Role of azathioprine in severe ulcerative colitis: one-year, placebo-controlled, randomized trial

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Objective: To investigate the efficacy of azathioprine in treating patients with severe ulcerative colitis. Design: One-year, randomized, placebo-controlled trial. Subjects: 83 patients with severe ulcerative colitis were enrolled. Fifty patients who relapsed within two months on corticosteroid withdrawal were randomized into two groups. The azathioprine group received oral sulfasalazine (6-8 g/day), oral prednisolone (1 mg/Kg/day) and oral azathioprine (2 mg/Kg/day). The placebo group received oral sulfasalazine (6-8 g/day), oral prednisolone (1 mg/Kg/day) and placebo. Corticosteroids were tapered over 12-16 weeks. Results: Five patients (2 in azathioprine group, 3 in placebo group) dropped out of the study. Three patients in the azathioprine group had side effects. The number of patients going into complete remission and partial remission was not significantly different in the two groups. The proportion of relapses in the azathioprine group was lower than in the placebo group (p<0.05). Conclusions: In patients with ulcerative colitis, azathioprine had no effect in achieving remission, when given in combination with prednisolone; however, it lowers the proportion of relapses. Side effects like pancreatitis and hepatitis are mild and respond promptly to drug withdrawal. [Indian J Gastroenterol 2000; 19:14-16]

Key words: Inflammatory bowel disease, idiopathic ulcerative colitis

After an encouraging report on the use of the immunomodulatory drug azathioprine in ulcerative colitis in 1966 by Bowen and colleagues,1 a number of case reports and small series describing a beneficial role of this drug in ulcerative colitis were published.2,3,4 However, subsequent controlled trials have produced conflicting results.5-10 No data are available from India.

We conducted this prospective, randomized, single-blind, placebo-controlled trial to assess the efficacy of azathioprine in patients with severe ulcerative colitis.

Methods

The study was performed in accordance with the declaration of Helsinki and was approved by the ethical committee of the hospital. All patients gave written informed consent. Eligible patients were those who had a confirmed diagnosis of severe ulcerative colitis on the basis of clinical examination (Truelove and Witt's criteria) and endoscopic and histological criteria and had suffered a relapse within two months of corticosteroid withdrawal. Exclusion criteria included pregnancy, bone marrow suppression, drug allergy and liver disease.

A total of 83 patients with severe disease attended our hospital during the period January 1993 to August 1997. They were given intensive treatment comprising (a) parenteral corticosteroids (hydrocortisone 100 mg 6 hourly) followed by oral prednisolone (1 mg/Kg), (b) sulfasalazine (6-8 g/day) and (c) parenteral ciprofloxacin and metronidazole for 7 days. Corticosteroids were tapered off over 12-16 weeks. Fifty patients relapsed within two months of corticosteroid withdrawal and were entered into the study. Clinical and demographic data of these 50 patients are given in Table 1. The disease was said to be continuous when disease activity persisted and there was no remission for any appreciable time, episodic when there were intermittent attacks and remission in between, and unspecified when the course was not categorized because of irregular treatment.

The study drugs consisted of 50 mg azathioprine tablets and identical matched placebo drugs (prepared by Indilima Pharmaceuticals, Ludhiana). The drugs were provided by a single coordinator (VK) to the patients in identical blister packs. Compliance was monitored by diary records of tablet consumption. Noncompliant patients, who did not take the study medication as prescribed, were considered as drop-outs.

Study design

The was a 1-year, prospective, randomized, placebo-control}

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<td>Women</td>
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<td>Age (years)</td>
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<td>Duration of disease at study entry (years)</td>
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<td>Disease extent</td>
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Values are mean (SD). *p<0.05

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trolled trial. Patients were randomized into two groups using pseudorandom numbers ranging from 0-1 generated by a scientific calculator (Casio fx-82D). The azathioprine group (n=25) received oral sulfasalazine 6-8 g/day, oral prednisolone (1 mg/Kg/day) (tapered over 12-16 weeks) and oral azathioprine (2 mg/Kg/day); whereas the placebo group (n=25) received oral sulfasalazine (6-8 g/day), oral prednisolone (1 mg/kg/day) (tapered over 12-16 weeks) and placebo. The treating physician was aware of the drug treatment.

Patients were assessed at entry into the trial and then every month or earlier in the event of relapse till 1 year. They maintained a daily symptom diary, which was reviewed at each hospital visit. The patients were withdrawn from the study in case of relapse, significant side effects, loss to follow up or noncompliance. At alternate visits, complete blood counts and transaminases were estimated. Sigmoidoscopy or colonoscopy was performed at entry, at 12 months, and earlier if warranted, by one endoscopist (AS). Endoscopic findings were scored in accordance with Baron’s criteria as follows: 0 - normal mucosa; 1 (mild) - hyperemic mucosa, indistinct vascular pattern; 2 (moderate) - friability, bleeding to light touch; 3 (severe) - spontaneous bleeding, ulceration, muco-pus. Rectal biopsy was done in those who achieved endoscopic remission.

The end point of the study was 1 year and the outcome response was characterized as complete remission, partial remission and relapse. Complete remission was defined as clinical improvement with absence of symptoms of active disease (rectal bleeding, bowel frequency) with sigmoidoscopic appearance of grade 0-1 and normal histological pattern. Partial remission was defined as clinical improvement with stool frequency still increased but less than 50% of previous, and sigmoidoscopy showing downgrading of severity and granular nonfriable mucosa (grade 0-2). Relapse was defined as remission followed by worsening of symptoms recognized by the patient as active disease (such as rectal bleeding, loose motions or bowel frequency) with sigmoidoscopic appearance of active colitis.

Statistical analysis

Homogeneity of baseline characteristics of the two groups was analyzed using Student’s t test for unpaired data. Clinical outcome was compared using χ² test, and on an intention-to-treat basis. To study the difference between complete remission, partial remission and relapse, Z test for proportions was applied. The sensitivity, specificity and predictive accuracy rates of the study were worked out. Absolute as well as relative risk reduction were also computed.

Results

The two groups were matched for age, sex, extent and disease description (Table 1). The duration of disease before entry into the trial was significantly higher in the azathioprine group (p<0.05).

Five patients (2 on azathioprine, 3 on placebo) were excluded because of noncompliance and violation of treatment protocol (use of other medications). Three patients in the azathioprine group experienced adverse effects causing early withdrawal of the drug. Two patients had mild acute pancreatitis requiring hospital admission for one day. One patient developed jaundice with increase in transaminases after having been in the trial for 3 weeks. Rechallenge with drug again caused increase in transaminases. Serial hematological observations showed no evidence of bone marrow suppression.

Treatment outcome (Table 2)

Fourteen (56%) of 25 patients in the azathioprine group were in complete remission at the end of the study, compared with 10 of 25 (40%) in the placebo treated group (Z=1.13, p=ns). Partial remission was seen in 3 patients (12%) in the azathioprine-treated group and in 6 patients (24%) in the placebo group (Z=1.1, p=ns).

Till 4 months after start of treatment, the two groups did not differ in the proportion of patients entering remission (Z=1.22, p=ns). However, after 4 months, the proportion was higher in the azathioprine treated group as compared to the placebo group (4-6 months: Z=2.43, p<0.05; 6-8 months: Z=2.01, p<0.05). All patients who achieved complete clinical remission in the azathioprine group had done so by 8 months whereas in the placebo group they achieved complete remission by 10 months after entry (Fig).

By the end of one year, 3 patients (12%) taking azathioprine had relapsed compared to 6 patients (24%) taking placebo. The relative risk (relative protective effect of azathioprine) was 11.1%. Overall, the response in the two groups was not significantly different (χ²=0.37, p=ns).

The study had a significant overall predictive accuracy (52%), the positive predictive accuracy being 68% while negative predictive accuracy was 36%. The sensitivity and specificity of the study was 51.5% and 53.0%, respectively. The study’s statistical power to detect the specified minimum important difference was only 36%.
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In conclusion, azathioprine does not affect the rate of achieving remission when given in combination with prednisolone, but brings down the proportion of relapses in patients with ulcerative colitis. Side effects like pancreatitis and hepatitis occur but are mild and respond promptly to drug withdrawal.

References

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Fig: Cumulative number of patients achieving remission in azathioprine and placebo groups at different time points

Discussion
Azathioprine has been used as a therapeutic option in the management of patients who relapse on withdrawal of corticosteroids despite maximal dosage of 5-aminosalicylic acid. Its role as a steroid-sparing agent and in maintenance therapy of patients with chronic ulcerative colitis has been demonstrated previously. To our knowledge, this is the first randomized, controlled study on the efficacy of azathioprine in patients with ulcerative colitis from India. A significantly higher number of patients achieved remission earlier in the azathioprine group as compared to the placebo group. The addition of azathioprine also reduced the relapse rate in a subset of patients (12% vs 24%). This trial, however, failed to detect an overall significant benefit with azathioprine; this may be related to a small sample size and low statistical power. We are continuing this study with a larger sample size and for a longer follow up.

There have been previous reports on the effectiveness of azathioprine in ulcerative colitis. Jewell and Truelove reported a reduction in the one-year relapse rate in a subgroup of patients with established disease. In another study, a beneficial effect of azathioprine as maintenance treatment was noticed since its withdrawal in patients with complete remission resulted in a doubling of the relapse rate.

The concern about toxicity of azathioprine has been addressed in several reports. The major concerns associated with immunosuppressive therapy, such as infections and malignancy, have not been of much significance. In our study also, toxic side effects were not a serious problem. Only 3 patients (2 with mild acute pancreatitis, 1 hepatitis) needed drug withdrawal. None of our patients had bone marrow suppression. However, a close and regular monitoring of hemogram is necessary.