Low dose of azathioprine is effective to induce and maintain remission in active Crohn disease
A prospective observational study
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Abstract
Azathioprine (AZA) 2 to 2.5 mg/kg/d is recommended for European patients with Crohn disease (CD), but several Asian studies reported that low dose of AZA was also effective to treat CD. To confirm these observations, we performed this prospective observational study to compare the efficacy and safety of low and standard doses of AZA in the treatment of active CD.

This was a prospective, open-labeled observational study. Two hundred twenty-six active CD patients were divided into two groups and treated with AZA 1.5 or 2.0 mg/kg/d respectively, combined with steroid therapy. Patients were followed up for 96 weeks. The complete remission (CR) rate, response rate, relapse rate, and adverse effect rate were assessed at weeks 24, 48, and 96 by intention-to-treat (ITT) analysis.

Azathioprine 1.5 mg/kg/d showed no significant difference compared with AZA 2 mg/kg/d in CR rate, response rate and relapse rate by ITT analysis at week 24, 48, or 96 (all \( P > .05 \)). Their adverse effect rates had no significant difference either (\( P > .05 \)). Up to 21.7\% (49/226) of the patients reported adverse events and 69.4\% (34/49) of them were myelosuppression.

Azathioprine 1.5 mg/kg/d combined with steroids is as effective as AZA 2.0 mg/kg/d to induce remission of active CD in the first 6 months, and to maintain remission of inactive CD in the first 2 years, without increasing the recurrence of active CD after clinical remission. The most common adverse effect is myelosuppression.

Abbreviations: AZA = azathioprine, CD = Crohn disease, CR = complete remission, ITT = intention-to-treat.

Keywords: azathioprine, Crohn disease, dose, efficacy, remission

1. Introduction
Inflammatory bowel disease (IBD) mainly manifests as ulcerative colitis (UC) and Crohn disease (CD). Abnormality of the immune system is observed in most IBD patients.\textsuperscript{[1]} Azathioprine (AZA) is a commonly used nonspecific immunosuppressant, and it was first introduced into the treatment of IBD about 40 years ago.\textsuperscript{[2]} Many studies have demonstrated its efficacy in the treatment of IBD. Currently, AZA is widely used to induce and maintain remission in IBD, especially in developing countries, because it is effective, much less expensive than infliximab, and can be orally administered. However, the initial indications for thiopurines have been progressively challenged by wider use of anti-TNF-alpha agents.\textsuperscript{[3]}

The consensus in Europe, Asia-pacific region, and China all recommend AZA as a first-line medicine for the maintenance therapy for IBD.\textsuperscript{[4–6]} The European Crohn’s and Colitis Organization (ECCO) recommends a dose of 2.0 to 2.5 mg/kg/d for the European population with IBD.\textsuperscript{[5]} The Asia-pacific consensus on Crohn disease states that AZA at a dose of 2 to 2.5 mg/kg/d is superior to 1 mg/kg/d.\textsuperscript{[6]} However, a lower dose of AZA (0.6–1.2 mg/kg/d) for the treatment of UC is recommended by another Asia-pacific consensus on UC and a Japanese study,\textsuperscript{[7,8]} which is quite confusing for physicians. In an open prospective study with no controls, Yu et al\textsuperscript{[9]} proved that low-dose (1.0–1.5 mg/kg/d) AZA improved mucosal healing effectively in patients with small bowel CD. A more recent study conducted in Hong Kong proved that low-dose (<2 mg/kg/d) AZA was effective to maintain remission in steroid-dependent UC patients, while the standard-dose (≥2 mg/kg/d) of AZA was associated with a more than 3-fold increased risk of leucopenia.\textsuperscript{[10]}

With the fact that the consensus from ECCO and Asia-pacific region are inconsistent with each other, and the clinical reports are controversial, it seems interesting work to investigate the real efficacy of low dose of AZA to treat Chinese IBD patients. In this prospective observational study with open labels, we compared the efficacy and safety of 1.5 and 2.0 mg/kg/d of AZA to treat active CD in a Chinese cohort.
2. Methods

2.1. Patient selection

This study was conducted from February 2014 to January 2015. A diagnosis of CD was made according to the Chinese consensus on inflammatory bowel disease and the ECCO consensus on CD. The Crohn Disease Activity Index (CDAI) was employed to evaluate the activity of CD, and a score ≥150 was defined as "active CD." All enrolled CD patients were undergoing systemic steroid therapy when enrolled. Patients with bowel obstruction, severe liver or renal dysfunction, heart failure, lymphoma, active tuberculosis, viral hepatitis, severe bacterial or viral infection, a history of AZA therapy in the past 3 months, resistant to steroid therapy, pregnant or trying to conceive, were excluded initially.

All patients provided written informed consent. This study was approved by the ethics committee of the Renji Hospital, School of Medicine, Shanghai Jiao Tong University.

2.2. Study design

Two hundred twenty-six enrolled patients first underwent a screening test with AZA (Imuran, Pro-metheus Laboratories, San Diego, CA) 25 mg/d for 7 days. Only those patients who showed great gastrointestinal tolerance, no allergic reaction, no myelosuppression symptoms or liver toxicity were entered into the subsequent study. Myelosuppression was defined as white blood count (WBC) <3.5 × 10^9/L for 2 successive tests or blood platelets <100 × 10^9/L. Liver toxicity was defined as alanine aminotransferase or aspartate aminotransferase >2 × upper limit of normal. Patients with myelosuppression symptoms or liver toxicity were half-dosed with AZA, and they were categorized into the “withdrawal” group in the final statistical analysis. If the myelosuppression symptoms or liver toxicity still persisted, the patients were switched to other therapies such as 6-mercaptopurine, methotrexate, or biological agents.

After fully informed about the therapeutic effects and adverse effects of AZA treatment of 1.5 and 2 mg/kg/d, patients were divided into 2 groups, and administered with AZA 1.5 (1.5 mg group) or 2 mg/kg/d (2.0 mg group) respectively (Fig. 1).

At the start, all patients were treated with the steroids combined with AZA to induce remission of active CD. Patients were treated with prednisone 0.75 to 1 mg/kg/d by oral administration. After complete remission (CR) was achieved, the steroid dose was tapered gradually by 2.5 (<20 mg/d) or 5 mg/wk (≥20 mg/d). Steroids were

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Figure 1. Flow of patients in the present study. AZA=azathioprine, CD=Crohn disease, CR=complete remission, PR=partial remission. *: data was no included in statistical analysis.
withdrawn by week 12 for most patients. For those patients who were unable to withdraw steroids by week 12, steroids were continued until week 16. By that time point, if their steroid doses were ≤50% of their initial doses and ≤10 mg/d, then they were considered as partial remission (PR) and continued with steroid therapy. Otherwise, they were considered “treatment failure” and quit the study. Steroid-dependent was defined as steroid dose kept ≥10 mg/d within 12 weeks or disease relapsed after steroid withdrawal within 12 weeks. Steroid-resistant was defined as steroid dose kept ≥0.75 mg/kg/d for over 4 weeks with no response (decline in the CDAI by < 70 scores), and those patients were not included in statistical analysis (Fig. 1). After steroid withdrawal, AZA was continued to maintain remission of CD until week 96, which was the end-point of the study.

2.3. Follow-up

Patients were followed up every 4 weeks until week 24, and every 12 weeks thereafter until week 96. Baseline clinical data of week 0 were collected, including routine blood tests with WBC counts, high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), liver biochemical parameters (such as aminotransferase and albumin), purified protein derivative test, chest X-ray, colonoscopy and computed tomography enterography or capsule endoscopy or double-balloon enteroscopy. Routine blood tests were conducted every 2 weeks until week 12, and every 4 weeks thereafter. Colonoscopy and computed tomography enterography were re-conducted at week 48 and 96.

The end-point of follow-up was defined as AZA therapy for 96 weeks, or other cases including relapse, AZA withdrawal, poor medication compliance (<70% of the dose), loss to follow-up, steroid-resistance, and misdiagnosis.

2.4. Evaluation of efficacy

CR was defined as complete withdrawal of steroids and CDAI < 150. PR was defined as steroid dose of 50% of its initial dose and ≤10 mg/d, and CDAI < 150. Failure was defined as those cases that did not reach CR or PR. The response rate = CR rate + PR rate. Relapse was defined as the recurrence of the symptoms, with increased CDAI > 150 by ≥70 after CR.

Intention-to-treat (ITT) analysis was performed to assess the response rate, relapse rate, and adverse effect rate of the 2 groups at week 24, 48, and 96. The denominator of ITT analysis was the number of patients in each group at week 4, not including those steroid-resistant. The numerator of ITT was the number of patients achieved CR or response at week 24, 48, or 96.

2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and discrete variables as count and percent (%). Continuous variables with a normal distribution were compared using the Student t test, and those with no normal distribution were compared with Mann–Whitney–Wilcoxon test. χ² and Fisher exact test were employed to compare discrete variables. P < .05 was considered statistically significant. All statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient characteristics

In total, 226 active CD patients were enrolled in the study at the start. In the initial AZA 2.5 mg/d screening test, 14 patients were excluded due to severe myelosuppression, and another 4 patients showed live toxicity. The remaining 208 patients were divided equally into 2 groups with different doses of AZA. The patient characteristics at baseline were listed in Table 1. Note that 8 cases in 1.5 mg group and 6 cases in 2.0 mg group were steroid-resistant and 1 case in 2.0 mg group were lost to follow-up in the first 4 weeks. They did not meet the criteria of study design, so they were excluded in statistical analysis. Thereby, the baseline numbers of patients were 96 in 1.5 mg group and 97 in 2.0 mg group at week 4. There were no significant differences between the 2 groups, including age, sex, duration of disease, hs-CRP, ESR, serum albumin, WBC counts, and CDAI scores. Fourteen of 208 patients (6.7%) were lost to follow-up by week 96 (Fig. 1). One hundred fifty-five, 133, and 121 patients (74.5%, 63.9%, and 58.2%) were followed up until weeks 24, 48, and 96 respectively. Ten and 14 patients experienced relapses by weeks 48 and 96 respectively. Thirty-one patients withdrew their AZA therapy because of severe adverse effects such as myelosuppression (20 cases) and liver toxicity (7 cases) (Fig. 1) (Table 2).

By week 96, several clinical and biological parameters were re-evaluated. The results showed that there were no significant differences in hs-CRP, serum albumin, ESR, WBC counts, or CDAI scores (all P > .05) between the 2 groups.

3.2. Efficacy evaluation

At week 24, the CR rate showed no significant difference by ITT analysis (20.8% vs 28.9%, P = .20). The response rate showed no significant difference by ITT analysis (81.3% vs 79.4%, P = .74) either (Table 2). These results indicated that AZA 1.5 mg/kg/d combined with steroids was as effective as AZA 2.0 mg/kg/d to induce remission of active CD in the first 6 months of AZA administration.

At week 48, the CR rate showed no significant difference by ITT analysis (20.8% vs 25.8%, P = .42). The response rate showed no significant difference by ITT analysis (70.8% vs 67.0%, P = .57) either (Table 2). These results indicated that AZA 1.5 mg/kg/d was as effective as AZA 2.0 mg/kg/d to maintain remission of inactive CD in the first year of AZA administration.

| Baseline and end-point characteristics of patients with active Crohn disease. |
|---------------------------------|------------------|------------------|-----|
| **Baseline** & **1.5mg group N=96** | **2.0mg group N=97** | **P** |
| Sex | Male | 20 | 26 | 0.31 |
| | Female | 32 | 28 | 0.05 |
| Age, mean±SD, y | 32.1±11.0 | 37.6±11.9 | 0.33 |
| Duration, mean±SD, y | 2.9±2.1 | 2.1±1.8 | 0.50 |
| hs-CRP, mean±SD, mg/L | 16.1±3.2 | 13.5±3.0 | 0.15 |
| ESR, mean±SD, mm/h | 28.1±6.4 | 30.2±5.6 | 0.82 |
| Serum albumin, mean±SD, g/L | 29.7±5.1 | 27.5±5.2 | 0.72 |
| WBC counts, mean±SD, ×10⁹/L | 8.2±2.2 | 7.7±1.1 | 0.54 |
| CDAI scores, mean±SD | 242.5±60.4 | 256.2±62.9 | 0.65 |
| End-point (wk 96) | N=64 | N=57 | 0.02 |
| hs-CRP, mean±SD | 4.2±2.1 | 2.5±1.9 | 0.13 |
| ESR, mean±SD | 15.1±7.6 | 15.8±4.2 | 0.73 |
| Serum albumin, mean±SD | 36.8±7.7 | 39.8±5.3 | 0.14 |
| WBC counts, mean±SD, ×10⁹/L | 5.2±1.3 | 6.4±1.1 | 0.63 |
| CDAI scores, mean±SD | 75.8±20.2 | 62.7±25.2 | 0.49 |

hs-CRP = high-sensitivity C-reactive protein, ESR = erythrocyte sedimentation rate, WBC = white blood cell, CDAI = Crohn disease activity index.
Gastroenterological Association Institute recommends that AZA 1.5mg/kg/d was as effective as AZA 2.0mg/kg/d to maintain remission in the first 2 years of AZA administration. The relapse rate showed no significant difference by ITT analysis by week 48 (4.2% vs 6.2%, P = .53) or week 96 (5.2% vs 9.3%, P = .28) (Table 2). These results indicated that AZA 1.5 mg/kg/d did not increase the recurrence of active CD after clinical remission compared with AZA 2.0 mg/kg/d in the first 2 years of AZA administration.

### 3.3. Adverse effects

Eighteen cases of adverse effects (14 cases of severe myelosuppression and 4 cases of liver toxicity) were observed in the initial AZA 2.0 mg/kg/d administration. The relapse rate showed no significant difference by ITT analysis by week 96 compared with AZA 2.0 mg/kg/d in the first 2 years of AZA administration.

| Week 24 | CR rate (%) | Response rate (%) | Relapse rate (%) |
|---------|-------------|-------------------|-----------------|
|         | N = 96      | n/N               |                 |
| CR rate | 20.8        | 20/96             |                 |
| Response rate | 81.3 | 78/96             |                 |
| Relapse rate | 4.2 | 4/96              |                 |

| Week 48 | CR rate (%) | Response rate (%) | Relapse rate (%) |
|---------|-------------|-------------------|-----------------|
|         | N = 97      | n/N               |                 |
| CR rate | 20.8        | 20/97             |                 |
| Response rate | 70.8 | 68/97             |                 |
| Relapse rate | 4.2 | 4/97              |                 |

| Week 96 | CR rate (%) | Response rate (%) | Relapse rate (%) |
|---------|-------------|-------------------|-----------------|
|         | N = 97      | n/N               |                 |
| CR rate | 26.0        | 25/97             |                 |
| Response rate | 66.7 | 64/97             |                 |
| Relapse rate | 5.2 | 5/96              |                 |

CR = complete remission, ITT = intention-to-treat.

### 4. Discussion

It is an intricate work for physicians to balance the benefits and risks in medical treatment of IBD. Certain studies and meta-analyses reported that higher levels of 6-thioguanine nucleotide (6-TGN), one of the metabolites of AZA, were associated with a higher rate of clinical remission of IBD and higher rate of severe adverse events such as myelosuppression, liver toxicity, arthritis, pancreatitis, etc. [12,13] Consensus in America, Europe, Asia-Pacific region, and China propose different suggestions of the dose of AZA in the treatment of IBD. [5–7,14] American Gastroenterological Association Institute recommends that AZA at a dose of 2.0 to 3.0 mg/kg/d is most effective for treating CD. [14] The ECCO recommends a dose of 2.0 to 2.5 mg/kg/d for most European population with IBD. [5] Asian Pacific Association of Gastroenterology recommends that lower starting doses in Asian compared with Caucasian populations, along with close monitoring of complete blood count and liver function in UC patients. [15] For CD patients, Asian Pacific Association of Gastroenterology recommends that AZA at a dose of 2.0 to 2.5 mg/kg/d is superior to 1 mg/kg/d, and the dose of thiopurine should be optimized for the individual, according to toxicity and tolerability, and be different between individuals. [16] The latest version of Chinese consensus on IBD proposes a wider dose range (1.0–2.5 mg/kg/d) and suggests close monitoring during administration. [15] The reason of difference between these consensuses still remains unclear, may be partly attributed to the variety of ethnic groups and genotypes, lower tolerability of Asians to high dose of AZA, and higher sensitivity of Asians to low dose of AZA. [10,16] A randomized, double-blind, controlled withdrawal trial in CD patients in long-term remission on AZA conducted in France and Belgium proved that AZA 1.7 ± 0.4 mg/kg/d was superior to placebo in maintenance therapy. [17] A multicenter prospective trial performed in Japan involving 22 patients with UC with the presence of remission for 3 months or more found that low dose of AZA (50 mg/d, 0.6–1.2 mg/kg/d) could maintain remission in 88% of the patients at 6 months. [18] Also, a previous study reported that a 24-month low-dose (1.0–1.5 mg/kg/d) AZA regimen as maintenance treatment in moderate small bowel CD could achieve a high mucosal healing rate. [19] Another study reported that low-dose (<2 mg/kg/d) AZA proved to be effective to maintain remission in steroid-dependent UC patients, while the standard-dose (≥2 mg/kg/d) of AZA was associated with a more than 3-fold increased risk of leucopenia. [10] More recently, a prospective randomized study on standard-dose (2 mg/kg/d) versus low-dose AZA (1 mg/kg/d) in the treatment of CD in a Chinese population indicated that AZA 2 mg/kg/d achieved significantly higher CR rate and response rate than 1 mg/kg/d with lower recurrence rate and no increased adverse events. [18] In the present study, we enrolled 226 active CD patients to compare the remission rate and relapse rate of 2 different doses of AZA, with a follow-up period up to 96 weeks. We only employed ITT analysis to assess the efficacy of different doses of AZA to treat active CD. Theoretically, per-protocol analysis has a better reference value for a noninferiority study, but ITT analysis is more in line with the actual application, especially for this descriptive and prospective study. [18] Our results showed that AZA 1.5 mg/kg/d had a comparable CR rate and response rate to that of AZA 2 mg/kg/d at weeks 24, 48, and 96, by ITT analysis.
(all $P > .05$). We also noted that there was a clear tendency to a lower CR rate at week 24 in 1.5 mg group, though the ITT analysis showed no statistical difference. It is likely that there may be a statistical error type beta due to the small sample size of our study, and a proper way to get a more solid conclusion is to expand the sample size. Benmassaoud et al.$^{[19]}$ reported that adult CD patients with normal thiopurine S-methyltransferase (TPMT) levels starting at full dose of AZA (2–2.565 mg/kg) had better clinical response compared with patients starting at low dose of AZA (69% vs 27%, $P = .0542$), though there was no statistical difference, which was quite similar to our results. Furthermore, the relapse rate between AZA 1.5 and 2.0 mg group showed no statistically significant difference by ITT analysis (all $P > .05$). Thus, we could safely conclude that AZA 1.5 mg/kg/d combined with steroids was as effective as AZA 2.0 mg/kg/d to induce remission of active CD in the first 6 months, and to maintain remission of inactive CD in the first 2 years, without increasing the recurrence of active CD after clinical remission. However, much longer observation up to 3 to 5 years may reveal a lower remission rate and higher recurrence rate in 1.5 mg group. Our study provided a strong support for the Asian-Pacific consensus and Chinese consensus for their recommendations of lower dose of AZA in the treatment of CD. And, we recommend that clinical readers of this article in Asia could try to start with lower initial dose of AZA for their CD patients, instead of a high initial dose of 2.0 to 2.5 mg/kg/d.

We also noted that some latest systemic reviews in the Cochrane Database had different suggestions about AZA in the treatment of CD. One review points out that low-quality evidence suggests that AZA is more effective than placebo to maintain the remission of inactive CD, and its use is limited by adverse effects.$^{[20]}$ Another review suggests that AZA and 6-mercaptopurine have no advantage over placebo for induction of remission or clinical improvement in active CD. Antimetabolite therapy may allow patients to reduce the consumption of steroids. Adverse events are more common in patients receiving antimetabolites although differences with placebo were not statistically significant.$^{[21]}$ A third review finds that purine analogues may be superior to placebo for maintenance of surgically induced remission in inactive CD patients, although this is based on 2 small studies.$^{[22]}$ Although these systemic reviews have different opinions with our study due to different population of enrolled patients, they provide the latest convincing opinions of experts about AZA in the treatment of CD and should be paid attention to.

It takes a mean time of 3.1 months for AZA to show its efficacy.$^{[23]}$ Studies indicated that the odds ratio of efficacy increased significantly after at least 17 weeks of AZA treatment.$^{[24]}$ Therefore, in our study, the efficacy was evaluated at weeks 24, 48, and 96 to investigate its long-term outcome. At least 4 years of AZA treatment was recommended for those patients who could maintain clinical remission after steroid withdrawal.$^{[15]}$ Considering its potential risk of lymphoma and severe infection, patients should consult with their physicians if they wish to continue with AZA. Most studies suggest that the benefits of long-term use of AZA outweigh its potential risk of lymphoma.$^{[25]}$ In this study, no lymphoma was discovered during 96 weeks of follow-up.

Many adverse effects have been observed in patients treated with AZA, including allergy, gastrointestinal discomfort, pancreatitis, arthritis, facial rashes, and flu-like symptoms. The most common side effect is myelosuppression. High doses (2 mg/kg/d) of AZA increase the incidence of myelosuppression in IBD.$^{[26]}$ A more recent review article revealed that myelosuppression was the most commonly observed adverse event and it was dose-dependent.$^{[27]}$ In our study, 49 of 226 patients (18 in screening test, 31 in subsequent study) had adverse event, including 34 cases of severe myelosuppression and 11 cases ofilexicity by week 96. No arthritis or pancreatitis was observed in either group. There was no significant difference in adverse effects between the 2 groups ($P = .17$). Thus, in our cohort, AZA 1.5 mg/kg/d seemed not to significantly reduce the incidence of adverse effects compared with AZA 2 mg/kg/d in the first 2 years. However, much longer observation up to 3 to 5 years may reveal a lower adverse effect rate in 1.5 mg group.

Our study had several limitations. First, this was a prospective, single-center study with open labels that enrolled only 226 patients. A multicenter double-blind, randomized prospective cohort study with more patients is warranted to draw more convincing conclusions. Second, the follow-up discontinued after 96 weeks. More results might be revealed if the follow-up lasted up to 3 to 5 years or even longer, such as opportunistic infections, aplastic anemia, lymphoma, and so on. Third, the ECCO recommends that the TPMT genotype should be examined before AZA treatment for Western populations; and for patients with TPMT mutations, AZA should be avoided or used under strict monitoring.$^{[15]}$ For the Chinese Han population, the TPMT genotype was highly specific to predict the incidence of myelosuppression; however, its sensitivity was rather low.$^{[28]}$

Considering its limitations, the TPMT genotype was not examined before the study. Determination of the phenotype of TPMT would lead to a reduced dose to the minimum efficient level.$^{[29]}$ Instead, we employed the AZA 2.5 mg/d screening test to exclude a part of patients with low tolerance in the first 7 days. Recent studies indicated that a new biomarker NUDT15 may be more sensitive than TPMT to predict the risk of AZA-induced leucopenia.$^{[30,31]}$ Fourth, the 6-TGN concentration in blood was not determined, while higher levels of 6-TGN concentration were reported to be associated with a higher rate of clinical remission of IBD.$^{[12]}$ Finally, 14 of 208 patients (6.7%) were lost to follow-up by week 96 with unknown reasons. The rate of loss to follow-up was acceptable, but it still had influence of some degree to the final conclusions, because those patients might have severe adverse effects, treatment failure, and relapse of disease, so the actual rates of adverse effects, treatment failure, and relapse might be higher than those of observation, and the actual rates of CR and response might be lower than those of observation.

5. Conclusions

In summary, AZA 1.5 mg/kg/d combined with steroids is as effective as AZA 2.0 mg/kg/d to induce remission of active CD in the first 6 months, and to maintain remission of inactive CD in the first 2 years, without increasing the recurrence of active CD after clinical remission. The most common adverse effect is myelosuppression.

Author contributions

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References

[1] Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology 1998;115:182–205.
[2] Brooke BN, Javett SL, Davison OW. Further experience with azathioprine for Crohn’s disease. Lancet 1970;2:1030–3.
[3] Motter G, Schoepfer AM, Juillerat P, et al. Experts opinion on the practical use of azathioprine and 6-mercaptopurine in inflammatory bowel disease. Inflamm Bowel Dis 2016;22:2733–47.
[4] Ouyang Q, Hu PJ, Qian JM, et al. Consensus on the management of inflammatory bowel disease in China in 2007. J Dig Dis 2008;9:52–62.
[5] Dignass A, Asche GV, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn’s disease: current management. J Crohns Colitis 2010;4:28–62.
[6] Ooi CJ, Makihara GK, Hilti I, et al. Asia-Pacific consensus statements on Crohn’s disease. Part 2: Management. J Gastroenterol Hepatol 2016;31:56–68.
[7] Ooi CJ, Fock KM, Makharia GK, et al. The Asia-Pacific consensus on ulcerative colitis. J Gastroenterol Hepatol 2010;25:453–68.
[8] Hibi T, Naganuma M, Kitahora T, et al. Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. J Gastroenterol 2003;38:740–6.
[9] Yu LF, Zhong J, Cheng SD, et al. Low-dose azathioprine effectively improves mucosal healing in Chinese patients with small bowel Crohn’s disease. J Dig Dis 2014;15:180–7.
[10] Shi HY, Chan FK, Leung WK, et al. Low-dose azathioprine is effective in maintaining remission in steroid-dependent ulcerative colitis: results from a territory-wide Chinese population-based IRD registry. Ther Adv Gastroenterol 2016;9:449–56.
[11] Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn’s disease: definitions and diagnosis. J Crohns Colitis 2010;4:7–27.
[12] Goldenberg BA, Raw throne P, Bernstein CN. The utility of 6-thioguanine metabolite levels in managing patients with inflammatory bowel disease. Am J Gastroenterol 2004;99:1744–8.
[13] Moreau AC, Paul S, Del Tedesco E, et al. Association between 6-thioguanine nucleotides levels and clinical remission in inflammatory disease: a meta-analysis. Inflamm Bowel Dis 2014;20:464–71.
[14] Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association/American Gastrointestinal Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006;130:940–87.
[15] Hu PJ. The consensus on the diagnosis and management of inflammatory bowel disease of China (2012, Guangzhou) (in Chinese). Chin J Gastroenterol 2012;17:763–81.
[16] Ueno F, Matsui T, Matsumoto T, et al. Evidence-based clinical practice guidelines for Crohn’s disease, integrated with formal consensus of experts in Japan. J Gastroenterol 2013;48:31–72.
[17] Lemann M, Mary JY, Colombel JF, et al. A randomized, double-blind, controlled withdrawal trial in Crohn’s disease patients in long-term remission on azathioprine. Gastroenterology 2005;128:1812–8.
[18] Zang Y, Xia JJ, Xiao P, et al. Standard-dose versus low-dose azathioprine in the treatment of Crohn’s disease: a prospective randomized study. J Dig Dis 2016;17:747–55.
[19] Bennmassaoud A, Xie X, Ayaafi M, et al. Thiopurines in the management of Crohn’s disease: safety and efficacy profile in patients with normal TPMT activity—a retrospective study. Can J Gastroenterol 2016;2016:1034834.
[20] Chande N, Patton PH, Tsoulis DJ, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn’s disease. Cochrane DB Syst Rev 2015;10.
[21] Chande N, Townsend CM, Parker CE, et al. Azathioprine or 6-mercaptopurine for induction of remission in Crohn’s disease. Cochrane Database Syst Rev 2016;10.
[22] Gordon M, Taylor K, Akobeng AK, et al. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn’s disease. Cochrane Database Syst Rev 2014;CD010233.
[23] Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn’s disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980;302:981–7.
[24] Pearson DC, May GR, Fick GH, et al. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med 1995;123:132–42.
[25] Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn’s disease: benefits outweigh the risk of lymphoma. Gastroenterology 2000;118:1018–24.
[26] Connell WR, Kamm MA, Ritchie JK, et al. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut 1993;34:1081–5.
[27] Dubinsky MC. Azathioprine, 6-mercaptopurine in inflammatory bowel disease: pharmacology, efficacy, and safety. Clin Gastroenterol Hepatol 2004;2:731–43.
[28] Cao Q, Zhu Q, Shang Y, et al. Thiopurine methyltransferase gene polymorphisms in Chinese patients with inflammatory bowel disease. Digestion 2009;79:58–63.
[29] Willert N, Roblin X. Trend towards dose reduction of azathioprine as monotherapy in inflammatory bowel disease patients: what about for combination therapy? Therap Adv Gastroenterol 2017;10:5–10.
[30] Lee YJ, Hwang EH, Park JH, et al. NUDT15 variant is the most common variant associated with thiopurine-induced early leukopenia and alopecia in Korean pediatric patients with Crohn’s disease. Eur J Gastroenterol Hepatol 2016;28:475–8.
[31] Zhu X, Wang XD, Chao K, et al. NUDT15 polymorphisms are better than thiopurine S-methyltransferase as predictor of risk for thiopurine-induced leukopenia in Chinese patients with Crohn’s disease. Aliment Pharmacol Ther 2016;44:967–75.