Jiménez 2000 did find a statistically significant difference in efficacy between oral methotrexate and oral 5-ASA. Twenty per cent (3/15) of patients administered methotrexate and 86% (6/7) of patients administered 5-ASA failed to enter remission (RR 0.23, 95% CI 0.08 to 0.67). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (9 events) and lack of blinding (See Summary of findings 3). Ardizzone 2003 found no statistically significant difference in induction of remission between patients treated with methotrexate (intravenous followed by oral administration) and oral azathioprine. Forty-four per cent (12/27) of methotrexate patients failed to enter remission compared to 37% (10/27) of azathioprine patients (RR 1.20, 95% CI 0.63 to 2.29). A GRADE analysis indicated that the quality of the evidence supporting this outcome was very low due to sparse data (22 events) and investigator-only blinding (See Summary of findings 2).

Schröder 2006 found no advantage for induction of remission with the combination of intravenous and oral methotrexate with infliximab compared to infliximab alone. Forty-five per cent (5/11) of patients in the combination group failed to enter remission compared to 63% (5/8) of patients in the infliximab only group (RR 0.73, 95% CI 0.31 to 1.69). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (10 events) and lack of blinding (See Summary of findings 4) Feagan 2014 also found no advantage for induction of remission with the combination of subcutaneous methotrexate with infliximab compared to infliximab alone. Twenty-four per cent (15/63) of patients receiving subcutaneous methotrexate and infliximab failed to enter remission compared to 22% (14/63) of patients receiving infliximab (RR 1.07, 95% CI 0.57 to 2.03). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to sparse data (29 events, See Summary of findings 4).

The three trials that employed low dose oral methotrexate (Arora 1999; Maté-Jiménez 2000; Oren 1997), and two trials which employed a higher dose of intravenous and oral methotrexate (Ardizzone 2003; Schröder 2006), included relatively small numbers of patients and may have lacked power to show a benefit of this form of therapy if such a benefit exists. In two of these trials it was difficult to be certain from the published results of the precise numbers of patients who were in clinical remission and the status of these patients with respect to continued steroid treatment (Arora 1999; Oren 1997). The term 'possible remission' has been used to reflect this uncertainty.

Two studies reported the proportion of patients who experienced at least one adverse event (Ardizzone 2003; Schröder 2006). The proportion of patients who experienced at least one adverse event was significantly higher in methotrexate patients compared to azathioprine. Ardizzone 2003 reported that 63% (17/27) of methotrexate patients experienced at least one adverse event compared to 26% (7/27) of azathioprine patients (RR 2.43, 95% CI 1.21 to 4.89). Schröder 2006 reported no significant difference in adverse events between the combination of methotrexate and infliximab compared to infliximab monotherapy. Sixty-four per cent (7/11) of patients in the combination therapy group experienced at least one adverse event compared to 63% (5/8) of patients in the infliximab monotherapy group (RR 1.02, 95% CI 0.51 to 2.05).

Withdrawal due to adverse events was significantly more common with high dose intramuscular methotrexate therapy than with placebo. Feagan 1995 reported that 17% (16/94) of methotrexate patients withdrew due to adverse events compared to 2% (1/47) of placebo patients (RR 8.00, 95% CI 1.09 to 58.51).A GRADE analysis indicated that the quality of the evidence supporting this outcome was low due to very sparse data (17 events, see Summary of findings for the main comparison). Withdrawal due to adverse events may be more common with high dose intramuscular therapy than with low dose oral drug. Arora 1999 reported that 20% (3/15) of methotrexate patients withdrew due to an adverse event compared to 0% (0/18) of placebo patients (RR 8.31, 95% CI 0.46 to 149.21). A GRADE analysis indicated that the quality of the evidence supporting this outcome was low due to very sparse data (3 events, See Summary of findings for the main comparison). Oren 1997 reported that 4% (1/26) of methotrexate patients withdrew due to adverse events compared to 0% (0/26) of placebo patients (RR 3.00, 95% CI 0.13 to 70.42). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data and and unknown risk of bias for random sequence generation and allocation concealment (1 event, See Summary of findings

for the main comparison). Moreover, there were no statistically significant differences in withdrawal due to adverse events in the trials looking at the efficacy of methotrexate compared to active comparators. Ardizzone 2003 reported that 11% (3/27) of methotrexate patients withdrew due to adverse events compared to 11% (3/27) of azathioprine patients (RR 1.00, 95% CI 0.22 to 4.52). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (6 events) and single blinding (See Summary of findings 2). Maté-Jiménez 2000 reported that 13% (2/15) of methotrexate patients withdrew due to adverse events compared to 6% (1/16) of 6-mercaptopurine patients (RR 2.13, 95% CI 0.22 to 21.17). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (2 events) and lack of blinding. (see Summary of findings 2). Furthermore, Oren 1997 reported 4% (1/26) and 3% (1/32) of patients receiving methotrexate and 6-mercaptopurine, respectively, withdrew due to adverse events (RR 1.23, 95% CI 0.08 to 18.74). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (2 events) and an unknown risk of bias for random sequence generation and allocation concealment (See Summary of findings 2). Maté-Jiménez 2000 reported that 13% (2/15) of methotrexate patients withdrew due to adverse events compared to 0% (0/7) of 5-ASA patients (RR 2.50, 95% CI 0.14 to 46.14). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (2 events) and lack of blinding (see Summary of findings 3). With respect to the combination of methotrexate and infliximab, Schröder 2006 reported no withdrawals due to adverse events in either group (0/11 combination therapy; 0/8 infliximab alone). Feagan 2014 reported no statistically significant difference in withdrawals due to adverse events between patients receiving combination therapy with methotrexate and infliximab and infliximab alone. Three per cent (2/63) of patients receiving methotrexate and infliximab withdrew due to adverse events compared to 2% (1/63) of patients receiving infliximab alone (RR 2.00, 95% CI 0.19 to 21.50). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (3 events, See Summary of findings 4).

One trial reported on serious adverse events (Schröder 2006). There was no statistically significant difference in the incidence of serious adverse events between infliximab and methotrexate and infliximab alone. Zero per cent (0/11) of patients receiving methotrexate and infliximab experienced a serious adverse event compared to 13% (1/8) of patients who received infliximab alone (RR 0.25, 95% CI 0.01 to 5.45). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to very sparse data (1 event) and no blinding (see Summary of findings 4). Common adverse events reported in the studies included nausea and vomiting (Feagan 1995; Ardizzone 2003; Feagan 2014), abdominal pain (Feagan 1995; Feagan 2014), diarrhea (Feagan 1995; Feagan 2014), skin rash (Feagan 1995; Feagan 2014) and headache (Feagan 1995; Ardizzone 2003; Schröder 2006).

DISCUSSION

Crohn's disease is a chronic idiopathic inflammatory disorder characterized by recurrent exacerbations and remissions. Corticosteroids have been the mainstay of therapy for the induction of remission in patients with Crohn's disease. However, 20% of patients become steroid dependent (Binder 1985). Physicians attempt to avoid prolonged steroid therapy because of the frequency and severity of adverse effects. As a result, many physicians attempt to introduce steroid sparing agents such as methotrexate, azathioprine or 6-mercaptopurine.

The interest in methotrexate for the treatment of inflammatory bowel disease originated from an uncontrolled study in which 12 weeks of intramuscular methotrexate at a dose of 25 mg/wk resulted in a significant response in 5 of 7 patients with refractory ulcerative colitis and 11 of 14 patients with Crohn's disease (Kozarek 1989). Randomized trials were subsequently performed.

Seven randomized controlled trials were identified. Methotrexate was superior to placebo in one trial (Feagan 1995), which included the largest number of patients and utilized intramuscular administration of the drug at a high dose. Two other trials (Oren 1997; Arora 1999) showed no statistically significant difference between low dose oral methotrexate and placebo treated patients (Oren 1997; Arora 1999). These trials may have failed to show a benefit of methotrexate in refractory Crohn's disease because they used lower doses of the drug (12.5 to 15 mg/week compared to 25 mg/week) and oral administration. Both studies included relatively small numbers of patients and the failure to show a difference between the treatment and control groups may have been due to insufficient statistical power. One trial assessed quality of life and demonstrated a clinically significant improvement in quality of life in methotrexate patients compared to placebo (Feagan 1995).

Two studies looked at the efficacy of methotrexate compared to azathioprine (Ardizzone 2003), 6-mercaptopurine (Maté-Jiménez 2000), and 5-ASA (Maté-Jiménez 2000). These trials included small numbers of patients and the failure to show a difference between treatment groups may be due to a lack of statistical power. The statistically significant result favouring methotrexate over 5-ASA for induction of remission reported by Maté-Jiménez 2000 needs to be interpreted with caution due to the small numbers of patients enrolled. Oren 1997 attempted to compare response rates of azathioprine, oral methotrexate and placebo. This study used low doses of both drugs, enrolled small numbers of patients and did not show any statistically significant difference with placebo for either drug. None of these trials provide sufficient evidence to assess the efficacy of oral or intravenous methotrexate compared to other active medications used for the treatment of Crohn's disease. To compare the relative efficacy of azathioprine and 6-mercaptopurine to methotrexate the randomization of large numbers of patients would be required.

In clinical practice, intramuscular administration is associated with higher costs and compromised patient quality of life because of the need for increased clinic visits. Subcutaneous injection can be used as an alternative method of parenteral administration. It has been shown to have similar pharmacokinetics to intramuscular injection, is easier to administer and leads to greater patient comfort and reduced local complication rate at the injection site than intramuscular injection (Balis 1988; Brooks 1990; Egan 1999b).

Two studies compared the combination of methotrexate and infliximab to infliximab monotherapy. Schröder 2006 was a small, open label trial and found no difference in efficacy between infliximab monotherapy and the combination of methotrexate (intravenous infusions and oral) and infliximab. Feagan 2014 was a larger, double-blind trial which also found no difference in efficacy between the combination of methotrexate (subcutaneous) and

infliximab and infliximab monotherapy. Further research is needed to determine whether the addition of methotrexate to infliximab or other biological therapies has any benefit for patients with refractory Crohn's disease. Future research should also determine which route of administration is most effective.

Adverse events were observed in approximately equal frequency in the methotrexate treated (45%) and control (42%) groups in the study reported by Feagan 1995. However, 17% of the methotrexate treated patients were withdrawn from treatment because of adverse events, compared to 2% in the placebo group (P = 0.012). The most common reasons for withdrawal were nausea and vomiting (6 patients) and asymptomatic elevation of liver enzymes (7 patients). No serious adverse effects were observed. Although the design of this study resulted in withdrawal of these patients, in clinical practice in patients with rheumatoid disease, adverse effects such as nausea are often dealt with or prevented by the concomitant administration of folic acid (Griffith 2000, Lorenzi 2000), and asymptomatic elevations of transaminases are not considered to reflect or predict existing or future hepatic disease (Kremer 1994).

In the three trials that employed lower doses of oral methotrexate no serious adverse effects were observed (Arora 1999; Maté-Jiménez 2000; Oren 1997). However, in one trial ALT levels were increased in 53% of patients receiving methotrexate, compared to 22% of patients receiving placebo (Arora 1999). No clinically significant hepatotoxicity was observed in any patient.

On the basis of a single large randomized trial methotrexate appears to be safe and effective medication for induction of remission in patients with refractory Crohn's disease when administered parenterally at a dose of 25 mg weekly. There is no evidence that lower doses administered orally are effective.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from a single large randomized trial which suggests that intramuscular methotrexate (25 mg/week) provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory Crohn's disease. Lower dose oral methotrexate does not appear to provide any benefit relative to relative to placebo or active comparator (e.g. azathioprine or 6-mercaptopurine). The addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infiximab monotherapy.

Implications for research

Trials of lower doses of methotrexate administered orally may be justified. Comparative studies of methotrexate to other immunomodulatory drugs such as azathioprine and 6-mercaptopurine would require the randomization of large numbers of patients. Further research is needed to determine the role of methotrexate when used in conjunction with infliximab or other biological therapies.

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* Egan LJ, Sandborn WJ, Leighton JA, Mays DC, Pike MG, Zinsmeister AR, et al. A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 1999;**13**:1597-604. [PUBMED: 10594394]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ardizzone 2003

Methods	Randomized, investigator blind, 1 center, 2 arm: (methotrexate, azathioprine)
Participants	Patients with chronic active Crohn's disease defined as the need for steroid therapy of ≥ 10 mg/day for at least 4 months during preceding 12 months, with at least one attempt to discontinue treatment. Crohn's disease had to be clinically active at entry (CDAI ≥ 200) No immunosuppressives 3 months prior to entry N = 54
Interventions	Intraveneous methotrexate 25 mg/wk (n = 27) or oral azathioprine 2 mg/kg/day (n = 27) for 6 months After 3 months the methotrexate was switched to oral administration maintaining the same dose At entry, all patients received prednisolone (40 mg once a day) for 2 weeks, then 30 and 20 mg/day for the following 2 and 4 weeks After 8 weeks if the patients condition was stable or improved prednisolone was tapered by 5 mg/week until withdrawal For patients whose condition worsened prednisolone dosage was increased to a maximum daily dose of 40 mg after which tapering was attempted as described above

Ardizzone 2003 *(Continued)*

	During the study the use of oral and topical aminosalicylates, other immunosuppressive agents, antibiotics for perianal disease, tube feeding, parenteral nutrition, or topical corticosteroids was not permitted
Outcomes	The primary outcome was the proportion of patients entering first remission after 3 and 6 months of treatment Secondary outcomes: decrease in steroid requirements, decrease in mean CDAI scores, decrease in mean CRP and ESR, fistula closure
Notes	Clinical remission was defined as lack of need for steroid treatment and CDAI ≤ 150 at each scheduled visit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by a computer-generated list
Allocation concealment (selection bias)	Unclear risk	Not described in published report
Blinding (performance bias and detection bias) All outcomes	High risk	The study was investigator-blind Patients and Chief of the Institute (GBP), who supervised the randomization, were aware of the treatment The principal investigator (SA), who was blinded to treatment assignment, evaluated the efficacy of treatment at each scheduled visit and at the end of the study, according to the information provided by the other physicians in the investigation team (SB, GM, VB, EC), all of whom were also blinded and evaluated each patient's clinical condition, computed the CDAI on the basis of patient diaries, recorded all the biochemical parameters considered in the study, and monitored compliance and toxicity
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up Six patients (three in AZA and three in MTX group) discontinued treatment due to adverse events Withdrawal from the trial medication was considered to be a treatment failure
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues

Arora 1999

Methods	Randomized, double blind placebo-control Two centers with different protocols for steroid dosage
Participants	Prednisone dependent for at least 6 months and CDAI > 150 on prednisone 10 mg/day or CDAI < 150 on prednisone ≥ 15 mg/day N = 33

Arora 1999 *(Continued)*

Interventions	Oral methotrexate 15 mg/wk (n = 15) or placebo (n = 18) for 1 year Dose adjusted up to 22.5 mg/week at discretion of senior investigator, adjusted down by 50% for clinical adverse effects or laboratory abnormalities Prednisone co-intervention: All patients on at least 10 mg/day Prednisone tapered according to clinical status (physician's decision) either after 12 weeks (MTX 6 patients, placebo 12 patients),or at any time during the study (MTX 9 patients, placebo 6 patients) 5-aminosalicylates: not described
Outcomes	Treatment failure: no improvement in CDAI with no reduction in steroid dose or the development of severe clinical illness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized through a code directed through the hospital pharmacy
Allocation concealment (selection bias)	Low risk	Centralized pharmacy randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Twenty-six of 33 patients withdrew from the study (11 from methotrexate, 15 from placebo) However, there were predetermined withdrawal criteria: including treatment failure with a flare of Crohn's disease, significant side effects, non-compliance, serious concomitant disease, pregnancy, or presence of Clostridium difficile toxin in the stool Eighteen of 26 patients withdrew due to disease flare The remainder withdrew for other reasons, as described in the published study
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues

Feagan 1995

Methods	Randomized, double-blind placebo-control 7 centers
Participants	Active disease, symptoms at least 3 months despite prednisone $\geq$ 12.5 mg/day, at least one attempt to discontinue Stratified according to prednisone dose < or > 20 mg/day N = 141
Interventions	Intramuscular methotrexate 25 mg/week (n = 94) or placebo (n = 47) for 16 weeks

Feagan 1995 *(Continued)*

	Prednisone co-intervention: all patients, dose adjusted to 20 mg daily at the start of the study, constant dose 2 weeks, then tapered 2.5 mg/week, dose increased to maximum 40 mg/week for worsening; tapering 5 mg/week until 20 mg, then 2.5 mg/week 5-aminosalicylates: not permitted
Outcomes	Remission: prednisone stopped and CDAI < 150 Mean CDAI score Quality of life (IBDQ) Steroid sparing effect
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind The placebo was identical in appearance to the active drug and the investigators were unaware of the treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up The same proportion of patients were withdrawn from treatment prematurely in the two groups (28%)
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues

Feagan 2014

Methods	Randomized, double-blind placebo controlled trial 15 centers
Participants	Patients with active symptoms for six weeks N = 126
Interventions	Subcutaneous methotrexate (n = 63, 10 mg/wk, increased at week 3 to 20 mg/wk, increased at week 5 to 25 mg/wk) or placebo (n = 63) for 50 weeks All patients received intraveneous infliximab (5 mg/kg at weeks 1, 3, 7, 14, 22, 30, 38, and 46), and 200 mg of intravenous hydrocortisone 30 minutes prior to infliximab dose All patients received prednisone, it was tapered after week 1 (patients with > 20 mg decreased by 5 mg/day until dose of 20 mg; patients with ≤ 20mg decreased by 2.5 mg/day) Aminosalicylates, budesonide, probiotics, systemic antibiotics, immunosuppressives, investigational agents, parenteral nutrition, topical aminosalicylates or corticosteroids were not permitted

Feagan 2014 *(Continued)*

Outcomes	Primary outcome: failure to achieve steroid free remission (CDAI < 150) at week 14 or failure to maintain remission through week 50 Secondary outcomes: the proportion of patients who achieved overall treatment success, prednisone-free remission at week 14, mean change in the CDAI and SF36 scores, median change in serum CRP concentration, median serum infliximab concentration, the proportion of patients who developed antibodies to infliximab, and adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by computer
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with identically appearing placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six patients withdrew from the study for reasons not related to treatment failure; two patients were assigned to methotrexate (both due to adverse events) and four patients were assigned to placebo (two withdrew consent, one due to adverse event, one lost to follow-up)
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues

Maté-Jiménez 2000

Methods	Randomized 1 center 3 arm: (methotrexate, 6-MP, 5-ASA)
Participants	Radiological or endoscopic diagnosis of CD or UC and steroid dependent Steroid dependent was defined as those patients whose prednisone could not be lowered to 20 mg/day without presenting inflammatory activity determined by a CDAI score of 200 or more or having presented more than two episodes in the last 6 months or more than 3 in the last 12 months None of the patients had received 6-MP or methotrexate prior to entry N = 72 numbers for Crohn's participants: 6-MP (n = 16), methotrexate (n = 15), 5-ASA (n = 7)
Interventions	Oral methotrexate 15 mg/wk or 6-MP 1.5 mg/kg/day or 5-ASA 3 g/day for 30 weeks For 2 weeks after randomization no attempt was made to decrease prednisone dose, thereafter prednisone was decreased by 8 mg/week, prednisone was reduced if the condition of the patient remained stable or improved and discontinued if clinical remission was achieved Methotrexate was reduced to 10 mg/week and the 6-MP dose to 1 mg/kg/day if clinical remission was achieved

Maté-Jiménez 2000 *(Continued)*

	Patients in the 5-ASA group continued to receive 3 g/day after achieving remission and stopping prednisone
Outcomes	Remission: prednisone stopped and CDAI < 150 and normal serum orosomucoid concentration
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in published study
Allocation concealment (selection bias)	Unclear risk	Not described in published study
Blinding (performance bias and detection bias) All outcomes	High risk	Not mentioned in published study. Authors assumed the study was unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	24/72 patients dropped out in the first 30 weeks of the trial. Worst outcome assumed
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were reported. Some *post hoc* outcomes were also reported
Other bias	Low risk	No other issues

Oren 1997

Methods	Randomized, double blind placebo-control 12 centers 3 arm: (methotrexate, 6-MP, placebo)
Participants	Active disease (HBI > 7), on steroids and/or immunosuppressives at least 4/12 preceding months, no immunosuppressives 3 months prior to entry N = 84
Interventions	Oral methotrexate 12.5 mg/wk (n = 26) or 6-mercaptopurine 50 mg/day (n = 32) or placebo (n = 26) for 9 months Prednisone co-intervention: continued at discretion of physician: MTX 20/26 patients, placebo 19/26 patients No steroid tapering regimen was described in this study, although reduction in steroid dose was described as an outcome measure 5-aminosalicylates: permitted as clinically indicated (MTX 18/26 patients, placebo 18/26 patients)
Outcomes	Remission (HBS < 3) and not receiving steroids Maintenance of remission in patients entering remission Decrease in steroid requirement General well being

Oren 1997 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the published study
Allocation concealment (selection bias)	Unclear risk	Not described in the published study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, the investigators were blinded to treatment assignment An unblinded independent observer and the pharmacist were the only persons who had access to the "drug key" in cases in which there was a compelling medical reason to break the code (and discontinue the trial)
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 27/84 patients withdrew from the study (MTX, n = 13; 6-MP n = 9; placebo n = 5) All analyses were performed on an intention-to-treat basis (the Harvey-Bradshaw Index and monthly steroid dose of patients dropping out for whatever reason were included for as long as they continued the study)
Selective reporting (reporting bias)	Low risk	All outcome were reported
Other bias	Low risk	No other issues

Schröder 2006

Methods	Randomized, open-label, controlled trial 1 center 2 arms: infliximab alone and infliximab plus methotrexate
Participants	Patients with chronic active Crohn's disease (steroid-refractory or -dependent and resistant/intolerant to azathioprine) Patients could not be receiving: 5-aminosalicylates > 4g/day or corticosteroids < 40 mg/day N = 19
Interventions	All patients received infliximab (5mg/kg) infusion at weeks 0 and 2 Those in the methotrexate plus infliximab group (n = 11) also received methotrexate by infusion for weeks 0 to 5 (6 infusions at 20 mg/week) then oral methotrexate (20 mg/week) This treatment lasted the remaining 48 weeks of the trial
Outcomes	Clinical remission (CDAI < 150) Time to achieve clinical remission Corticosteroid-tapering effect

Schröder 2006 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in published study
Allocation concealment (selection bias)	Unclear risk	Not described in published study
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/8 receiving infliximab alone and 4/11 receiving infliximab plus methotrexate discontinued therapy by the end of the trial. The sole reason leading to the discontinuation of study treatment in both groups was lack of efficacy
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other issues

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

Study	Reason for exclusion
Clark 2009	A retrospective chart review
Domènech 2008	A retrospective chart review
Egan 1999	A dose finding pharmacokinetic study comparing two doses of methotrexate
Feagan 2000	A maintenance of remission study, not applicable to induction review
Hayee 2005	A case series report
Houben 1994	Retrospective study examining patients treated with intramuscular methotrexate
Kurnik 2003	A pharmacokinetic study
Laharie 2011	Not a randomized trial. The study evaluated mucosal healing in patients
Lampen-Smith 2011	Retrospective chart review
Lémann 2000	No control group and no randomization
Schröder 1996	A commentary on the Feagan 1995 study
Suares 2012	No randomization and no control group
Sun 2005	A review article

Study	Reason for exclusion
Wilson 2013	A pharmacokinetic study on bioequivalence of oral and subcutaneous methotrexate in Crohn's disease

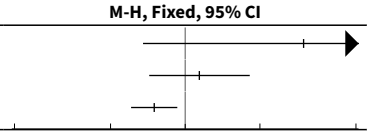
DATA AND ANALYSES

Comparison 1. Methotrexate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to enter remission or possible remission at 16 weeks	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Withdrawal due to adverse event	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

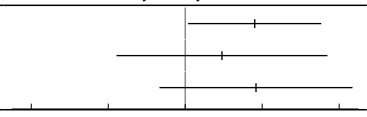
Analysis 1.1. Comparison 1 Methotrexate versus placebo, Outcome 1 Failure to enter remission or possible remission at 16 weeks.

Study or subgroup	Methotrexate n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Arora 1999	5/15	2/18		3[0.68,13.31]
Oren 1997	16/26	14/26		1.14[0.72,1.82]
Feagan 1995	57/94	38/47		0.75[0.61,0.93]



Analysis 1.2. Comparison 1 Methotrexate versus placebo, Outcome 2 Withdrawal due to adverse event.

Study or subgroup	Methotrexate n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Feagan 1995	16/94	1/47		8[1.09,58.51]
Oren 1997	1/26	0/26		3[0.13,70.42]
Arora 1999	3/15	0/18		8.31[0.46,149.21]



Comparison 2. Methotrexate versus 6-MP or Azathioprine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to enter remission or possible remission at 24-36 weeks	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Withdrawal due to adverse event	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

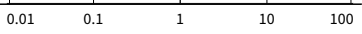
Analysis 2.1. Comparison 2 Methotrexate versus 6-MP or Azathioprine, Outcome 1 Failure to enter remission or possible remission at 24-36 weeks.

Study or subgroup	Methotrexate n/N	6-MP or Azathioprine n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Oren 1997	16/26	19/32		1.04[0.68,1.57]
Maté-Jiménez 2000	3/15	1/16		3.2[0.37,27.49]
Ardizzone 2003	12/27	10/27		1.2[0.63,2.29]

Favours methotrexate — Favours 6-MP or aza

Analysis 2.2. Comparison 2 Methotrexate versus 6-MP or Azathioprine, Outcome 2 Adverse events.

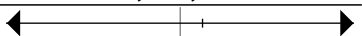
Study or subgroup	Methotrexate n/N	Azathioprine n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Ardizzone 2003	17/27	7/27		2.43[1.21,4.89]



Favours azathioprine — Favours methotrexate

Analysis 2.3. Comparison 2 Methotrexate versus 6-MP or Azathioprine, Outcome 3 Withdrawal due to adverse event.

Study or subgroup	Methotrexate n/N	6-MP or Azathioprine n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Oren 1997	1/26	1/32		1.23[0.08,18.74]
Maté-Jiménez 2000	2/15	1/16		2.13[0.22,21.17]
Ardizzone 2003	3/27	3/27		1[0.22,4.52]



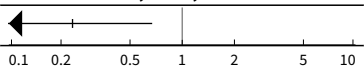
Favours methotrexate — Favours 6-MP or aza

Comparison 3. Methotrexate versus 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to enter remission or possible remission at 30 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Withdrawal due to adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

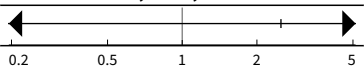
Analysis 3.1. Comparison 3 Methotrexate versus 5-ASA, Outcome 1 Failure to enter remission or possible remission at 30 weeks.

Study or subgroup	methotrexate n/N	5-ASA n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Maté-Jiménez 2000	3/15	6/7		0.23[0.08,0.67]



Analysis 3.2. Comparison 3 Methotrexate versus 5-ASA, Outcome 2 Withdrawal due to adverse event.

Study or subgroup	methotrexate n/N	5-ASA n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Maté-Jiménez 2000	2/15	0/7		2.5[0.14,46.14]



Comparison 4. Methotrexate and Infliximab versus Infliximab

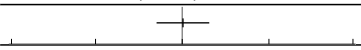
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to enter remission at 14 weeks or 24 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Withdrawals due to adverse event	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Methotrexate and Infliximab versus Infliximab, Outcome 1 Failure to enter remission at 14 weeks or 24 weeks.

Study or subgroup	MTX+IFX n/N	IFX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Schröder 2006	5/11	5/8		0.73[0.31,1.69]
Feagan 2014	15/63	14/63		1.07[0.57,2.03]

Analysis 4.2. Comparison 4 Methotrexate and Infliximab versus Infliximab, Outcome 2 Adverse events.

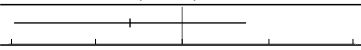
Study or subgroup	MTX+IFX n/N	IFX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Schröder 2006	7/11	5/8		1.02[0.51,2.05]



Favours IFX — Favours MTX+IFX

Analysis 4.3. Comparison 4 Methotrexate and Infliximab versus Infliximab, Outcome 3 Serious adverse events.

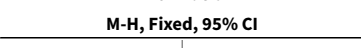
Study or subgroup	MTX+IFX n/N	IFX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Schröder 2006	0/11	1/8		0.25[0.01,5.45]



Favours IFX — Favours MTX+IFX

Analysis 4.4. Comparison 4 Methotrexate and Infliximab versus Infliximab, Outcome 4 Withdrawals due to adverse event.

Study or subgroup	MTX+IFX n/N	IFX n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Schröder 2006	0/11	0/8		Not estimable
Feagan 2014	2/63	1/63		2[0.19,21.5]



Favours IFX — Favours MTX+IFX

APPENDICES

Appendix 1. Search strategies

MEDLINE search strategy

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19 (CROHN or crohn's).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

20. inflammatory bowel disease*.ti. or inflammatory bowel disease*.ab. or IBD.ti. or IBD.ab.

21. 19 or 20

22. 18 and 21

23. methotrexate.mp. or exp methotrexate derivative/ or exp methotrexate/ or exp methotrexate gamma aspartic acid/ or exp methotrexate polyglutamate/

24. 22 and 23

EMBASE search strategy

1. random$.tw.

2. factorial$.tw.

3. (crossover$ or cross over$ or cross-over$).tw.

4. placebo$.tw.

5. single blind.mp.

6. double blind.mp.

7. triple blind.mp.

8. (singl$ adj blind$).tw.

9. (double$ adj blind$).tw.

10. (tripl$ adj blind$).tw.

11. assign$.tw.

12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19 (CROHN or crohn's).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

20. inflammatory bowel disease*.ti. or inflammatory bowel disease*.ab. or IBD.ti. or IBD.ab.

21. 19 and 20

22. 18 and 21

23. methotrexate.mp. or exp methotrexate derivative/ or exp methotrexate/ or exp methotrexate gamma aspartic acid/ or exp methotrexate polyglutamate/

24. 22 and 23

CENTRAL search strategy

#1 crohn* or "inflammatory bowel disease" or IBD

#2 methotrexate

#3 #1 and #2

SR-IBD

Crohn AND methotrexate

WHAT'S NEW

Date	Event	Description
27 July 2015	Amended	Correction of minor data extraction error

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 1, 2003

Date	Event	Description
24 June 2014	New search has been performed	New literature search conducted on June 9, 2014
24 June 2014	New citation required but conclusions have not changed	Updated review with one new author

DECLARATIONS OF INTEREST

Brian Feagan and John WD McDonald are authors of two manuscripts that were included in this review. Brian Feagan has received fee(s) from Abbott/AbbVie, Amgen, Astra Zeneca, Avaxia Biologics Inc., Bristol-Myers Squibb, Celgene, Centocor Inc., Elan/Biogen, Ferring, JnJ/Janssen, Merck, Novartis, Novonordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Takeda, Teva, Tillotts Pharma AG, UCB Pharma for Board membership; fee(s) from Abbott/AbbVie, Actogenix, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics Inc., Axcan, Baxter Healthcare Corp., Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging Inc., GSK, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Merck, Millennium, Nektar, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharma, Tillotts, UCB Pharma, Vertex Pharma, Warner-Chilcott, Wyeth, Zealand, and Zyngenia for consultancy; and lecture fee(s) from: Abbott/AbbVie, JnJ/Janssen, Takeda, Warner-Chilcott, and UCB Pharma. All of these activities are outside the submitted work.

The other authors have no known declarations of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [therapeutic use]; Azathioprine [therapeutic use]; Crohn Disease [*drug therapy]; Immunosuppressive Agents [*therapeutic use]; Induction Chemotherapy [*methods]; Infliximab; Mercaptopurine [therapeutic use]; Methotrexate [*therapeutic use]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic; Steroids [therapeutic use]

MeSH check words

Humans