# A Systematic Review of the Clinical Effectiveness of Azathioprine in Patients with Ulcerative Colitis

Keiko Ohno,*,[a] Yukari Masunaga,[d] Ryuichi Ogawa,[b]
Masayuki Hashiguchi,[a,1] and Hiroyasu Ogata[c]

*Departments of Medication Use Analysis and Clinical Research,[a] Pharmacotherapy,[b] Biopharmaceutics,[c]
and Postgraduate School of Clinical Pharmacy,[d] Meiji Pharmaceutical University,
2–522–1 Noshio, Kiyose, Tokyo, 204–8588 Japan*

To clarify the effectiveness and safety of azathioprine (AZA) and 6-mercaptopurine (6MP) in the induction and maintenance of remission in ulcerative colitis (UC) by using a systematic review of published studies. Studies were searched for from within the 1966 to March 2003 MEDLINE database, Cochrane Library 2003 issue 1, and the 1981 to March 2003 Japana Centra Revuo Medicina database. References from published studies and reviews were also obtained. Randomized, placebo-controlled trials of oral AZA or 6MP therapy in adult patients with active or quiescent UC were included. Ratios for the induction and maintenance of remission, the steroid-sparing effect, and the incidence of adverse drug reactions (ADRs) were compared and evaluated between the two study arms and expressed by the odds ratio (OR) specific for the individual studies and the meta-analytic summary for the OR. We could find no randomized controlled trial for 6MP therapy. However, four clinical trials for AZA therapy were included in this meta-analysis. For the induction of remission, the pooled OR of the response to AZA therapy compared with placebo in active UC was 1.45 (95% Confidence Interval (CI): 0.68 to 3.08). For the maintenance of remission, the pooled OR for AZA therapy was 2.26 (95% CI: 1.27 to 4.01). The number needed to treat (NNT) to prevent one recurrence was 6 patients. The pooled OR for AZA therapy's ADRs compared with placebo was 2.11 (95% CI: 0.92 to 4.84). From the viewpoint of effectiveness and safety, this meta-analysis suggests that AZA might be useful in the maintenance of remission in UC patients.

**Key words**——ulcerative colitis; azathioprine; inducing remission; maintaining remission; meta-analysis

## INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are types of idiopathic inflammatory bowel disease (IBD) characterized by an up-regulated intestinal immune defense with an apparently uncontrolled inflammatory action. UC and CD are treated with currently available standard agents including symptomatic medications, sulfasalazine, and corticosteroids (steroids) to relieve the inflammatory process. These first-line agents are usually effective, except in patients with steroid resistancy or steroid dependency, for which additional medications are required. More than 50% of patients with CD have been found to be steroid resistant or steroid dependent.[2,3] Presently a combination therapy of a steroid and azathioprine (AZA) or 6-mercaptopurine (6MP) for the treatment of steroid-resistant and steroid-dependent cases of IBD is recommended in the guidelines that were published by the UC and CD research committee of the Ministry of Health and Welfare of Japan in 1998.[4] These agents are mainly recommended for the treatment of patients with chronic, active, and non-surgical stages of IBD in order to allow for discontinuation or reduction of the dose of steroids required for inducing or maintaining the remission.

The efficacy of immunosuppressives for the treatment of CD has been previously reported and the implementation of the therapy already established.[5,6] However there are only a few studies that have examined potential UC treatments. In this report, we assessed the effectiveness of AZA or 6MP in the induction and maintenance of UC remissions by using a systematic review of literature, including the use of the meta-analysis method.

## METHODS

**Literature Search**  We searched the literature using the MEDLINE (1966 to March 2003), Cochrane Library (2003 issue 1), and Japana Centra Revuo Medicina (1981 to March 2003) databases with the Medical Subject Headings (MeSH) "anti-

e-mail: k-kato@my-pharm.ac.jp

metabolites", "azathioprine", or "6-mercaptopurine" and "ulcerative colitis", and with a publication type of "randomized controlled trials". We also searched the literature using references from the studies and reviews obtained from the above-described databases.

**Inclusion Criteria**    Two investigators (KO, YM) applied the following inclusion criteria independently and where disagreements occurred, they were resolved by consensus. When methodology was inadequate or when description of data was insufficient, the study was excluded from this meta-analysis.

*Types of studies*: Randomized, single-blind or double-blind, placebo-controlled trials.

*Types of participants*: Patients greater than 18 years of age with active or quiescent UC were selected. The diagnosis of UC was made according to the criteria for each trial. Active UC was defined as the presence of serious or worsening UC symptoms. Quiescent UC, or disease in remission, was defined as the presence of mild or no symptoms in patients that had prior documented UC before the start of the study, regardless of the use of prophylactic medication.

*Types of intervention*: Oral AZA or 6MP therapy with minimum treatment durations of one month for induction of remission or three months for maintenance of remission.

*Types of outcome measures*: The two primary endpoints were: (1) the induction of remission that was categorized as entering clinical remission as defined by the studies, and (2) the maintenance of remission that was categorized as the maintenance of clinical remission as defined by the studies. The secondary endpoint was the presence of a steroid-sparing effect, which was defined as the ability to reduce the steroid dose while maintaining remission as per the criteria of each trial. Other outcomes were the adverse drug reactions (ADRs) induced by the AZA or 6MP treatments.

**Quality Assessment of Studies**    The quality analysis of the literature was performed according to the previously reported procedure of Jadad et al.[6] The analysis focused on the randomization, double blinding of the study design, and the description of withdrawals and dropouts in each study.

**Data extraction**    We extracted study design, the daily dose, therapy duration for AZA or 6MP, follow-up duration, and data on the concurrent therapy

with sulfasalazine, 5-aminosalicylic acid, and steroids. We recorded the number of patients with active UC that had induction of clinical remission, and the number of quiescent UC patients that maintained clinical remission. The number of patients able to taper steroids as a steroid-sparing effect was also recorded. Furthermore we extracted the number of patients who incurred each of the ADRs induced by the AZA or 6MP treatments.

**Statistical Analysis**    The active UC therapy and quiescent UC groups were not combined, and each group was analyzed separately. We used both random- and fixed-effects models to derive the pooled odds ratio (OR) from combinations of studies in order to allow for any heterogeneity across the studies. Heterogeneity among the studies was assessed using the Q statistic and by comparing both random- and fixed-effects estimates. In the case where there was no detectable heterogeneity among the OR estimates within the quartiles ($p > 0.10$) in both disease-state groups (i.e., active and quiescent), we used a standard fixed-effects model of meta-analysis to estimate the overall ORs and the 95% confidence intervals (CI) for the estimates of effectiveness of the drug therapy using the Excel 2000 software program (Microsoft Corporation, Redmond, WA, USA). For the primary analysis, the studies were weighted according to the total number of participants.

## RESULTS

Of the 81 studies we reviewed, 5 clinical trails met the inclusion criteria.[8—12] The included studies only dealt with AZA therapy, as we could find no studies that reported data for 6MP therapy. All quality assessment scores were greater than 4 as determined by the procedure reported by Jadad et al. One study[8] out of the total group that met the qualifications was excluded from our analysis because the data was judged to be a part of another study.[9]

Table 1 shows the summary of the 4 clinical studies used for the meta-analysis. A total of 244 patients were included in the analysis. The daily doses of AZA were 100 mg/day or 2.0—2.5 mg/kg/day, which are similar to the recommended doses that are used in Japan. Duration of therapy was 1 year for all studies. The concomitantly administered drugs were steroid and sulfasalazine or mesalazine in three studies,[10—12] and steroids in one study.[9]

**Induction of Remission in UC with AZA**    Of

Table 1.   Summary of Clinical Studies Included in the Meta-analysis

| Study | Study design | Immunosuppressive drug (dosage) | No. of subjects | Control | No. of subjects | Duration of therapy (year) | Coadministrated drug | Inducing remission | Maintaining remission | Steroid-sparing effect | Duration of follow-up | Assessment of quality (Jadad's score) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sood et al. 2002[11)] | DB | AZA (2.5 mg/kg/day) | 17 | placebo | 18 | 1 | SSZ, corticosteroids | NR | ○ | NR | Maintaining: 1 year | 5 |
| Sood et al. 2000[10)] | SB | AZA (2 mg/kg/day) | 25 | placebo | 25 | 1 | SSZ, PSL | ○ | ○ | NR | Inducing: Up to 1 year  Maintaining: 1 year | 5 |
| Hawthorne et al. 1992[9)] | DB | AZA (100 mg/day) | 40 | placebo | 39 | 1 | SSZ or MSZ, PSL | NR | ○ | NR | Maintaining: 1 year | 4 |
| Jewell et al. 1974[8)] | DB | AZA (2.5 mg/kg/day) | 40 | placebo | 40 | 1 | PSL | ○ | ○ | NR | Inducing: 1 month  Maintaining: 1 year | 4 |

The "Endpoints" header spans the Inducing remission, Maintaining remission, and Steroid-sparing effect columns.

DB: double blind, SB: single blind, AZA: azathioprine, SSZ: sulfasalazine, PSL: prednisolone, MSZ: mesalazine, NR: Not reported.

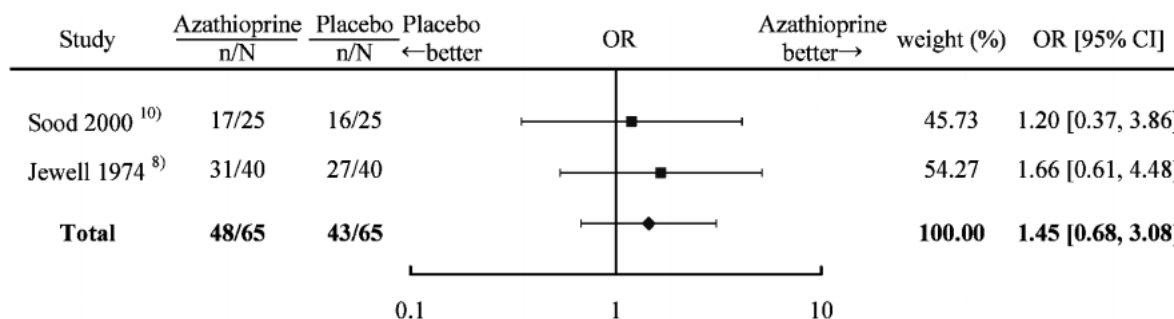| Study | Azathioprine n/N | Placebo n/N | Placebo ←better | OR | Azathioprine better→ | weight (%) | OR [95% CI] |
|---|---|---|---|---|---|---|---|
| Sood 2000 [10)] | 17/25 | 16/25 | | | | 45.73 | 1.20 [0.37, 3.86] |
| Jewell 1974 [8)] | 31/40 | 27/40 | | | | 54.27 | 1.66 [0.61, 4.48] |
| **Total** | **48/65** | **43/65** | | | | **100.00** | **1.45 [0.68, 3.08]** |

0.1    1    10

Fig. 1.   Effectiveness of Azathioprine in Inducing Remission in Patients with UC
OR: odds ratio, CI: confidence interval, $n/N$: number of patient remissions/number of total patients evaluated.

the 4 studies, two were randomized placebo-controlled trials[9,11)] that used AZA therapy in adult patients. The daily doses were 2—2.5 mg/kg/day. The pooled OR of the response to AZA therapy compared with placebo in active UC was 1.45 (95% CI: 0.68 to 3.08) (Fig. 1).

**Maintenance of Remission in UC with AZA**
All of the 4 studies were randomized placebo-controlled trials[9—12)] that used AZA therapy in adult patients. Four studies were single blind or double blind, and the follow-up period was 1 year. Daily doses were 2.0—2.5 mg/kg/day or 100 mg/day. All studies that examined remission maintenance in UC were designed so that patients who were in remission with AZA were randomized to receive a one-year course of either AZA or placebo. The pooled OR of the response to the AZA therapy compared with

placebo was 2.26 (95% CI: 1.27 to 4.01) (Fig. 2). The number needed to treat (NNT) to prevent one relapse was 6 patients.

**Steroid-sparing Effects with AZA**     There were no studies found on the steroid-sparing effects of AZA therapy during the 1-year follow-up.

**Adverse Drug Reactions with AZA**     Bone marrow suppression, gastrointestinal disturbance, mild acute pancreatitis, jaundice, hair loss, and rash were reported as the ADRs of AZA. The pooled OR of the ADRs of AZA therapy compared with placebo was 2.11 (95% CI: 0.92 to 4.84), indicating a tendency for AZA treatment to be worse than placebo treatment, although this was not found to be significant (Fig. 3).
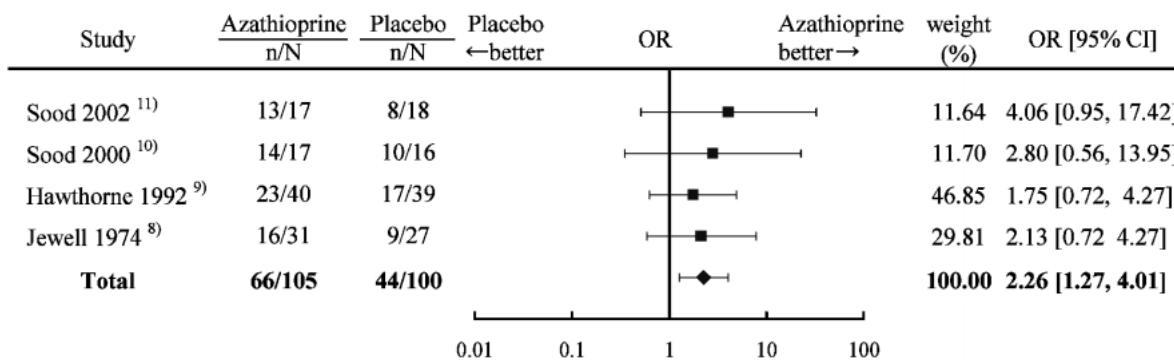
| Study | Azathioprine n/N | Placebo n/N | Placebo ←better | OR | Azathioprine better→ | weight (%) | OR [95% CI] |
|---|---|---|---|---|---|---|---|
| Sood 2002 [11] | 13/17 | 8/18 | | | | 11.64 | 4.06 [0.95, 17.42] |
| Sood 2000 [10] | 14/17 | 10/16 | | | | 11.70 | 2.80 [0.56, 13.95] |
| Hawthorne 1992 [9] | 23/40 | 17/39 | | | | 46.85 | 1.75 [0.72, 4.27] |
| Jewell 1974 [8] | 16/31 | 9/27 | | | | 29.81 | 2.13 [0.72 4.27] |
| **Total** | **66/105** | **44/100** | | | | **100.00** | **2.26 [1.27, 4.01]** |

0.01    0.1    1    10    100

Fig. 2.  Effectiveness of Azathioprine in Maintaining Remission in Patients with UC
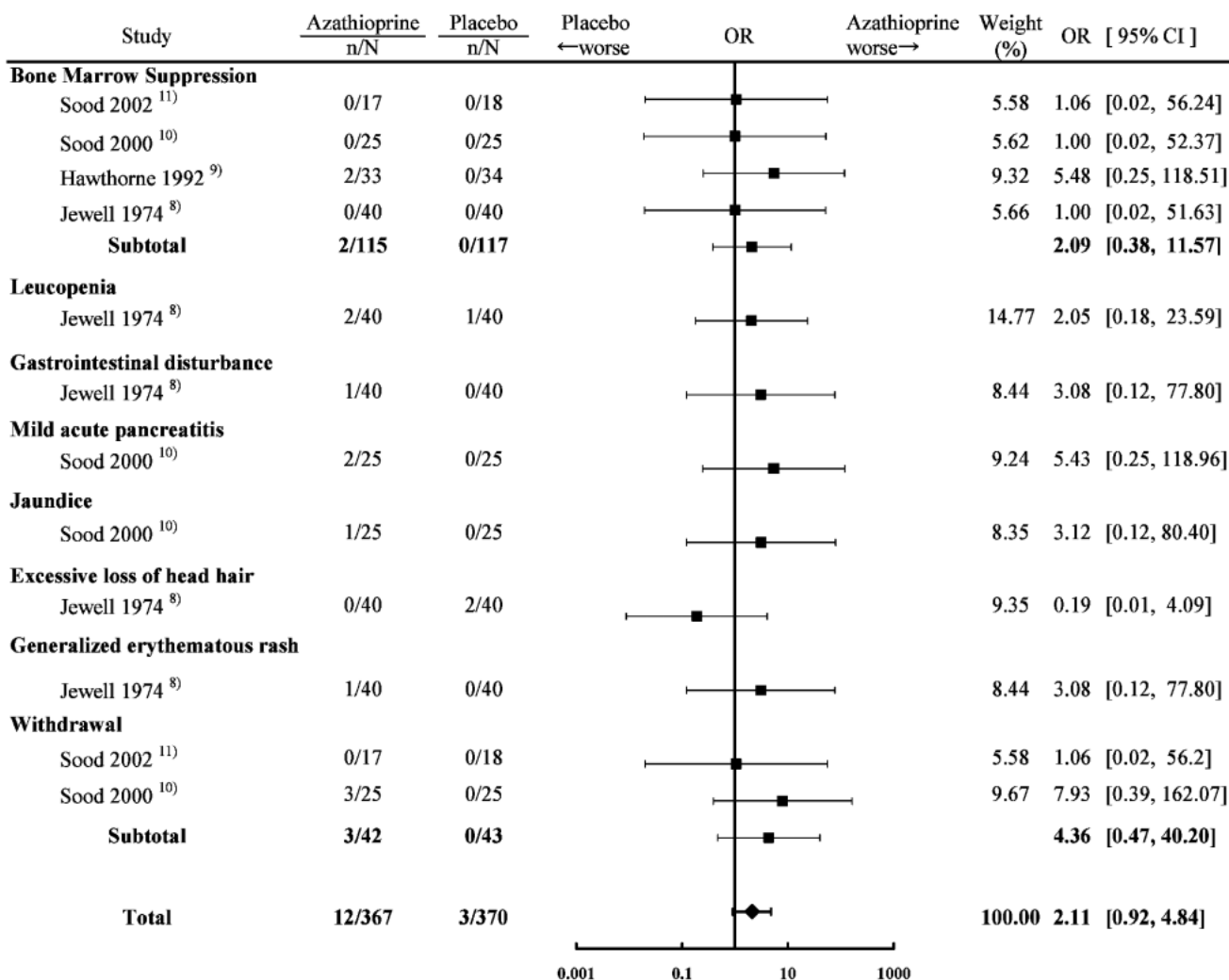OR: odds ratio, CI: confidence interval, $n/N$: number of patient remissions/number of total patients evaluated.

| Study | Azathioprine n/N | Placebo n/N | Placebo ←worse | OR | Azathioprine worse→ | Weight (%) | OR [95% CI] |
|---|---|---|---|---|---|---|---|
| **Bone Marrow Suppression** | | | | | | | |
| Sood 2002 [11] | 0/17 | 0/18 | | | | 5.58 | 1.06 [0.02, 56.24] |
| Sood 2000 [10] | 0/25 | 0/25 | | | | 5.62 | 1.00 [0.02, 52.37] |
| Hawthorne 1992 [9] | 2/33 | 0/34 | | | | 9.32 | 5.48 [0.25, 118.51] |
| Jewell 1974 [8] | 0/40 | 0/40 | | | | 5.66 | 1.00 [0.02, 51.63] |
| **Subtotal** | **2/115** | **0/117** | | | | | **2.09 [0.38, 11.57]** |
| **Leucopenia** | | | | | | | |
| Jewell 1974 [8] | 2/40 | 1/40 | | | | 14.77 | 2.05 [0.18, 23.59] |
| **Gastrointestinal disturbance** | | | | | | | |
| Jewell 1974 [8] | 1/40 | 0/40 | | | | 8.44 | 3.08 [0.12, 77.80] |
| **Mild acute pancreatitis** | | | | | | | |
| Sood 2000 [10] | 2/25 | 0/25 | | | | 9.24 | 5.43 [0.25, 118.96] |
| **Jaundice** | | | | | | | |
| Sood 2000 [10] | 1/25 | 0/25 | | | | 8.35 | 3.12 [0.12, 80.40] |
| **Excessive loss of head hair** | | | | | | | |
| Jewell 1974 [8] | 0/40 | 2/40 | | | | 9.35 | 0.19 [0.01, 4.09] |
| **Generalized erythematous rash** | | | | | | | |
| Jewell 1974 [8] | 1/40 | 0/40 | | | | 8.44 | 3.08 [0.12, 77.80] |
| **Withdrawal** | | | | | | | |
| Sood 2002 [11] | 0/17 | 0/18 | | | | 5.58 | 1.06 [0.02, 56.2] |
| Sood 2000 [10] | 3/25 | 0/25 | | | | 9.67 | 7.93 [0.39, 162.07] |
| **Subtotal** | **3/42** | **0/43** | | | | | **4.36 [0.47, 40.20]** |
| **Total** | **12/367** | **3/370** | | | | **100.00** | **2.11 [0.92, 4.84]** |

0.001    0.1    10    1000

Fig. 3.  Adverse Drug Reactions with Azathioprine as Compared with Placebo in Patients with UC
OR: odds ratio, CI: confidence interval, $n/N$: number of patients with adverse drug reactions/number of total patients evaluated.

## DISCUSSION

The efficacy of AZA and 6MP for use in CD has been already been reported and shown to be statistically effective.[5,6] In contrast, there has been no clarification on the efficacy of AZA and 6MP for the treatment of UC.

In this report, we attempted to evaluate the efficacy and safety of AZA and 6MP treatment for UC by us-

ing the meta-analysis method. However, as we were unable to find any randomized controlled trials for 6MP treatment, this meta-analysis only evaluated AZA's effect on the induction of remission, maintenance of remission and safety during the treatment of UC patients.

The results of this systematic review found 4 studies that met the inclusion criteria. The concomitantly administered drugs were steroid and sulfasalazine or mesalazine in three studies,[10—12] and steroids in one study.[9] Therefore, the meta-analysis was performed according to the types of concomitant drugs seen during the AZA therapy. The results of the meta-analysis showed that the pooled OR for maintaining remission during AZA therapy as compared with placebo was 2.31 (95% CI: 1.17 to 4.56) and the pooled OR for ADRs was 3.49 (95% CI: 1.04 to 11.73). Based on these results, we chose four clinical trials for the purpose of evaluating the outcomes.

We could find no evidence that AZA was effective in the induction of remission, but did find it was statistically effective in the maintenance of remission. The NNT needed to prevent one recurrence was estimated to be 6 patients. It has also been reported that AZA therapy in patients with CD is efficacious in the maintenance of remission, with a NNT estimated to be 7 patients.[6] Based on these results, AZA seems to have an equivalent efficacy for either UC or CD.

A steroid-sparing effect has been previously noted,[13] and in some cases, the steroids could be discontinued in patients taking AZA.[14] However, we were unable to examine AZA's steroid-sparing effects since there was no mention of this in the included studies. Therefore, further double-blind randomized controlled studies are needed to clarify which immunosuppressive therapies in patients with IBD have steroid-sparing effects.

Our results indicated that the incidence of ADRs, such as bone marrow suppression, gastrointestinal disturbance, mild acute pancreatitis, jaundice, and rash, tended to be higher, although not significantly, in patients treated with AZA as compared to those given placebo (Fig. 3). The ADRs induced by AZA and 6MP in patients with IBD can be categorized as being dose-dependent (e.g., bone marrow suppression with leucopenia and/or thrombocytopenia) or dose-independent (e.g., pancreatitis, allergic reactions or hepatitis).[15,16] All of the above-mentioned ADRs are reversible with early detection and cessation of drug administration. Other major concerns such as infections or malignancies associated with the immunosuppressive therapy have not been found to be of significance.[15—17]

In conclusion, this systematic review could not clarify either the effectiveness of AZA in the induction of UC remission or the steroid-sparing effects that have been seen previously in some UC patients. However, AZA might have clinical usefulness in the maintenance of remission for these patients. Further clinical trials are needed to clarify and confirm these findings.

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