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Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease (Review)

Chande N, Townsend CM, Parker CE, MacDonald JK

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[Intervention Review]

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

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ABSTRACT

Background

The results from controlled clinical trials investigating the efficacy of azathioprine and 6-mercaptopurine for the treatment of active Crohn's disease have been conflicting and controversial. An updated meta-analysis was performed to assess the effectiveness of these drugs for the induction of remission in active Crohn's disease.

Objectives

The primary objective was to determine the efficacy and safety of azathioprine and 6-mercaptopurine for induction of remission in active Crohn's disease.

Search methods

We searched MEDLINE, EMBASE and the Cochrane Library from inception to 30 October 2015. Review articles and conference proceedings were also searched to identify additional studies.

Selection criteria

Randomized controlled trials (RCTs) of oral azathioprine or 6-mercaptopurine compared to placebo or active therapy involving adult patients with active Crohn's disease were selected for inclusion.

Data collection and analysis

Data were extracted by two independent observers based on the intention-to-treat principle. Outcomes of interest included: clinical remission, clinical improvement, fistula improvement or healing, steroid sparing, adverse events, withdrawals due to adverse events and serious adverse events. We calculated the pooled relative risk (RR) and 95% confidence intervals (95% CI) for each outcome. The methodological quality of included studies was evaluated using the Cochrane risk of bias tool. The overall quality of the evidence supporting each outcome was assessed using the GRADE criteria.

Main results

Thirteen RCTs (n = 1211 patients) of azathioprine and 6-mercaptopurine therapy in adult patients were identified: nine included placebo comparators and six included active comparators. The majority of included studies were rated as low risk of bias. There was possibly a modest difference in clinical remission rates between azathioprine or 6-mercaptopurine and placebo. Forty-eight per cent (95/197) of patients receiving antimetabolites achieved remission compared to 37% (68/183) of placebo patients (5 studies, 380 patients; RR 1.23, 95% CI 0.97 to 1.55; moderate quality evidence). There was possibly a modest difference in clinical improvement rates between azathioprine

or 6-mercaptopurine and placebo. Forty-eight per cent (107/225) of patients receiving antimetabolites achieved clinical improvement or remission compared to 36% (75/209) of placebo patients (8 studies, 434 patients; RR 1.26, 95% CI 0.98 to 1.62; moderate quality evidence). There was possibly a modest difference in steroid sparing (defined as prednisone dose < 10 mg/day while maintaining remission) between azathioprine and placebo. Sixty-four per cent (47/73) of azathioprine patients were able to reduce their prednisone dose to < 10 mg/day compared to 46% (32/70) of placebo patients (RR 1.34, 95% CI 1.02 to 1.77; moderate quality evidence). GRADE analyses rated the overall quality of the evidence for the outcomes clinical remission, clinical improvement and steroid sparing as moderate due to sparse data.

There was possibly a modest difference in withdrawals due to adverse events or serious adverse events between antimetabolites and placebo. Ten percent of patients in the antimetabolite group withdrew due to adverse events compared to 5% of placebo patients (8 studies, 510 patients; RR 1.70, 95% CI 0.94 to 3.08; moderate quality evidence). Serious adverse events were reported in 14% of patients receiving azathioprine compared to 4% of placebo patients (2 studies, 216 patients; RR 2.57, 95% CI 0.92 to 7.13; low quality evidence). Common adverse events reported in the placebo controlled studies included: allergic reactions, leukopenia, pancreatitis and nausea. Azathioprine was probably inferior to infliximab for induction of steroid-free clinical remission. Thirty per cent (51/170) of azathioprine patients achieved steroid-free remission compared to 44% (75/169) of infliximab patients (1 study, 339 patients; RR 0.68, 95% CI 0.51 to 0.90; moderate quality evidence). The combination of azathioprine and infliximab was probably superior to infliximab alone for induction of steroid-free clinical remission. Sixty per cent (116/194) of patients in the combined azathioprine and infliximab group achieved steroid-free remission compared to 48% (91/189) of infliximab patients (2 studies, 383 patients; RR 1.23, 95% CI 1.02 to 1.47; moderate quality evidence). Azathioprine or 6-mercaptopurine therapy was found to be possibly superior at inducing steroid free clinical remission compared to methotrexate (RR 1.13, 95% CI 0.85 to 1.49; low quality evidence) and the evidence was very uncertain as regards the comparison with 5-aminosalicylate or sulfasalazine (RR 1.24, 95% CI 0.80 to 1.91; very low quality evidence). The estimates for withdrawals due to adverse events between the various drugs were as follows: azathioprine or 6-mercaptopurine versus methotrexate: RR 0.78, 95% CI 0.23 to 2.71; very low quality evidence; azathioprine or 6-mercaptopurine versus 5-aminosalicylate or sulfasalazine: RR 0.98, 95% CI 0.38 to 2.54; low quality evidence; azathioprine versus infliximab: RR 1.47, 95% CI 0.96 to 2.23; moderate quality evidence and the combination of azathioprine and infliximab versus infliximab: RR 1.16, 95% CI 0.75 to 1.80; moderate quality evidence. Common adverse events in the active comparator trials included nausea, abdominal pain, pyrexia and headache.

Authors' conclusions

Azathioprine and 6-mercaptopurine possibly offer a modest advantage over placebo for induction of remission or clinical improvement in active Crohn's disease. Antimetabolite therapy possibly allows patients to reduce steroid consumption. Adverse events are possibly more common in patients receiving antimetabolites compared to those receiving placebo. Azathioprine therapy is probably inferior to infliximab for induction of steroid-free remission. However, the combination of azathioprine and infliximab is probably superior to infliximab alone for induction of steroid-free remission.

PLAIN LANGUAGE SUMMARY

Azathioprine or 6-mercaptopurine for the treatment of active Crohn's disease

Azathioprine and 6-mercaptopurine are immunosuppressive drugs that are thought to reduce inflammation by blocking the immune system. This review includes 13 randomized trials with a total of 1211 participants. Azathioprine and 6-mercaptopurine were found to be possibly more effective than placebo (fake medicine) for inducing remission in Crohn's disease. There is evidence to suggest that the combination of azathioprine and infliximab is superior to infliximab used as a single drug for induction of steroid-free remission in active Crohn's disease. Tumor necrosis factor (TNF) alpha blocking drugs like infliximab may provide an alternative treatment for patients who do not respond to corticosteroid or immunosuppressive drug treatment. Azathioprine and 6-mercaptopurine may reduce the need for steroid treatment and their use may therefore lead to a lower incidence of steroid related side effects. However, these drugs are slow acting and are associated with some rare, but serious side effects. In some patients they suppress formation of blood cells that fight off infection and allow blood to clot and they occasionally cause inflammation of the pancreas. These drugs have also been associated with an increased risk of lymphoma. For these reasons careful consideration needs to be given to the use of these drugs in patients with active Crohn's disease.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Azathioprine or 6-mercaptopurine versus placebo for induction of remission in Crohn's disease

Azathioprine (AZA) or 6-mercaptopurine (6-MP) versus placebo for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease

Settings: Outpatients

Intervention: Azathioprine or 6-mercaptopurine versus 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				
	Control	AZA or 6-MP versus placebo				
Clinical remission	372 per 1000 ¹	458 per 1000 (361 to 577)	RR 1.23 (0.97 to 1.55)	380 (5 studies)	⊕⊕⊕⊖ Moderate ²	
Clinical remission or improvement	359 per 1000 ¹	452 per 1000 (352 to 582)	RR 1.26 (0.98 to 1.62)	434 (8 studies)	⊕⊕⊕⊖ Moderate ³	
Fistula improvement or healing	286 per 1000 ¹	572 per 1000 (192 to 1696)	RR 2.00 (0.67 to 5.93)	18 (3 studies)	⊕⊕⊖⊖ Low ⁴	
Steroid sparing effect	457 per 1000 ¹	612 per 1000 (466 to 809)	RR 1.34 (1.02 to 1.77)	143 (4 studies)	⊕⊕⊕⊖ Moderate ⁵	
Withdrawals due to adverse events	53 per 1000 ¹	90 per 1000 (50 to 163)	RR 1.70 (0.94 to 3.08)	510 (8 studies)	⊕⊕⊕⊖ Moderate ⁶	
Serious Adverse events	38 per 1000 ¹	98 per 1000 (35 to 271)	RR 2.57 (0.92 to 7.13)	216 (2 studies)	⊕⊕⊖⊖ 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 estimates come from control arm of meta-analysis, based on included trials
- ² Sparse data (163 events)
- ³ Sparse data (182 events)
- ⁴ Sparse data (8 events) and very wide confidence intervals
- ⁵ Sparse data (79 events)
- ⁶ Sparse data (41 events)
- ⁷ Sparse data (19 events) and very wide confidence intervals

Summary of findings 2. Azathioprine versus infliximab for induction of remission in Crohn's disease

Azathioprine (AZA) versus infliximab (IFX) for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease

Settings: Outpatients

Intervention: Azathioprine versus 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				
	Control	AZA versus IFX				
Clinical remission	479 per 1000 ¹	316 per 1000 (244 to 417)	RR 0.66 (0.51 to 0.87)	339 (1 study)	⊕⊕⊕⊖ Moderate ²	
Clinical remission off steroids	444 per 1000 ¹	302 per 1000 (226 to 400)	RR 0.68 (0.51 to 0.90)	339 (1 study)	⊕⊕⊕⊖ Moderate ³	
Mucosal healing	283 per 1000 ¹	156 per 1000 (93 to 266)	RR 0.55 (0.33 to 0.94)	214 (1 study)	⊕⊕⊕⊖ Moderate ⁴	
Adverse events	890 per 1000 ¹	899 per 1000 (828 to 961)	RR 1.01 (0.93 to 1.08)	324 (1 study)	⊕⊕⊕⊖ Moderate ⁵	
Withdrawals due to adverse events	178 per 1000 ¹	262 per 1000 (171 to 397)	RR 1.47 (0.96 to 2.23)	324 (1 study)	⊕⊕⊕⊖ Moderate ⁶	
Serious adverse events	239 per 1000 ¹	268 per 1000 (184 to 387)	RR 1.12 (0.77 to 1.62)	324 (1 study)	⊕⊕⊕⊖ Moderate 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 estimates come from control arm of the study
- ² Sparse data (135 events)
- ³ Sparse data (126 events)
- ⁴ Sparse data (46 events)
- ⁵ Sparse data (289 events)
- ⁶ Sparse data (71 events)
- ⁷ Sparse data (82 events)

Summary of findings 3. Azathioprine + infliximab versus infliximab for induction of remission in Crohn's disease

Azathioprine (AZA) + infliximab (IFX) versus infliximab for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease

Settings: Outpatients

Intervention: Azathioprine + infliximab versus 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				
	Control	AZA + IFX versus IFX				
Clinical remission	479 per 1000 ¹	603 per 1000 (493 to 738)	RR 1.26 (1.03 to 1.54)	338 (1 study)	⊕⊕⊕⊕ Moderate ²	
Clinical remission off steroids	482 per 1000 ¹	593 per 1000 (492 to 708)	RR 1.23 (1.02 to 1.47)	383 (2 studies)	⊕⊕⊕⊕ Moderate ³	
Mucosal healing	283 per 1000 ¹	424 per 1000 (289 to 620)	RR 1.50 (1.02 to 2.19)	210 (1 study)	⊕⊕⊕⊕ Moderate ⁴	
Adverse events	890 per 1000 ¹	899 per 1000	RR 1.01	342	⊕⊕⊕⊕	

	(837 to 970)		(0.94 to 1.09)	(1 study)	Moderate ⁵
Withdrawals due to adverse events	178 per 1000 ¹	206 per 1000 (134 to 320)	RR 1.16 (0.75 to 1.80)	342 (1 study)	⊕⊕⊕⊕ Moderate ⁶
Serious adverse events	239 per 1000 ¹	151 per 1000 (98 to 234)	RR 0.63 (0.41 to 0.98)	342 (1 study)	⊕⊕⊕⊕ Moderate 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 estimates come from control arm of the study

² Sparse data (183 events)

³ Sparse data (207 events)

⁴ Sparse data (75 events)

⁵ Sparse data (306 events)

⁶ Sparse data (66 events)

⁷ Sparse data (66 events)

Summary of findings 4. Azathioprine or 6-mercaptopurine versus methotrexate for induction of remission in Crohn's disease

Azathioprine (AZA) or 6-mercaptopurine (6-MP) versus methotrexate (MTX) for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease

Settings: Outpatients

Intervention: Azathioprine or 6-mercaptopurine versus methotrexate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	AZA or 6-MP versus MTX				
Clinical remission ¹	500 per 1000 ²	565 per 1000 (425 to 1210)	RR 1.13 (0.85 to 1.49)	143 (3 studies)	⊕⊕⊕⊕ Low ^{3,4}	

Adverse events	452 per 1000²	190 per 1000 (95 to 371)	RR 0.42 (0.21 to 0.82)	85 (2 studies)	⊕⊕⊕⊕ Low ^{5,6}
Withdrawals due to adverse events	119 per 1000²	93 per 1000 (27 to 322)	RR 0.78 (0.23 to 2.71)	85 (2 studies)	⊕⊕⊕⊕ Very low ^{7,8}

*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 Definition of clinical remission includes withdrawal from steroids.

2 Control group risk estimates come from control arm of meta-analysis, based on included trials

3 Sparse data (75 events)

4 Two of the studies in the pooled analysis were rated as having a high risk of bias due to single-blind and open label designs

5 Sparse data (27 events)

6 The two studies in the pooled analysis were rated as having a high risk of bias due to single-blind and open label designs

7 Sparse data (9 events) and very wide confidence intervals

8 The two studies in the pooled analysis were rated as having a high risk of bias due to single-blind and open label designs

Summary of findings 5. Azathioprine or 6-mercaptopurine versus 5-ASA or Sulfasalazine for induction of remission in Crohn's disease

6-mercaptopurine (6-MP) versus 5-ASA for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease

Settings: Outpatients

Intervention: Azathioprine or 6-mercaptopurine versus 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				
	Control	6-MP versus 5-ASA				
Clinical remission	358 per 1000¹	444 per 1000 (286 to 684)	RR 1.24 (0.80 to 1.91)	156 (2 studies)	⊕⊕⊕⊕ Very low ^{2,3,4}	

Withdrawals due to adverse events	99 per 1000¹	97 per 1000 (38 to 251)	RR 0.98 (0.38 to 2.54)	156 (2 studies)	⊕⊕○○ Low ^{3,5}
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*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 estimates come from control arm of study

² Sparse data (65 events)

³ [Maté-Jiménez 2000](#) was rated as having a high risk of bias due to open label design

⁴ Unexplained heterogeneity

⁵ Sparse data (15 events)

BACKGROUND

6-Mercaptopurine (6-MP) (predominantly used as a chemotherapeutic agent) and its prodrug azathioprine (AZA) (an immune modifier agent) are purine analogues that competitively interfere with nucleic acid metabolism (Lennard 1992; Sahasranaman 2008). Consequently, both drugs reduce cell proliferation and have immune modulating properties. A deficiency of thiopurine methyltransferase (TPMT) enzyme appears to account for some dose- and metabolism-dependent toxicities such as leukopenia (and possible subsequent infection), thrombocytopenia, and malignancy (Lennard 1983; Lennard 1989; Weinsilbom 1980). Other toxicities such as rash, fever, arthralgias, pancreatitis, hepatitis, nausea, non-pancreatic abdominal pain and diarrhea appear to be hypersensitivity reactions (Sandborn 1996).

Azathioprine and 6-mercaptopurine have both been used to treat patients with active, steroid-refractory, and steroid-dependent Crohn's disease, and patients with fistulizing Crohn's disease. Uncontrolled trials suggested efficacy for azathioprine (Avery-Jones 1966; Brooke 1969; Brooke 1970; Brooke 1976; Brown 1970; Colonna 1994; D'Haens 1995; D'Haens 1997; Drucker 1970; Fausa 1971; Javett 1972; Kessler 1995; Korelitz 1985; Korelitz 1993; Lemann 1990; Lennard-Jones 1972; Markowitz 1990; Nyman 1985; O'Brien 1991; Patterson 1971; Papp 1974; Perrault 1991; Rhodes 1971; Shah 1991; Verhave 1990; Wallensten 1972). Placebo controlled clinical trials have been performed in order to determine whether the results of these uncontrolled studies are valid (Candy 1995; Ewe 1993; Klein 1974; Oren 1997; Present 1980; Reinisch 2008; Rhodes 1971; Summers 1979; Willoughby 1971). The results from these controlled trials were conflicting and controversies regarding efficacy developed (Korelitz 1981; Lennard-Jones 1981). Much of the controversy centered on design flaws in some of the studies, which failed to take into account the prolonged time to onset of drug action (3 to 4 months minimum). Careful analysis of the controlled data, paying attention to duration of therapy, concomitant medications, and drug dosage, may reveal logical explanations for conflicting data and allow more valid conclusions to be reached regarding efficacy. There have also been studies comparing AZA or 6-MP to other active treatments or in combination with these treatments (Ardizzone 2003; Colombel 2010; Maté-Jiménez 2000; Oren 1997; Summers 1979). This systematic review is an update of a previously published Cochrane review (Chande 2013).

OBJECTIVES

The primary objective was to assess the efficacy and safety of azathioprine and 6-mercaptopurine used for induction of remission in active Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized placebo-controlled or active comparator trials were considered for inclusion.

Types of participants

Adult patients with Crohn's disease defined by conventional clinical, radiographic, and endoscopic criteria which was categorized as acute (active) inflammatory disease (CDAI $\geq$ 150 points or Harvey-Bradshaw Index score $\geq$ 7 points or presence of moderate to severe symptoms at the time of entry into the trial).

Types of interventions

Trials of oral azathioprine or 6-mercaptopurine therapy were considered for inclusion.

Types of outcome measures

The primary outcome was the proportion of patients with clinical remission as measured with a validated outcome (e.g. Crohn's Disease Activity Index score $<$ 150 points or a Harvey-Bradshaw Index score $\leq$ 3). The proportion of patients with clinical improvement or remission was a secondary outcome. The definitions of remission and improvement varied from study to study making exact comparisons across studies difficult. Therefore, the definition of improvement or remission used in each study was used for data extraction. Other outcomes of interest included fistula improvement or healing, steroid sparing effect, adverse events, withdrawals due to adverse events, and serious adverse events. Included studies were also reviewed for adverse events commonly associated with antimetabolites including: leukopenia, infection, thrombocytopenia, malignancy, rash, fever, arthralgias, pancreatitis, hepatitis, nausea, non-pancreatic abdominal pain, and diarrhea.

Search methods for identification of studies

Electronic searches

We searched MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Library from inception to 30 October 2015. Conference proceedings were also searched to identify additional studies. The search strategy is reported in [Appendix 1](#).

Searching other resources

We also searched conference proceedings and reference lists to identify additional studies.

Data collection and analysis

Study Selection:

Potentially relevant articles were reviewed in an independent unblinded fashion by two authors (CMT and CEP) to determine if they met the criteria specified above. For crossover studies, only data from the first portion of the study were incorporated to avoid possible carry-over effects of medication into the second part of the study, and to make these studies more comparable to those not of a crossover design. All results were tabulated on an intention-to-treat basis. Reviewers rated each article as being eligible, ineligible, or not applicable to the current review. Any disagreement among reviewers was resolved by consensus. Trials published in abstract form only were not included unless full details of the protocol and results could be obtained from the authors.

Data Collection:

Eligible articles were reviewed in duplicate and the results of the primary research trials were abstracted. Data were then extracted onto specially designed data extraction forms.

We used the Cochrane risk of bias tool to assess the methodological quality of the included studies ([Higgins 2011](#)). The following study characteristics were assessed:

1. Randomization sequence generation;
2. Allocation concealment;
3. Blinding of participants, outcome assessors and investigators;
4. Incomplete outcome reporting (i.e. there was an acceptable method of dealing with attrition);
5. Selective outcome reporting (i.e. all outcomes described in the methods were included in the analysis); and
6. Other potential sources of bias.

Based on these characteristics, studies were judged to have a high, low or unclear risk of bias.

We used the GRADE approach to assess the overall quality of evidence for the primary outcome and selected secondary outcomes of interest. Outcomes from pooling of randomized trials start as high quality evidence, but may be downgraded due to: (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The overall quality of evidence for each outcome was determined after considering each of these elements, and categorized as high quality (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate quality (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low quality (i.e. 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); or very low quality (i.e. we are very uncertain about the estimate) ([Guyatt 2008](#); [Schünemann 2011](#)).

Statistical Analysis:

Data were analyzed using Review Manager (RevMan 5). The risk ratio (RR) and 95% confidence intervals (95% CI) were calculated for each dichotomous outcome. Data from individual trials were combined for meta-analysis if the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). A fixed-effect model was used to pool data in the absence of heterogeneity. A random-effects model was used when significant heterogeneity was detected. Heterogeneity was assessed using the Chi² test (a P value of 0.10 will be regarded as statistically significant). The I² statistic was used to estimate the degree of heterogeneity. This measure describes the percentage of total variation across studies that results from heterogeneity rather than chance. A value of 25% is considered to indicate low heterogeneity, 50% moderate heterogeneity and 75% high heterogeneity ([Higgins 2003](#)). Sensitivity analyses were used to explore potential sources of heterogeneity.

RESULTS

Description of studies

A literature search conducted on October 30, 2015 identified 1609 records. Seven additional studies were identified through searching of conference abstracts. After duplicates were removed, a total of 1161 trials remained for review of titles and abstracts. Two authors (CMT and CEP) independently reviewed the titles and abstracts of these trials and 59 studies were selected for full text review (see [Figure 1](#)). Thirty-two reports of 23 studies were excluded (See: [Characteristics of excluded studies](#)). Twenty-seven reports of 13 trials met the pre-defined inclusion criteria and were included in the review ([Ardizzone 2003](#); [Candy 1995](#); [Colombel 2010](#); [Ewe 1993](#); [Klein 1974](#); [Mantzaris 2004](#); [Maté-Jiménez 2000](#); [Oren 1997](#); [Present 1980](#); [Reinisch 2008](#); [Rhodes 1971](#); [Summers 1979](#); [Willoughby 1971](#)).

Figure 1. Study flow diagram.

The 13 selected trials ($n = 1211$ patients) had a variety of designs: seven were exclusively concerned with therapy of active disease (Colombel 2010; Ewe 1993; Klein 1974; Maté-Jiménez 2000; Present 1980; Reinisch 2008; Rhodes 1971) and two trials had separate arms for patients with active and quiescent disease (Summers 1979; Willoughby 1971). Oren 1997 compared therapy with 6-mercaptopurine, methotrexate, or placebo for active disease and subsequently for quiescent disease (if the patient responded) without randomizing for maintenance of remission therapy. In three trials patients were treated with 6-mercaptopurine (Maté-

Jiménez 2000; Oren 1997; Present 1980). All the other included studies treated patients with azathioprine. Azathioprine is rapidly converted to 6-mercaptopurine in vivo, and the clinical indications for using azathioprine and 6-mercaptopurine are similar so it was decided that these trials could be pooled for meta-analysis. The authors of the National Co-operative Crohn's Disease Study (Summers 1979) divided their study into three parts and compared azathioprine, prednisone, sulfasalazine and placebo. Part I phase one dealt with patients with active disease, while part I phase two examined the ability of these patients to maintain their remission.

Part II patients entered the study in remission. This review deals only with part I phase one for remission and all of part I for adverse event data (Summers 1979). Candy 1995 was divided into two parts. The first part treated active disease and the second part enrolled those who had successfully completed part one and examined their ability to maintain remission. This review deals only with part one of the Candy study.

Six studies included active comparators (Colombel 2010; Mantzaris 2004; Maté-Jiménez 2000; Oren 1997; Reinisch 2008; Summers 1979). As described above, Oren 1997 compared 6-mercaptopurine to placebo or methotrexate; and Summers 1979 examined azathioprine, prednisone, sulfasalazine and placebo. Colombel 2010 had three treatment arms including azathioprine, infliximab and infliximab plus azathioprine. Patients were followed for induction at 30 weeks and maintenance of remission at week 50 (Colombel 2010). Mantzaris 2004 compared treatment with infliximab to the combination of infliximab and azathioprine for active disease. Patients who were successfully induced at six weeks were entered into a one year maintenance phase and were treated with either infliximab or azathioprine alone (Mantzaris 2004). Maté-Jiménez 2000 randomized patients to one of three treatments: 6-mercaptopurine, azathioprine or 5-aminosalicylic acid. Patients were followed for induction of remission at 30 weeks and then for maintenance through 76 weeks. Reinisch 2008 had three different treatment arms: everolimus, azathioprine and placebo. This trial was stopped early (at seven months) due to lack of efficacy of everolimus.

All patients were symptomatic: some had an acute exacerbation of previously quiescent disease (Ewe 1993), other patients had chronic disease unresponsive to other therapy such as steroids (Ardizzone 2003; Colombel 2010; Klein 1974; Maté-Jiménez 2000; Willoughby 1971), and some (Candy 1995; Oren 1997; Present 1980; Reinisch 2008; Rhodes 1971; Summers 1979) were evaluated only on the severity of their symptoms at the time of randomization. The steroid sparing effect of therapy was a primary end point for some studies (Ewe 1993; Klein 1974; Oren 1997; Present 1980; Willoughby 1971), while others (Candy 1995; Rhodes 1971) were concerned only with clinical response and did not consider the effect of concurrent medications. For some trials steroid free remission was the endpoint considered (Colombel 2010; Maté-Jiménez 2000). The National Cooperative Crohn's Disease Study (Summers 1979) measured only clinical response and by design excluded concurrent therapy.

Remission was measured at various time points in the included studies. Remission was measured at 16 weeks in two studies (Ewe 1993; Klein 1974). Candy 1995 and Reinisch 2008 measured

remission at 12 weeks. Oren 1997 measured remission every month. Mantzaris 2004 measured remission at six weeks. Rhodes 1971 and Present 1980 were cross-over trials and the remission data before crossing over were used. Rhodes 1971 measured remission at two months and Present 1980 measured remission at one year. Summers 1979 measured remission at 17 weeks. Colombel 2010 measured remission at 26 weeks. Willoughby 1971 reported remission at 24 weeks. Maté-Jiménez 2000 reported remission at 30 weeks.

Risk of bias in included studies

The risk of bias for the included studies is summarized in Figure 2. Overall the studies were of low risk of bias for most assessed items. All of the trials were described as randomized, however only four studies explained the method used for sequence generation (Ardizzone 2003; Colombel 2010; Present 1980; Reinisch 2008). Four trials were rated as low risk of bias for allocation concealment (Colombel 2010; Present 1980; Reinisch 2008; Summers 1979). The remaining studies did not explain methods used for allocation concealment and were rated as unclear for this item (Ardizzone 2003; Candy 1995; Ewe 1993; Klein 1974; Maté-Jiménez 2000; Mantzaris 2004; Oren 1997; Rhodes 1971; Willoughby 1971). Seven studies were rated as low risk for blinding (Candy 1995; Colombel 2010; Klein 1974; Present 1980; Reinisch 2008; Summers 1979; Willoughby 1971). Ardizzone 2003 was single-blind (investigator) and was rated as high risk for blinding. Maté-Jiménez 2000 was rated as high risk of bias for blinding because it was open label. Blinding was not discussed in Mantzaris 2004 and this study was rated as unclear for this study. Three studies were described as double-blind but did not explain the methods used for blinding. These studies were rated as unclear for blinding (Ewe 1993; Oren 1997; Rhodes 1971). Nine studies were rated as low risk for incomplete outcome data (Ardizzone 2003; Candy 1995; Colombel 2010; Ewe 1993; Klein 1974; Mantzaris 2004; Maté-Jiménez 2000; Oren 1997; Willoughby 1971). Four studies were rated as unclear for incomplete outcome data (Rhodes 1971; Summers 1979; Present 1980; Reinisch 2008). Twelve studies reported all expected outcomes (Rhodes 1971; Willoughby 1971; Klein 1974; Summers 1979; Present 1980; Ewe 1993; Candy 1995; Oren 1997; Ardizzone 2003; Mantzaris 2004; Reinisch 2008; Colombel 2010). Maté-Jiménez 2000 reported some additional *post hoc* analyses and was rated as unclear for selective reporting. No additional items of concern were noted and all studies were rated as low risk for other sources of bias (Ardizzone 2003; Candy 1995; Colombel 2010; Ewe 1993; Klein 1974; Mantzaris 2004; Maté-Jiménez 2000; Oren 1997; Present 1980; Rhodes 1971; Reinisch 2008; Summers 1979; Willoughby 1971).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ardizzone 2003	+	?	-	+	+	+
Candy 1995	?	?	+	+	+	+
Colombel 2010	+	+	+	+	+	+
Ewe 1993	?	?	?	+	+	+
Klein 1974	?	?	+	+	+	+
Mantzaris 2004	?	?	?	+	+	+
Maté-Jiménez 2000	?	?	-	+	?	+
Oren 1997	?	?	?	+	+	+
Present 1980	+	+	+	?	+	+
Reinisch 2008	+	+	+	?	+	+
Rhodes 1971	?	?	?	?	+	+
Summers 1979	?	+	+	?	+	+
Willoughby 1971	?	?	+	+	+	+

Effects of interventions

See: [Summary of findings for the main comparison Azathioprine or 6-mercaptopurine versus placebo for induction of remission in Crohn's disease](#); [Summary of findings 2 Azathioprine versus infliximab for induction of remission in Crohn's disease](#); [Summary of findings 3 Azathioprine + infliximab versus infliximab for induction of remission in Crohn's disease](#); [Summary of findings 4 Azathioprine or 6-mercaptopurine versus methotrexate for induction of remission in Crohn's disease](#); [Summary of findings 5 Azathioprine or 6-mercaptopurine versus 5-ASA or Sulfasalazine for induction of remission in Crohn's disease](#)

Azathioprine or 6-Mercaptopurine versus Placebo

Five placebo-controlled studies ([Candy 1995](#); [Ewe 1993](#); [Oren 1997](#); [Reinisch 2008](#); [Summers 1979](#)) involving 380 patients reported clinical remission at 12 to 17 weeks as an outcome using validated outcome measures (i.e. CDAI < 150 or HBI ≤ 3). The pooled analysis showed that 48 per cent (95/197) of patients receiving antimetabolites achieved remission compared to 37% (68/183) of placebo patients (RR 1.23, 95% CI 0.97 to 1.55; [Analysis 1.1](#)). No statistically significant heterogeneity was detected for this comparison ($P = 0.35$; $I^2 = 9\%$). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome (clinical remission) was moderate due to sparse data (163 events, see [Summary of findings table 1](#)). Subgroup analysis showed no statistically significant difference in remission rates between azathioprine and placebo (4 studies, 322 patients) or 6-mercaptopurine and placebo (1 study, 58 patients): $P = 0.97$; $I^2 = 0\%$. Fifty-two per cent (86/165) of azathioprine patients achieved remission compared to 40% (62/157) of placebo patients (RR 1.24, 95% CI 0.94 to 1.64). Twenty-eight per cent (9/32) of 6-mercaptopurine patients achieved remission compared to 23% (6/26) of placebo patients (RR 1.22, 95% CI 0.50 to 2.98).

Nine placebo-controlled studies ($n = 506$ patients) reported clinical remission or improvement as an outcome ([Candy 1995](#); [Ewe 1993](#); [Klein 1974](#); [Oren 1997](#); [Present 1980](#); [Reinisch 2008](#); [Rhodes 1971](#); [Summers 1979](#); [Willoughby 1971](#)). The pooled analysis showed that 51 per cent (133/261) of patients receiving antimetabolites achieved clinical remission or improvement compared to 33% (80/245) of placebo patients (RR 1.53, 95% CI 1.05 to 2.22; [Analysis 1.2](#)). However, statistically significant heterogeneity was detected for this comparison ($P = 0.006$; $I^2 = 64\%$). Subgroup analysis showed no statistically significant difference in remission or improvement rates between azathioprine and placebo (7 studies, 376 patients) or between 6-mercaptopurine and placebo (2 studies, 130 patients): $P = 0.36$; $I^2 = 0\%$. Fifty-one per cent (98/193) of azathioprine patients achieved remission compared to 38% (69/183) of placebo patients (RR 1.28, 95% CI 0.96 to 1.71). No statistically significant heterogeneity was detected for the azathioprine subgroup comparison ($P = 0.17$; $I^2 = 35\%$). Fifty-one per cent (35/68) of 6-mercaptopurine patients achieved remission compared to 18% (11/62) of placebo patients (RR 2.54, 95% CI 0.60 to 10.68). However, a large statistically significant amount of heterogeneity was detected for the 6-mercaptopurine subgroup comparison ($P = 0.02$; $I^2 = 82\%$). The heterogeneity appears to be a result of the inclusion of the [Present 1980](#) study in the pooled analysis. The [Present 1980](#) study was quite different than the other studies in the pooled analysis, as it did not use a validated outcome measure (e.g. CDAI) and it measured clinical improvement at one

year whereas the other studies measured clinical remission or improvement between 6 and 28 weeks. To investigate if this study was the source of the heterogeneity the analysis was repeated excluding this trial. The pooled analysis now included 8 studies involving 434 patients. No statistically significant heterogeneity was detected for the overall comparison ($P = 0.26$; $I^2 = 22\%$). Forty-eight per cent (107/225) of patients receiving antimetabolites achieved clinical remission or improvement compared to 36% (75/209) of placebo patients (RR 1.26, 95% CI 0.98 to 1.62; [Analysis 1.3](#)). A GRADE analysis indicated that the quality of evidence was moderate due to sparse data (182 events, see [Summary of findings table 1](#)).

[Present 1980](#) reported that the mean time to response with 6-mercaptopurine therapy in active Crohn's disease was 3.1 months, and that 19% of patients who responded took more than 16 weeks to respond. We therefore investigated the effect of duration of therapy on response ([Analysis 1.4](#)). When the active disease therapy data were analysed for the effect of duration of therapy (range 6 weeks to 12 months), the pooled risk ratio for response within 1 to 16 weeks was 1.08 (95% CI 0.83 to 1.40) and response with ≥ 17 weeks was 1.59 (95% CI 1.05 to 2.41). These risk ratios are not significantly different from one another as the confidence intervals overlap ($P = 0.12$; $I^2 = 59\%$). Thus no conclusion can be drawn with respect to the length of therapy.

Four placebo-controlled studies reported fistula response as an outcome ([Klein 1974](#); [Present 1980](#); [Rhodes 1971](#); [Willoughby 1971](#)). Two trials ([Ewe 1993](#); [Summers 1979](#)) reported no statistically significant difference in healing rates between placebo and therapy groups but did not include numerical data. [Present 1980](#) reported the number of fistulae that responded rather than the number of patients with fistulae that responded, so their results could not be pooled for analysis. We defined fistula response as complete healing or decreased discharge. If a fistula developed during the study, it was included as "unhealed". The pooled analysis included 3 studies and 18 patients. Fifty-four per cent (6/11) of azathioprine patients had a fistula response compared to 29% (2/7) of placebo patients (RR 2.00, 95% CI 0.67 to 5.93; [Analysis 1.5](#)). No statistically significant heterogeneity was detected for this comparison ($P = 1.00$, $I^2 = 0\%$). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to serious imprecision (very sparse data - 8 events and wide confidence intervals).

The ability to reduce prednisone or prednisolone dose was an important outcome measure for some studies. It was defined as the ability to follow a pre-defined steroid tapering regimen, and the ability to reduce steroid dose to < 10 mg/day while maintaining remission. Five studies reported the reduction of steroid consumption as an outcome ([Candy 1995](#); [Ewe 1993](#); [Klein 1974](#); [Present 1980](#); [Willoughby 1971](#)). However, [Present 1980](#) reported only cross-over results for this outcome and we decided that it should not be included in the pooled analysis. The pooled analysis (4 studies, 143 patients) showed that sixty-four per cent (47/73) of patients receiving azathioprine were able to reduce their prednisone dose to < 10 mg/day compared to 46% (32/70) of placebo patients (RR 1.34, 95% CI 1.02 to 1.77; [Analysis 1.6](#)). No statistically significant heterogeneity was detected for this comparison ($P = 0.40$; $I^2 = 0\%$). A GRADE analysis indicated that the overall quality of the evidence was moderate for this outcome due to sparse data. [Present 1980](#) reported that during treatment with

6-mercaptopurine in 44 patients, steroids could be discontinued in 23 patients and reduced in five (28/44). In 39 placebo patients steroids could be discontinued in five and reduced in one (6/39); RR 4.14, 95% CI 1.92 to 8.93. [Oren 1997](#) reported no statistically significant difference in steroid consumption or ability to taper steroids between 6-mercaptopurine and placebo (data not shown).

Commonly reported adverse events in the placebo-controlled studies included allergic reactions (consisting of fever or rash or both and arthritis), leukopenia, pancreatitis and nausea. One study involving 80 patients reported the proportion of patients who experienced at least one adverse event ([Reinisch 2008](#)). Sixty-nine per cent of patients in the azathioprine group experienced at least one adverse event compared to 86% of placebo patients (RR 0.81, 95% CI 0.64 to 1.02; [Analysis 1.7](#)). Eight placebo-controlled trials reported the proportion of patients who withdrew due to adverse events ([Candy 1995](#); [Ewe 1993](#); [Klein 1974](#); [Present 1980](#); [Reinisch 2008](#); [Rhodes 1971](#); [Summers 1979](#); [Willoughby 1971](#)). The adverse events reported from [Present 1980](#) include both arms of the cross-over since data from the individual arms were not reported. All other data from cross-over studies were reported from the period prior to cross-over. The adverse events from [Willoughby 1971](#) include both an induction of remission for active disease arm and a maintenance of remission arm since data from the individual arms were not reported. [Summers 1979](#) reported adverse events from each part of the trial and did not split part I in to its phases. [Oren 1997](#) did not report adverse event data. The pooled analysis (8 studies, 510 patients) showed that ten per cent (28/266) of patients receiving antimetabolites withdrew due to adverse events compared to 5% (13/244) of placebo patients (RR 1.70, 95% CI 0.94 to 3.08; [Analysis 1.8](#)). No statistically significant heterogeneity was detected for this comparison ($P = 0.68$; $I^2 = 0\%$). A GRADE analysis indicated that the overall quality of the evidence for this outcome was moderate due to sparse data (41 events, See [Summary of findings table 1](#)). Two studies ([Reinisch 2008](#); [Summers 1979](#)) including 216 patients reported the proportion of patients who experienced serious adverse events ([Reinisch 2008](#); [Summers 1979](#)). The pooled analysis showed that fourteen per cent (15/111) of patients in the antimetabolite group had a serious adverse event compared to 4% of placebo patients (RR 2.57, 95% CI 0.92 to 7.13; [Analysis 1.9](#)). There was no statistically significant heterogeneity detected for this analysis ($P = 0.44$; $I^2 = 0\%$). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to very sparse data (19 events) and very wide confidence intervals (See [Summary of findings table 1](#)).

Azathioprine versus Infliximab

[Colombel 2010](#) was the only study that compared azathioprine with infliximab. Clinical remission was a secondary outcome in this study. Patients with active Crohn's disease (CDAI 220 to 450) were included in the study. Clinical remission rates were higher in those randomized to receive infliximab compared to azathioprine. Thirty-two per cent (54/170) of azathioprine patients achieved clinical remission at week 26 compared to 48% (81/169) of infliximab patients (339 patients, RR 0.66, 95% CI 0.51 to 0.87; [Analysis 2.1](#)). A GRADE analysis indicated that the quality of evidence was moderate due to sparse data (135 events, see [Summary of findings 2](#)). Steroid free remission was the primary outcome in the [Colombel 2010](#) study. More infliximab patients than azathioprine patients were able to achieve steroid free remission. Thirty per cent of azathioprine patients (51/170) achieved steroid free remission at

26 weeks compared to 44% (75/169) of infliximab patients (339 patients, RR 0.68, 95% CI 0.51 to 0.90; [Analysis 2.2](#)). A GRADE analysis indicated that the quality of evidence was moderate due to sparse data (126 events, see [Summary of findings 2](#)).

[Colombel 2010](#) reported mucosal healing by colonoscopy as an outcome. Mucosal healing was defined as the absence of mucosal ulceration at week 26 in patients who had confirmed mucosal ulceration at baseline ([Colombel 2010](#)). Mucosal healing rates were higher in those randomized to receive infliximab compared to azathioprine. Twenty-eight per cent (28/99) of infliximab patients had mucosal healing at week 26 compared to 16% (18/115) of azathioprine patients (RR 0.55, 95% CI 0.33 to 0.94; [Analysis 2.3](#)). A GRADE analysis indicated that the overall quality of evidence was moderate due to sparse data (46 events, see [Summary of findings 2](#)).

[Colombel 2010](#) reported adverse events through week 54 of their trial. Eighty-nine per cent (144/161) of patients in the azathioprine group experienced at least one adverse event compared to 89% (145/163) of patients in the infliximab group (RR 1.01, 95% CI 0.93 to 1.08; [Analysis 2.4](#)). Common adverse events included nausea, abdominal pain, pyrexia and headache. Twenty-six per cent (42/161) of azathioprine patients withdrew from the study because of an adverse event compared to 18% (29/163) of infliximab patients (RR 1.47, 95% CI 0.96 to 2.23; [Analysis 2.5](#)). Twenty-seven per cent of azathioprine patients (43/161) experienced a serious adverse event compared to 24% (39/163) of infliximab patients (RR 1.12, 95% CI 0.77 to 1.62; [Analysis 2.6](#)). The overall quality of the evidence supporting these outcomes was moderate due to sparse data (see [Summary of findings 2](#)).

Azathioprine and Infliximab versus Infliximab

Two studies compared the combination of azathioprine and infliximab to infliximab alone ([Colombel 2010](#); [Mantzaris 2004](#)). Only [Colombel 2010](#) reported the outcome of clinical remission. Sixty per cent (102/169) of patients in the combination therapy group achieved clinical remission compared to 48% (81/169) of infliximab patients (338 patients, RR 1.26, 95% CI 1.03 to 1.54; [Analysis 3.1](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due to sparse data (183 events, See [Summary of findings 3](#)). Both studies ([Colombel 2010](#); [Mantzaris 2004](#)) reported steroid-free clinical remission as an outcome. Sixty per cent (116/194) of patients in the combination therapy group achieved steroid-free clinical remission compared to 48% (91/189) of infliximab patients (383 patients, RR 1.23, 95% CI 1.02 to 1.47; [Analysis 3.2](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due to sparse data (207 events, See [Summary of findings 3](#)). [Colombel 2010](#) reported mucosal healing. After 26 weeks of therapy, 42% (47/111) of patients in the combination therapy group achieved mucosal healing compared to 28% (28/99) of patients in the infliximab group (RR 1.50, 95% CI 1.02 to 2.19; [Analysis 3.3](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due to sparse data (75 events, see [Summary of findings 3](#)).

[Colombel 2010](#) reported that ninety per cent (161/179) of patients in the combination therapy group experienced an adverse event compared to 89% (145/163) of infliximab patients (RR 1.01, 95% CI 0.94 to 1.09; [Analysis 3.4](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due

to sparse data (306 events, see [Summary of findings 3](#)). Twenty-one per cent (37/179) of patients in the combination therapy group withdrew due to adverse events compared to 18% (29/163) of infliximab patients (RR 1.16, 95% CI 0.75 to 1.80; [Analysis 3.5](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due to sparse data (66 events, see [Summary of findings 3](#)). Fifteen per cent of patients in the combination therapy group (27/179) experienced a serious adverse event compared to 24% (39/163) of infliximab patients (RR 0.63, 95% CI 0.41 to 0.98; [Analysis 3.6](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was moderate due to sparse data (66 events, see [Summary of findings 3](#)).

Azathioprine or 6-Mercaptopurine versus Methotrexate

Two studies compared 6-MP to methotrexate ([Maté-Jiménez 2000](#); [Oren 1997](#);). [Oren 1997](#) used the Harvey-Bradshaw Index to evaluate disease activity. Those with a score of ≥ 7 were included in the study and remission was defined as a Harvey-Bradshaw score of ≤ 3 and no steroid use. [Maté-Jiménez 2000](#) included patients with steroid dependent Crohn's disease, defined as the inability to taper steroids below 20 mg/day without presenting symptoms of active disease (e.g. CDAI > 200). Remission was defined as CDAI < 150 with normal orosomucoid serum concentrations after discontinuing steroids. [Ardizzone 2003](#) compared azathioprine to methotrexate. [Ardizzone 2003](#) enrolled patients with active Crohn's disease (CDAI ≥ 200) with the need for steroids. [Ardizzone 2003](#) defined remission as CDAI ≤ 150 and the discontinuation of steroid treatment. A pooled analysis (3 studies, $n = 143$ patients) revealed that 60% (45/75) of patients in the antimetabolites group achieved steroid-free remission compared to 57% (39/68) of methotrexate patients (RR 1.13, 95% CI 0.85 to 1.49; [Analysis 4.1](#)). No statistically significant heterogeneity was detected for this comparison ($P = 0.95$; $I^2 = 0\%$). A GRADE analysis indicates that the overall quality of the evidence for this outcome was low due to sparse data (75 events) and a high risk of bias in two of the studies in the pooled analysis (See [Summary of findings 4](#)).

These studies provided little data on adverse events. [Oren 1997](#) did not report adverse event data. [Maté-Jiménez 2000](#) pooled adverse event data for Crohn's disease and ulcerative colitis, therefore only some of the adverse events were interpretable for Crohn's disease. [Ardizzone 2003](#) provided adequate information with respect to adverse events. A pooled analysis (2 studies, 85 patients) showed that adverse events were more likely in patients receiving methotrexate compared to azathioprine or 6-MP. Overall, adverse events occurred in 19% (8/43) of azathioprine or 6-MP patients compared to 45% (19/42) of methotrexate patients (RR 0.42, 95% CI 0.21 to 0.82; [Analysis 4.2](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was low due to sparse data (27 events) and a high risk of bias in two of the studies in the pooled analysis. Adverse events leading to withdrawal occurred in 9% (4/43) of azathioprine or 6-MP patients compared to 12% (5/42) of methotrexate patients (RR 0.78, 95% CI 0.23 to 2.71; [Analysis 4.3](#)). A GRADE analysis indicates that the overall quality of the evidence for this outcome was very low due to sparse data (9 events), very wide confidence intervals and a high risk of bias in two of the studies in the pooled analysis. No serious adverse events were reported in these studies.

Azathioprine or 6-Mercaptopurine versus 5-Aminosalicylic Acid or Sulfasalazine

[Maté-Jiménez 2000](#) compared 6-MP to 5-ASA. [Summers 1979](#) compared azathioprine to sulfasalazine. A pooled analysis of two studies ($n = 156$) revealed that forty-eight per cent (36/75) of patients in the antimetabolite group achieved remission compared to 36% (29/81) of patients who received 5-ASA or sulfasalazine (RR 1.24, 95% CI 0.80 to 1.91; [Analysis 5.1](#)). There was statistically significant heterogeneity detected for this analysis ($P = 0.03$; $I^2 = 79\%$). A GRADE analysis indicates that the overall quality of the evidence for this outcome was very low due to sparse data (65 events), a high risk of bias in the [Maté-Jiménez 2000](#) study, and unexplained heterogeneity (See [Summary of findings 5](#)). Nine per cent of 6-MP patients (7/75) withdrew due to adverse events compared to 10% of patients (8/81) in the aminosalicylates group (156 patients, RR 0.98, 95% CI 0.38 to 2.54; [Analysis 5.2](#)). There was no statistically significant heterogeneity detected for this comparison ($P = 0.81$; $I^2 = 0\%$). A GRADE analysis indicates that the overall quality of the evidence for this outcome was low due to sparse data (15 events) and a high risk of bias in the [Maté-Jiménez 2000](#) study. [Maté-Jiménez 2000](#) did not report serious adverse events and neither of the studies reported the proportion of patients who experienced at least one adverse event ([Maté-Jiménez 2000](#); [Summers 1979](#);). [Summers 1979](#) reported serious adverse events as an outcome. Seven per cent of patients in the 6-MP group experienced a serious adverse event compared to 0% of 5-ASA patients (RR 11.25, 95% CI 0.62 to 204.86; [Analysis 5.3](#)).

DISCUSSION

This updated review includes 13 randomized controlled trials ($n = 1211$ patients) which examined the efficacy of azathioprine or 6-mercaptopurine for inducing remission in Crohn's disease. These trials compared these antimetabolites to placebo and various active therapies including infliximab, methotrexate and 5-aminosalicylate. The definitions of remission and improvement varied from study to study making exact comparisons across studies difficult. Only 5 of 9 ([Candy 1995](#); [Ewe 1993](#); [Oren 1997](#); [Reinisch 2008](#); [Summers 1979](#)) placebo-controlled studies used generally accepted and validated criteria (either a Crohn's Disease Activity Index score < 150 points or a Harvey-Bradshaw Index score ≤ 3 points) to define remission. The other four studies used subjective improvement or other non-validated outcome measures ([Klein 1974](#); [Present 1980](#); [Rhodes 1971](#); [Willoughby 1971](#)). Azathioprine or 6-mercaptopurine therapy was possibly modestly better than placebo (5 studies, 380 patients, RR 1.23, 95% CI 0.97 to 1.55, moderate certainty evidence) for achieving clinical remission. When clinical remission or improvement is considered as an outcome, azathioprine or 6-mercaptopurine therapy was possibly better than placebo (434 patients, RR 1.26, 95% CI 0.98 to 1.62, moderate certainty evidence). These results suggest that azathioprine and 6-mercaptopurine possibly offer a modest advantage over placebo for induction of remission or clinical improvement in active Crohn's disease. We believe that the methodological basis for these conclusions is sound. The quality of the individual trials was assessed using the Cochrane risk of bias tool and the possibility of bias was judged to be low for these studies. A GRADE analysis indicated that the overall quality of the evidence supporting these outcomes is moderate due to sparse data, hence we cannot have complete certainty in the

estimates. These findings agree with a recent meta-analysis of immunosuppressives in inflammatory bowel disease (Khan 2011).

The ability to taper or discontinue corticosteroids is an important outcome to consider when treating Crohn's disease. Four older trials (Candy 1995; Ewe 1993; Klein 1974; Willoughby 1971) reported steroid-sparing (e.g. final prednisone dose < 10 mg/day) as an outcome. A pooled analysis of these studies showed that azathioprine was possibly effective compared to placebo (143 patients, RR 1.34, 95% CI 1.02 to 1.77). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate. The role of combined antimetabolite and steroid therapy in active disease has been controversial. The National Cooperative Crohn's Disease Study (Summers 1979) failed to show a statistically significant benefit for azathioprine monotherapy and has been criticised for not allowing concurrent steroid therapy during the lag period before azathioprine could act, and for not allowing sufficient time to assess the response to azathioprine (Korelitz 1981). Combination therapy with azathioprine and steroids may lead to a higher response rate with less steroid use.

More recent trials comparing antimetabolites to other active therapies reported steroid-free clinical remission as an outcome (Ardizzone 2003; Colombel 2010; Mantzaris 2004; Maté-Jiménez 2000; Oren 1997; Reinisch 2008). The evidence is very uncertain about the effectiveness of 6-Mercaptopurine in inducing steroid-free remission compared to 5-aminosalicyclates (23 patients, RR 6.56, 95% CI 1.06 to 40.46). This uncertainty is due to the small number of patients included in the analysis and the poor methodological quality of the Maté-Jiménez 2000 study. The overall quality of the evidence was rated as very low using the GRADE approach due to this risk of bias, imprecision and inconsistency. The Oren 1997 study is not adequate to determine the relative benefits of 6-mercaptopurine versus methotrexate. The sample size was small, both drugs were probably underdosed (6-mercaptopurine 50 mg/day and methotrexate 12.5 mg/week orally), and neither drug was reported to be superior to placebo. A trial comparing oral 6-mercaptopurine 1.5 mg/kg/d or azathioprine 2 to 3 mg/kg/d with parenteral methotrexate 25 mg/wk for chronic active Crohn's disease would be of interest. A pooled analysis including three studies found a difference in steroid-free clinical remission between azathioprine or 6-mercaptopurine and methotrexate (143 patients, RR 1.13, 95% CI 0.85 to 1.49). However, the results of this pooled analysis need to be interpreted with caution due to the small number of patients included in the analysis and because of a high risk of bias in two of the studies in the pooled analysis (Ardizzone 2003; Maté-Jiménez 2000). Furthermore, none of the three studies in the pooled analysis were designed as formal non-inferiority studies. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low. Azathioprine and 6-mercaptopurine may be better choices as first line steroid sparing agents than methotrexate due to the propensity for adverse effects. A pooled analysis of two studies found that patients taking methotrexate may be more likely than patients taking azathioprine or 6-mercaptopurine to experience an adverse event (85 patients, RR 0.42, 95% CI 0.21 to 0.82; low quality evidence). More high quality trials comparing azathioprine or 6-mercaptopurine with 5-aminosalicyclates or methotrexate are required to determine the true comparative efficacy and safety of these interventions.

Azathioprine was found to be probably less effective than infliximab (339 patients, RR 0.66, 95% CI 0.51 to 0.87) for achieving clinical remission. The addition of azathioprine to infliximab probably improved clinical remission rates (338 patients, RR 1.26, 95% CI 1.03 to 1.54) compared to azathioprine alone. The combination of azathioprine and infliximab was found to be probably superior to infliximab alone (383 patients, RR 1.23, 95% CI 1.02 to 1.47) for induction of steroid-free remission. Azathioprine was found to be probably inferior to infliximab therapy (339 patients, RR 0.68, 95% CI 0.51 to 0.90) for induction of steroid-free remission. The reason for the uncertainty in these estimate is our GRADE analysis which rated the overall quality of the evidence for these comparison as moderate. Colombel 2010 also reported mucosal healing as an outcome. Azathioprine was found to be probably inferior to infliximab for mucosal healing (RR 0.55, 95% CI 0.33 to 0.94). The combination of azathioprine and infliximab was found to be probably superior to infliximab alone for mucosal healing (RR 1.50, 95% CI 1.02 to 2.19). Again, the reason for the uncertainty is that our GRADE analysis rated the overall quality of the evidence for these outcomes as moderate due to sparse data. More high quality trials comparing the combination of azathioprine with infliximab to infliximab alone are required to confirm the benefit of this combination.

The use of azathioprine for refractory fistulae was originally based on uncontrolled reports (Avery-Jones 1966; Brown 1970; Brooke 1970; Drucker 1970; Korelitz 1985). For three placebo controlled trials that reported numerical results (Klein 1974; Rhodes 1971; Willoughby 1971;), azathioprine therapy was found to have a possible advantage over placebo for fistula healing (RR 2.00, 95% CI 0.67 to 5.93). However, this pooled analysis included only 18 patients and further research is necessary to determine if azathioprine provides a benefit for fistula healing. In the Present 1980 study, forty fistulae were observed in 36 patients, and 9/29 (31%) of fistulae closed completely during treatment with 6-mercaptopurine compared with 1/17 (6%) of fistulae which closed during treatment with placebo (these numbers represent overlapping patients, some who crossed over and some who did not). The Present 1980 data were not included in this systematic review because the data were reported as the number of fistulae closing, rather than the number of patients who had complete fistulae closure, and because the fistulae data were not presented in a way that made separation of the results from the first phase of the crossover study possible. The principal author of this study was contacted, and the original data are no longer available to address these issues. The results from two other studies which reported no significant effect (Ewe 1993; Summers 1979) also could not be included in the analysis because the fistulae data were not available. The lack of specific reporting on fistula response in these two trials may represent publication bias, as negative results were not reported. A randomized, double-blind, placebo-controlled trial of azathioprine designed to specifically address the question of efficacy in the subgroup of patients with fistulizing (perforating) Crohn's disease would be of interest.

The adverse effects of antimetabolite therapy are well recognised (Alstead 1990; Haber 1986 Rhodes 1971; Rosman 1973). Patients with Crohn's disease may have similar symptoms, so a comparison with a control group is useful to estimate the incidence of adverse effects attributable to therapy. Patients receiving azathioprine or 6-mercaptopurine may be more likely to withdraw due to an adverse event. Present 1989 reviewed their extensive experience with 6-

mercaptopurine in 396 patients with inflammatory bowel disease and approximately 1800 patient-years of follow-up. [Present 1989](#) reported a higher incidence of adverse reactions, presumably due to the longer duration of therapy and observation: significant infection (7.4%), pancreatitis (3.3%), neoplasm (3.1%), bone marrow suppression (2.0%), allergy (2.0%), and drug-induced hepatitis (0.3%). [O'Brien 1991](#) reported an overall 10% incidence of adverse events sufficiently severe to justify stopping azathioprine or 6-mercaptopurine in their uncontrolled series of 78 patients with Crohn's disease. Two studies detailing the low toxicity of azathioprine with respect to bone marrow suppression and cancer risk in 755 patients with inflammatory bowel disease treated over 27 years have been reported ([Connell 1993](#); [Connell 1994](#)). A follow-up report of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine for up to 166 months did not show an increase in toxicity with long term use ([Bouhnik 1996](#)). More recent studies confirm the low risk of bone marrow suppression and cancer in IBD patients treated with azathioprine ([Fraser 2002](#); [Gisbert 2008](#)). The time course for the occurrence of adverse events is variable. Allergic reactions and pancreatitis usually occur within a few weeks of beginning therapy, whereas bone marrow suppression, infection, and hepatitis may occur at any time. It was not possible to ascertain from the controlled trials reviewed for this meta-analysis what the time course was for the various forms of drug toxicity observed.

Four active comparator trials reported the proportion of patients who experienced at least one adverse event ([Ardizzone 2003](#); [Colombel 2010](#); [Mantzaris 2004](#); [Maté-Jiménez 2000](#)). The difference in adverse events rates between azathioprine and infliximab was probably negligible (RR 1.01, 95% CI 0.93 to 1.08). Furthermore, the combination of azathioprine and infliximab was found to probably have a similar rate of adverse events compared to infliximab alone (RR 1.01, 95% CI 0.94 to 1.09). Data on withdrawals due to adverse events were available for all of the comparisons. The differences in withdrawals secondary to adverse events between the various drugs were as follows: azathioprine or 6-mercaptopurine and methotrexate: RR 0.78, 95% CI 0.23 to 2.71; 6-mercaptopurine and aminosaliclates: RR 0.98, 95% CI 0.38 to 2.54 and azathioprine and infliximab: RR 1.47, 95% CI 0.96 to 2.23. The risk ratio for combined therapy with infliximab and azathioprine compared to infliximab alone was 1.16, 95% CI 0.75 to 1.80. The rate of serious adverse events was only reported in one study ([Colombel 2010](#)). Azathioprine was found to probably have a similar serious adverse event rate compared to infliximab (RR 1.12, 95% CI 0.77 to 1.62). However, the addition of azathioprine to infliximab was found to probably decrease the risk of a serious adverse event compared to infliximab alone (RR 0.63, 95% CI 0.41 to 0.98). The reason for uncertainty is that GRADE analyses indicated that the overall quality of the evidence supporting these outcomes was low to moderate due to sparse data ([Colombel 2010](#)) or high risk of bias ([Ardizzone 2003](#); [Maté-Jiménez 2000](#)). Further research is necessary to assess the long term safety of azathioprine and 6-mercaptopurine.

The above findings from the present meta-analysis highlight some of the problems with the use of azathioprine or 6-mercaptopurine in active Crohn's disease. First and foremost, our meta-analysis shows that antimetabolite therapy possibly provides a modest benefit over placebo for induction of remission or clinical improvement in active Crohn's disease, but the evidence is of moderate quality due to the imprecision of the effect estimate.

Antimetabolite therapy may take a few months before onset of drug action (e.g. approximately three months, [Present 1980](#); [Sahasranaman 2008](#)). To explore this we analyzed placebo-controlled trials by the time point when remission or clinical improvement was measured. Azathioprine or 6-mercaptopurine patients evaluated at 17 weeks or later were probably more likely to be in remission than those taking placebo (RR 1.59, 95% CI 1.05 to 2.41). When remission or clinical improvement was measured before 17 weeks there was probably a smaller difference between antimetabolites and placebo (RR 1.08, 95% CI 0.83 to 1.40). These results suggest that a period of 17 weeks may be the minimum time period for an adequate trial of antimetabolite therapy. It had been postulated that the apparent long duration of therapy required to achieve benefit may be due to a requirement for equilibration of the active metabolite of the drug within tissues. It was also suggested that a high intravenous loading dose of the drug might overcome this problem ([Sandborn 1995](#)). However, a placebo-controlled trial of intravenous azathioprine loading (40 mg/kg over 36 hours) in patients with active steroid-refractory Crohn's disease receiving oral azathioprine did not show any benefit ([Sandborn 1999](#)).

Apart from potentially expediting induction of steroid-free remission, azathioprine may have a role as an adjunctive therapy to infliximab. This was illustrated by the likely superiority of the combination of infliximab and azathioprine to monotherapy with azathioprine or infliximab. Therapy with azathioprine and 6-mercaptopurine may help to prevent the development of antibodies to infliximab. The development of antibodies to infliximab has been associated with a loss of response to infliximab and the development of infusion reactions. An analysis of the ACCENT I data by Hanauer and colleagues found that patients who received immunosuppressive therapy (i.e. azathioprine, 6-mercaptopurine or methotrexate) in conjunction with infliximab had a significantly lower chance of developing antibodies to infliximab than patients who received infliximab monotherapy ([Hanauer 2004](#)). However, patients who were found to be positive for these antibodies were not less likely to have a clinical response or be in clinical remission at the end of the study. These results should be interpreted with caution as only 80 patients had positive antibodies ([Hanauer 2004](#)). Future trials should evaluate the interaction between antimetabolite therapy and infliximab with respect to antibody formation and efficacy.

AUTHORS' CONCLUSIONS

Implications for practice

Azathioprine and 6-mercaptopurine possibly offer a modest advantage over placebo for induction of remission or clinical improvement in active Crohn's disease. Antimetabolite therapy possibly allows patients to reduce steroid consumption. There is evidence to suggest that the combination of azathioprine and infliximab is probably superior to infliximab monotherapy for induction of steroid-free remission in active Crohn's disease. Adverse events are possibly more common in patients receiving antimetabolites compared to those receiving placebo.

Implications for research

All of the studies reported in this analysis used clinical improvement or remission as the primary outcome. It would be of interest to know whether azathioprine or 6-mercaptopurine can induce mucosal healing. Preliminary uncontrolled observations

have suggested that azathioprine does result in endoscopic healing of active Crohn's disease (D'Haens 1997; Sandborn 1995;). Future studies should assess time to steroid-free remission as an outcome. The available data on fistulae closure in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine is not adequate to make definite conclusions regarding efficacy. A randomized, double-blind, placebo-controlled trial of azathioprine therapy in patients with active fistulizing Crohn's disease would be of interest. More high quality trials comparing azathioprine or 6-mercaptopurine with 5-aminosalicylates or methotrexate are

required to determine the true comparative efficacy and safety of these interventions. Further research is required to confirm the superiority of combination of azathioprine and infliximab to infliximab monotherapy. Future research should also assess the efficacy and safety of the use of azathioprine with other biologics.

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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, controlled trial with blinded investigators Intention to treat 6 month trial; all patients given standard prednisolone dose at the beginning of the trial
Participants	Patients (18 to 75 years old) with confirmed Crohn's disease on steroids for ≥ 4 months in the last year and active (CDAI ≥ 200) disease at entry (N = 54)
Interventions	Intravenous methotrexate for 3 months then oral administration for 3 months (25 mg/week) (n = 27) or oral azathioprine for 6 months (2.5 mg/kg) (n = 27)
Outcomes	Primary: steroid free clinical remission Secondary: decreased steroid use, decreased CDAI, CRP or ERS, closure of fistulae
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by a computer-generated list"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "investigator-blind" Quote: "patients and Chief of the Institute (GBP), who supervised the randomization, were aware of the treatment" Quote: "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 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"

Ardizzone 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patients were lost to follow-up. Six patients (three in azathioprine and three in methotrexate group) discontinued treatment due to adverse events. Withdrawal from the trial medication was considered as a treatment failure"
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Candy 1995

Methods	Randomized, double-blind, placebo-controlled Intention to treat 12 weeks induction with tapering prednisolone dose, Month 3-15, no prednisolone, maintenance with azathioprine (N = 63)
Participants	Patients with active disease, CDAI > 150
Interventions	Azathioprine (2.5 mg/kg/day) (n = 33) versus placebo (n = 30). All patients received a tapering dose of prednisolone (1 mg/kg)
Outcomes	Remission (CDAI <150) at 12 weeks and maintenance at 15 months
Notes	Unknown 5ASA use during trial and unknown previous steroid use before trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "patients were presented with tablets of identical appearance" Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	20/63 participants withdrew by week 12 (azathioprine = 9/33, placebo = 11/30); 47/63 withdrew by month 15 (azathioprine = 19/33, placebo = 28/30). Data were analyzed by intention to treat and the reasons for withdrawal were reported
Selective reporting (reporting bias)	Low risk	<i>A priori</i> outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Colombel 2010

Methods	Randomized, double-blind trial comparing azathioprine, infliximab or combination of both Intention to treat 30 weeks with a 20 week blinded extension option given Primary outcome reported at 26 weeks (N = 508)
Participants	Adult patients (≥ 21 years old) with CDAI between 220 and 450 Exclusion criteria: short bowel syndrome, ostomy, symptomatic stricture, abscess, recent abdominal surgery, history of tuberculosis or other granulomatous infection, positive chest x-ray or tuberculin skin test, recent opportunistic infection, active hepatitis C or V or HIV infection, multiple sclerosis, cancer or homozygous/heterozygous mutation to thiopurine methyltransferase phenotype
Interventions	Azathioprine 2.5 mg/kg (n = 170) versus infliximab 5 mg/kg (n = 169) versus combination of azathioprine and infliximab (n = 169)
Outcomes	Primary outcome: steroid-free remission rate Secondary outcomes: mucosal healing (measured at week 26 in those who had ulcers at baseline), rate of clinical remission, response, IBDQ scores, corticosteroid dose, change in CRP from baseline Remission was defined as < 150 CDAI

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of an adaptive randomization procedure"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of an adaptive randomization procedure"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind" Quote: "daily oral placebo" Quote: "placebo infusions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	190/508 were withdrawn in the first 30 weeks. 280 patients entered the extension trial. Patients lost to follow up were assumed to not be in remission
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in either the report or appendices
Other bias	Low risk	The study appears to be free of other sources of bias

Ewe 1993

Methods	Randomized, double-blind, placebo-controlled Intention to treat
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Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease (Review)

Ewe 1993 (Continued)

16 weeks
(N = 42)

Participants	Patients with active disease, CDAI > 150
Interventions	Azathioprine (2.5 mg/kg/day) (n = 21) versus placebo (n = 21). All patients started with 60 mg prednisolone daily, reduced weekly to: 40, 30, 25, 20, 15, 10 mg. If taper successful, maintained at 10 mg/day prednisolone for the remainder of the trial
Outcomes	Remission (CDAI < 150) at 17 weeks. No data on fistulae
Notes	Steroid sparing effect found: azathioprine group more likely to follow tapering schedule and reinstitution of prednisolone more frequent in control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described (Quote: "allocation to each group was double blinded")
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "None of the patients dropped out during the course of the trial"
Selective reporting (reporting bias)	Low risk	The primary outcome (remission) was reported, along with all lab values
Other bias	Low risk	The study appears to be free of other sources of bias

Klein 1974

Methods	Randomized, double-blind, placebo-controlled Cross-over design: only data prior to cross-over used Intention to treat 17 weeks (N = 26)
Participants	Patients with active disease unresponsive to other forms of medical management
Interventions	Azathioprine 3 mg/kg/day (n = 13) versus placebo (n = 13). Concomitant steroid therapy at discretion of attending physician, but a conscious effort was made to taper steroids
Outcomes	Remission defined as a subjective sense of improvement
Notes	

Risk of bias

Klein 1974 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind" Quote: "control subjects took a similar amount of dummy tablets (placebo)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/13 patients from each group were unable to complete the study. Reasons for withdrawal were given
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mantzaris 2004

Methods	Randomized controlled trial (N = 47) comparing infliximab alone (n = 20) to infliximab and azathioprine (n = 25) for induction phase (6 weeks). Patients who were successfully induced were entered into the maintenance phase and were treated with infliximab (5 mg/kg) every eight weeks (n = 16) or azathioprine alone (n = 20) for 1 year
Participants	Adult patients with active Crohn's disease (CDAI > 150) at entry
Interventions	Infliximab (5 mg/kg at week 0, 2, 6) or infliximab with azathioprine (2.5 mg/kg)
Outcomes	Induction of remission at week 6 (CDAI < 150 and off steroids) and maintenance of remission at 1 year
Notes	It is not clear which group the missing two patients were assigned to

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seven patients withdrew, intention to treat followed

Mantzaris 2004 (Continued)

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Maté-Jiménez 2000

Methods	Randomized trial of 6-mercaptopurine, methotrexate and 5-aminosalicylic acid in patients with inflammatory bowel disease 38 patients with Crohn's disease, 34 patients with ulcerative colitis Induction for 30 weeks, followed for maintenance for 76 weeks (N = 38 with Crohn's)
Participants	Patients with steroid-dependent inflammatory bowel disease between 15 and 70 years old Exclusion criteria: cardiac, hepatic or renal disease; bacterial infection; pregnancy, lactating or no use of reliable contraception, use of allopurinol, nonsteroidal anti-inflammatory drugs, tetracyclines or phenytoin; extensive surgery in the past
Interventions	6-mercaptopurine (n = 16 with Crohn's), methotrexate (n = 15 with Crohn's) or 5-aminosalicylic acid (n = 7 with Crohn's)
Outcomes	Primary outcome was clinical remission
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	The use of blinding was not described in the manuscript. We assume that blinding was not used
Incomplete outcome data (attrition bias) All outcomes	Low risk	24/72 patients withdrew in the first 30 weeks, reasons described, worst outcome assumed
Selective reporting (reporting bias)	Unclear risk	Primary outcome was reported, as well as a number of other <i>post hoc</i> outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Oren 1997

Methods	Randomized, double-blind, three arm study (6-mercaptopurine, methotrexate, placebo) Intention to treat
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Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease (Review)

Oren 1997 (Continued)

9 months
(N = 84)

Participants	Patients with active disease, Harvey-Bradshaw Index ≥ 7
Interventions	6-mercaptopurine 50 mg/day (n = 32) versus methotrexate 12.5 mg/week (n = 26) versus placebo (n = 26). 5-aminosalicylate and/or steroids continued at the discretion of the attending physician. Treating physicians were instructed to taper steroids and try to discontinue them within 2-3 months of entering the trial
Outcomes	Remission defined as a Harvey-Bradshaw Index score ≤ 3 on the condition that the patient was not receiving steroids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind" Quote: "The investigators were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition over the 9 month study were 13/26 for the methotrexate group, 9/32 for the 6-mercaptopurine group and 5/26 for the placebo. Data were analyzed by intention to treat and the method for dealing with missing data was outlined
Selective reporting (reporting bias)	Low risk	The primary outcome (remission) was reported, along with all secondary outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Present 1980

Methods	Randomized, double-blind, placebo-controlled Crossover design, only data prior to cross over used for analysis of disease activity, data from both arms used to assess fistula effect, steroid sparing effect, and adverse effects Intention to treat 52 weeks (N = 83)
Participants	Patients with chronically active Crohn's disease, unresponsive to corticosteroids and sulfasalazine but surgery not imminent
Interventions	6-mercaptopurine 1.5 mg/kg/day versus placebo
Outcomes	Improvement in disease, healing of fistulae, steroid sparing effect
Notes	

Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease (Review)

Present 1980 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random-number tables"
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Both tablets...were identical in appearance and taste" Quote: "patients and gastroenterologists were unaware of which treatment was being given"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/83 patients dropped out early. 8 from the 6-mercaptopurine group
Selective reporting (reporting bias)	Low risk	Effects on fistulas and steroid doses are explicitly discussed. Effect on signs and symptoms is discussed partially in the "Factors That Influenced the Response to 6-MP" section
Other bias	Low risk	Some problems with the cross-over protocol being followed, but no other issues

Reinisch 2008

Methods	Randomized, double blind , controlled trial 7 months (N = 96) Study stopped early because of lack of efficacy of everolimus
Participants	Adult patients (18 to 80 years old) with active Crohn's disease (CDAI 220 to 450) Exclusion criteria listed in the study
Interventions	Azathioprine 2.5 mg/kg/day (n = 36), everolimus 6mg/day (n = 38) or placebo (n = 22)
Outcomes	Treatment success and safety of everolimus
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " randomization was performed using a validated interactive voice response randomization system that automated the random assignment of patient numbers to randomization numbers"

Reinisch 2008 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "randomization was performed using a validated interactive voice response randomization system that automated the random assignment of patient numbers to randomization numbers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "A double-blind, double-dummy design was used to overcome the different forms of everolimus and azathioprine"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A large proportion of the patients initially enrolled (n = 144) appear not to be in remission after 3 months (n = 48). Furthermore, 54 patients withdrew from the study for various reasons. However, intention to treat was followed for the remaining 96 patients
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Rhodes 1971

Methods	Randomized, double-blind, placebo-controlled Intention to treat Crossover, only data from first arm of cross over used in analysis 8 weeks (N = 12)
Participants	Patients with active Crohn's disease
Interventions	Azathioprine 4 mg/kg/day versus placebo for 10 days, then 2 mg/kg/day versus placebo for a total of 8 weeks of therapy
Outcomes	Response to treatment, fistulae improvement
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/16 withdrew Quote: "two were withdrawn because of complications" The group assignment was not provided for one of the withdrawals

Rhodes 1971 (Continued)

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Summers 1979

Methods	Randomized, double-blind, placebo-controlled Intention to treat 17 weeks N = 136
Participants	Patients with active disease, CDAI >150
Interventions	Azathioprine 2.5 mg/kg/day versus placebo
Outcomes	Remission (CDAI <150) at 17 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "all prepared in uncoated tablets of identical external and internal appearance"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition appears to be low but is not balanced across intervention groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Willoughby 1971

Methods	Randomized, double-blind trial 24 weeks N = 22
Participants	Group 1: patients with active disease (subgroup included in this review) (n = 12)

Willoughby 1971 (Continued)

Group 2: patients with disease controlled on prednisone (n = 10)

Interventions	Azathioprine 2 mg/kg or placebo; prednisone was tapered in both groups	
Outcomes	Withdrawal from trial because of deterioration in condition	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind" Quote: "Only the pharmacist dispensing the tablets knew whether azathioprine or placebo had been selected for a given case"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the final analysis, withdrawal (as defined above) was the endpoint of the trial
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bianchi Porro 1982	Not a randomized trial.
Broekman 2015	Included patients with both Ulcerative Colitis and Crohn's disease. Not a randomized controlled trial. Analyzed data from an existing study to determine incidence of side effects in thiopurine naive patients who were started on thiopurine therapy.
Chebli 2007	Not a randomized controlled trial. Patients (N = 69) were given azathioprine after induction of remission with steroids and followed to see if they would maintain remission
Colombel 2003	Report detailing mucosal healing 5 years after patients participated in GETAID trial. Not a new trial.
Cosnes 2012	All patients (N = 147) received azathioprine. Study compared accelerated step-care (steroids + early azathioprine) to conventional step-care (steroids + azathioprine based on guidelines)
D'Haens 2008	All patients (N = 133) received azathioprine. Study compared early combined immunosuppression (step-down: infliximab + azathioprine) to conventional step-up care (steroids for induction followed in sequence by azathioprine and infliximab)

Study	Reason for exclusion
Dassopoulos 2014	All patients (n=50) received azathioprine. Studied differences between individualized dosing vs weight based dosing
Dejaco 2003	Not a randomized trial. Patients (N = 52) with perianal fistulas received an antibiotic and azathioprine
Eigner 2015	Azathioprine not used in trial. Patients intolerant to azathioprine
Israeli 2015	Trial compared one formulation of 6-MP to another
Khanna 2014	Compared conventional management plan to early combined immunosuppression. Used a combination of medications in trial but focus was on comparing management plans not comparing medications
Lloyd-Still 1990	Pediatric study population.
Ludwig 1999	Not a randomized controlled trial. Patients (N = 89) were enrolled in an uncontrolled, investigator-blind study and received azathioprine therapy for 1 year, for induction of remission. Seventy-five per cent of patients were in remission at the end of 1 year
Lémann 2006	All patients (N = 113) received AZA or 6-MP. Study compared efficacy of infliximab + azathioprine or 6-mercaptopurine versus placebo + azathioprine or 6-mercaptopurine
Mantzaris 2009	Induction of remission was achieved by conventional steroids. Patients (N = 77) were randomized to receive azathioprine or budesonide to assess efficacy for maintenance of remission
Markowitz 2000	A pediatric study. Patients (N = 55) were enrolled in a double-blind, placebo-controlled study and randomized to receive 6-mercaptopurine (1.5 mg/kg/day) and prednisone (40 mg/day) or placebo and prednisone (40 mg/day) for induction of remission. After 18 months, remission was induced in 89% of patients in both groups and was maintained in 91% of 6-MP patients compared to 53% of placebo patients. 6-MP also had a steroid-sparing effect compared to placebo
Miehlsler 2001	Not a randomized controlled trial. Forty-five patients were enrolled in this retrospective study comparing mycophenolate mofetil and azathioprine for induction of remission. All patients who completed the treatment achieved remission after 1 year. MMF had a faster steroid-sparing effect compared to AZA but had almost twice as many flare-ups as AZA
Neurath 1999	The primary outcome for the review (clinical remission) was not reported. The primary outcome for the study was change in CDAI
Panés 2013	Maintenance trial
Reinshagen 2007	Randomized trial comparing standard dosing of azathioprine to adapted dosing of azathioprine
Rosenberg 1975	Maintenance trial, remission already induced with steroids. Trial was monitoring for relapses when patients (n=20) were started on azathioprine.
Sans 2011	Pediatric study
Watson 1974	An abstract publication. Eleven patients enrolled into a randomised, double blind placebo controlled cross-over study of maintenance therapy, 1 year per arm Intervention: azathioprine 50 mg TID. Never published as a full paper, so unable to properly evaluate the methods and data. Preliminary analysis of the data showed no therapeutic advantage of azathioprine over placebo. No statistically significant change in objective disease score, but patients on azathioprine felt better, 1 patient in each group flared and required surgery

DATA AND ANALYSES

Comparison 1. Azathioprine or 6-Mercaptopurine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission	5	380	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.97, 1.55]
1.1 Azathioprine	4	322	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.94, 1.64]
1.2 6-Mercaptopurine	1	58	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.50, 2.98]
2 Clinical remission or improvement	9	506	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.05, 2.22]
2.1 Azathioprine	7	376	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.96, 1.71]
2.2 6-Mercaptopurine	2	130	Risk Ratio (M-H, Random, 95% CI)	2.54 [0.60, 10.68]
3 Clinical remission or improvement (sensitivity analysis)	8	434	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.98, 1.62]
3.1 Azathioprine	7	376	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.96, 1.71]
3.2 6-Mercaptopurine	1	58	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.50, 2.98]
4 Clinical remission or improvement by trial duration	8	434	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.98, 1.62]
4.1 trials ≥17 weeks	4	216	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.05, 2.41]
4.2 trials <17 weeks	4	218	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.40]
5 Fistula improvement or healing	3	18	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.67, 5.93]
6 Steroid sparing effect (final prednisone dose < 10 mg/day)	4	143	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.02, 1.77]
7 Adverse events	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.02]
8 Withdrawals due to adverse events	8	510	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.94, 3.08]
9 Serious adverse events	2	216	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.92, 7.13]

Analysis 1.1. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 1 Clinical remission.

Analysis 1.2. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 2 Clinical remission or improvement.

Analysis 1.3. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 3 Clinical remission or improvement (sensitivity analysis).

Analysis 1.4. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 4 Clinical remission or improvement by trial duration.

Analysis 1.5. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 5 Fistula improvement or healing.

Analysis 1.6. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 6 Steroid sparing effect (final prednisone dose < 10 mg/day).

Analysis 1.7. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 7 Adverse events.

Analysis 1.8. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 8 Withdrawals due to adverse events.

Analysis 1.9. Comparison 1 Azathioprine or 6-Mercaptopurine versus placebo, Outcome 9 Serious adverse events.

Comparison 2. Azathioprine versus Infliximab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission through 26 weeks	1	339	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.51, 0.87]
2 Steroid-free remission through 26 weeks	1	339	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.90]
3 Mucosal healing through 26 weeks	1	214	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.33, 0.94]
4 Adverse events	1	324	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.08]
5 Withdrawals due to adverse events	1	324	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.96, 2.23]
6 Serious adverse events through 54 weeks	1	324	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.77, 1.62]

Analysis 2.1. Comparison 2 Azathioprine versus Infliximab, Outcome 1 Clinical remission through 26 weeks.

Analysis 2.2. Comparison 2 Azathioprine versus Infliximab, Outcome 2 Steroid-free remission through 26 weeks.

Analysis 2.3. Comparison 2 Azathioprine versus Infliximab, Outcome 3 Mucosal healing through 26 weeks.

Analysis 2.4. Comparison 2 Azathioprine versus Infliximab, Outcome 4 Adverse events.

Analysis 2.5. Comparison 2 Azathioprine versus Infliximab, Outcome 5 Withdrawals due to adverse events.

Analysis 2.6. Comparison 2 Azathioprine versus Infliximab, Outcome 6 Serious adverse events through 54 weeks.

Comparison 3. Azathioprine and Infliximab versus Infliximab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission	1	338	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.03, 1.54]
2 Steroid-free clinical remission	2	383	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.02, 1.47]
3 Mucosal healing through 26 weeks	1	210	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.02, 2.19]
4 Adverse events	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
5 Withdrawals due to adverse events	1	342	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.75, 1.80]
6 Serious adverse events	1	342	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.41, 0.98]

Analysis 3.1. Comparison 3 Azathioprine and Infliximab versus Infliximab, Outcome 1 Clinical remission.

Analysis 3.2. Comparison 3 Azathioprine and Infliximab versus Infliximab, Outcome 2 Steroid-free clinical remission.

Analysis 3.3. Comparison 3 Azathioprine and Infliximab versus Infliximab, Outcome 3 Mucosal healing through 26 weeks.

Analysis 3.4. Comparison 3 Azathioprine and Infliximab versus Infliximab, Outcome 4 Adverse events.

Analysis 3.5. Comparison 3 Azathioprine and Infliximab versus Infliximab, Outcome 5 Withdrawals due to adverse events.

Analysis 3.6. Comparison 3 Azathioprine and Infliximab versus Infliximab, Outcome 6 Serious adverse events.

Comparison 4. Azathioprine or 6-Mercaptopurine versus Methotrexate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Steroid-free remission	3	143	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.85, 1.49]
2 Adverse events	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.21, 0.82]
3 Withdrawals due to adverse events	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.23, 2.71]

Analysis 4.1. Comparison 4 Azathioprine or 6-Mercaptopurine versus Methotrexate, Outcome 1 Steroid-free remission.

Analysis 4.2. Comparison 4 Azathioprine or 6-Mercaptopurine versus Methotrexate, Outcome 2 Adverse events.

Analysis 4.3. Comparison 4 Azathioprine or 6-Mercaptopurine versus Methotrexate, Outcome 3 Withdrawals due to adverse events.

Comparison 5. Azathioprine or 6-Mercaptopurine versus 5-Aminosalicylic acid or Sulfasalazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Steroid-free clinical remission	2	156	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.80, 1.91]
2 Withdrawals due to adverse events	2	156	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.38, 2.54]
3 Serious adverse events	1	133	Risk Ratio (M-H, Fixed, 95% CI)	11.25 [0.62, 204.86]

Analysis 5.1. Comparison 5 Azathioprine or 6-Mercaptopurine versus 5-Aminosalicylic acid or Sulfasalazine, Outcome 1 Steroid-free clinical remission.

Analysis 5.2. Comparison 5 Azathioprine or 6-Mercaptopurine versus 5-Aminosalicylic acid or Sulfasalazine, Outcome 2 Withdrawals due to adverse events.

Analysis 5.3. Comparison 5 Azathioprine or 6-Mercaptopurine versus 5-Aminosalicylic acid or Sulfasalazine, Outcome 3 Serious adverse events.

APPENDICES

Appendix 1. Search strategies

EMBASE

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. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
 20. 18 not 19
 21. exp Crohn disease/
 22. Crohn.mp.
 23. (inflammatory bowel disease* or IBD).mp.
 24. 21 or 22 or 23
 25. 20 and 24
 26. (anti-metabolite* or anti-metabolite* or antimetabolite*).mp.
 27. (AZA or azathioprine).mp.
 28. (6-mercaptopurine or mercaptopurine or 6-MP or 6MP).mp.
 29. azathioprine.mp. or exp azathioprine/
 30. or/26-29
 31. 25 and 30
- = 990

MEDLINE

1. exp Crohn disease/
2. crohn*.mp.
3. (inflammatory bowel disease* or IBD).mp.
4. 1 or 2 or 3
5. random\$.mp.
6. factorial\$.mp.
7. (crossover\$ or cross over\$ or cross-over\$).mp.

8. placebo\$.mp.
9. single blind.mp.
10. double blind.mp.
11. triple blind.mp.
12. (singl\$ adj blind\$).mp.
13. (double\$ adj blind\$).mp.
14. (tripl\$ adj blind\$).mp.
15. assign\$.mp.
16. allocat\$.mp.
17. crossover procedure/
18. double blind procedure/
19. single blind procedure/
20. triple blind procedure/
21. randomized controlled trial/
22. or/4-21
23. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
24. 22 not 23
25. exp antimetabolite/
26. anti*metabolite*.mp.
27. (6-mercaptopurine or mercaptopurine or 6-MP or 6MP).mp.
28. exp mercaptopurine/
29. (AZA or azathioprine).mp.
30. exp azathioprine/
- 31 or/25-30
32. 24 and 31

= 260

Cochrane Library

- #1 anti*metabolite*
- #2. 6-mercaptopurine or mercaptopurine or 6-MP or 6MP
- #3 AZA or azathioprine
- #4 Crohn*
- #5 IBD or inflammatory bowel disease
- #6 #1 or #2 or #3
- #7 #4 or #5
- #8 #6 and #7

Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease (Review)

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= 259

IBD Group Specialized Register

Title or abstract search: metabolite or 6-MP or mercaptopurine or aza or azathioprine

= 100

FEEDBACK

Comment, 4 November 2019

Summary

The first line of the implications for practice section of this review states: Azathioprine and 6-mercaptopurine offer no advantage over placebo for induction of remission or clinical improvement in active Crohn's disease. However, the SoF table shows that this is uncertainty not evidence of no effect. Indeed I would interpret the first three outcomes as possibly demonstrating moderate (or low in the case of fistula improvement) evidence of a benefit (which might or might not be clinically important). It seems an example of overreliance on statistical significance. I am editing this topic for BMJ Best Practice and the author of this topic has used the Cochrane Review to repeat the conclusion of no benefit.

Reply

Thank you for this feedback. edits have been made to the Abstract and Implications for practice sections to reflect the quality of the evidence.

Contributors

Comment contributor: David Tovey, Freelance Editor, BMJ Best Practice

Response: Nilesh Chande, contact author

WHAT'S NEW

Date	Event	Description
10 March 2020	Amended	Edits made to the Abstract following feedback

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 4, 1997

Date	Event	Description
30 October 2015	New search has been performed	New literature search conducted on October 30, 2015. The search did not identify any new studies
30 October 2015	New citation required but conclusions have not changed	Updated review with new authors

DECLARATIONS OF INTEREST

Nilesh Chande has received fees for consultancy from Abbott/AbbVie and Ferring, fees for lectures from Abbott and Janssen, travel expenses from Merck and has stock/stock options in Pfizer, Glaxo Smith Kline, Proctor and Gamble and Johnson and Johnson. All of these financial activities are outside the submitted work.

Cassandra M Townsend: None known

Claire E Parker: None known

John K MacDonald: None known

INDEX TERMS

Medical Subject Headings (MeSH)

Antimetabolites [adverse effects] [*therapeutic use]; Azathioprine [adverse effects] [*therapeutic use]; Crohn Disease [*drug therapy]; Glucocorticoids [administration & dosage]; Immunosuppressive Agents [adverse effects] [*therapeutic use]; Induction Chemotherapy [*methods] [statistics & numerical data]; Infliximab [therapeutic use]; Mercaptopurine [adverse effects] [*therapeutic use]; Mesalamine [therapeutic use]; Prednisone [administration & dosage]; Randomized Controlled Trials as Topic; Sulfasalazine [therapeutic use]; Withholding Treatment

MeSH check words

Adult; Humans