CURRENT USE OF IMMUNOSUPPRESSIVE AGENTS IN INFLAMMATORY BOWEL DISEASE PATIENTS IN EAST CHINA

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AIM: To investigate immunosuppressive agents used to treat inflammatory bowel disease (IBD) in East China.

METHODS: A retrospective review was conducted, involving 227 patients with IBD admitted to Sir Run Run Shaw Hospital, College of Medicine Zhejiang University from June 2000 to December 2007. Data regarding demographic, clinical characteristics and immunosuppressants usage were analyzed.

RESULTS: A total of 227 eligible patients were evaluated in this study, including 104 patients with Crohn's disease and 123 with ulcerative colitis. Among the patients, 61 had indications for immunosuppressive agents use. However, only 21 (34.4%) received immunosuppressive agents. Among the 21 patients, 6 (37.5%) received a subtherapeutic dose of azathioprine with no attempt to increase the dosage. Of the 20 patients that received immunosuppressive agent treatment longer than 6 mo, 15 patients went into remission, four patients were not affected and one relapsed. Among these 20 patients, four patients suffered from myelotoxicity and one suffered from hepatotoxicity.

CONCLUSION: Immunosuppressive agents are used less frequently to treat IBD patients from East China compared with Western countries. Monitoring immunosuppressive agent use is recommended to optimize dispensation of drugs for IBD in China.

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Key words: Inflammatory bowel disease; Immunosuppressive agents; Azathioprine

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic disorder of the gastrointestinal tract. There have been no large scale epidemiological studies on the incidence and prevalence of IBD in China, but reports indicate that rates are increasing. According to data collected from multiple hospitals, the prevalence rate of UC and CD can be speculatively estimated to be 11.6/10⁵ and 1.4/10⁵, respectively; however, the numbers may be underestimated[1]. An investigation from one hospital showed that the definitive cases of IBD during the past 10 years have increased five-fold[2].

Immunosuppressive agents, such as Azathioprine (AZA), play an essential role in drug therapy of IBD. Evidence-based medicine has shown that immunosuppressive agents can control active inflammation, allow for the withdrawal of steroids, and ultimately maintain long-term remission of IBD[3-5]. However, great interpatient variability has been found when assessing the efficacy and toxicity of these drugs. In the treatment of active disease, about 2/3 of the patients achieve remission, but this results is not achieved in approximately 15% of cases, and serious...
drug toxicity leads to cessation of therapy in 9%-28% of patients, such as myelotoxicity and hepatotoxicity. Uncertainty regarding the risk of interpatient variability and serious drug toxicity prevent the use of AZA and other immunosuppressants, and therefore affects the quality of care in IBD patients. Domestically, the paradox is quite a problem. Currently, there are no reports about the status of usage of AZA and other immunosuppressive agents in Chinese IBD patients.

Sir Run Run Shaw Hospital is a teaching hospital affiliated to Zhejiang University, China. Together with 12 other large hospitals and numerous smaller district hospitals, it provides health care to 48 million people living in Zhejiang Province in eastern China. Our IBD study group has set up an IBD database to collect IBD patients’ data in East China. The purpose of the current study was to do a retrospective study of the therapeutic status of immunosuppressive agents, such as AZA used in patients with IBD in hospitals, to investigate the therapeutic implications of IBD in eastern China, to arouse the attention of clinicians, to apply immunosuppressive drugs optimally and to enhance the quality of therapy delivered to IBD patients.

MATERIALS AND METHODS

Subjects
IBD patients admitted to Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, from June 2000 to December 2007, were enrolled in this study.

The diagnosis of IBD was confirmed by the criteria established by Chinese Society of Gastroenterology in 2000 and the guidelines issued by the Clinical Services Committee of the British Society of Gastroenterology (BSG) in 2004. Patients not under the care of a gastroenterologist were excluded.

Data collection
A retrospective review was performed. Clinical data on demographic information, clinical characteristics of IBD patients, as well as endoscopic, radiologic, surgical and pathological records, confirmed diagnoses, duration and severity of disease, and use of immunomodulatory agents were collected from the inpatient and follow-up clinic visit records and collated in an IBD database.

Statistical analysis
The data were expressed as mean values, and the enumeration data were expressed by percentages. All statistical analyses were performed by SPSS V 13.0 (Statistical Product and Service Solutions).

RESULTS

Patient characteristics
According to the inclusion and exclusion criteria, 104 patients with CD and 123 patients with UC were enrolled in the study. All the patients were Han Chinese.

UC was categorized by extent, activity and severity of disease. Extent of disease at diagnosis was defined macroscopically by the proximal limit of inflammation at colonoscopy and was divided into the following four categories: (1) Proctitis, inflammation confined to the rectum only; (2) Distal colitis, inflammation involving to the rectum and sigmoid colon; (3) Left-sided colitis, inflammation extending the rectum to and including the splenic flexure; (4) Extensive colitis, inflammation proximal to the splenic flexure.

Patients with Crohn’s disease were classified by age of onset, disease location and behaviour according to the Truelove & Witts’ criteria for UC and the criteria established by the Chinese Society of Gastroenterology for CD.

Severe UC was defined as the passage of ≥ 6 bloody stools daily with one or more of the following criteria: temperature ≥ 37.8°C, pulse > 90/min, haemoglobin < 10.5 g/dL, or erythrocyte sedimentation rate (ESR) > 30 mm/h.

Mild CD was defined when the patient had no fever, abdominal tenderness, abdominal mass and obstruction, while severe CD was defined when the patient had persistent high fever, weight loss, nausea, vomiting, abdominal pain, diarrhea, anemia, and complications. Characteristics of the patients and the information about the location of disease are given in Table 1.

Table 1  Clinical characteristics of the study population

| Crohn’s disease | Ulcerative colitis |
|-----------------|-------------------|
| Number of patients | 104               | 123               |
| Female           | 42 (40.4%)        | 56 (45.5%)        |
| Age (yr)         | 36 (13-70)        | 45 (15-80)        |
| Disease duration (yr) | 4.8 (0.5-24)     | 5.5 (0.5-23)     |
| Non-smoking      | 82 (78.8%)        | 90 (73.2%)        |
| Severity, n (%)  | 24 (23.1%)        | 62 (50.4%)        |
| Mild             | 51 (49)           | 42 (34.1)         |
| Moderate         | 29 (27.9)         | 19 (15.5)         |
| Disease distribution, n (%) | 44 (42.3)     | 41 (33.3)         |
| Small intestine  | 17 (16.3)         | 24 (19.5)         |
| Left side colon  | 40 (38.5)         | 58 (47.2)         |
| Systemic or pan-colon | 5 (4.1)   | 4 (3.2)           |
| History of any intestinal operation | 46 (44.2)     | 5 (4.1)           |
mg/d for more than 2 wk) and 28 (45.9%) had postsurgery fistulating CD. Twenty-one patients (21/61, 34.4%) received immunosuppressive agents (19 cases with AZA, two cases with cyclosporin) as shown in Figure 1A. The mean dose of AZA was 1.47 mg/kg per day (range 0.83-2.22 mg/kg per day). A suboptimal dose of AZA was defined as a dose less than 1.5 mg/kg per day in the absence of myelotoxicity or hepatotoxicity. AZA-related myelotoxicity is defined as WBC < 3.0 × 10^9/L or neutrophil < 1.5 × 10^9/L, while AZA-related hepatotoxicity is defined as ALT and/or GGT levels greater than 5 times the upper normal limit, or ALP levels greater than 3 times the upper normal limit, excluding viral hepatitis. When withdrawing AZA or reducing the dose, the above indexes recover to normal. According to this criterion, among the 19 patients treated with AZA, there were two with myelotoxicity and one with hepatotoxicity, before the clinician adjusted the dosage. The other 16 residual cases received AZA therapy, and six of those cases (37.5%) received subtherapeutic therapy, with no attempt to increase this dosage (Figure 1B).

The effectiveness of the immunosuppressant therapy (disease remission) is defined as follows: for Crohn’s disease, the HBI value was less than five or for UC the Sutherland index was less than three. According to this definition, of the 20 patients who received immunosuppressant therapy for more than 6 mo, 15 (75%) patients went into remission, four (20%) patients had no benefit and one (5%) relapsed.

According to the definitions of AZA-related myelotoxicity and hepatotoxicity, four (20%) patients suffered from myelotoxicity (two cases occurred within 3 mo after receiving AZA therapy; one case each occurred one and two years after drug therapy) and one (5%) patient suffered from hepatotoxicity.

**DISCUSSION**

IBD, which includes CD and UC, is a complicated disease of the digestive tract. In recent years, because of the rapid development of evidence-based medicine, the therapy guidelines of IBD in China and abroad have been updated constantly. Reddy et al[12] analyzed the therapeutic condition of American patients with IBD according to the American College of Gastroenterology (ACG) practice guidelines[13,14]. They found that the dose of aminosalicylic acid agents was not adequate and enema therapy and immunosuppressive agents were not applied effectively[13,14]. With the lack of relative data in China, we carried out this study to reflect the current therapeutic condition of patients with IBD in eastern China.

Although glucocorticoids are effective in the induction of remission for IBD, more than 20% of patients may be steroid-refractory or become steroid-dependent[15-17]. Meta-analyses showed that glucocorticoids are not effective for medical maintenance. The frequency and severity of well-recognized adverse effects also preclude their long-term use.

Immunosuppressive agents such as AZA can induce and maintain remission of IBD and have steroid sparing effects in patients who are steroid dependent or who have refractory IBD[7,18-20].

In our study, the use of immunosuppressive agents was restricted to a minority of IBD patients (19.6%) who adapted to use these drugs, which is distinctly less frequent compared with that in Western countries. Furthermore, more than half of the patients did not receive recommended doses of AZA. We found that the percentage of serious drug toxicity was 5/20 in AZA therapy. Because of the lack of data from large-scale studies in China, the adverse reaction rate of AZA in Han nationality Chinese with IBD is not clear. Results of our study are consistent with the conclusions reported outside of China[21].

At present, many researchers presume that interpatient and interracial variability, which are based on thiopurine methyltransferase (TPMT) gene polymorphisms and enzyme activity, exist and affect the efficacy and toxicity of AZA. Whether TPMT gene

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**Figure 1** Drug therapeutic status of IBD patients who received immunosuppressant therapy. A: Twenty one IBD patients; B: AZA therapeutic status of 16 IBD patients.
Innovations and breakthroughs

The use of immunosuppressive agents in IBD patients in China has not been reported. The authors designed this study to address this problem and provide data to improve the quality of IBD treatment in China.

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