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Review Article

Azathioprine/6-mercaptopurine versus 5-aminosalicylic for treatment of inflammatory bowel disease

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Abstract: Background: Debate exists regarding to whether thiopurine therapy is as effective as 5-aminosalicylic (5-ASA, mesalazine) in inflammatory bowel disease (IBD). In this study, we aimed to review the efficacy of azathioprine (AZA) and 6-mercaptopurine (6-MP) in inflammatory bowel disease (IBD), and to conduct a meta-analysis of randomized controlled trials to compare the efficacy and safety of AZA/6-MP and 5-ASA in IBD. Methods: Selection of studies: Randomized controlled trials comparing AZA/6-MP with 5-ASA was included in the meta-analysis. Search strategy: Electronic and manual. Study quality: Independently assessed by two reviewers. Data synthesis: By "intention-to-treat". Results: Eight trials (572 IBD patients) were included in the meta-analysis. All trials stated random allocation and reported withdrawal and dropout. Most of the trials reported blind, allocation concealment, intention-to-treat analysis, the calculation of sample size. Six studies showed that AZA/6-MP had lower relapse rate than 5-ASA (RR: 0.72, 95% CI: 0.55-0.95). Three studies showed that AZA/6-MP had higher remission rate than 5-ASA (RR: 3.30, 95% CI: 1.80-6.05). Compared with 5-ASA, AZA/6-MP did not show significant differences for endoscopic recurrence rate and therapeutic failure rate. Compared with 5-ASA, AZA/6-MP did not increase adverse events (RR: 1.16, 95% CI: 0.87-1.55). Conclusion: All the eligible trials were of high methodological quality. Thiopurine drugs (AZA/6-MP) are more effective than 5-ASA for the treatment of IBD.

Keywords: Inflammatory bowel disease, azathioprine, 6-mercaptopurine, 5-aminosalicylic, meta-analysis

Introduction

Steroids relieve symptoms of inflammatory bowel disease (IBD) patients promptly and efficiently, which include both Crohn's disease (CD) and ulcerative colitis (UC). Most patients initially respond to corticosteroids, but patients become steroid-dependent [1, 2] and presented complications of the disease and chronic toxicity [3]. To reduce the side effects of steroid, alternative pharmacological approaches have been attempted.

5-aminosalicylic acid (5-ASA) and immunomodulatory agents such as azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate and ciclosporin, have been used in selected patients who was inadequately response to steroids [4-7]. Although these purine analogues promote remission in CD [8], the efficacy of AZA and 6-MP in UC is still controversial. Several open studies demonstrated AZA or 6-MP's efficacy in UC [9-14], but controlled trials produced conflicting results [15, 16]. Furthermore, there is no controlled trials compared the efficacy and safety of AZA/6-MP with 5-ASA in IBD.

Therefore, we review systematically the efficacy of AZA and 6-MP in IBD, and conduct a meta-analysis of randomized clinical trials comparing the efficacy and safety of AZA/6-MP and 5-ASA in IBD.

Methods

Literature search

Pubmed/Medline, EMBASE, ISI Web of Knowledge, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Chinese Clinical Trial Register (ChiCTR) were searched for the eligible trials up to 25th May, 2014. Search strategy was constructed using a combination of the following words: "inflammatory bowel disease" (inflammatory bowel disease, ulcerative colitis or Crohn's disease), "5-ASA" (mesalamine, 5-aminosalicylic acid, or 5-ASA) and "azathioprine, 6-mercaptopurine or thiopurine". Articles published in any language were included. In case of duplicate reports, or studies obviously reporting results from the same study population, only the latest published results were used. This study was performed according to the preferred reporting items for systematic reviews and meta-Analysis [17, 18].

Study selection criteria

Studies evaluating AZA or 6-MP and 5-ASA treatment for the IBD were considered for the systematic review. The inclusion and exclusion criteria for the meta-analysis were: (a) Patients were diagnosed as IBD, either UC or CD. Patients with irritable bowel syndrome, other types of colitis (e.g., infectious colitis, ischaemic colitis) were excluded. (b) Include at least two branches of treatment consisting of (i) AZA or 6-MP therapy and (ii) 5-ASA. The treatment with other immunomodulators (e.g., Tacrolimus, Cyclosporine) or biologic agents (e.g., infliximab, adalimumab) was considered exclusion criteria. (c) The outcomes included clinical relapse, remission rate, endoscopic recurrence, and the adverse events. The Studies with at least one of the outcomes were included. (d) Randomized controlled trials were considered for inclusion. Cross-sectional study, cohort study, and case-control study were excluded. The selection criteria were applied independently by two reviewers according to the eligibility criteria and disagreements were resolved by consensus.

Quality assessment

The methodological qualities were evaluated using the Jadad scale [19], which included randomization, double blinding, and description of withdrawals and dropouts. Points (0 to 2) awarded for items 1 and 2 based on the quality of the methods used to generate the randomization and the double blinding, respectively. The third item including withdrawals and dropouts, was awarded as 0 and 1 points for a negative and positive answer, respectively. Each trial was graded as low (0-2 points) or high (3-5 points) quality. Quality assessment of studies was conducted independently by two reviewers and discrepancies were resolved by consensus.

Data extraction

The titles and abstracts of all the articles were screened by two reviewers independently. The eligible or uncertain articles were retrieved for the full texts. Two reviewers read the full texts, and identified the eligible trials. The articles included in the following variables: the first author, types of disease, research design, types of treatments, publication time, sample sizes, effectiveness outcomes, the adverse events and the methodological qualities. Any disagreements in data collection were resolved by consensus.

Data synthesis

The primary outcome considered in this review was 'success of treatment', defined as the clinical relapse rate and clinical remission rate. The mean percentage of AZA/6-MP efficacy was calculated and expressed as weighted mean (and corresponding 95% confidence interval, 95% CI). Categorical variables were compared by the chi-squared (χ^2) test and $P<0.05$ was considered statistically significant.

All calculations were performed using Reviewer Manager (RevMan) (Computer program, Version 5.3). All the outcomes (e.g., clinical remission, clinical response) were estimated using the risk ratio (RR) and its 95% confidence intervals (CI). For the meta-analysis, the homogeneity of effects throughout studies was tested by a homogeneity test based on the Cochran Q test, and $P\leq0.05$ was considered as significant heterogeneity. In addition, the I^2 statistic was used to assess the impact of heterogeneity on the results and the value >50% was considered substantial heterogeneity [20]. In the presence of significant homogeneity, the fixed-effects

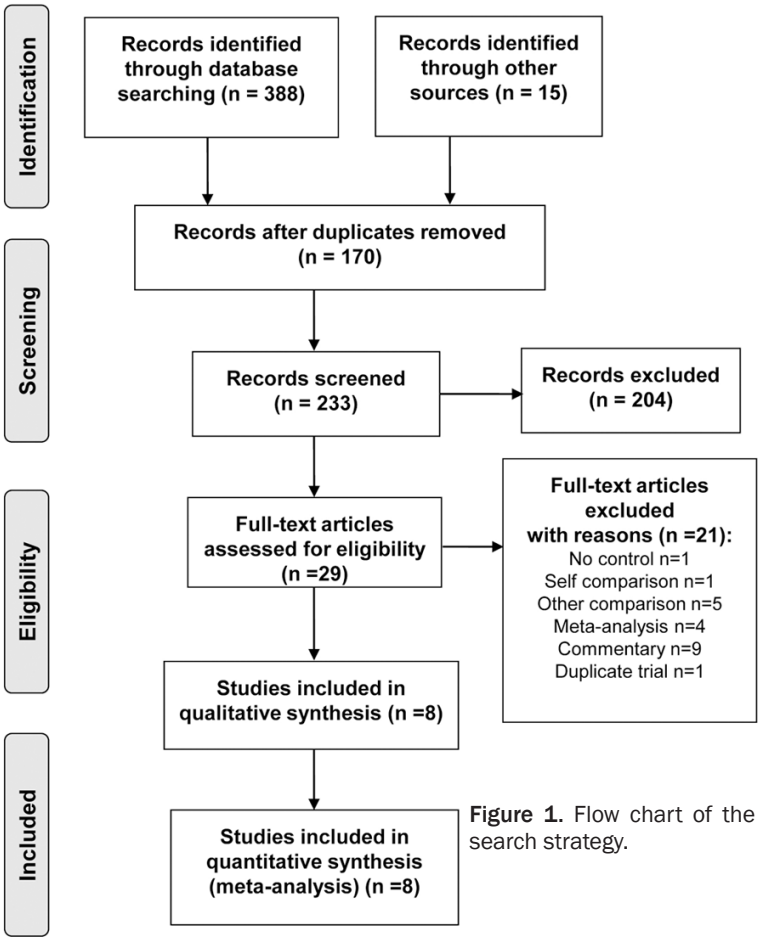

Figure 1. Flow chart of the search strategy.

model was applied. If any heterogeneity existed, random-effects model was employed.

Results

Description of studies

The initial search strategy identified 403 potentially eligible papers through database. 170 papers were excluded because of duplication. 204 studies were excluded because, although the title suggested that they could fulfill the inclusion criteria, the detailed review of the abstract finally ruled them out. The remaining 29 studies were evaluated for the full text. Nine studies were enrolled, but one more studies was considered duplicate reports and therefore excluded [21]. Eventually, we included 8 trials in our meta-analysis (**Figure 1** and **Table 1**) [22-29].

All the eligible trials were based on RCTs. Among the 8 trials, 6 trials were about Crohn's disease [22-27], 1 trial was about ulcerative colitis [28], and 1 trial was about inflammatory bowel disease [29]. Seven trials were from developed countries [22-25, 27-29], and only one trial were from Brazil [26]. A total of 572 IBD patients were randomly assigned, of whom 296 patients received AZA or 6-MP treatment, and 276 patients received 5-ASA treatment.

Methodological qualities

All the trials stated random allocation and reported withdrawal and dropout (**Table 2**). Two trial did not report the method of blind [27, 29], and one trial used the method of open-label [22]. Five trials reported allocation concealment and intention-to-treat analysis [21-23, 26, 28]. Only one trial did not reported sample sizes [24]. Baseline comparability was achieved in all the trials.

Meta-analysis of clinical relapse rate

The results of the meta-analysis comparing AZA/6-MP vs. 5-ASA for the clinical relapse rate in IBD are summarized in **Figure 2A**. Six studies were included, with a total of 218 patients being treated with AZA/6-MP. Mean efficacy (pooled data) with AZA/6-MP was 27.1% and 35.4% in 5-ASA group. The RR for this comparison was 0.72 (95% CI: 0.55-0.95, P=0.02), results being statistically homogeneous (χ^2= 9.32, P=0.16, I^2=36%). Subgroup analysis was used to evaluate the efficacy according to different disease. The pooled RR was 0.74 (95% CI =0.46-0.98, n=6) for CD patients, and the pooled RR was 0.35 (95% CI =0.13-0.97, n=1) for UC patients.

Meta-analysis of remission rate

The results of the meta-analysis comparing AZA/6-MP vs. 5-ASA for the remission rate in IBD are summarized in **Figure 2B**. Three stud-

Table 1. The characteristics of the included trials

	Country	Patients	Desige	Outcomes	Intervention (duration)	Number of Patients	Sex (M/F)	Age (year)	Disease duration (year)
Ardizzone S 2004 [22]	Italy	CD, 18~70 years, underwent surgery	Open-label, randomised controlled trial	CRR, Surgical relapse, AEs	AZA 2.0 mg/kg/day, 2 years	71	45/26	NR	NR
					Mesalazine 3 g/day, 2 years	71	50/21	NR	NR
Hanauer SB 2004 [23]	USA	CD, underwent ileocolic resection	Multicentre, randomized, double-blind, double-dummy, controlled trial	CRR, ERR AEs	6-MP 50 mg/day, 2 years	47	23/24	34.9±11.5	9.4±7.8
					Mesalazine 3 g/day, 2 years	44	19/25	34.1±10.9	10.0±8.8
Herfarth H 2006 [24]	Germany	CD after surgery	Multicentre, randomised, double-blind, double-dummy trial	CRR, Therapeutic failure, AEs	AZA 2.0~2.5 mg/kg/day, 1 year	18	NR	NR	NR
					Mesalazine 4 g/day, 1 year	19	NR	NR	NR
Reinisch W 2010 [25]	Austria	CD with moderate or severe endoscopic recurrence, 18~70 years, CDAI score <200	Multicentre, randomised, double-blind, double-dummy trial	CRR, ERR, TF, CDEIS, IBDQ score, AEs	AZA 2.0~2. mg/kg/day, 1 year	41	24/17	35.5±13.6	NR
					Mesalazine 4 g/day, 1 year	37	20/17	36.0±10.7	NR
de Souza GS 2013 [26]	Brazil	CD, 18~65 years	Randomised, investigator-blind, controlled trial	Hospitalization proportion, AEs	AZA 2.0-3.0 mg/kg/day, 3 years	36	18/18	36±12.5	5.8±2.9
					Mesalazine 3.2 g/day, 3 years	36	17/19	38±12.5	5.9±2.7
Savarino E 2013 [27]	Italy	CD undergoing resection,	Randomized, three-armed, unblinded controlled trial	ERR, CRR, IBDQ, Radiological relapse, CDAI, CRP, AEs	AZA 2 mg/kg every day, 2 years	17	9/8	49	7.9
					Mesalamine, 3 g/day, 2 years	18	8/10	46	6.9
Ardizzone S 2006 [28]	Italy	Active steroid dependent UC, Powell-Tuck index >8 and Baron index >2	Randomised, investigator-blind, controlled trial	CER, Remission rate, Powell-Tuck index, Baron index, AEs	AZA 2 mg/kg/day, 0.5 year	36	20/16	43±14	5.4±4.6
					Mesalazine 3.2 g/day, 0.5 year	36	19/17	45±17	5.6±5.5
Maté-Jiménez J 2000 [29]	Spain	Steroid-dependent IBD, 15~70 years	Single-centre, randomised, controlled trial	CER, Remission rate, AEs	6-MP 1.5 mg/kg/day + prednisone, 2 years	30 (UC:14, CD:16)	14/16	38 (25-60)	UC:3.4±2 CD:4.5±3
					Mesalazine 3 g/day + prednisone, 3 years	15 (UC:8, CD:7)	9/6	39 (19-65)	UC:3.5±4 CD:3.5±2

Note: IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; AZA: Azathioprine; 6-MP: 6-Mercaptopurine; CDAI: Crohn's disease activity index; CRR: clinical relapse rate; CER: clinical and endoscopic remission; ERR: Endoscopic Recurrence Rate; TF: Therapeutic failure; CDEIS: Crohn's Disease Endoscopic Index of Severity; IBDQ: Infammatory Bowel Disease Questionnaire; AEs: adverse events.

Table 2. The methodological quality of the included trials

	Randomization	Blind	Dropout/ withdrawal	Allocation concealment	ITT	Sample size calculation	Baseline compatability
Ardizzone S 2004 [22]	1	0	1	0	1	1	1
Hanauer SB 2004 [23]	1	1	1	1	1	1	1
Herfarth H 2006 [24]	1	1	1	NR	NR	NR	NR
Reinisch W 2010 [25]	1	1	1	1	1	1	Partial*
de Souza GS 2013 [26]	1	1	1	1	1	1	1
Savarino E 2013 [27]	1	0	1	1	1	1	1
Ardizzone S 2006 [28]	1	1	1	1	1	1	1
Maté-Jiménez J 2000 [29]	1	NR	1	NR	NR	1	1

*Baseline characteristics were similar between two groups apart from CDAI score and disease behavior. 1: high quality; 0: low quality; NR: not report.

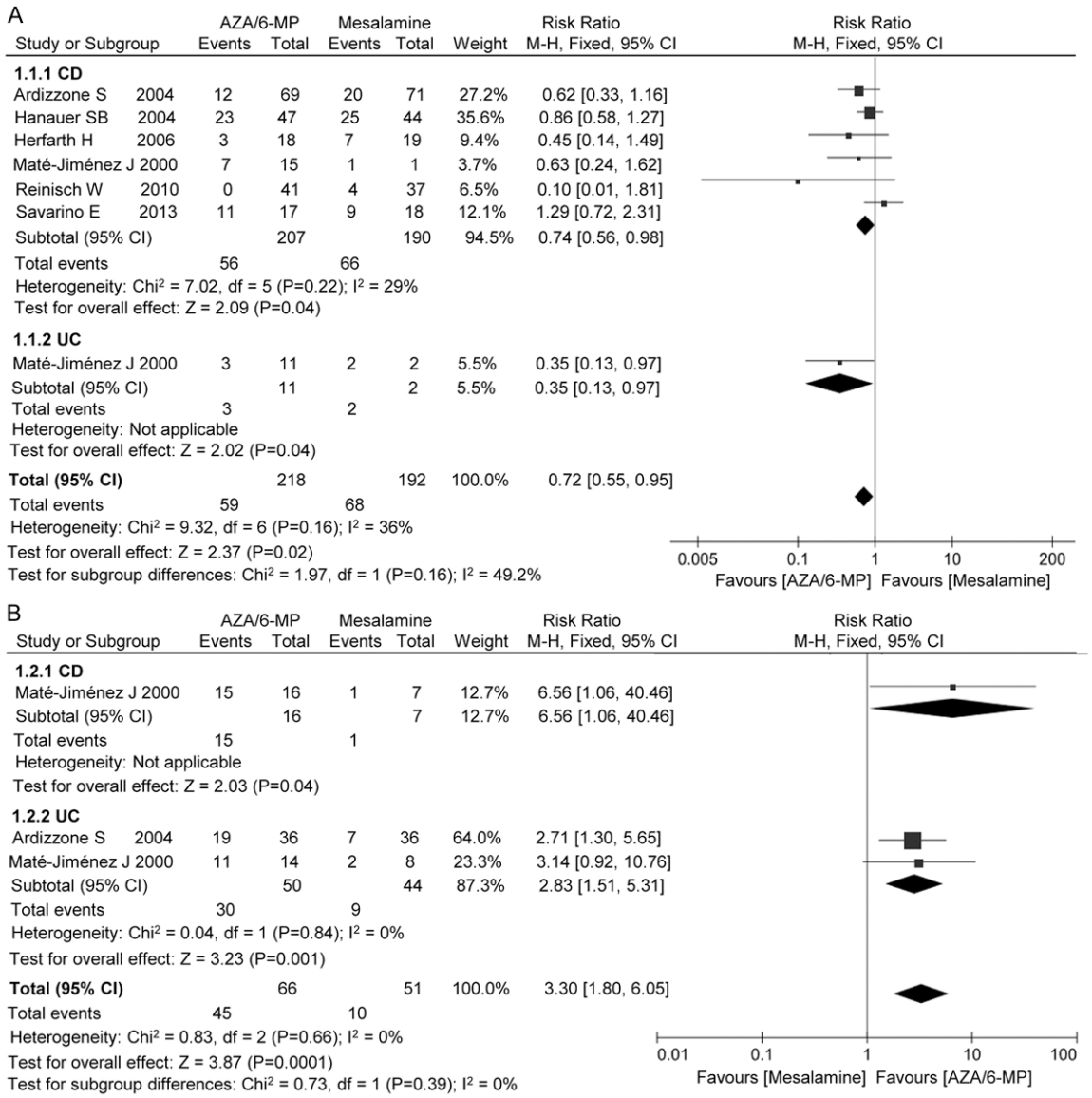

Figure 2. Meta-analysis of randomized clinical trials evaluating the efficacy of AZA/6-MP and mesalazine for the clinical relapse rate (A) and the remission rate (B).

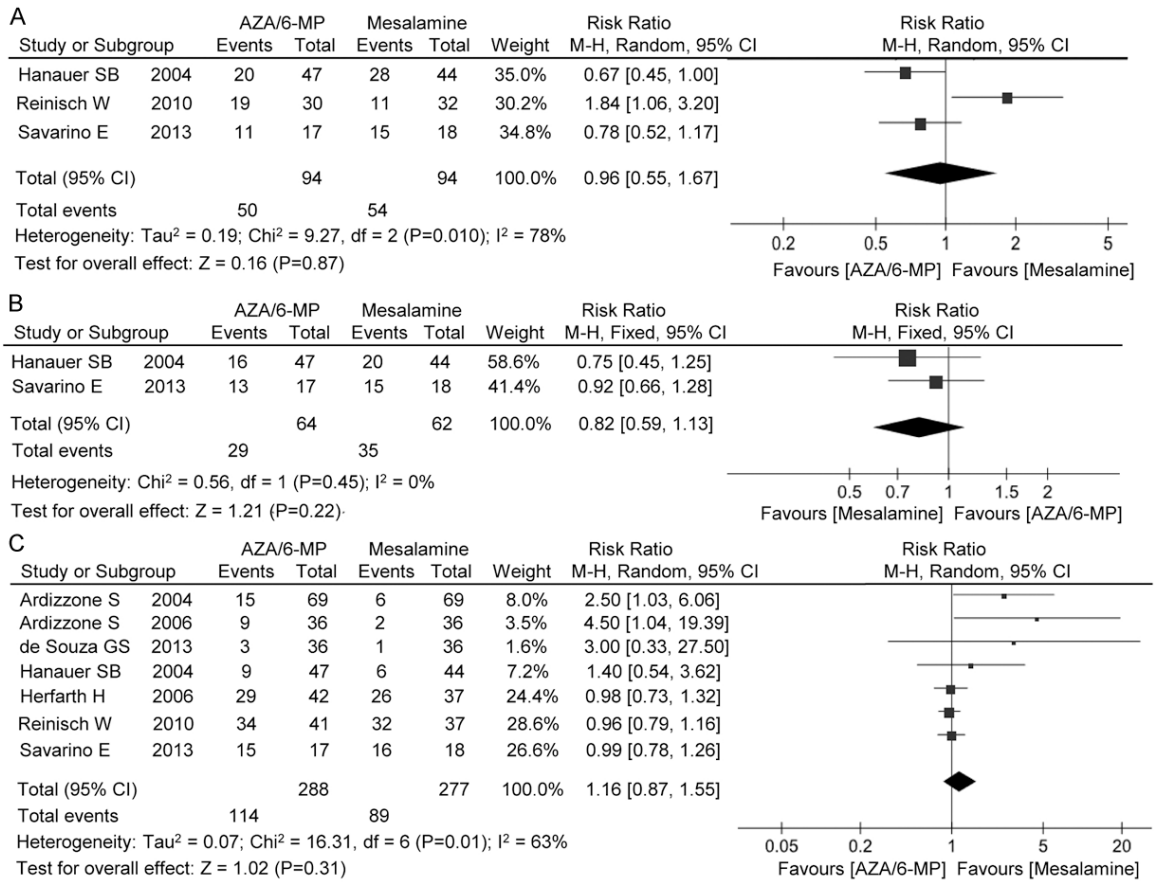

Figure 3. Meta-analysis of randomized clinical trials evaluating the efficacy of AZA/6-MP and mesalazine for the endoscopic recurrence rate (A) and the radiological recurrence rate (B) and the adverse rate (C) in IBD.

ies were included, with a total of 66 patients being treated with AZA/6-MP. Mean efficacy (pooled data) with AZA/6-MP was 68.2% and 19.6% in 5-ASA group. The RR for this comparison was 3.30 (95% CI, 1.80-6.05), results being statistically homogeneous (χ^2=0.83, P=0.66, I^2=0%). Subgroup analysis was used to evaluate the efficacy according to different disease. The pooled RR was 6.56 (95% CI, 1.06-40.46, n=1) for CD patients, and the pooled RR was 2.83 (95% CI, 1.51-5.31, n=2) for UC patients.

Meta-analysis of endoscopic recurrence rate and therapeutic failure rate

The endoscopic recurrence rate, radiological recurrence rate and therapeutic failure rate were only reported in CD patients. The results of the meta-analysis comparing AZA/6-MP vs. 5-ASA for the endoscopic recurrence rate in IBD are summarized in **Figure 3A**. Three studies were included, with a total of 94 patients being treated with AZA/6-MP. Mean efficacy (pooled data) with AZA/6-MP was 53.2% and 60.0% in 5-ASA group. The RR for this comparison was 0.96 (95% CI, 0.55-1.67), results being statistically heterogeneous (χ^2=9.27, P=0.010, I^2=78%).

Two studies reported radiological recurrence rate. The two studies were statistically homogeneous (χ^2=0.56, P=0.45, I^2=0%). The RR for this comparison was 0.82 (95% CI, 0.59-1.13, P=0.22), **Figure 3B**.

Assessment of safety

All the trials reported the adverse events [22-29]. The adverse events mainly included fever, headache, nasopharyngitis, leucopenia, proctalgia, nausea, and vomiting. The results of the meta-analysis comparing AZA/6-MP vs. 5-ASA for the incidence rate of adverse events in IBD are summarized in **Figure 3C**. Seven studies were included, with a total of 288 patients

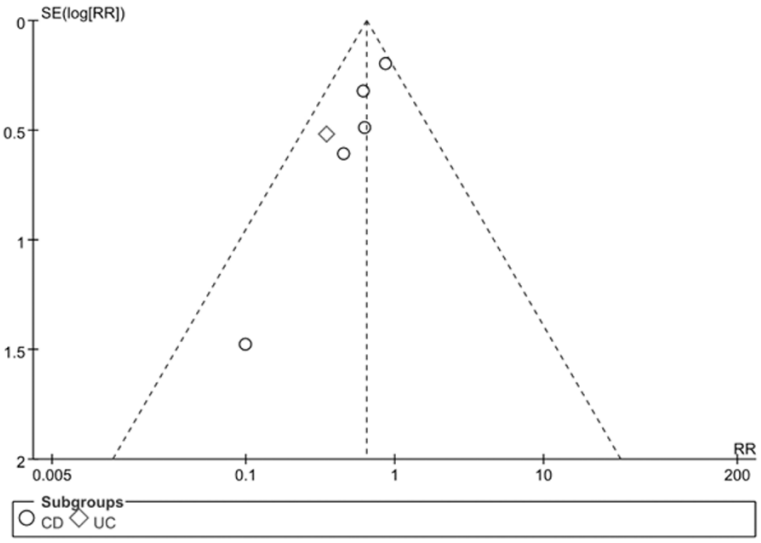

Figure 4. Begg's funnel plot for the assessment of publication bias.

being treated with AZA/6-MP. Mean efficacy (pooled data) with AZA/6-MP was 39.6% and 32.1% in 5-ASA group. The RR for this comparison was 1.16 (95% CI, 0.87-1.55), results being statistically heterogeneous (χ^2=16.31, P=0.01, I^2=63%).

Publication bias

A funnel plot was provided to assess the publication bias. The funnel plot was a slightly asymmetrical distribution (**Figure 4**).

Discussion

Significant advances have been made in the therapy of IBD and new treatments are being introduced. Randomized controlled trials showing that immunomodulatory agents, such as AZA and 6-MP, are effective in inducing and maintaining remission of IBD [30, 31]. Meta analysis [9] have also established the efficacy of AZA or 6-MP in reducing the usage of steroids and maintaining remission in IBD. Several open uncontrolled and retrospective studies showed the efficacy of AZA in active UC [9, 10, 13, 14], all reporting data suggested AZA or 6-MP's efficacy in patients with steroid resistant and steroid dependent UC.

The results of our meta-analysis comparing AZA/6-MP with 5-ASA for the clinical relapse rate in IBD (**Figure 1**), including six studies, showed a therapeutic benefit of AZA/6-MP, both overall (RR =0.72; 95% CI, 0.55-0.95) and, particularly, when AZA/6-MP was compared with 5-ASA in UC (RR=0.35; 95% CI, 0.13-0.97), results being statistically homogeneous. The remission rate of AZA/6-MP group was significantly higher than that of 5-ASA group (RR=3.30; 95% CI, 1.80-6.05, P=0.0001). These favorable results were confirmed by the non-controlled study: when these drugs were evaluated for the maintenance of remission of UC, the efficacy rate was 76% [32].

Although a benefit of safety has been suggested, the magnitude of benefit remains unclear because it always took a long time (several months of treatment with AZA/6-MP) to reach the maximal efficacy. Our meta-analysis comparing AZA/6-MP with 5-ASA for the adverse rate in IBD, which included only 288 patients treated with AZA/6-MP, could not find a statistically significant benefit of AZA/6-MP over 5-ASA (RR=1.16; 95% CI, 0.87-1.55). The low sample size of the studies (low number of studies and patients) could explain the lack of statistically significant differences for safety assessment.

Several meta-analysis have reported the efficacy of AZA/6-MP in patients with UC [33, 34]. A meta-analysis [34] showed the efficacy of AZA/6-MP to be superior for the maintenance of remission over placebo, but the literature search was up to the year 2006. Another study identified only four clinical trials and included studies up to the year 2003 and was published in a Japanese journal [33]. The pooled OR of the response to AZA compared with placebo was 1.45 and 2.26 for the induction and maintenance of remission, respectively [33]. However, few studies have directly compared thiopurine therapy efficacy in UC with that in CD. It was reported that AZA was more likely to achieve remission in patients with UC than with CD [14, 35]. However, Bastida et al. [36] showed that the benefit of AZA was independent of either CD or UC. Additionally, it was also reported that patients with UC treated with AZA responded similarly to their CD counterparts [37, 38] and AZA led to a similar reduction in

the number of hospitalizations and surgical operation in CD and UC [38]. In summary, it may be concluded that AZA seems at least as effective in UC as in CD patients, indicating thiopurine therapy is effective in treatment of IBD.

The low risks of bias of the trials were acknowledged according to the Jadad scale and the Cochrane criteria. All the trials stated random allocation and presented withdrawal and dropout and most of them were described in details. However, some limitations of the meta-analysis should be commented: relatively small number of trials and patients; uniform disease's severity; and varied definition of disease's response and remission to treatment among the studies.

Taken together, our meta-analysis has confirmed that AZA/6-MP is more effective than 5-ASA for the prevention of relapse and inducing remission in IBD. AZA/6-MP seem to be more safe than 5-ASA for the treatment of IBD, supporting the conclusion that thiopurine immunossuppresants represent the first option in the management of steroid-resistant and steroid-dependent UC. Additionally, the American Gastroenterology Association has concluded that patients with steroid-dependent UC should be treated with AZA or 6-MP [39].

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Disclosure of conflict of interest

None.

Abbreviations

IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; 6-MP, 6-mercaptopurine.

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