Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease (Review)

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[Intervention Review]

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

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ABSTRACT

Background

Crohn's disease (CD) is a chronic relapsing inflammatory condition. Many patients fail to achieve remission with medical management and require surgical interventions. Purine analogues have been used to maintain surgically-induced remission in CD, but the effectiveness of these agents is unclear.

Objectives

The objectives were to evaluate the efficacy and safety of purine analogues for maintenance of surgically-induced remission in CD.

Search methods

We searched the following databases from inception to 30 April 2014: PubMed, MEDLINE, EMBASE, CENTRAL, and the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register). We also searched the reference lists of all included studies, and contacted personal sources and drug companies to identify additional studies. The searches were not limited by language.

Selection criteria

Randomised controlled trials (RCTs) that compared purine analogues to placebo or another intervention, with treatment durations of at least six months were considered for inclusion. Participants were patients of any age with CD in remission following surgery.

Data collection and analysis

Two authors independently assessed trial eligibility and extracted data. Methodological quality was assessed using the Cochrane risk of bias tool. The primary outcome measures were clinical and endoscopic relapse as defined by the primary studies. Secondary outcomes included adverse events, withdrawal due to adverse events and serious adverse events. Data were analysed on an intention-to-treat basis where patients with missing final outcomes were assumed to have relapsed. We calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI) for dichotomous outcomes. The Chi^2 and I^2 statistics were used to assess heterogeneity. The overall quality of the evidence supporting the primary outcomes and selected secondary outcomes was assessed using the GRADE criteria.

Main results

Seven RCTs (n = 584 patients) were included in the review. Three studies compared azathioprine to 5-aminosalicylic acid (5-ASA). One small study compared azathioprine to both 5-ASA and adalimumab. One study compared azathioprine to placebo and another study compared 6-mercaptopurine to 5-ASA and placebo. One small study compared azathioprine to infliximab. Three studies were judged to be at low risk of bias. Four studies were judged to be at high risk of bias due to blinding. The study (n = 22) comparing azathioprine to infliximab found that the effects on the proportion of patients who had a clinical (RR 2.00, 95% CI 0.21 to 18.98) or endoscopic relapse (RR 4.40, 95% CI 0.59 to 3.07) were uncertain. One study (n = 33) found decreased clinical (RR 5.18, 95% CI 1.35 to 19.83) and endoscopic relapse (RR 10.35, 95% CI 1.50 to 71.32) rates favouring adalimumab over azathioprine. A pooled analysis of two studies (n = 168 patients) showed decreased clinical relapse rates at one or two years favouring purine analogues over placebo. Forty-eight per cent of patients in the purine analogue group experienced a clinical relapse compared to 63% of placebo patients (RR 0.74, 95% CI 0.58 to 0.94). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to high risk of bias (one study was single-blind) and sparse data (93 events). One study (87 patients) found a reduction in endoscopic relapse rates favouring 6-mercaptopurine over placebo. Seventeen per cent of 6-mercaptopurine patients had an endoscopic relapse at two years compared to 42% of placebo patients (RR 0.40, 95% CI 0.19 to 0.83). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to very sparse data (25 events). A pooled analysis of five studies (n = 425 patients) showed no difference in clinical relapse rates at one or two years between purine analogues and 5-ASA agents. Sixty-three per cent of patients in the purine analogues group experienced a clinical relapse compared to 54% of 5-ASA patients (RR 1.15, 95% CI 0.99 to 1.34). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias (two open-label studies), sparse data (249 events) and moderate heterogeneity (I^2 = 45%). There was no difference in endoscopic relapse at 12 months between azathioprine and 5-ASA (RR 0.78, 95% CI 0.52 to 1.17; 1 study, 35 patients). A GRADE analysis indicated that the overall quality of the evidence for this outcome was very low due to high risk of bias (open-label study) and very sparse data (26 events). There was a reduction in endoscopic relapse at 24 months favouring 6-mercaptopurine over 5-ASA patients. Seventeen per cent of 6-mercaptopurine patients had an endoscopic relapse compared to 48% of 5-ASA patients (RR 0.36, 95% CI 0.18 to 0.72; 1 study, 91 patients). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to very sparse data (29 events). Adverse events that required withdrawal were more common in the purine analogue group compared to 5-ASA. Twenty per cent of patients in the purine analogue group withdrew due to adverse events compared to 10% of 5-ASA patients (RR 2.07, 95% CI 1.26 to 3.39; 5 studies, 423 patients).The results for withdrawal due to adverse events between purine analogues and placebo or for other comparisons were uncertain. Commonly reported adverse events across all studies included leucopenia, arthralgia, abdominal pain or severe epigastric intolerance, elevated liver enzymes, nausea and vomiting, pancreatitis, anaemia, exacerbation of Crohn's disease, nasopharyngitis, and flatulence.

Authors' conclusions

Purine analogues may be superior to placebo for maintenance of surgically-induced remission in patients with CD, although this is based on two small studies. The results for efficacy outcomes between purine analogues and 5-ASA agents were uncertain. However, patients taking purine analogues were more likely than 5-ASA patients to discontinue therapy due to adverse events. No firm conclusions can be drawn from the two small studies that compared azathioprine to infliximab or adalimumab. Adalimumab may be superior to azathioprine but further research is needed to confirm these results. Further research investigating the efficacy and safety of azathioprine and 6-mercaptopurine in comparison to other active medications in patients with surgically-induced remission of CD is warranted.

PLAIN LANGUAGE SUMMARY

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

Prevention of clinical relapse (resumption of symptoms of active disease) and endoscopic relapse (signs of mucosal inflammation upon examination with an endoscope) are key objectives in the management of Crohn's disease. There is no treatment currently available that completely prevents relapse and is without significant side-effects. The purpose of this systematic review was to examine the effectiveness and side effects of purine analogue medications (azathioprine and 6-mercaptopurine) used to prevent relapse in Crohn's patients in surgically-induced remission

This review identified seven studies that included a total of 584 participants. One study compared azathioprine to placebo (e.g. a sugar pill). Another study compared 6-mercaptopurine to 5-aminosalicylic acid (5-ASA) or placebo. Three studies compared azathioprine to 5-ASA drugs. One small study compared azathioprine to both 5-ASA and adalimumab (a biological drug that is a tumour necrosis

factor-alpha antagonist). One small study compared azathioprine to infliximab (a biological drug that is a tumour necrosis factor-alpha antagonist). The study that compared azathioprine to infliximab (22 patients) found that the effects on the proportion of patients who had a clinical or endoscopic relapse were uncertain. A small study (33 patients) found reduced clinical and endoscopic relapse rates favouring adalimumab over azathioprine. No firm conclusions can be drawn from the two small studies that compared azathioprine to infliximab or adalimumab. Adalimumab may be superior to azathioprine but further research is needed to confirm these results. A pooled analysis of two studies (168 patients) suggests that purine analogues may be superior to placebo for preventing clinical relapse in Crohn's patients in surgically-induced remission. One study (87 patients) found a reduction in endoscopic relapse rates favouring 6-mercaptopurine over placebo. A pooled analysis of five studies (425 patients) found no difference in clinical relapse rates between purine analogues and 5-ASA agents. One study (35 patients) found no difference in endoscopic relapse at 12 months between azathioprine and 5-ASA. Another study (91 patients) found reduced endoscopic relapse rates at 24 months favouring 6-mercaptopurine over 5-ASA patients. Patients taking purine analogues were more likely than 5-ASA patients to discontinue therapy due to side effects. Commonly reported side effects across the studies included leucopenia (a decrease in the number of white blood cells), arthralgia (joint pain), abdominal pain or severe epigastric intolerance, elevated liver enzymes, nausea and vomiting, pancreatitis (inflammation of the pancreas), anaemia (a decrease in the number of red blood cells), exacerbation (worsening) of Crohn's disease, nasopharyngitis (common cold), and flatulence. The results of this review need to be interpreted with caution as they are based on small numbers of patients and the overall quality of the evidence from the studies was rated as low or very low due to lack of precision of the results, inconsistent results across studies and the low methodological quality of some studies. Further research investigating the effectiveness and side effects of azathioprine and 6-mercaptopurine in comparison to other medications in patients with surgically-induced remission of Crohn's disease is warranted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

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

Patient or population: Patients in remission after surgery for Crohn's disease
Settings: Outpatient
Intervention: AZA or 6-MP 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 relapse	630 per 1000[1]	466 per 1000 (365 to 592)	RR 0.74 (0.58 to 0.94)	168 (2 studies)	⊕⊕◯◯ low[2,3]	
Endoscopic relapse (6-MP study)	425 per 1000[1]	170 per 1000 (81 to 353)	RR 0.40 (0.19 to 0.83)	87 (1 study)	⊕⊕◯◯ low[4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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

[1] Control group risk estimates come from control arm of meta-analysis, based on included trials.
[2] Sparse data (93 events).
[3] High risk of bias in one study in pooled analysis due to single-blind design.
[4] Very sparse data (25 events).

BACKGROUND

Description of the condition

Crohn's disease (CD) is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract. There is no cure for the disease, and management strategies are mainly focused on induction and maintenance of remission. Approximately 75% of patients with CD will eventually undergo surgical resection (Bernell 2000), and this can induce remission. However endoscopic recurrence of disease has been reported to be as high as 73% at one year post surgery (Rutgeerts 1990), and clinical relapse rates have been reported to range from 22 to 55% at five years post surgery (Williams 1990). There is no standard therapy for the prevention of postoperative recurrence in CD (Hanauer 2001). A number of agents have been studied, but considerable uncertainty remains as to the efficacy of such treatments.

Description of the intervention

Corticosteroids, the mainstay of treatment of acute exacerbations, are not effective for maintenance of remission in CD (Steinhart 2003), and chronic use is limited by numerous adverse events. 5-Aminosalicylic acid agents have been shown to be safe and may be effective for maintenance of post-surgical remission, although the existing data suggests that the efficacy of these agents may be limited (Gordon 2011). Probiotics and budesonide do not appear to provide any benefit for maintenance of surgically-induced remission (Rolfe 2006; Benchimol 2009; Doherty 2009). Nitroimidazole antibiotics may reduce the risk of relapse in surgically-induced remission (Doherty 2009). However these agents are not well tolerated and are associated with a higher risk of serious adverse events (Doherty 2009). TNF-alpha antagonists may provide a benefit in post-operative Crohn's disease but these agents are expensive. One small study suggests that infliximab may provide a benefit for reducing the risk of relapse in surgically-induced remission (Regueiro 2009). Another small study suggests that adalimumab my be superior to azathioprine for reducing the risk of relapse in post-operative CD patients (Savarino 2013). Further research is needed to confirm these benefits, Purine analogues such as azathioprine and 6-mercaptopurine have been extensively used for maintenance of remission in both Crohn's disease and ulcerative colitis and are relatively inexpensive.

How the intervention might work

Azathioprine is a prodrug which is non-enzymatically degraded to 6-mercaptopurine which in turn is metabolised to the active component, 6-thioguanine nucleotide (6-TGN). 6-TGN is thought to work by inhibiting the proliferation of T and B lymphocytes and reducing the numbers of cytotoxic T cells and plasma cells. There are some trial data which suggest that neutrophil count is a predictor of induction and maintenance of remission (Colonna 1994), which may suggest the mechanism of action, although this is not well understood. The major limiting factor for long term use has been the occurrence of adverse events in approximately 10% of patients leading to withdrawal of therapy (Hafraoui 2002), with dose-dependent and idiosyncratic adverse events occurring.

Why it is important to do this review

Relatively few studies have been published that investigate the role of azathioprine or 6-mercaptopurine for maintenance of remission following surgery in patients with CD. One multicentre randomised placebo controlled trial involving 81 patients found a significant reduction in endoscopic recurrence when azathioprine was used in conjunction with metronidazole in comparison to metronidazole alone (D'Haens 2008). In another multicentre randomised controlled trial, it was concluded that 6-mercaptopurine was more effective than either mesalamine or placebo at preventing postoperative recurrence at 24 months following surgery (Hanauer 2001). However, a single-center randomised open-label trial found no significant difference in clinical relapse rates between azathioprine and mesalamine (Ardizzone 2004). An up-to-date systematic review using the Cochrane Collaboration format is indicated to summarise the current evidence on the use of purine analogues for the maintenance of surgically induced remission in CD.

OBJECTIVES

The primary objective was to evaluate the efficacy and safety of azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in CD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were considered for inclusion.

Types of participants

Patients of any age with CD who were in remission following surgery, defined by a recognized CD activity index or endoscopy, or who had undergone a curative surgical resection, as defined by the authors of the primary studies were considered for inclusion.

Types of interventions

Trials which compared azathioprine or 6-mercaptopurine to placebo or another active intervention with treatment durations of at least six months were considered for inclusion.

Types of outcome measures

Primary outcomes

The primary outcome measure was clinical relapse or endoscopic relapse as defined by the primary studies.

Secondary outcomes

Secondary outcomes included the incidence of adverse events, withdrawal due to adverse events, and serious adverse events. Adverse events that are known to be associated with azathioprine or 6-mercaptopurine were reported. These adverse events could include:
a. Bone marrow suppression: pancytopenia, leucopenia, neutropenia, thrombocytopenia;
b. Hypersensitive reactions: malaise, vomiting, diarrhoea, rash, hypotension;
c. Malignancy
d. Liver function impairment, jaundice;
e. Pancreatitis;
f. Pulmonary: pneumonitis; and
g. Renal: interstitial nephritis.

Search methods for identification of studies

Electronic searches

A. Electronic searching
The following electronic databases were searched for relevant studies:
1. PubMed (from inception to April 30, 2014);
2. MEDLINE (from inception to April 30, 2014);
3. EMBASE (from inception to April 30, 2014);
4. Cochrane Central Register of Controlled Trials (CENTRAL, on 30 April 2014); and
5. Cochrane Inflammatory Bowel Disease and Functional Bowel Disortders Group Specialized Trials Register.
The search strategy was not limited by language. The search strategy used for each database is reported in Appendix 1. There is some evidence that data from abstracts can be inconsistent with data in published articles (Pitkin 1999). Thus studies that were reported in abstract form only were not included in this review.

Searching other resources

B. Reference searching
The references of all identified studies were inspected for more trials.
C. Personal contacts
Leaders in the field were contacted to try to identify other studies.
D. Drug companies
The manufacturers of azathioprine and 6-mercaptopurine were contacted for any additional data.

Data collection and analysis

All identified abstracts and results from searches were reviewed by two authors (MG and KV). If the reference appeared relevant, a full copy of the study was obtained.

Selection of studies

Two authors (MG and KV), after reading the full texts, independently assessed the eligibility of all trials identified based on the inclusion criteria above. Disagreement among authors was discussed and agreement reached by consensus.

Data extraction and management

A data extraction form was developed to extract information on relevant features and results of included studies. Two authors (MG and KV) independently extracted and recorded data on the predefined checklist. Extracted data included the following items:
a. characteristics of patients: age, sex, disease distribution, disease duration, disease activity index;
b. total number of patients originally assigned to each treatment group;
c. intervention: dose of azathioprine or 6-mercaptopurine;
d. control: placebo, other drugs;
e. concurrent medications; and
f. outcomes: time of assessment, length of follow up, type of Crohn's disease activity index used, definitions of remission and relapse, relapse rates, adverse events.

Assessment of risk of bias in included studies

The methodological quality of selected trials was assessed independently by two authors (MG and KV) using the Cochrane risk of bias tool (Higgins 2011).
Factors assessed included:
1. sequence generation (i.e. was the allocation sequence adequately generated?);
2. allocation sequence concealment (i.e. was allocation adequately concealed?);
3. blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?);

4. incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);
5. selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?);
6. other potential sources of bias (i.e. was the study apparently free of other problems that could put it at a high risk of bias?).
A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias. Disagreements were resolved by consensus. Study authors were contacted for further information when insufficient information was provided to determine the risk of bias.
The overall quality of evidence was assessed using the GRADE approach (Guyatt 2008; Schünemann 2011). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Randomised trials start as high quality evidence, but may be downgraded due to: risk of bias (methodological quality), indirectness of evidence, unexplained heterogeneity, imprecision (sparse data) and publication bias. The overall quality of the evidence for each outcome was determined after considering each of these factors and graded as:

- High: further research is very unlikely to change confidence in the estimate of effect;

- Moderate: further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate;

- Low: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; and

- Very low: any estimate of effect is very uncertain.

Measures of treatment effect

The Cochrane Collaboration review manager (RevMan) software (version 5.3) was used for data analysis (RevMan 2014). We calculated the risk ratio and corresponding 95% confidence interval (95% CI) for dichotomous outcomes. We planned to calculate the mean difference (MD) and corresponding 95% CI for continuous outcomes measured using the same units. We planned to calculate the standardized mean difference (SMD) and corresponding 95% CI for continuous outcomes where different scales were used to evaluate the same outcome.

Unit of analysis issues

When cross-over trials were included, data from the first phase of the study were extracted for analysis (i.e. before the cross-over occurred). Separate analyses were conducted for comparisons between azathioprine or 6-mercaptopurine versus placebo, and azathioprine or 6-mercaptopurine versus active comparator (e.g. mesalamine). If studies randomised subjects to more than one azathioprine or 6-mercaptopurine treatment arm, these were combined for the primary analysis. Although some studies reported more than one efficacy or safety event per subject, the primary analysis considered only the proportion of subjects who experienced at least one event.

Dealing with missing data

Data were analysed according to the intention-to-treat principle. Patients with final missing outcomes were assumed to have relapsed.

Assessment of heterogeneity

Heterogeneity among trial results was assessed by visual inspection of forest plots and by calculating the Chi^2 test (a P value of 0.10 was regarded as statistically significant heterogeneity). We also used the I^2 statistic to quantity the effect of heterogeneity (Higgins 2003). A random-effects model was used in situations of unexplained heterogeneity. We conducted sensitivity analyses as appropriate to investigate heterogeneity. For example, if a pooled analysis showed statistically significant heterogeneity and a visual inspection of the forest plot identified studies that may have contributed to this heterogeneity the analysis was repeated excluding these studies to see if this explained the heterogeneity.

Assessment of reporting biases

We planned to investigate the possibility of a publication bias through the construction of funnel plots (trial effects versus trial size), although this was not completed as the number of studies was small.

Data synthesis

Data from individual trials were combined for meta-analysis if the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). We calculated the pooled RR and corresponding 95% CI for dichotomous outcomes. Meta-analysis was carried out using a fixed-effect model. A random-effects model was used in situations of statistically significant heterogeneity. Data were not to be pooled for meta-analysis if a high degree of heterogeneity was detected (i.e. $I^2 > 75\%$).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to further study the effects of a number of variables on the outcomes, when appropriate data were available. However there were not sufficient studies to carry out such analyses. Planned subgroup analyses included:
a. Length of follow up; and
b. Drug type (i.e. azathioprine or 6-mercaptopurine).

Sensitivity analysis

Sensitivity analyses based on random-effects versus fixed-effect models were planned where appropriate data or numbers of studies were available. Sensitivity analysis was also undertaken to explore possible explanations for significant heterogeneity.

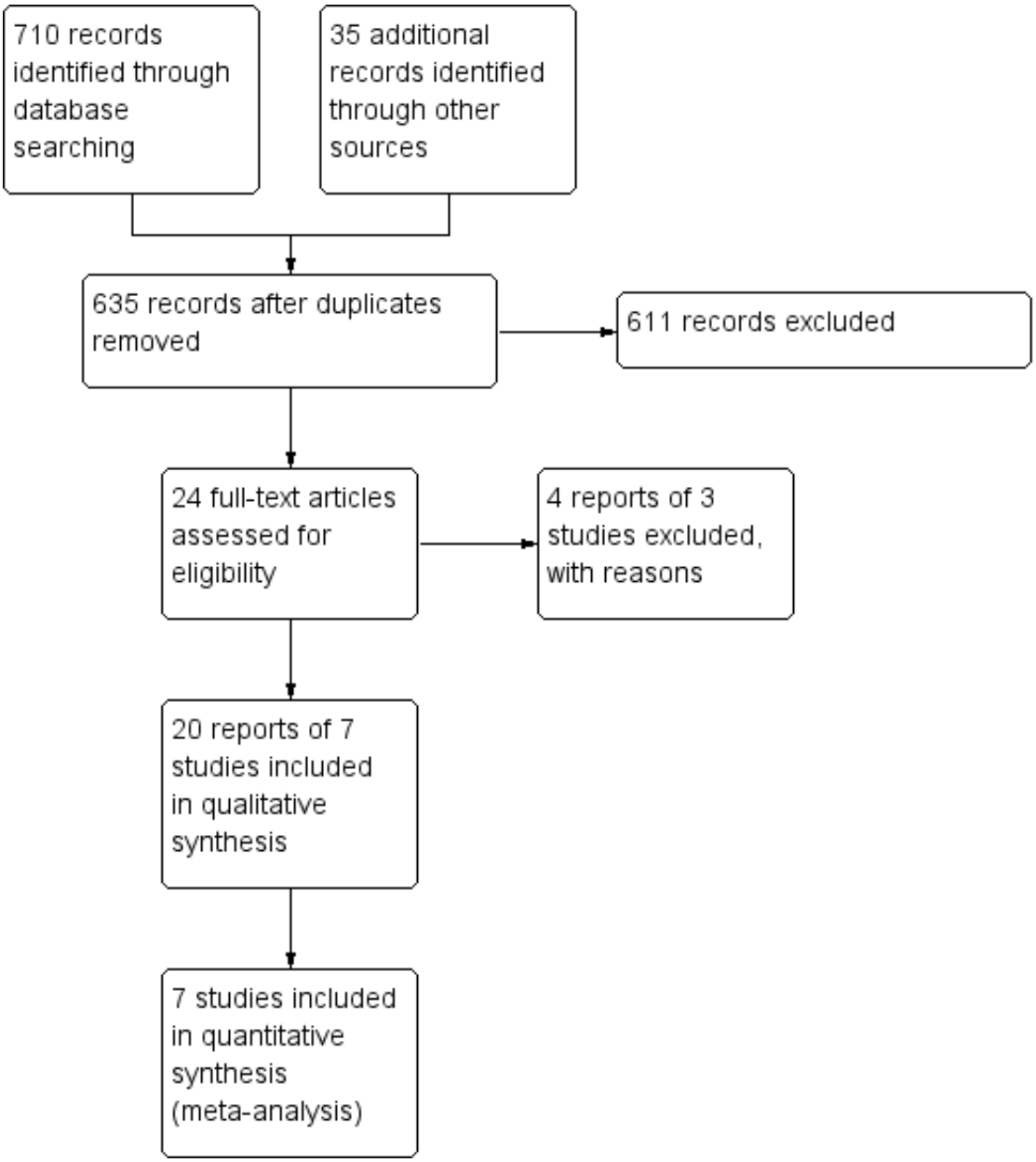
RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

The electronic database search on 30 April 2014 identified 745 studies. After removal of duplicates, 635 studies were screened for inclusion. Of these, 24 studies were judged to be potentially relevant and subjected to full text review (See Figure 1). Experts were contacted, but no responses were received and no further studies were identified from drug companies.

Figure 1. Study flow diagram.



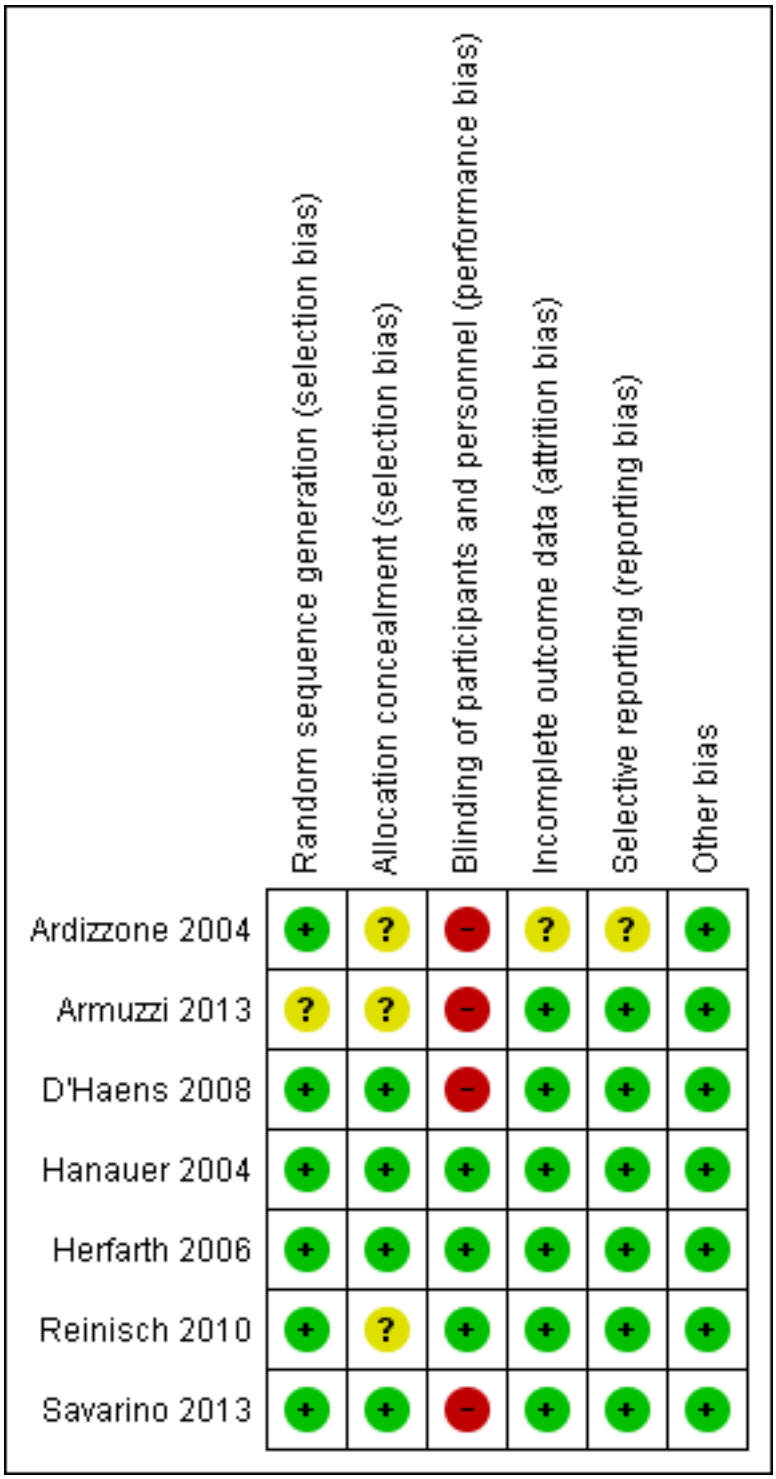
Four reports of three studies were excluded for failing to meet the inclusion criteria. One study was excluded because it was not a randomised controlled trial as confirmed by the author (Nos 2000). The other two studies were excluded because all patients received azathioprine as part of their post-surgical maintenance therapy (Mañosa 2013; Ferrante 2014).

Twenty reports of seven studies satisfied the inclusion criteria and were included in the review. Three studies compared azathioprine to 5-aminosalicylic acid (Ardizzone 2004; Herfarth 2006; Reinisch 2010). D'Haens 2008 compared azathioprine to placebo. All patients in this study were taking concurrent metronidazole or ornidazole. Hanauer 2004 compared 6-mercaptopurine to both 5-aminosalicylic acid and placebo. Savarino 2013 compared azathioprine to both 5-aminosalicylic acid and adalimumab. Armuzzi 2013 was a randomised open-label pilot study that compared azathioprine to infliximab. All patients in this study took oral metronidazole for two weeks post-surgery. There were no cross-over trials. The total number of participants in the seven studies was 584. All participants were adult patients with Crohn's disease, the majority of whom were recruited within two weeks of surgery or before hospital discharge after remission-inducing surgery. The 78 participants in one study were enrolled between 6 and 24 months postoperatively and were in clinical remission but had endoscopic recurrence as an inclusion criterion (Reinisch 2010).

Risk of bias in included studies

A summary of the risk of bias analysis is shown in Figure 2.

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



Six studies were rated as low risk for random sequence generation (selection bias) because these studies employed computer-generated randomisation (Ardizzone 2004; Hanauer 2004; Herfarth 2006; D'Haens 2008; Reinisch 2010; Savarino 2013). Armuzzi 2013 was rated as unclear risk of bias for random sequence generation because the method of randomisation was not described in the manuscript. Four studies were rated as low risk of bias for allocation concealment (selection bias) (Hanauer 2004; Herfarth 2006; D'Haens 2008; Savarino 2013). Three studies were rated as unclear risk of bias for allocation concealment as the methods were not clearly described in the manuscripts (Ardizzone 2004; Reinisch 2010; Armuzzi 2013). The authors were contacted, but no further information was given.

Three studies were double-blinded and were judged to be at low risk of bias for blinding of participants and personnel (performance bias) (Hanauer 2004; Herfarth 2006; Reinisch 2010). The D'Haens 2008 study was investigator-blinded and was judged to be at high risk of bias for blinding of participants. Three studies were open-label and were judged to be at high risk of bias for blinding of participants and personnel (Ardizzone 2004; Armuzzi 2013; Savarino 2013).

Six studies reported full and appropriate data and satisfactorily documented withdrawals and dropouts and were therefore judged to be at low risk of bias for incomplete outcome data (attrition bias) and selective reporting (reporting bias) (Hanauer 2004; Herfarth 2006; D'Haens 2008; Reinisch 2010; Armuzzi 2013; Savarino 2013). Ardizzone 2004 was judged to be at unclear risk of bias for incomplete outcome data and selective reporting owing to inadequately described outcomes and potentially selective data reporting.

All seven studies were judged to be a low risk of bias for other sources of bias. Reinisch 2010 was funded by a drug company with some of the authors employed by the drug company although the extent of their involvement was unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Azathioprine or 6-mercaptopurine versus placebo for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 2** Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 3** Azathioprine versus infliximab for maintenance of surgically-induced remission in Crohn's disease; **Summary of findings 4** Azathioprine versus adalimumab for maintenance of surgically-induced remission in Crohn's disease

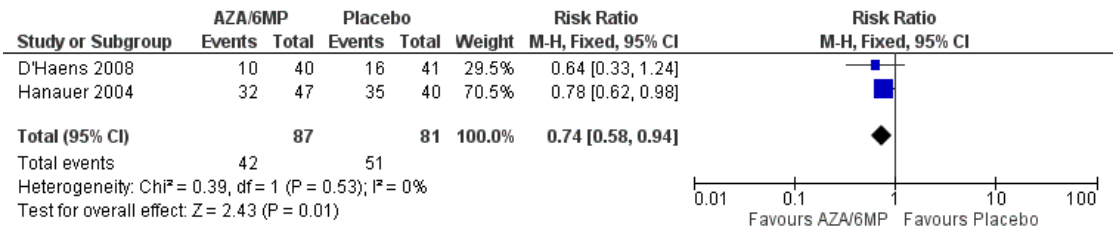
Azathioprine or 6-mercaptopurine versus placebo

Two studies with a total of 168 participants compared azathioprine or 6-mercaptopurine to placebo (Hanauer 2004; D'Haens 2008). In one of these studies all patients were also taking either metronidazole or ornidazole (D'Haens 2008).

Efficacy

Meta-analysis of two studies with 168 participants comparing azathioprine or 6-mercaptopurine to placebo, showed a statistically significant difference in clinical relapse rates favouring purine analogues. Forty-eight per cent of patients in the purine analogue group experienced a clinical relapse compared to 63% of placebo patients (RR 0.74, 95% CI 0.58 to 0.94; See Figure 3). No heterogeneity was detected for this comparison (P = 0.53, I^2 = 0%). However, there was clinical and methodological heterogeneity between these two studies, regarding the choice of purine analogue and the use of other medications. A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to high risk of bias (one study in the pooled analysis was single blind) and sparse data (93 events, See Summary of findings for the main comparison). A sensitivity analysis using a random-effects model showed a statistically significant difference in clinical relapse rates favouring purine analogues (RR 0.76, 95% CI 0.61 to 0.95).

Figure 3. Forest plot of comparison: 2 AZA or 6MP versus placebo, outcome: 2.1 Clinical relapse (fixed-effect).



One study reported on endoscopic relapse at two years as an outcome (Hanauer 2004). There was a statistically significant difference in endoscopic relapse rates favouring 6-mercaptopurine. Seventeen per cent of patients in the 6-mercaptopurine group had an endoscopic relapse at two years compared to 42% of placebo patients (RR 0.40, 95% CI 0.19 to 0.83). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to very sparse data (25 events, See Summary of findings for the main comparison).

Safety

Both studies reported on the proportion of patients who withdrew due to an adverse event. Adverse events leading to withdrawal were not significantly more common in the azathioprine or 6-mercaptupurine groups. Fifteen per cent of patients in the purine analogue group withdrew due to adverse events compared to 11% of placebo patients (RR 1.33, 95% CI 0.59 to 2.98). No heterogeneity was detected for this comparison (P = 0.32, I^2 = 1%).
Common adverse events reported in the study that compared azathioprine to placebo included metallic taste, headache, paraesthesias, epigastric pain, nausea, arthralgia, angina, skin rash, and elevated liver enzymes (D'Haens 2008). Common adverse events reported in the study that compared 6-mercaptopurine to placebo included leukopenia, alopecia, diarrhoea, flatus, gastrointestinal bleeding, phlebitis, abdominal pain, and headache (Hanauer 2004).

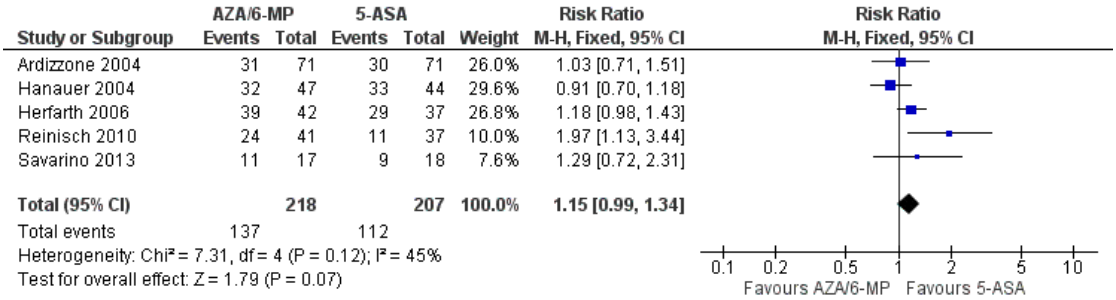
Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Five studies involving 425 participants compared either azathioprine or 6-mercaptopurine to 5-aminosalicylic acid (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013). Reinisch 2010 enrolled patients who were in clinical remission but had endoscopic recurrence as an inclusion criteria.

Efficacy

Five studies involving 425 patients reported on clinical relapse at one or two years as an outcome (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013). The pooled analysis showed no statistically significant difference in clinical relapse rates between purine analogues and 5-aminosalicylates. Sixty-three per cent (137/218) of patients in the purine analogues group experienced a clinical relapse compared to 54% (112/207) of patients in the 5-aminosalicylates group (RR 1.15, 95% CI 0.99 to 1.34; See Figure 4). Statistical heterogeneity was moderate (I^2 = 45%). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome (clinical relapse) was very low due to high risk of bias (two studies in the pooled analysis were not blinded), moderate heterogeneity and sparse data (249 events, see Summary of findings 2). A sensitivity analysis using a random-effects model showed no statistically significant difference in clinical relapse rates between the two groups (RR 1.14, 95% CI 0.93 to 1.41; see Analysis 2.2). A sensitivity analysis excluding the study that included patients with endoscopic recurrence (Reinisch 2010), showed no statistically significant difference in rates of clinical relapse (RR 1.06, 95% CI 0.91 to 1.24; see Analysis 2.3). However, there was far less statistical heterogeneity for this comparison (P = 0.36, I^2 = 6%) which suggests that the heterogeneity can be explained by the inclusion of the study that enrolled patients with endoscopic recurrence. A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to high risk of bias (two studies in the pooled analysis were not blinded) and sparse data (214 events, See Summary of findings 2).

Figure 4. Forest plot of comparison: 1 AZA/6MP vs 5-ASA, outcome: 1.1 Clinical relapse (fixed-effect).



A subgroup analysis by drug type suggests a statistically significant benefit for 5-aminosalicylates over azathioprine but no statistically significant difference for 5-aminosalicylates over 6-mercaptopurine. Sixty-eight per cent of 6-mercaptopurine patients had a clinical relapse compared to 75% of 5-aminosalicylate patients (RR 0.91, 95% CI 0.70 to 1.18; 91 patients 1 study). Sixty-one per cent of azathioprine patients experienced a clinical relapse compared to 48% of 5-aminosalicylate patients (RR 1.25, 95% CI 1.04 to 1.51; 4 studies, 334 patients). There was no significant statistical heterogeneity (P = 0.28, I^2= 22%) for this comparison. A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to high risk of bias (two studies in the pooled analysis were not blinded) and sparse data (184 events, See Summary of findings 2). A sensitivity analysis excluding the study that included patients with endoscopic recurrence (Reinisch 2010), showed no statistically significant difference in clinical relapse rates (RR 1.13, 95% CI 0.93 to 1.38; 3 studies, 256 patients).

A subgroup analysis by length of follow-up suggests a statistically significant benefit for 5-aminosalicylates over antimetabolites at 12 months but not at 24 months. Seventy-six per cent of patients in the antimetabolite group experienced a clinical relapse at 12 months compared to 54% of 5-aminosalicylate patients (RR 1.40, 95% CI 1.12 to 1.74; 2 studies, 157 patients). A high degree of heterogeneity was detected for this comparison (P = 0.04, I^2 = 77%). At 24 months, 55% of patients in the antimetabolite group experienced a clinical relapse compared to 54% of 5-aminosalicylate patients (RR 1.01, 95% CI 0.81 to 1.24; 3 studies, 268 patients). No heterogeneity was detected for this comparison (P = 0.51, I^2 = 0%). A sensitivity analysis excluding the study that included patients with endoscopic recurrence (Reinisch 2010), showed no statistically significant difference in rates of clinical relapse at one year (RR 1.18, 95% CI 0.98 to 1.43).

Two studies reported on endoscopic relapse at one or two years as an outcome (Hanauer 2004; Savarino 2013). These studies were not pooled for analysis due to a high degree of heterogeneity. There was no statistically significant difference in endoscopic relapse at 12 months between azathioprine and 5-aminosalicylate patients. Sixty-five per cent of azathioprine patients had an endoscopic relapse compared to 83% of 5-aminosalicylate patients (RR 0.78, 95% CI 0.52 to 1.17). A GRADE analysis indicated that the overall quality of the evidence for this outcome was very low due to high risk of bias (the study was not blinded) and very sparse data (26 events, See Summary of findings 2). There was a statistically significant difference in the rate of endoscopic relapse at 24 months between 6-mercaptopurine and 5-aminosalicylate patients. Seventeen per cent of 6-mercaptopurine patients had an endoscopic relapse compared to 48% of 5-aminosalicylate patients (RR 0.36, 95% CI 0.18 to 0.72). A GRADE analysis indicated that the overall quality of the evidence for this outcome was low due to very sparse data (29 events, See Summary of findings 2).

Safety

Four studies involving 334 patients reported on the proportion of patients who had at least one adverse event (Ardizzone 2004; Herfarth 2006; Reinisch 2010; Savarino 2013). The pooled analysis showed no statistically significant difference in the proportion of patients who experienced an adverse event. Sixty-two per cent (106/171) of patients in the azathioprine group experienced an adverse event compared to 56% (92/163) of patients in the 5-aminosalicylates group (RR 1.08, 95% CI 0.93 to 1.27). No significant heterogeneity was found for this comparison (P = 0.20, I^2 = 36%).

Five studies involving 423 patients reported on the proportion of patients who withdrew due to an adverse event (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013). Adverse events that required withdrawal were significantly more common in the purine analogue group compared to the 5-aminosalicylic acid group. Twenty per cent of patients in the purine analogue group withdrew due to an adverse event compared to 10% of 5-aminosalicylate patients (RR 2.07, 95% CI 1.26 to 3.39). No heterogeneity was detected for this comparison (P = 0.53, I^2 = 0%). A subgroup analysis by drug type suggests a significantly higher risk of withdrawal due to adverse events for patients receiving azathioprine but not for 6-mercaptopurine. Twenty per cent of patients in the azathioprine group withdrew due to an adverse event compared to 9% of 5-aminosalicylate patients (RR 2.35, 95% CI 1.31 to 4.22; 4 studies, 332 patients). No heterogeneity was detected for this comparison (P = 0.47, I^2 = 0%).

Nineteen per cent of 6-mercaptopurine patients withdrew due to an adverse event compared to 14% of 5-aminosalicylate patients (RR 1.40, 95% 0.54 to 3.62). Two studies involving 169 patients reported on the proportion of patients who had a serious adverse event (Hanauer 2004; Reinisch 2010). The pooled analysis showed no statistically significant difference in the proportion of patients who experienced a serious adverse event. Eleven per cent (10/88) of patients in the antimetabolite group experienced an adverse event compared to 1% (1/81) of patients in the 5-aminosalicylates group (RR 2.61, 95% CI 0.04 to 162.02). A high degree of heterogeneity was detected for this comparison (P = 0.05, I^2 = 74%).

Commonly reported adverse events included leucopenia (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010), arthralgia (Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013), abdominal pain or severe epigastric intolerance (Ardizzone 2004; Herfarth 2006; Reinisch 2010; Savarino 2013), elevated liver enzymes (Ardizzone 2004; Hanauer 2004; Herfarth 2006), nausea and vomiting (Herfarth 2006; Reinisch 2010; Savarino 2013), pancreatitis (Ardizzone 2004; Herfarth 2006; Reinisch 2010), anaemia (Herfarth 2006; Reinisch 2010), exacerbation of Crohn's disease (Reinisch 2010; Savarino 2013), nasopharyngitis (Reinisch 2010; Savarino 2013), and flatulence (Hanauer 2004; Reinisch 2010).

Azathioprine versus infliximab

Efficacy

One study with a total of 22 participants compared azathioprine to infliximab (Armuzzi 2013). There was no statistically significant difference in the proportion of patients who had a clinical relapse. Eighteen per cent (2/11) of patients in the azathioprine group relapsed clinically compared to 9% (1/11) of infliximab patients (RR 2.00, 95% CI 0.21 to 18.98). A GRADE analysis indicated that the overall quality of the evidence for this outcome was very low due to high risk of bias (the study was not blinded) and very sparse data (3 events, See Summary of findings 3). There was no statistically significant difference in the proportion of patients who had endoscopic relapse. Forty per cent (4/10) of patients in the azathioprine group relapsed endoscopically compared to 9% (1/11) of infliximab patients (RR 4.40, 95% CI 0.59 to 33.07). A GRADE analysis indicated that the overall quality of the evidence for this outcome was very low due to high risk of bias (the study was not blinded) and very sparse data (5 events, See Summary of findings 3).

Safety

There was no statistically significant difference in the proportion of patients who withdrew due to adverse events. One patient in the azathioprine group (1/11, 9%) withdrew due to an adverse event (i.e. nausea and epigastric pain) compared to no patients in the infliximab group (RR 3.00, 95% CI 0.14 to 66.53). No other adverse events were reported.

Azathioprine versus adalimumab

Efficacy

One study with a total of 33 participants compared azathioprine to adalimumab (Savarino 2013). There was a statistically significant difference in the proportion of patients who had a clinical relapse. Sixty-five per cent (11/17) of patients in the azathioprine group relapsed clinically compared to 12% (2/16) of adalimumab patients (RR 5.18, 95% CI 1.35 to 19.83). A GRADE analysis indicated that the overall quality of the evidence for this outcome was very low due to high risk of bias (the study was not blinded) and very sparse data (13 events, See Summary of findings 4). There was a statistically significant difference in the proportion of patients who had endoscopic relapse. Sixty-five per cent (11/17) of patients in the azathioprine group relapsed endoscopically compared to 6% (1/16) of adalimumab patients (RR 10.35, 95% CI 1.50 to 71.32). A GRADE analysis indicated that the overall quality of the evidence for this outcome was very low due to high risk of bias (the study was not blinded) and very sparse data (12 events, See Summary of findings 4).

Safety

Savarino 2013 reported on the proportion of patients who experienced at least one adverse event and on the proportion of patients who withdrew due to adverse events. There was no statistically significant difference in the proportion of patients who had an adverse event. Eight-eight per cent (15/17) had an adverse event compared to 69% (11/16) of adalimumab patients (RR 1.28, 95% CI 0.88 to 1.86). There was no statistically significant difference in the proportion of patients who withdrew due to adverse events. Twelve per cent (2/17) of azathioprine patients withdrew due to an adverse event compared to 6% (1/16) of patients in the adalimumab group (RR 1.88, 95% CI 0.19 to 18.80). Commonly reported adverse events included bronchitis, nasopharyngitis, flu, abdominal pain, nausea and vomiting, arthralgia, dermatitis, and abscess (Savarino 2013).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Azathioprine (AZA) or 6-mercaptopurine (6-MP) versus 5-aminosalicylic acid (5-ASA) for maintenance of surgically-induced remission in Crohn's disease

Patient or population: Patients in remission after surgery for Crohn's disease
Settings: Outpatient
Intervention: AZA or 6-MP 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	AZA or 6-MP versus 5-ASA				
Clinical relapse	**541 per 1000**[1]	**622 per 1000** (536 to 725)	**RR 1.15** (0.99 to 1.34)	425 (5 studies)	⊕○○○ **very low**[2,3,4]	
Clinical relapse (sensitivity analysis excluding study that enrolled patients with endoscopic recurrence)	**594 per 1000**[1]	**630 per 1000** (540 to 737)	**RR 1.06** (0.91 to 1.24)	347 (4 studies)	⊕⊕○○ **low**[2,5]	
Clinical relapse (subgroup analysis - AZA studies only)	**485 per 1000**[1]	**606 per 1000** (504 to 732)	**RR 1.25** (1.04 to 1.51)	334 (4 studies)	⊕⊕○○ **low**[2,6]	
Endoscopic relapse (AZA study)	**833 per 1000**[1]	**650 per 1000** (433 to 975)	**RR 0.78** (0.52 to 1.17)	35 (1 study)	⊕○○○ **very low**[7,8]	
Endoscopic relapse (6-MP study)	**477 per 1000**[1]	**172 per 1000** (86 to 343)	**RR 0.36** (0.18 to 0.72)	91 (1 study)	⊕⊕○○ **low**[9]	

*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] High risk of bias in two studies in pooled analysis due to lack of blinding.
[3] Sparse data (249 events).
[4] Moderate heterogeneity $I^2 = 45\%$.
[5] Sparse data (214 events).
[6] Sparse data (184 events).
[7] High risk of bias due to lack of blinding.
[8] Very sparse data (26 events) and wide confidence interval.
[9] Very sparse data (29 events) and wide confidence interval.

Azathioprine (AZA) versus infliximab for maintenance of surgically-induced remission in Crohn's disease

Patient or population: Patients in remission after surgery for Crohn's disease
Settings: Outpatient
Intervention: AZA 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 infliximab				
Clinical relapse	**91 per 1000**[1]	**182 per 1000** (19 to 1727)	**RR 2.00** (0.21 to 18.98)	22 (1 study)	⊕◯◯◯ **very low**[2,3]	
Endoscopic relapse	**91 per 1000**[1]	**400 per 1000** (54 to 3009)	**RR 4.40** (0.59 to 33.07)	21 (1 study)	⊕◯◯◯ **very low**[2,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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

[1] Control group risk estimates come from control arm of meta-analysis, based on included trial.
[2] High risk of bias due to lack of blinding.
[3] Very sparse data (3 events) and very wide confidence interval.
[4] Very sparse data (5 events) and very wide confidence interval.

Azathioprine (AZA) versus adalimumab for maintenance of surgically-induced remission in Crohn's disease

Patient or population: Patients in remission after surgery for Crohn's disease
Settings: Outpatient
Intervention: AZA versus adalimumab

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 adalimumab				
Clinical relapse	**125 per 1000**[1]	**648 per 1000** (169 to 2479)	**RR 5.18** (1.35 to 19.83)	33 (1 study)	⊕◯◯◯ **very low**[2,3]	
Endoscopic relapse (6-MP study)	**62 per 1000**[1]	**642 per 1000** (93 to 4422)	**RR 10.35** (1.50 to 71.32)	33 (1 study)	⊕◯◯◯ **very low**[2,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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

[1] Control group risk estimates come from control arm of meta-analysis, based on included trial.
[2] High risk of bias due to lack of blinding.
[3] Very sparse data (13 events) and very wide confidence interval.
[4] Very sparse data (12 events) and very wide confidence interval.

DISCUSSION

Summary of main results

The Hanauer 2004 and D'Haens 2008 studies compared azathioprine or 6-mercaptopurine to placebo, with meta-analysis suggesting the superiority of purine analogues over placebo for preventing clinical (2 studies, 168 patients) and endoscopic relapse (1 study, 87 patients). This small evidence base gives some support for the use of purine analogues for maintenance of surgically-induced remission in CD.

However, meta-analysis of five studies (n = 425 patients) comparing purine analogues to 5-aminosalicylic acid found no statistically significant differences in clinical relapse rates (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013). A subgroup analysis by drug type suggests that azathioprine may be significantly inferior to 5-aminosalicylic acid. Sixty-one per cent of azathioprine patients had a clinical relapse compared to 48% of 5-aminosalicylic acid patients (RR 1.25, 95% CI 1.04 to 1.51). There was no statistically significant difference in clinical relapse rates between 6-mercaptopurine and 5-aminosalicylic acid. However, clinical heterogeneity among the pooled studies was a concern. Reinisch 2010 enrolled patients with active endoscopic recurrence within 6 to 24 months of surgery, whereas the patients in the other three studies were enrolled within two weeks of surgery and were unlikely to have endoscopic recurrence. A sensitivity analysis excluding the Reinisch 2010 study found no statistically significant difference between azathioprine and 5-aminosalicyclic acid. A subgroup analysis by length of follow-up suggests a statistically significant benefit for 5-aminosalicylates over purine analogues at 12 months but not at 24 months. Seventy-six per cent of patients in the antimetabolite group experienced a clinical relapse at 12 months compared to 54% of 5-aminosalicylate patients (RR 1.40, 95% CI 1.12 to 1.74; 2 studies, 157 patients). However, a high degree of heterogeneity was detected for this comparison (P = 0.04, I^2 = 77%). A sensitivity analysis removing the Reinisch 2010 study found no statistically significant difference in clinical relapse rates between purine analogues and 5-aminosalicyclic acid at 12 months follow-up.

There are considerable concerns raised with the safety profile of azathioprine and 6-mercaptopurine. Adverse events requiring medication to be discontinued were significantly more common in the purine analogue group compared to 5-aminosalicylic acid. One small study (n = 22) compared azathioprine to infliximab and found no statistically significant differences in clinical relapse, endoscopic relapse or withdrawal due to adverse events (Armuzzi 2013). Savarino 2013 (n = 33) compared azathioprine to adalimumab and found statistically significant differences in clinical and endoscopic relapse favouring adalimumab over azathioprine. The results of these studies should be interpreted with caution due to the small number of patients.

Overall completeness and applicability of evidence

We consider the evidence from this review to be applicable to most patients with post-surgical remission of CD. However, the evidence base cannot be considered to be complete. This review has found a relatively small evidence base for the use of purine analogues in the maintenance of surgically-induced remission in CD, despite the widespread use of such medications in this setting. The two studies (n = 168 participants) comparing azathioprine or 6-mercaptopurine with placebo had significant clinical and methodological heterogeneity regarding the choice of purine analogue and the use of concurrent medications. There was considerable clinical and methodological heterogeneity across the five studies (n = 425 patients) that compared azathioprine or 6-mercaptopurine to 5-aminosalicylic acid. Most of the trials were relatively small and probably lacked sufficient power to detect any differences between intervention groups. One small study compared azathioprine to infliximab (n = 22) and one small study compared azathioprine to adalimumab. Therefore, the evidence base can clearly be seen as lacking.

Quality of the evidence

Four studies were judged to be at high risk of bias for blinding due to open-label (Ardizzone 2004; Armuzzi 2013; Savarino 2013), and single-blind design (D'Haens 2008). The results of the included studies need to be interpreted with caution as GRADE analyses rated the overall quality of the evidence for the primary outcomes (i.e. clinical relapse or endoscopic relapse) as low or very low due to high risk of bias (i.e. open-label or single-blind studies), heterogeneity and imprecision (i.e. very sparse data) (See Summary of findings 2; Summary of findings for the main comparison; Summary of findings 3; Summary of findings 4).

Potential biases in the review process

We attempted to reduce potential biases in the review process. A comprehensive literature search was performed to identify all eligible studies. Two review authors independently assessed studies for inclusion, extracted data and assessed study quality.

All analyses were completed using the intention-to-treat principle, whereby patients with final missing outcomes were assumed to have relapsed. Given the high attrition rate in the purine analogue groups compared to the 5-aminosalicylate groups, this may have affected the difference in clinical relapse rates between purine analogues and 5-aminosalicylates. However, it is arguably a moot point given that even if purine analogues do have superior efficacy, it is difficult to rationalise the use on the basis of the poor adverse event profile in the published evidence.

Agreements and disagreements with other studies or reviews

A recent Cochrane review assessing the use of azathioprine or 6-mercaptopurine for maintenance of medically-induced remission in CD disease revealed that the purine analogues are more effective than placebo, with higher response rates for azathioprine than 6-mercaptopurine (Prefontaine 2009). These findings are mirrored in the two studies comparing purine analogues to placebo. No difference in efficacy was found between azathioprine or 6-mercaptopurine and 5-aminosalicylic acid. This could be due to lower disease activity following resection of the gut than is achieved in medically-induced remission of CD, so that a milder anti-inflammatory agent such as 5-aminosalicylic acid, gives a better risk versus benefit ratio when compared to azathioprine and 6-mercaptopurine. It is also possible that the methodology of the included studies supports this hypothesis, with all but one study recruiting patients in the immediate post-surgical setting. As such, the patients are potentially at their lowest period of disease activity clinically and microscopically.

A Cochrane review (Gordon 2011) looking at the use of 5-aminosalicylic acid for the maintenance of surgically-induced remission in CD suggests that 5-aminosalicyclic acid may be superior to placebo (Gordon 2011). It also showed that 5-aminosalicylic acid is a safe and well tolerated drug, as the incidence of adverse events was not different in patients receiving 5-aminosalicylic acid compared to those receiving placebo. The results of this systematic review question the risk versus benefit balance of starting a purine analogue over 5-aminosalicylic acid in postoperative CD.

AUTHORS' CONCLUSIONS

Implications for practice

Purine analogues may be superior to placebo for maintenance of surgically-induced remission in patients with CD. The results for efficacy outcomes between purine analogues and 5-aminosalicylic acid were uncertain. However, patients taking purine analogues were more likely than 5-aminosalicylic acid patients to discontinue therapy due to adverse events. These results question the use of azathioprine and 6-mercaptopurine in patients with surgically-induced remission of CD. No firm conclusions can be drawn from the two small studies that compared azathioprine to infliximab or adalimumab. Adalimumab may be superior to azathioprine but further research is needed to confirm these results.There may be a role for other agents for maintenance of post-surgical remission in CD.

Implications for research

Using the GRADE criteria the overall quality of the evidence was judged to be low for the placebo controlled studies and low or very low for the active comparator studies.Therefore the strength of our conclusions is extremely limited. Further research investigating the efficacy and safety of azathioprine and 6-mercaptopurine in comparison to other active medications in patients with surgically-induced remission of CD is warranted. The use of TPMT monitoring as part of such research protocols may be beneficial. Only one of the five studies mentioned the use of TPMT monitoring which may be important in identifying patients who are more likely to tolerate azathioprine and 6-mercaptopurine. There could be a role for TMPT monitoring when weighing the risk versus benefit of using purine analogues, and future research could incorporate this.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ardizzone 2004

Methods	Open-label, single-centre, randomised, controlled trial
Participants	Crohn's disease patients were enrolled 2 weeks after elective stricturoplasty, minimal bowel resection or both (N = 142) Exclusion criteria included contraindications for use of azathioprine or mesalamine; significant preexisting conditions; the use of immunosuppressive drugs in the past 3 months or anti-tumour necrosis factor within the 6 months before surgery; any corticosteroid-dependant disease; as well as women who were pregnant, planning pregnancy or breast-feeding
Interventions	Azathioprine 2 mg/kg/day (n = 71) for 24 months or until relapse Mesalamine 3 g/day (n = 71) for 24 months or until relapse
Outcomes	Primary outcomes: clinical relapse (symptoms of active disease with laboratory, radiological or endoscopic findings and CDAI > 200 to warrant steroids) or surgical relapse (symptoms refractory to medical treatment and need for further surgery) at 24 months Secondary outcome: adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of 10
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear with data reported
Selective reporting (reporting bias)	Unclear risk	Unclear with data reported
Other bias	Low risk	None apparent

Armuzzi 2013

Methods	Open-label, single-centre, randomised, controlled pilot study
Participants	Consecutive Crohn's disease patients who underwent a curative ileocolonic resection and were considered to be at 'high risk' of postoperative recurrence (N = 22) Exclusion criteria: active perianal disease, presence of stoma, adverse events during previous therapy with infliximab or azathioprine, age > 70 years, surgical complications, active infectious diseases, history of cancer, renal, cardiac or hepatic failure, history of acute or chronic pancreatitis, severe leucopenia and pregnancy
Interventions	Infliximab 5 mg/kg at weeks 0, 2 and 6 weeks and then every 8 weeks for 1 year (n = 11) Azathioprine 2.5 mg/kg/day for 1 year (n =11) All patients received oral metronidazole (500 mg twice daily) for 2 weeks after surgery Treatment was started within 2 to 4 weeks of surgery No other drugs were allowed
Outcomes	Co-primary outcomes were endoscopic, histological and clinical recurrence at 12 months Secondary outcomes: Harvey-Bradshaw Index, laboratory tests and adverse events
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 of participants and personnel (performance bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient in the azathioprine group withdrew due to adverse events (severe nausea and epigastric pain), no other patients withdrew
Selective reporting (reporting bias)	Low risk	Appropriate data reported
Other bias	Low risk	None apparent

D'Haens 2008

Methods	Randomised controlled trial at 2 centres
Participants	Adult CD patients were enrolled within 2 weeks of curative ileal or ileocolonic resection with ileocolonic anastomosis (N = 81) Exclusion criteria: Patients with macroscopic evidence of pancolitis or disease proximal or distal to the site of resection or those who had an ileorectal anastomosis or stoma, contraindications for use of azathioprine or metronidazole; alcohol or drug abuse, leucopenia, malignancies or ongoing infectious disease (hepatitis, tuberculosis, AIDS); the use of azathioprine within 2 months of surgery and pregnancy
Interventions	Azathioprine 100 mg/day if patient weight was < 60 kg or 150 mg/day if patient weight was > 60 kg (n= 40) for 12 months (n = 40) Placebo for 12 months (n = 41) All patients received metronidazole 250 mg three times daily or ornidazole 500 mg twice daily for 3 months
Outcomes	Primary outcome: proportion of patients with endoscopic recurrence (> 2 Rutgeers endoscopic score) at 3 and 12 months Secondary outcomes: clinical relapse (CDAI > 250), the severity of endoscopic recurrence and adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Centralized pharmacy randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind: azathioprine dummy was provided in sealed containers so the investigator did not see the pills
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data reported
Selective reporting (reporting bias)	Low risk	Appropriate data reported
Other bias	Low risk	None apparent

Hanauer 2004

Methods	Randomised, multi-centre double-blind, double-dummy, controlled trial
Participants	CD patients before postoperative hospital discharge after ileocolic resection with a primary anastomosis for disease confined to the ileum and adjacent colon (N = 131) Patients were excluded if there was evidence of disease proximal or distal to the site of resection
Interventions	6-mercaptopurine 50 mg/day for 24 months (n = 47) mesalamine 3 g/day for 24 months (n = 44) placebo for 24 months (n = 40)
Outcomes	Primary outcomes: clinical relapse (score of > 2 on the clinical recurrence grading scale) at 6, 12 and 24 months, radiographic relapse (a score of > 2 on the radiological recurrence grading scale) or endoscopic recurrence (score of > 2 on the Rutgeerts endoscopic scoring system) at 12 and 24 months Secondary outcome: adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomisation in blocks of 6
Allocation concealment (selection bias)	Low risk	Centralized pharmacy randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Identical matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data reported
Selective reporting (reporting bias)	Low risk	Appropriate data reported
Other bias	Low risk	None apparent

Herfarth 2006

Methods	Randomised, double-blind, double-dummy, multi-centre trial
Participants	CD patients were enrolled within 2 weeks of surgery (N = 79) Patients with homozygous TPMT deficiency were excluded
Interventions	Azathioprine 2 to 2.5 mg/kg/day for 12 months (n = 42) 5-ASA 4 g/day for 12months (n = 37)

Herfarth 2006 (*Continued*)

Outcomes	Primary outcome: treatment failure end point was 12months clinical relapse (not defined) or endoscopic relapse (not defined) or withdrawal due to any relapse or adverse event. treatment failure: severe endoscopic relapse, withdrawal due to clinical relapse or adverse drug reaction
Notes	Ended prematurely because an interim analysis revealed that the hypothesis of superiority of AZA versus 5-ASA could not be tested with the planned sample size

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Centralized randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data reported
Selective reporting (reporting bias)	Low risk	Appropriate data reported
Other bias	Low risk	None apparent

Reinisch 2010

Methods	Randomised, double-blind, double-dummy, multi-centre trial
Participants	CD patients within 6 to 24 months of resection with a ileocolonic anastomosis who had no clinical recurrence with CDAI < 200 but with moderate or severe endoscopic recurrence Exclusion criteria: short bowel syndrome, stricture plasty or an ileocolonic stoma, TPMT deficiency; high serum creatinine; or the use of immunosuppressants or anti-tumour necrosis factor since resection, corticosteroids or oral antibiotics for > 4weeks since resection, or NSAIDs within the preceding 2 weeks
Interventions	Azathioprine 2 to 2.5 mg/kg/day for 12 months (n = 41) Mesalazine 4 g/day for 12 months (n = 37)
Outcomes	Primary outcome: clinical relapse (CDAI > 200 and an increase of > 60 points from baseline) at 12 months or withdrawal due to any relapse or adverse event Secondary outcomes: endoscopic improvement (>1 point reduction in Rutgeerts score) or any change in CDAI score, IBDQ score and CRP level from baseline

Reinisch 2010 (*Continued*)

Notes	Included despite endoscopic recurrence as inclusion criteria	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomisation in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data reported
Selective reporting (reporting bias)	Low risk	Appropriate data reported
Other bias	Low risk	None apparent although funded by drug company and some authors employed by drug company

Savarino 2013

Methods	Open-label, randomised, controlled trial	
Participants	Adult patients with ileal or ileocolonic CD undergoing resection (N = 51) Exclusion criteria: more than 10 years of Crohn's disease requiring first resection for short (10 cm) fibrostenotic stricture, macroscopically active disease not resected during surgery, or the presence of a stoma	
Interventions	Adalimumab 160/80 mg at weeks 0 and 2, followed by 40 mg every 2 weeks for 2 years (n = 16) Azathioprine 2.0 mg/kg/day for 2 years (n = 17) Mesalamine 3 g/day for 2 years (n = 18)	
Outcomes	Primary outcome: the proportion of patients with endoscopic and clinical recurrence at 2 years Secondary outcomes: quality of life (IBD-Q), adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Savarino 2013 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	"Patient allocation was concealed and performed by an independent nurse not involved with the trial"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient withdrew from the adalimumab group due to atopic dermatitis Two patients withdrew from the azathioprine group due to a severe exacerbation of Crohn's disease or an adverse event (severe abdominal pain and increase of pancreatic enzymes Two patients withdrew from the 5-ASA group due to severe exacerbation of Crohn's disease
Selective reporting (reporting bias)	Low risk	Appropriate data reported
Other bias	Low risk	None apparent

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

Study	Reason for exclusion
Ferrante 2014	Abstract publication All patients received azathioprine Study compared systematic azathioprine therapy to endoscopically driven azathioprine therapy
Mañosa 2013	All patients received azathioprine Study compared combination of azathioprine and metronidazole to azathioprine
Nos 2000	Not RCT after contacting author

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 relapse (fixed-effect)	2	168	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.94]
2 Clinical relapse, sensitivity analysis, (random-effects)	2	168	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.61, 0.95]
3 Endoscopic relapse (fixed-effect)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events requiring withdrawal (fixed-effect)	2	168	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.59, 2.98]

Comparison 2. Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse (fixed-effect)	5	425	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.34]
2 Clinical relapse,sensitivity analysis (random-effects)	5	425	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.93, 1.41]
3 Clinical relapse, sensitivity analysis excluding study that enrolled patients with endoscopic recurrence, (fixed-effect)	4	347	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.24]
4 Clinical relapse, subgroup analysis by drug type (fixed-effect)	5	425	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.34]
4.1 Azathioprine	4	334	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.04, 1.51]
4.2 6-mercaptopurine	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.18]
5 Clinical relapse, subgroup analysis by length of follow-up	5	425	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.34]
5.1 12 months	2	157	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.12, 1.74]
5.2 24 months	3	268	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.24]
6 Endoscopic relapse (fixed-effect)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Adverse events (fixed-effect)	4	334	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.27]
8 Adverse events requiring withdrawal (fixed-effect)	5	423	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [1.26, 3.39]
9 Adverse events requiring withdrawal, subgroup analysis by drug type (fixed-effect)	5	423	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [1.26, 3.39]
9.1 Azathioprine	4	332	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.31, 4.22]
9.2 6-mercaptopurine	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.54, 3.62]

10 Serious adverse events (random-effects)	2	169	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.04, 162.02]

Comparison 3. Azathioprine versus infliximab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Endoscopic relapse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events requiring withdrawal	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Azathioprine versus adalimumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Endoscopic relapse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events requiring withdrawal	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Azathioprine or 6-mercaptopurine versus placebo, Outcome 1 Clinical relapse (fixed-effect).

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

Comparison: 1 Azathioprine or 6-mercaptopurine versus placebo

Outcome: 1 Clinical relapse (fixed-effect)

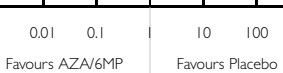
Study or subgroup	AZA/6MP n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
D'Haens 2008	10/40	16/41		29.5 %	0.64 [0.33, 1.24]
Hanauer 2004	32/47	35/40		70.5 %	0.78 [0.62, 0.98]
Total (95% CI)	**87**	**81**		**100.0 %**	**0.74 [0.58, 0.94]**

Total events: 42 (AZA/6MP), 51 (Placebo)

Heterogeneity: $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Azathioprine or 6-mercaptopurine versus placebo, Outcome 2 Clinical relapse, sensitivity analysis, (random-effects).

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

Comparison: 1 Azathioprine or 6-mercaptopurine versus placebo

Outcome: 2 Clinical relapse, sensitivity analysis, (random-effects)

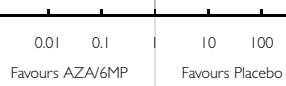
Study or subgroup	AZA/6MP n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
D'Haens 2008	10/40	16/41		10.7 %	0.64 [0.33, 1.24]
Hanauer 2004	32/47	35/40		89.3 %	0.78 [0.62, 0.98]
Total (95% CI)	**87**	**81**		**100.0 %**	**0.76 [0.61, 0.95]**

Total events: 42 (AZA/6MP), 51 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.47 (P = 0.014)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Azathioprine or 6-mercaptopurine versus placebo, Outcome 3 Endoscopic relapse (fixed-effect).

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

Comparison: 1 Azathioprine or 6-mercaptopurine versus placebo

Outcome: 3 Endoscopic relapse (fixed-effect)

Study or subgroup	6-MP n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Hanauer 2004	8/47	17/40		0.40 [0.19, 0.83]

Analysis 1.4. Comparison 1 Azathioprine or 6-mercaptopurine versus placebo, Outcome 4 Adverse events requiring withdrawal (fixed-effect).

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

Comparison: 1 Azathioprine or 6-mercaptopurine versus placebo

Outcome: 4 Adverse events requiring withdrawal (fixed-effect)

Study or subgroup	AZA/6MP n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
D'Haens 2008	4/40	5/41		53.3 %	0.82 [0.24, 2.84]
Hanauer 2004	9/47	4/40		46.7 %	1.91 [0.64, 5.75]
Total (95% CI)	**87**	**81**		**100.0 %**	**1.33 [0.59, 2.98]**
Total events: 13 (AZA/6MP), 9 (Placebo)					
Heterogeneity: Chi^2 = 1.01, df = 1 (P = 0.32); I^2 =1%					
Test for overall effect: Z = 0.70 (P = 0.49)					
Test for subgroup differences: Not applicable					

Analysis 2.1. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 1 Clinical relapse (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 1 Clinical relapse (fixed-effect)

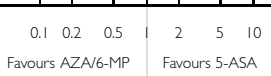
Study or subgroup	AZA/6-MP n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	31/71	30/71		26.0 %	1.03 [0.71, 1.51]
Hanauer 2004	32/47	33/44		29.6 %	0.91 [0.70, 1.18]
Herfarth 2006	39/42	29/37		26.8 %	1.18 [0.98, 1.43]
Reinisch 2010	24/41	11/37		10.0 %	1.97 [1.13, 3.44]
Savarino 2013	11/17	9/18		7.6 %	1.29 [0.72, 2.31]
Total (95% CI)	**218**	**207**		**100.0 %**	**1.15 [0.99, 1.34]**

Total events: 137 (AZA/6-MP), 112 (5-ASA)

Heterogeneity: $Chi^2 = 7.31$, df = 4 (P = 0.12); $I^2 = 45\%$

Test for overall effect: Z = 1.79 (P = 0.074)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 2 Clinical relapse,sensitivity analysis (random-effects).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 2 Clinical relapse,sensitivity analysis (random-effects)

Study or subgroup	AZA/6-MP n/N	5-ASA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ardizzone 2004	31/71	30/71		18.3 %	1.03 [0.71, 1.51]
Hanauer 2004	32/47	33/44		27.1 %	0.91 [0.70, 1.18]
Herfarth 2006	39/42	29/37		34.0 %	1.18 [0.98, 1.43]
Reinisch 2010	24/41	11/37		10.6 %	1.97 [1.13, 3.44]
Savarino 2013	11/17	9/18		10.0 %	1.29 [0.72, 2.31]
Total (95% CI)	**218**	**207**		**100.0 %**	**1.14 [0.93, 1.41]**

Total events: 137 (AZA/6-MP), 112 (5-ASA)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.31$, df = 4 (P = 0.12); $I^2 = 45\%$

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 3 Clinical relapse, sensitivity analysis excluding study that enrolled patients with endoscopic recurrence, (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 3 Clinical relapse, sensitivity analysis excluding study that enrolled patients with endoscopic recurrence, (fixed-effect)

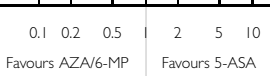
Study or subgroup	AZA/6-MP n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	31/71	30/71		28.9 %	1.03 [0.71, 1.51]
Hanauer 2004	32/47	33/44		32.9 %	0.91 [0.70, 1.18]
Herfarth 2006	39/42	29/37		29.7 %	1.18 [0.98, 1.43]
Savarino 2013	11/17	9/18		8.4 %	1.29 [0.72, 2.31]
Total (95% CI)	**177**	**170**		**100.0 %**	**1.06 [0.91, 1.24]**

Total events: 113 (AZA/6-MP), 101 (5-ASA)

Heterogeneity: $Chi^2 = 3.18$, df = 3 (P = 0.36); $I^2 = 6\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 4 Clinical relapse, subgroup analysis by drug type (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 4 Clinical relapse, subgroup analysis by drug type (fixed-effect)

Study or subgroup	AZA/6-MP n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Azathioprine					
Ardizzone 2004	31/71	30/71		26.0 %	1.03 [0.71, 1.51]
Herfarth 2006	39/42	29/37		26.8 %	1.18 [0.98, 1.43]
Reinisch 2010	24/41	11/37		10.0 %	1.97 [1.13, 3.44]
Savarino 2013	11/17	9/18		7.6 %	1.29 [0.72, 2.31]
Subtotal (95% CI)	**171**	**163**		**70.4 %**	**1.25 [1.04, 1.51]**
Total events: 105 (AZA/6-MP), 79 (5-ASA)					
Heterogeneity: Chi^2 = 3.85, df = 3 (P = 0.28); I^2 =22%					
Test for overall effect: Z = 2.35 (P = 0.019)					
2 6-mercaptopurine					
Hanauer 2004	32/47	33/44		29.6 %	0.91 [0.70, 1.18]
Subtotal (95% CI)	**47**	**44**		**29.6 %**	**0.91 [0.70, 1.18]**
Total events: 32 (AZA/6-MP), 33 (5-ASA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
Total (95% CI)	**218**	**207**		**100.0 %**	**1.15 [0.99, 1.34]**
Total events: 137 (AZA/6-MP), 112 (5-ASA)					
Heterogeneity: Chi^2 = 7.31, df = 4 (P = 0.12); I^2 =45%					
Test for overall effect: Z = 1.79 (P = 0.074)					
Test for subgroup differences: Chi^2 = 3.88, df = 1 (P = 0.05), I^2 =74%					

Analysis 2.5. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 5 Clinical relapse, subgroup analysis by length of follow-up.

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 5 Clinical relapse, subgroup analysis by length of follow-up

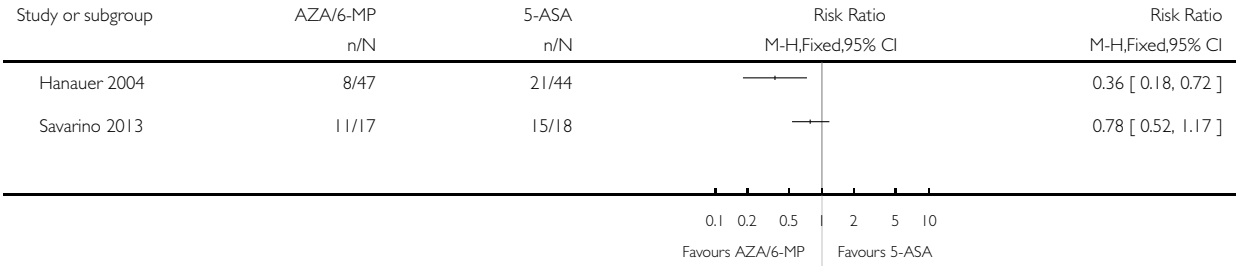
Study or subgroup	AZA/6-MP n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 12 months					
Herfarth 2006	39/42	29/37		26.8 %	1.18 [0.98, 1.43]
Reinisch 2010	24/41	11/37		10.0 %	1.97 [1.13, 3.44]
Subtotal (95% CI)	**83**	**74**		**36.8 %**	**1.40 [1.12, 1.74]**
Total events: 63 (AZA/6-MP), 40 (5-ASA)					
Heterogeneity: Chi^2 = 4.41, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 2.98 (P = 0.0029)					
2 24 months					
Ardizzone 2004	31/71	30/71		26.0 %	1.03 [0.71, 1.51]
Hanauer 2004	32/47	33/44		29.6 %	0.91 [0.70, 1.18]
Savarino 2013	11/17	9/18		7.6 %	1.29 [0.72, 2.31]
Subtotal (95% CI)	**135**	**133**		**63.2 %**	**1.01 [0.81, 1.24]**
Total events: 74 (AZA/6-MP), 72 (5-ASA)					
Heterogeneity: Chi^2 = 1.34, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
Total (95% CI)	**218**	**207**		**100.0 %**	**1.15 [0.99, 1.34]**
Total events: 137 (AZA/6-MP), 112 (5-ASA)					
Heterogeneity: Chi^2 = 7.31, df = 4 (P = 0.12); I^2 =45%					
Test for overall effect: Z = 1.79 (P = 0.074)					
Test for subgroup differences: Chi^2 = 4.48, df = 1 (P = 0.03), I^2 =78%					

Analysis 2.6. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 6 Endoscopic relapse (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 6 Endoscopic relapse (fixed-effect)

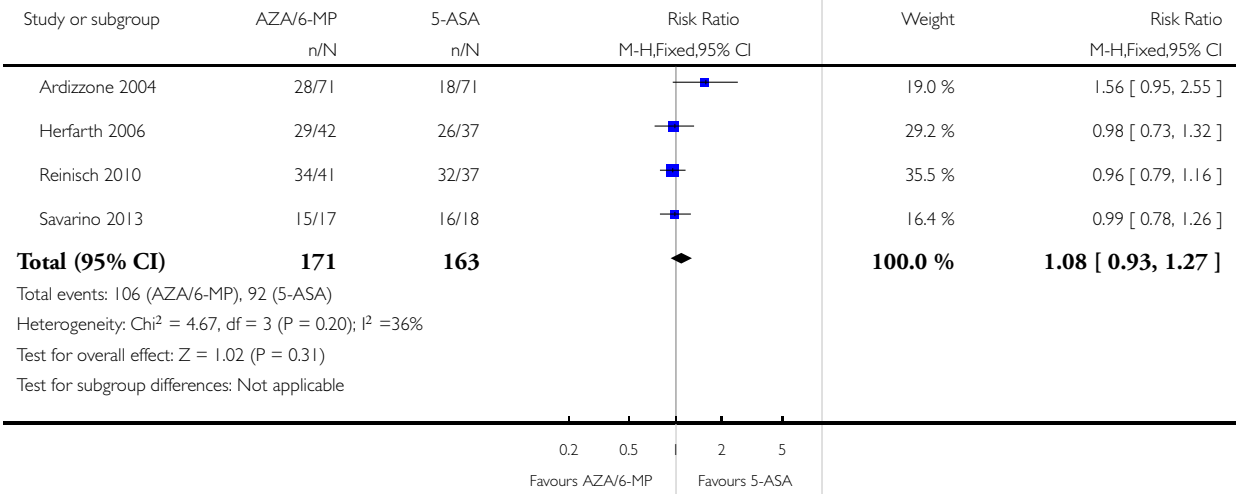


Analysis 2.7. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 7 Adverse events (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 7 Adverse events (fixed-effect)



Analysis 2.8. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 8 Adverse events requiring withdrawal (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 8 Adverse events requiring withdrawal (fixed-effect)

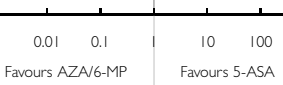
Study or subgroup	AZA/6-MP n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	15/71	6/71		29.1 %	2.50 [1.03, 6.07]
Hanauer 2004	9/47	6/44		30.1 %	1.40 [0.54, 3.62]
Herfarth 2006	7/42	4/37		20.6 %	1.54 [0.49, 4.85]
Reinisch 2010	11/41	2/37		10.2 %	4.96 [1.18, 20.94]
Savarino 2013	2/17	2/16		10.0 %	0.94 [0.15, 5.91]
Total (95% CI)	**218**	**205**		**100.0 %**	**2.07 [1.26, 3.39]**

Total events: 44 (AZA/6-MP), 20 (5-ASA)

Heterogeneity: $Chi^2 = 3.19$, df = 4 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.88 (P = 0.0040)

Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 9 Adverse events requiring withdrawal, subgroup analysis by drug type (fixed-effect).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 9 Adverse events requiring withdrawal, subgroup analysis by drug type (fixed-effect)

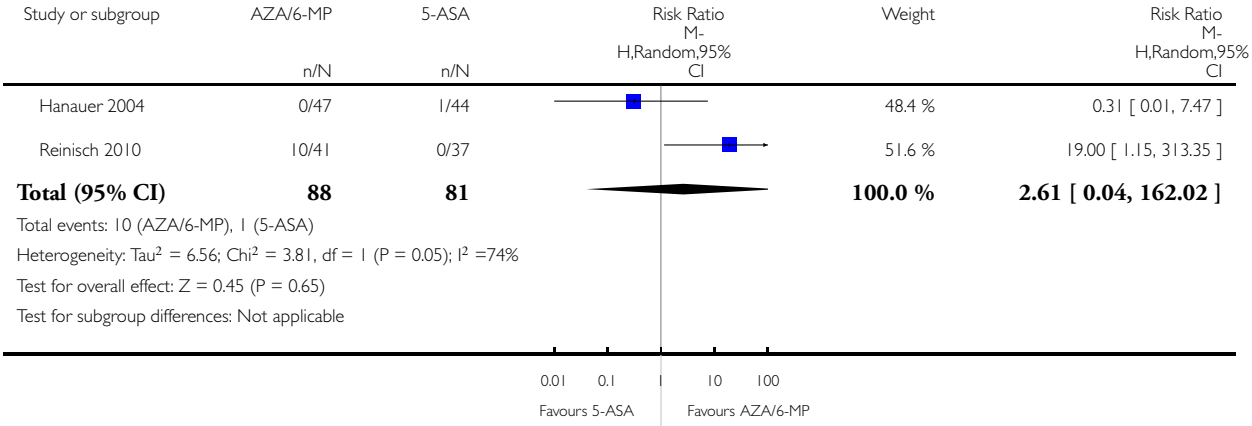
Study or subgroup	AZA n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Azathioprine					
Ardizzone 2004	15/71	6/71		29.1 %	2.50 [1.03, 6.07]
Herfarth 2006	7/42	4/37		20.6 %	1.54 [0.49, 4.85]
Reinisch 2010	11/41	2/37		10.2 %	4.96 [1.18, 20.94]
Savarino 2013	2/17	2/16		10.0 %	0.94 [0.15, 5.91]
Subtotal (95% CI)	**171**	**161**		**69.9 %**	**2.35 [1.31, 4.22]**
Total events: 35 (AZA), 14 (5-ASA)					
Heterogeneity: Chi^2 = 2.53, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.88 (P = 0.0040)					
2 6-mercaptopurine					
Hanauer 2004	9/47	6/44		30.1 %	1.40 [0.54, 3.62]
Subtotal (95% CI)	**47**	**44**		**30.1 %**	**1.40 [0.54, 3.62]**
Total events: 9 (AZA), 6 (5-ASA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
Total (95% CI)	**218**	**205**		**100.0 %**	**2.07 [1.26, 3.39]**
Total events: 44 (AZA), 20 (5-ASA)					
Heterogeneity: Chi^2 = 3.19, df = 4 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 2.88 (P = 0.0040)					
Test for subgroup differences: Chi^2 = 0.83, df = 1 (P = 0.36), I^2 =0.0%					

Analysis 2.10. Comparison 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid, Outcome 10 Serious adverse events (random-effects).

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

Comparison: 2 Azathioprine or 6-mercaptopurine versus 5-aminosalicylic acid

Outcome: 10 Serious adverse events (random-effects)

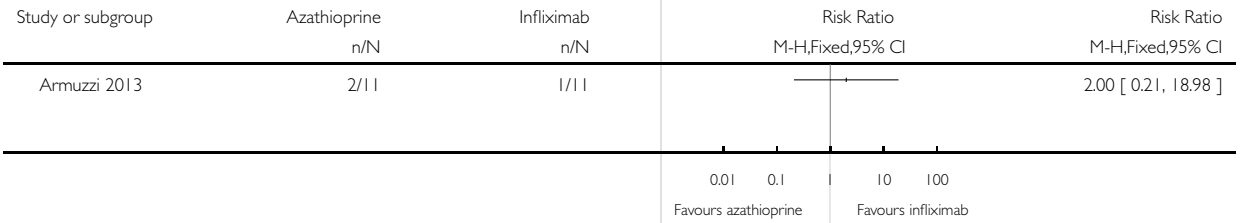


Analysis 3.1. Comparison 3 Azathioprine versus infliximab, Outcome 1 Clinical relapse.

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

Comparison: 3 Azathioprine versus infliximab

Outcome: 1 Clinical relapse



Analysis 3.2. Comparison 3 Azathioprine versus infliximab, Outcome 2 Endoscopic relapse.

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

Comparison: 3 Azathioprine versus infliximab

Outcome: 2 Endoscopic relapse

Study or subgroup	Azathioprine n/N	Infliximab n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Armuzzi 2013	4/10	1/11		4.40 [0.59, 33.07]

Analysis 3.3. Comparison 3 Azathioprine versus infliximab, Outcome 3 Adverse events requiring withdrawal.

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

Comparison: 3 Azathioprine versus infliximab

Outcome: 3 Adverse events requiring withdrawal

Study or subgroup	Azathioprine n/N	Infliximab n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Armuzzi 2013	1/11	0/11		3.00 [0.14, 66.53]

Analysis 4.1. Comparison 4 Azathioprine versus adalimumab, Outcome 1 Clinical relapse.

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

Comparison: 4 Azathioprine versus adalimumab

Outcome: 1 Clinical relapse

Study or subgroup	Azathioprine n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	11/17	2/16		5.18 [1.35, 19.83]

Analysis 4.2. Comparison 4 Azathioprine versus adalimumab, Outcome 2 Endoscopic relapse.

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

Comparison: 4 Azathioprine versus adalimumab

Outcome: 2 Endoscopic relapse

Study or subgroup	Azathioprine n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	11/17	1/16		10.35 [1.50, 71.32]

Analysis 4.3. Comparison 4 Azathioprine versus adalimumab, Outcome 3 Adverse events.

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

Comparison: 4 Azathioprine versus adalimumab

Outcome: 3 Adverse events

Study or subgroup	Azathioprine n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	15/17	11/16		1.28 [0.88, 1.86]

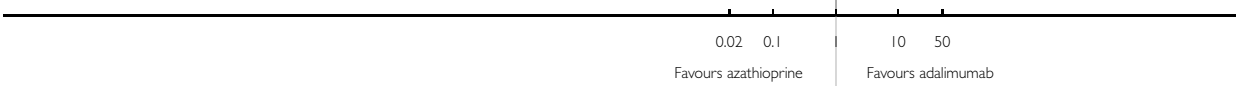
Analysis 4.4. Comparison 4 Azathioprine versus adalimumab, Outcome 4 Adverse events requiring withdrawal.

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

Comparison: 4 Azathioprine versus adalimumab

Outcome: 4 Adverse events requiring withdrawal

Study or subgroup	Azathioprine n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	2/17	1/16		1.88 [0.19, 18.80]



APPENDICES

Appendix 1. Search Strategies

PubMed

#1 crohn* OR IBD OR "inflammatory bowel disease" OR regional enteritis OR ileitis
2 singl* OR doubl* OR tripl* OR trebl* OR blind* OR mask* OR placebo* OR single-blind* OR double-blind* OR triple-blind* OR random* OR (controlled clinical)
3 #1 AND # 2
4 AZA or azathioprine
5 6-mercaptopurine or mercaptopurine or 6-MP or 6MP
6 anti-metabolite* or antimetabolite*
7 #4 OR #5 OR #6
8 #3 AND #7
9 surgery or surgic* or post-surgical or post-surgery or postoperative or post-operative or resection or operation
10 #8 AND #9

MEDLINE

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 Crohn disease/ or crohn*.mp.
20. inflammatory bowel disease.mp.
21. IBD.mp.
22. 19 or 20 or 21
23. 18 and 22
24. azathioprine.mp. or exp azathioprine derivative/ or exp azathioprine/
25. 6-mercaptopurine.mp. or exp mercaptopurine/
26. (AZA or 6-MP or 6MP).mp.
27. exp antimetabolite/ or anti-metabolite*.mp.
28. antimetabolite*.mp.
29. 24 or 25 or 26 or 27 or 28
30. 23 and 29
31. surgery.mp. or surgery/
32. (surgical or surgically).mp.
33. surgic*.mp.
34. (post-surgical or post-surgery).mp.
35. (postoperative or post-operative).mp.
36. resection.mp. or surgery/

37. operation.mp. or surgery/
38. 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 30 and 38

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 Crohn disease/ or crohn*.mp.
20. inflammatory bowel disease.mp.
21. IBD.mp.
22. 19 or 20 or 21
23. 18 and 22
24. azathioprine.mp. or exp azathioprine derivative/ or exp azathioprine/
25. 6-mercaptopurine.mp. or exp mercaptopurine/
26. (AZA or 6-MP or 6MP).mp.
27. exp antimetabolite/ or anti-metabolite*.mp.
28. antimetabolite*.mp.
29. 24 or 25 or 26 or 27 or 28
30. 23 and 29
31. surgery.mp. or surgery/
32. (surgical or surgically).mp.
33. surgic*.mp.
34. (post-surgical or post-surgery).mp.
35. (postoperative or post-operative).mp.
36. resection.mp. or surgery/
37. operation.mp. or surgery/
38. 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 30 and 38

CENTRAL

#1 crohn* or “inflammatory bowel disease” or IBD
#2 anti-metabolite* or antimetabolite*
#3 6-mercaptopurine or mercaptopurine or 6-MP or 6MP
#4 AZA or azathioprine
#5 #2 or #3 or #4
6 #1 and #5
#7 surgery or surgic* or post-surgical or post-surgery or postoperative or post-operative or resection or operation
#8 #6 and #7

SR-IBD

Crohn AND 6-mercaptopurine or 6-MP or 6MP or azathioprine AND surgery or surgic* or post* or resection or operation

WHAT'S NEW

Last assessed as up-to-date: 30 April 2014.

Date	Event	Description
24 September 2014	Amended	Correction of minor typo

CONTRIBUTIONS OF AUTHORS

Morris Gordon led the review and was involved in all phases. Kelly Taylor co-searched, led the write up of the results and discussion. Anthony Akobeng and Adrian Thomas commented on and supported all stages of the review.

DECLARATIONS OF INTEREST

Morris Gordon has received travel grants from Warner Chilcott Pharmaceuticals, Cassen Fleet, Vifor Pharma, Ferring Pharmaceuticals and Abbott to attend Digestive Disease Week (DDW), and other scientific meetings to present results of systematic reviews. He has also acted a clinical editor for Danone nutrition, and has received lecture fees from Warner Chilcott Pharmaceuticals for a presentation at DDW. These companies had no involvement in the review process or write up of this or any previous works.

The other authors have no known interests to declare.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following sensitivity analyses were planned but not carried out due to lack of data and small number of studies:

a. only including patients' whose outcome was known i.e. number of patients who completed the study used as denominator;

b. allocation concealment;

c. dose of AZA/6-MP; and

d. concurrent medications (5-aminosalicylic acid and other concurrent immunosuppressants such as methotrexate, cyclosporine, mycophenolate mofetil, infliximab, or adalimumab).

INDEX TERMS

Medical Subject Headings (MeSH)

6-Mercaptopurine [*therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized [therapeutic use]; Azathioprine [*therapeutic use]; Crohn Disease [*drug therapy; prevention & control; surgery]; Immunosuppressive Agents [*therapeutic use]; Maintenance Chemotherapy [*methods]; Mesalamine [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction [methods]; Secondary Prevention

MeSH check words

Humans