Compared azathioprine efficacy in ulcerative colitis and in Crohn’s disease

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SUMMARY

Aim — To compare the 6-month efficacy and tolerance of azathioprine in 68 patients with steroid-resistant or steroid-dependent chronic ulcerative colitis (n = 30) or Crohn’s disease (n = 38).

Methods — Clinical remission was defined as a Crohn’s Disease Activity Index < 150 for Crohn’s disease and number of non-bloody stools ≤ 3/day for ulcerative colitis, associated with prednisone requirement ≤ 10 mg/day.

Results — Seventy-three per cent of patients with ulcerative colitis had distal or left-sided colitis and 84% of patients with Crohn’s disease had pancolitis. Azathioprine was discontinued early for side-effect in 8 (26.7%) patients with ulcerative colitis and in 8 (21.1%) patients with Crohn’s disease (NS). In patients treated at least 6 months by azathioprine, clinical remission rates were 77.3% and 70% for chronic ulcerative colitis and Crohn’s disease (NS). Complete corticosteroids weaning was obtained significantly more often in ulcerative colitis patients than in Crohn’s disease patients (59.1% vs 30%; P < 0.05).

Conclusion — Azathioprine seems to be at least as effective and equally tolerated in steroid-resistant or steroid-dependent chronic ulcerative colitis or Crohn’s disease patients.

Azathioprine and its derivative 6-mercaptopurine are the gold-standard treatments for steroid-dependent and steroid-resistant Crohn’s disease (CD) [1, 2]. Their use in ulcerative colitis (UC) is more controversial. There are at least three reasons clinicians are not particularly inclined to prescribe immunosuppressors: the lack of sufficient evidence of efficacy provided by a limited number of studies with questionable methodologies [3-9], the fact that surgical cure of UC is theoretically possible, and fear of an increased risk of cancer. But new data are now available, allowing a re-evaluation of the efficacy of azathioprine and its derivative 6-mercaptopurine for the treatment of ulcerative colitis [10]. Several recent studies have demonstrated that patients with refractory disease can be maintained in remission with 6-mercaptopurine [9, 11] and that azathioprine is effective in about two-thirds of patients with steroid-dependent and steroid-resistant ulcerative colitis [12]. In addition, after cyclosporin-induced remission in severe ulcerative colitis [13], azathioprine appears to be the best treatment to maintain remission [14, 15]. It is also noted that the beneficial effect expected after ileal pouch-anal anastomosis is not always observed. After 10 years follow-up, approximately 50% of the patients who undergo surgical cure of UC develop chronic pouchitis and approximately 10% of them require definitive ileostomy [16]. Finally, the risk of cancer appears to be equivalent for extensive ulcerative colitis and Crohn’s disease [17]. These different considerations led us to propose azathioprine for patients with chronic steroid-dependent or steroid-resistant UC. We have used azathioprine since 1995 for our UC patients selected on the same basic criteria as patients with Crohn’s disease. The purpose of the present work was to compare clinical remission and steroid sparing effects as well as the efficacy and safety of azathioprine in patients with steroid-dependent or steroid-resistant ulcerative colitis or Crohn’s disease.

Patients and methods

The following inclusion criteria were used: a) steroid-dependent or steroid-resistant UC or CD with colonic involvement in outpatients or inpatients seen by the same clinician (PB) between January 1995 and April 2000; b) institution of azathioprine treatment starting with 2 mg/kg/d and continued for at least six months; c) no prior treatment with azathioprine. Steroid-dependence was defined as a requirement for corticosteroid treatment at a prednisone-equivalent dose of more than 10 mg/d on the average for at least 6 months [18] to control inflammatory bowel disease after failure of at least one attempt to withdraw corticosteroids. Steroid-resistance was defined as clinical signs of persistent active inflammatory bowel disease despite 6 weeks treatment with corticosteroids at a dose ≥ 30 mg/d during the 6 preceding months [18]. Patients given azathioprine after surgery (multiple operations for CD), or after cyclosporin treatment (severe UC) were included among the steroid-resistant patients. The following data were recorded at inclusion: age, sex, disease duration, disease localization, cumulative dose and adverse effects of corticosteroids.

ABBREVIATIONS:
UC : ulcerative colitis
CD : Crohn’s disease
All patients were seen at 2 and 6 months to assess the efficacy and safety of azathioprine. Patients were considered to be in clinical remission if their Crohn's Disease Activity Index was less than 150 (for CD patients), or had ≤ 3 bloody stools per day (for UC patients) and their prednisone dose was ≤ 10 mg/d (for CD and UC patients). Laboratory tests included blood cell counts and serum alanine aminotransferase (ALAT) activity weekly during the first month then monthly for 3 months and once every 3 months thereafter. Side effects of azathioprine were reported as follows: a) allergic immune reactions: skin rash, fever, pancreatitis, b) hematological reactions: leukopenia (< 4,000/mm³), thrombopenia (< 150,000/mm³); c) hepatic: serum ALAT > 2 upper limit of normal (NL); d) infectious: any infection (excluding common ENT infection) during the treatment course; e) other: alopecia, epigastric pain unrelated to allergic reactions. Azathioprine was discontinued in patients who developed an allergic immune reaction. Doses were generally reduced by half if the white cell count fell below 4,000/mm³, platelet count fell below 100,000/mm³, or serum ALAT was elevated with no other sign of liver disease, then adapted to laboratory results. Prednisone dose was maintained during the first month of treatment, then tapered off in order to achieve, when possible, complete withdrawal by the end of the third month of azathioprine. For patients with UC involving the left colon or rectum, local treatments were continued using the same schema as for oral steroids depending on their presumed efficacy. Patients exhibiting intolerance to azathioprine were not given 6-mercaptopurine.

### Statistical analysis

The Chi-square test was used to compare qualitative variables and Student’s t test for paired or unpaired variables to compare quantitative variables. The threshold of significance was set at 0.05.

### Results

Sixty-eight patients, 30 with UC and 38 with CD, were included in the study. Their clinical features at onset of azathioprine treatment are summarized in Table I. Patients with UC were significantly older and had a significantly shorter disease course than those with CD. There was no significant difference between the UC and CD patients for steroid-dependence or steroid-resistance. Four patients with UC had achieved clinical remission with cyclosporin. Three patients with CD were given azathioprine on parenteral nutrition catheter (n = 1). Two patients, one ileal and one ano-perineal 0 15 (39.5)

<table>
<thead>
<tr>
<th>Localization, n (%)</th>
<th>UC</th>
<th>CD</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>— rectal</td>
<td>9 (30.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>— ileal</td>
<td>0</td>
<td>28 (73.5)</td>
<td></td>
</tr>
<tr>
<td>— ano-perineal</td>
<td>0</td>
<td>15 (39.5)</td>
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<tr>
<td>Steroid-dependent (%)</td>
<td>46.5</td>
<td>53.5</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid-resistant (%)</td>
<td>53.5</td>
<td>47.5</td>
<td>NS</td>
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<tr>
<td>Cumulative dose of prednisone at onset of azathioprine treatment (g)</td>
<td>7.4 ± 4.4</td>
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No patient had severe acute colitis at the time of commencing of azathioprine.

Azathioprine was discontinued in 8 of the patients with UC (26.7%) and 8 of those with CD (21.0%) because of adverse effects after a mean 1.6 months (range 0.5-3) and 2.1 months (0.2-5) treatment, respectively. On an intention-to-treat basis, the rate of clinical remission at 6 months was not significantly different between UC and CD patients (56.7% and 55.3%, respectively). Among treated patients, the rate of clinical remission at 6 months was 77.3% for UC and 70% for CD (NS). Expressed in terms of mean prednisone dose (table II) the efficacy of azathioprine at 6 months was equivalent for UC and CD. Azathioprine was significantly more efficacious for UC than for CD for complete steroid withdrawal (59.1% vs 30%, P < 0.05). Mean delay to complete steroid withdrawal was 3.9

months (range, 1-6) for UC and 4 months (range, 1-6) for CD. The efficacy of azathioprine to induce clinical remission of steroid-dependent and steroid-resistant disease was 76.9% and 77.8% respectively for UC and 78.6% and 62.5% respectively for CD. There was no significant difference between steroid-dependent and steroid-resistant UC or CD concerning steroid dose after 6 months treatment with azathioprine or steroid withdrawal. Among the 17 patients with UC who achieved clinical remission with azathioprine, 16 had had at least one colonoscopy exploration 1 to 6 months after onset of azathioprine: endoscopic-proven remission in 14 patients (grade I according to Baron et al. [19]) and minor grade II lesions in 2.

The adverse effects observed in patients taking azathioprine are given in Table III. There was no significant difference between UC and CD patients. Approximately half of the early discontinuations of azathioprine were related to adverse effects. In UC patients, the following adverse effects were observed: allergic reactions (n = 3), elevated ALAT (n = 4), lung abscess with neutropenia (n = 1). In CD patients, the following adverse effects were observed: allergic reactions (n = 3), cytopenia involving two lines and not responsive to reduced dose of azathioprine (n = 2), elevated ALAT (n = 2), Staphylococcus aureus septicaemia on parenteral nutrition catheter (n = 1). Two patients, one

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Table II – Efficacy of azathioprine in change in corticoid dose for the patients having received the treatment during at least 6 months.

controlled trial, found that the rate of relapse in UC given azathioprine [4, 6-8]. Hawthorne et al. [9], in a double-blind controlled trial, found that the rate of relapse in patients given azathioprine [3-8]. Several groups have however demonstrated a real steroid-sparing effect and/or a lower relapse rate in patients with severe chronic inflammatory bowel disease, as reflected by the number of steroid-resistant cases, the high cumulative steroid-doses, and the number of patients with adverse reactions to corticosteroid treatment. The CD patients included in this study all had predominantly colonic disease. Most of the CD patients (84%) had pancolitis and in three-quarters of the UC patients, inflammation was limited to the rectum or the left colon and azathioprine is generally proposed for this type of disease extent. Despite the retrospective nature of this study, the mono- or double-blind controlled trial of indications, criteria of efficacy, decision to pursue or discontinue treatment was relatively homogeneous since the same clinician provided care from the onset of azathioprine treatment. The main methodological difficulty with this type of study lies in the criteria used to define clinical remission: the same criteria cannot be used for UC and CD. The endoscopic and histological criteria for UC remission are not necessary to define remission in CD. Although colonoscopy data was available for most of our patients with UC, we chose to define remission from UC solely on the basis of clinical criteria in order to obtain comparable results for the two diseases. For our UC patients, clinical remission was confirmed at colonoscopy in 1 of 16 patients examined. A reduction in the steroid dose, and/or complete steroid withdrawal, appears to be a pertinent criterion for defining remission in both diseases.

Our findings confirm that azathioprine is as least as effective in chronic active UC as in chronic active CD, with comparable tolerance. Complete steroid weaning was achieved at 6 months in twice as many UC as CD patients. The rate of clinical remission after a 6-month treatment with azathioprine was 73.3% for UC patients and 78.9% for CD patients. These results are in keeping with two earlier retrospective series reporting 46% and 75% remission at 6 and 12 months in patients with chronic UC [11, 12, 20-22].

Azathioprine had to be interrupted because of adverse effects in 26.5% of the UC patients and 21% of the CD patients. These rates are relatively high compared with the 10% generally reported in the literature [23, 24]. Others have however reported discontinuation in 20% of patients in prospective [25] and retrospective [26] series. Apart from the allergic immune reactions, the causal relationship was only probable for many events, especially infectious episodes that are also favored by associated corticosteroid treatment. It is also important to note that because of the drug’s long delay to the onset of action, clinicians or patients may hesitate to prolong azathioprine after an apparently benign side effect. Two of our patients declined continuing azathioprine treatment when informed of moderately elevated ALAT levels on a routine test. It is also likely that early in our experience we decided to interrupt azathioprine quite readily in our UC and CD patients. In any case, the rates of adverse early and easy discontinuation of azathioprine were similar in the two diseases.

The 6-month duration of this study is sufficient to test the efficacy of azathioprine despite the fact that response may appear late in some patients [2, 26]. A recent retrospective study [27] suggests that the efficacy of azathioprine in UC appears to deteriorate with time: remission rate was 41% at three years (below that observed in CD) and more than half the patients had colectomy at 5 years. These observations are not, in our opinion, in contradiction with the efficacy of azathioprine in chronic active UC. They could simply be the expression of earlier and more common decision for surgery in UC than in CD.

Growing indications for azathioprine in UC are partly related to a more critical attitude concerning ileo-anal anastomosis [2, 16, 28, 29]. It is however difficult to define with precision the respective indications for azathioprine and surgery in UC. It would appear logical to propose azathioprine as first-line treatment for patients with steroid-dependent or steroid-resistant UC of the rectum and left colon who are unresponsive to well-conducted local treatment and to reserve surgery for failure of medical treatment [2]. This type of indication accounted for

Table III. - Side effects of azathioprine.

<table>
<thead>
<tr>
<th>Type of side effect, n (%)</th>
<th>Ulcerative colitis n = 30</th>
<th>Crohn’s disease n = 38</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least one side effect n (%)</td>
<td>15 (50)</td>
<td>14 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of patients who interrupted azathioprine due to side effects n (%)</td>
<td>8 (26.5)</td>
<td>8 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Type of side effect, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— allergic immune reaction</td>
<td>2 (7)</td>
<td>3 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>— infectious</td>
<td>2 (7)</td>
<td>8 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>— hepatic b</td>
<td>6 (20)</td>
<td>3 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>— hematologic</td>
<td>5 (17)</td>
<td>3 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>— others c</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

a 5 patients had 2 side effects. b ALAT >2 N. c Alopecia, digestive intolerance. NS = not significant.
75% of our UC patients given azathioprine. Prescription of azathioprine for long-standing pancolitis or as a relay after cyclosporin for severe acute colitis is a new strategy that we applied in four patients but long-term results of such strategies need to be evaluated [14, 15].

The risk of prolonged immunosuppression must not be overlooked. There has however been much debate about the risk of immunosuppressors in patients with chronic inflammatory bowel disease [30, 31]. Although the significance increased risk of lymphoma has not been definitively proven in UC or CD patients treated with azathioprine [30, 31], certain cohort studies suggest that immunosuppression could increase the risk of lymphoma by 5-fold [30]. The risk of Hodgkin’s disease also appears to be increased in UC independently of immunosuppressors treatment [32]. For inflammatory bowel disease, it has been recently demonstrated that the risk of lymphoma is about 0.03% per patient and per year [30]. This risk is higher than in the general population but can be considered as low and should be balanced against the expected benefit of treatment. In CD, the beneficial effect of azathioprine has been recently measured using the Markov model which shows that the relative risk for lymphoma is 3 [33]. Lewis et al. [33] thus demonstrated that giving azathioprine to patients with steroid-dependent CD lengthens life expectancy by 0.03 years, which expressed in quality-of-life adjusted life expectancy, yields a gain of 0.05 years. In addition, as was demonstrated for mesalazine [34], azathioprine-induced maintenance of prolonged UC remission could possibly reduce the risk of colorectal cancer in these patients.

In conclusion, our study and recent reports in the literature argue in favor of more widespread and earlier use of azathioprine in UC patients, following the indications and with equivalent results as observed in CD. Despite the warranted concern about the risks of prolonged immunosuppression, we can expect to see wider use of azathioprine for UC patients, following the approach used by teams with more extensive experience with this drug [35].

REFERENCES


