Crohn's disease outcome in patients under azathioprine: A tertiary referral center experience

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Azathioprine;
Real-life study

Abstract
Background and aims: Azathioprine is of major importance in the treatment of Crohn's disease; its efficacy has been showed in several works, but real-life data regarding its use is scarce. Our aim was to address the outcome of patients with Crohn's disease under azathioprine in the real-life setting.

Methods: Crohn's disease patients followed at an Inflammatory Bowel Disease Outpatient Clinic under azathioprine were consecutively enrolled, being allocated in one of four groups. Two groups included patients on treatment with this drug, regarding its two major indications — prevention of post-operative recurrence and steroid-dependent disease; a third group included patients who needed infliximab in addition to azathioprine and a fourth group comprised patients who did not tolerate azathioprine.

Results: A total of 221 patients were enrolled, 180 on azathioprine due to steroid-dependency (64 needing additional treatment with infliximab) and 41 for prevention of post-operative recurrence. Steroid-free remission was obtained in 48%. Immunosuppression decreased the number of hospitalized patients (64% vs 36%; p < 0.001), but not the surgery rates per person per year. Azathioprine as a post-operative drug was effective in decreasing hospitalizations. The addition of infliximab decreased the number of patients hospitalized (p = 0.009) and hospitalization rates per
1. Introduction

Purine analogs, namely azathioprine (AZA) and 6-mercaptopurine (6-MP), are immunosuppressive drugs widely used in the treatment of Crohn’s disease (CD). Their efficacy in maintenance of remission and their steroid-sparing effect were established in controlled clinical trials.1–4 Furthermore, thiopurines have also shown to reduce the incidence of postoperative recurrence in CD.5,6 These drugs are an inexpensive treatment option in comparison with biological therapy; however, their efficacy fails in more than half of the patients and the occurrence of adverse events leads to drug discontinuation in up to 20% of the patients.4

Despite the substantial progress made in the medical treatment of CD and the more frequent use of immunosuppressive drugs, the rate of patients needing intestinal surgery did not decrease.7,8 The available data on effectiveness, failure and toxicity of thiopurine in real-life inflammatory bowel disease (IBD) cohorts is scarce. Herein, we report a real-life experience on long-term outcomes of AZA treatment in a cohort of 260 patients with CD followed for a median time of 8 years (Interquartile Range [IQR] 3–12 years); the oldest patient in our series had a follow-up of 21 years on AZA. The patients’ outcome was assessed in terms of clinical remission free of corticosteroids, time to hospitalizations and surgeries and rate of surgeries and hospitalizations per person per year.

2. Material and methods

2.1. Population

Data of patients followed at an IBD outpatient clinic between January 1991 and December 2011 was retrospectively analyzed. Patients were consecutively enrolled in this real-life study and their medical records concerning demographic data, disease phenotype, treatment, hospitalizations and surgeries were prospectively registered in an electronic database (www.gediibasedados.med.up.pt). The same gastroenterologist followed all the patients. Inclusion criteria were the definite diagnosis of Crohn’s disease and indication for maintenance treatment with AZA, either because of steroid-dependency or for prevention of postoperative recurrence. Patients who had indication for treatment with AZA but had side effects that precluded its use were not analyzed in terms of drug efficacy. Excluding criteria were age below 18 years-old and pregnancy.

Patients enrolled could be in one of four groups: two groups included patients on treatment with this drug, regarding the two major indications for its use — prevention of post-operative recurrence and steroid-dependent disease; a third group included patients who needed infliximab in addition to azathioprine and a fourth group comprised patients who did not tolerate azathioprine, that were only mentioned for descriptive purposes and that were not included in further analysis. Thiopurine methyltransferase (TMPT) was not routinely measured. Patients started AZA in a low dose (50 mg/day) and were clinically and analytically evaluated 2 weeks after. Higher dosages were gradually prescribed if there were no side effects, with full dose being achieved at 2 months after starting it. We did not perform serological markers of disease activity. Patients were clinically and analytically assessed every 3–6 months and colonoscopy was performed whenever considered necessary during follow-up. The results regarding hospitalizations or surgeries before and after the introduction of AZA were analyzed, as well as the need for hospitalization or surgery before AZA, after AZA and after anti-tumor necrosis factor (anti-TNF) treatments in the combo group. Rate of surgeries and hospitalizations, rate of surgeries and hospitalizations per person per year and the median time to these events were measured.

In order to calculate the incidence of hospitalizations or surgeries (expressed in rates per person per year), we divided the number of these events between two time periods by the time in years between those dates.

2.2. Definitions

Steroid-free clinical remission was defined as no need of oral steroids (either prednisolone or budesonide) for at least one year and a Harvey-Bradshaw score less than 5. Only hospitalizations or surgeries related with IBD were reported.

Steroid-dependent patients were those who were either i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting steroids, without recurrent active disease, or ii) who had a relapse within 3 months of stopping steroids.9

For the post-operative recurrence group we included patients that started AZA therapy in the first 2 months after surgery.

Pancreatitis was defined as typical abdominal pain with amylase or lipase above three-times the upper limit of normal.

2.3. Statistical analysis

Categorical variables were described as absolute frequencies (n) and relative frequencies (%); median and percentiles were used for continuous variables. The normality of the continuous variables was tested using the Kolmogorov–Smirnov test and the respective histogram. The distribution...
of continuous variables for two independent groups with non-normal distribution was tested using the Mann–Whitney test for two independent groups and Kruskal–Wallis test for more than two independent groups. The Pearson Chi-square test was used to test independence between categorical variables. The McNemar test was used to test differences in the same outcome between two different time periods in matched paired cases, in order to determine whether the row and column marginal frequencies were equal. To compare survival times between two or more groups, the Log-rank method was applied to test the survival curves for both hospitalizations and surgery time and presented graphically the respective ROC curves. Statistical significance was considered at $p < 0.05$. SPSS(r) 19.0 was used for statistical analysis.

3. Results

3.1. Population

A total of 260 patients with CD with indication for treatment with AZA were identified; of those, 39 patients (15%) developed adverse side effects that precluded its use, not achieving the time or dose needed for AZA efficacy. The remaining 221 patients were on treatment with AZA due to steroid-dependency ($n = 180$, 81%) or for prevention of post-operative recurrence ($n = 41$, 19%) (Fig. 1). Median follow-up after diagnosis was 8 years (IQR 3–12 years) and median duration of follow-up since the beginning of AZA therapy was 5 years (IQR 2–8 years). Baseline characteristics of these patients are summarized in Table 1.

Of the 180 steroid-dependent patients on AZA, 64 needed additional treatment with IFX after a median time of 48 months (range, 1–241 months); in contrast, patients previously submitted to surgery did not need additional therapy besides AZA (Fig. 1). The median dose of AZA was 2.08 mg/kg per day. Among patients only treated with AZA, the median dose was 2.05 mg/kg and in the combination group (AZA + IFX) the mean dose was 2.21 mg/kg. The median dose of steroids before AZA was 40 mg/day (IQR 20–40) for the AZA group and 20 mg (IQR 10–60 mg) for the combo group. The median duration of AZA therapy was 4 years (IQR, 2–7 years) in the AZA group and 7 years (IQR 3–9 years) in the AZA + IFX patients. The median length of IFX treatment in the AZA + IFX group was 4 years. The median number of IFX infusions was 14 (range, 5–26). The median time from diagnosis to beginning of AZA was 2 years (IQR, 0.5–7 years) and to beginning of IFX was 5 years (IQR, 2–8 years) (Table 1).

3.2. Clinical remission

Overall, steroid-free remission was achieved in 106 of 221 (48%) patients. In fact, 32% ($n = 37$) of patients treated with AZA due to steroid-dependency and 61% ($n = 25$) of post-operative patients ($p < 0.001$) did not need any cycle of steroids for induction of disease remission. In patients treated with IFX due to AZA refractoriness, 44 (69%) maintained steroid-free remission. In patients treated with IFX monotherapy, after azathioprine side effects, steroid-free remission was achieved in 62% of patients.

3.3. Endoscopic evaluation

Regarding endoscopic findings in patients taking AZA for post-operative recurrence, we found that before surgery they had ileal or colonic stenosis (22%) or erosions/ulcers (88%). After surgery and under an adequate time on AZA, most of the patients have consistently normal or almost normal endoscopies (Rutgeerts $i^0$ and $i^1$, 58%), while the other patients had at least one colonoscopy with disease recurrence (Rutgeerts $i^2$, 42%). In the group of steroid-dependent patients, they had mostly superficial ulceration (46%) in the time they began AZA, while the others had normal endoscopies (31%), stenosis (14%) or deep ulceration (8%). After AZA, they had normal endoscopies (58%), superficial ulceration (32%), stenosis (8%) or deep ulceration (2%). In patients with normal endoscopy before beginning AZA treatment all of them had CT-enterography, MR-enterography or intestinal follow-through showing CD activity. In most of them the terminal ileum was not achieved due to technical reasons (not possible to go through the ileocecal valve) or stenosis.

![Figure 1](https://academic.oup.com/ecco-jcc/article-abstract/8/7/617/565721)

**Figure 1** Schematic representation of the follow-up of the patients enrolled in the study. AZA — Azathioprine, IFX — Infliximab, ADA — Adalimumab, 5-ASA — 5-Aminosalicylates, SFR — Steroid-free remission.
Table 1  Characteristics of the population enrolled in the study.

<table>
<thead>
<tr>
<th>Groups (n)</th>
<th>AZA (total) (n = 221)</th>
<th>AZA mono (n = 157)</th>
<th>IFX + AZA (n = 64)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male, n (%) 128 (58)</td>
<td>91 (58)</td>
<td>37 (58)</td>
<td>0.984</td>
</tr>
<tr>
<td></td>
<td>Female, n (%) 93 (42)</td>
<td>66 (42)</td>
<td>27 (42)</td>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis (years; P25–75)</td>
<td>25 (20–32)</td>
<td>26 (21–34)</td>
<td>22 (17–27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time of follow-up (years; P25–75)</td>
<td>8 (3–12)</td>
<td>8 (3–14)</td>
<td>9 (4–12)</td>
<td>0.305</td>
</tr>
<tr>
<td>Median AZA dosage (mg/Kg) (P25–75)</td>
<td>2.08 (1.83–2.36)</td>
<td>2.05 (1.79–2.27)</td>
<td>2.21 (2.00–2.68)</td>
<td>0.003</td>
</tr>
<tr>
<td>Therapy length (years) (P25–75)</td>
<td>5 (2–8)</td>
<td>4 (2–7)</td>
<td>7 (3–9)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Median time from diagnosis until beginning AZA (P25–75)</td>
<td>2 (0–7)</td>
<td>2 (0–7)</td>
<td>2 (0–5)</td>
<td>0.192</td>
</tr>
<tr>
<td>Median time from diagnosis until beginning IFX (P25–75)</td>
<td>5 (2–8)</td>
<td>–</td>
<td>5 (2–8)</td>
<td></td>
</tr>
</tbody>
</table>

AZA - Azathioprine  
IFX - Infliximab  
P – Percentile.  
\(^a\) Chi-square test.  
\(^b\) Mann–Whitney test.

Before Azathioprine  

During Azathioprine  

Figure 2  Hazard Curves for hospitalization or surgery in patients before and during treatment with azathioprine, stratified in the two main indications (steroid-dependent disease and prevention of post-operative recurrence).
3.4. Hospitalization

3.4.1. AZA group

The median time to hospitalization (patients were censored at the first one) before starting immunosuppression with AZA was 137 months (Confidence Interval [CI] 95%: 106–167 months) for patients that after fell into the steroid-dependent group and 81 months (CI 95%: 50–113 months) for patients that needed surgery (p = 0.05) (Fig. 2). For the same patients, the median time to hospitalization after AZA was similar: 138 (CI 95%: 110–165) and 83 (CI 95%: 57–129) months respectively. Immunosuppression did not reduce the time to the first hospitalization, but it significantly decreased the number of patients that needed hospitalization (64% [n = 97] of patients before and 36% [n = 57] under AZA; p = 0.001) (Table 2), particularly in those treated for surgical recurrence (85% [n = 33] of patients before and 46% [n = 19] under AZA; p = 0.001) (Table 3). Hospitalization rates per person per year also decreased following the beginning of AZA, but only in the post-operative group (Tables 4 and 5).

Patients were stratified regarding the time between diagnosis and introduction of AZA (≤1 year, 1–3 years, or >3 years) and no significant differences were found in the median time to hospitalization, number of patients needing hospitalization and hospitalization rates per person per year among groups (p = 0.508).

3.4.2. AZA and IFX group

In patients on combination treatment (IFX + AZA), the addition of IFX to AZA decreased the number of patients hospitalized (56% [n = 36] before IFX and 29% [n = 17] after IFX, respectively; p = 0.009) (Table 2). The median time to hospitalization before IFX was 71 months (CI 95% 57–85 months) and after IFX was 82 months (CI 95% 69–95 months) (Fig. 3). Hospitalization rates per person per year dropped with the beginning of AZA (0.50 to 0.23) and further with the combination with IFX (0.07), p < 0.001 (Table 4).

3.5. Surgery

3.5.1. AZA group

The beginning of this drug decreased the number of patients needing surgery (37% [n = 58] before and 17% [n = 27] after AZA, p < 0.001) – Table 2 – but not the surgery rates per person per year (either globally or when stratified, Tables 4 and 5). Patients on AZA due to steroid-dependence had the highest cumulative hazard for surgery: 328 months (CI 95%: 295–361 months), (Fig. 2). The median time to surgery in patients on AZA for steroid-dependency was 172 months (CI 95%: 145–200 months) and 141 months (CI 95%: 123–160 months) for post-operative recurrence. There were no significant differences between the groups regarding time to surgery (Fig. 2). Once more, time from diagnosis to the beginning of AZA was analyzed (≤1 year, 1–3 years, or >3 years) and no significant differences were found in the time and rate of surgeries (p = 0.590).

3.5.2. AZA and IFX group

In the patients needing combo strategy, AZA therapy and, subsequently, the addition of IFX to AZA seemed to have no effect in the number of patients that needed surgery (Table 2). Similarly, these drugs had no effect in the surgery rates per person per year (Table 4) and in the median time to surgery (Fig. 3).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>AZA (n = 157; 71%)</th>
<th>IFX + AZA (n = 64; 29%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before AZA treatment</td>
<td>During AZA treatment</td>
</tr>
<tr>
<td>Surgery</td>
<td>58 (37)</td>
<td>27 (17)</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>97 (64)</td>
<td>57 (36)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(a) Comparison for the IFX + AZA Treatment group Before and During AZA treatment (McNemar test).

(b) Comparison for the IFX + AZA Treatment group During AZA and During IFX treatment (McNemar Test).

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>n (%)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>Surgery</td>
<td>21 (18)</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>64 (57)</td>
<td>33 (85)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Before AZA treatment</th>
<th>During AZA treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AZA Steroid Dependency</td>
<td>AZA Post-Op</td>
</tr>
<tr>
<td>Surgery</td>
<td>21 (18)</td>
<td>NA</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>64 (57)</td>
<td>33 (85)</td>
</tr>
<tr>
<td>p</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(1) Comparison between AZA Steroid Dependency group and AZA Post-Op group Before AZA treatment (Chi-square test).

(2) Comparison between AZA Steroid Dependency group and AZA Post-Op During AZA treatment (Chi-square test).

(a) Comparison between AZA Steroid Dependency group between Before and During AZA treatment (McNemar test).

(b) Comparison between AZA Post-Op group between Before and During AZA treatment (McNemar test).
3.6. Adverse events

Globally, 60 patients experienced adverse effects with AZA, representing 23% of the population. The most frequent reactions were pancreatitis (31 patients, 12% of the total population), gastrointestinal intolerance (nausea/vomiting/diarrhea, 10 patients, 4%), hepatotoxicity \( (n = 5, 2\%) \), and myelotoxicity \( (n = 5, 2\%) \). Among the 39 patients who had a serious adverse reaction that required the suspension of AZA (hepatitis, pancreatitis, myelotoxicity), treatment with IFX was needed in 26 patients (three of them changed posteriorly to Adalimumab), 8 started Adalimumab, one was submitted to surgery for intra-abdominal abscess and four maintained treatment only with 5-ASA (needing at least one cycle of steroids).

4. Discussion

AZA is superior to placebo for maintenance of remission in patients with CD, as shown by Candy et al. in a randomized controlled trial (RCT) published in 1995. After 15 months of follow-up, a higher proportion of patients on AZA were in remission comparing to the placebo group \( (42\% vs 7\%; p = 0.001) \). A recent meta-analysis including data from seven RCTs of AZA therapy and one of 6-MP confirmed this result. 

<p>| Table 4 | Surgery and Hospitalization rates per person per year in AZA (overall) and combo groups. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Before AZA treatment</th>
<th>During AZA treatment</th>
<th>Before AZA treatment</th>
<th>During AZA treatment</th>
<th>During IFX treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>AZA (n = 157; 71%)</td>
<td>Mdn (P25–P75)</td>
<td>Mdn (P25–P75)</td>
<td>p*</td>
<td>Mdn (P25–P75)</td>
<td>Mdn (P25–P75)</td>
</tr>
<tr>
<td></td>
<td>Surgery rates per person (per year)</td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 59</td>
<td>0.20 (0.11–0.50)</td>
<td>0.50 (0.20–0.50)</td>
<td>0.024</td>
<td>0.50 (0.25–1.00)</td>
<td>0.23 (0.13–0.27)</td>
</tr>
<tr>
<td></td>
<td>n = 27</td>
<td>0.20 (0.14–0.33)</td>
<td>0.33 (0.20–0.50)</td>
<td>0.216</td>
<td>0.25 (0.13–0.43)</td>
<td>0.20 (0.08–0.11)</td>
</tr>
<tr>
<td></td>
<td>n = 10</td>
<td>0.23 (0.13–0.27)</td>
<td>0.05 (0.08–0.11)</td>
<td>0.147</td>
<td>0.20 (0.13–0.25)</td>
<td>0.10 (0.08–0.25)</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>0.10 (0.08–0.11)</td>
<td>0.10 (0.08–0.25)</td>
<td>0.07</td>
<td>0.23 (0.17–0.25)</td>
<td>0.17 (0.08–0.25)</td>
</tr>
<tr>
<td></td>
<td>n = 5</td>
<td>0.10 (0.08–0.11)</td>
<td>0.17 (0.08–0.25)</td>
<td>0.147</td>
<td>0.26 (0.17–0.25)</td>
<td>0.17 (0.08–0.25)</td>
</tr>
</tbody>
</table>

** Mdn — median; P — Percentile; * Comparison between rates Before and During AZA treatment in the AZA group treatment only for the cases that had any Surgery or Hospitalization, respectively. ** Comparison between rates Before, During AZA treatment and During IFX treatment in the IFX + AZA group treatment only for the cases that had any Surgery or Hospitalization, respectively.

| Table 5 | Surgery and Hospitalization rates per person per year in AZA (stratification). |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | AZA group (n = 157; 71%) | Before AZA treatment | During AZA treatment | During AZA treatment | During AZA treatment |
|                | AZA Steroid Dependency | Mdn (P25–P75) | p (1) | Mdn (P25–P75) | p (2) | p* | p** |
| Surgery        | n = 22          | 0.18 (0.10–0.33) | 0.20 (0.12–0.50) | 0.216           | 0.860          | 0.262          | 0.932 |
| Surgery rates per person (per year) | n = 64 | 0.37 (0.20–1.00) | 0.26 (0.25–1.00) | 0.262           | 0.07           | 0.428          | 0.007 |
| Hospitalization | n = 64          | 0.37 (0.20–1.00) | 0.26 (0.25–1.00) | 0.262           | 0.07           | 0.428          | 0.007 |

Mdn — median; P — Percentile; * Comparison between rates Before and During AZA treatment in the AZA Steroid Dependency group treatment; ** Comparison between rates Before and During AZA treatment in AZA Post-Op group treatment.

(1) Comparison between AZA Steroid Dependency and AZA Post-Op group Before AZA treatment (Mann–Whitney test).
(2) Comparison between AZA Steroid Dependency and AZA Post-Op group During AZA treatment (Mann–Whitney test).
(3) Surgery rates per person per year = (Number of surgeries between the two dates) / (Time Duration in years between two time periods).
(4) Hospitalization rates per person per year = (Number of hospitalizations between the two dates) / (Time Duration in years between two time periods).
Figure 3  Hazard Curves for hospitalization or surgery in patients before and during treatment with azathioprine, and after the addition of infliximab.
RCTs are essential for the drug development process but they are not representative of clinical practice. Observational studies provide real life complementary information on management and outcomes of healthcare problems. In this paper we assessed the long-term therapeutic and safety profiles of AZA treatment in a real life cohort of 260 CD patients from a tertiary hospital with a maximum follow-up time of 21 years. Eighty-one percent of the patients in our sample were treated with AZA due to steroid-dependency and only a minority for post-operative recurrence prevention. This is similar to previous reports.10,11

CD is a chronic destructive disease that warrants medical intervention prior to the onset of gut damage (stricture, fistula or abscess) to improve the outcome and avoid loss of gastrointestinal function and disability. Nowadays, the main goals of the medical treatment in CD are steroid-free sustained clinical remission, reduction of hospitalization rate and prevention of surgery. The efficacy of biological therapy, namely, anti-TNF agents, questioned the relevance of conventional immunosuppression, as they have been shown to improve symptoms and to induce mucosal healing.12,13 However, as shown in RCTs, 25% to 40% of patients who initially benefit from treatment with an anti-TNF agent develop adverse events or lose their response during maintenance therapy.14

To our knowledge, the long-term outcome of thiopurine treatment for CD in the real world was showed by 7 observational studies.11,15–20 Four of them reported data from CD and ulcerative colitis. Herein, 33% of patients on AZA therapy due to steroid-dependency were in clinical remission at the end of follow-up. The meta-analysis from Pearson et al., which included five randomized, placebo-controlled trials, reported higher rates of success for AZA treatment,21 but the more recent SONIC trial22 found a steroid-free clinical remission rate of 30% at week 26. The therapeutic effectiveness of thiopurines reported in older real-life studies from O’Brien et al.,20 Korelitz et al.19 and Fraser et al.16 was between 45% and 76%. More recent studies depicted higher effectiveness rates up to 80%11,15,17,18; however, they assessed remission and in our work remission without corticosteroids for at least one year was noticed.

The number of patients hospitalized decreased significantly after AZA, either in the steroid-dependency group or in the post-operative group. Concerning hospitalization rates per person per year, AZA was also effective, but only in the post-operative group. The results of our study regarding surgery were less optimistic than hospitalization; the introduction of AZA, even reducing the number of patients submitted to surgery, was not effective when analyzing the steroid-dependent group separately or when calculating the surgery rates per person per year. The data supporting the early use of immunosuppressors to prevent surgery or complications are difficult to interpret since no randomized studies have evaluated this outcome. Some retrospective studies evaluated the benefit of the early use of immunosuppressors, being controversial, with some suggesting a reduction in surgery rates23–25 while others failed to show it.9 In our cohort, the early use of AZA did not decrease the median time to surgery.

Concerning safety, 15% of our patients failed thiopurine maintenance therapy due to side effects, mainly pancreatitis and gastrointestinal intolerance. This result is consistent with previous reports, showing that up to one third of patients on thiopurine therapy have side effects that preclude its use.16,26 Thirty-one patients from our series (12%) had to discontinue AZA due to pancreatitis, which is considerably more than the 2.6–4.9% previously reported by others.27,28 We did not find any particular explanation for this high number of pancreatitis, but it was diagnosed using consensual criteria. All patients were hospitalized, and all cases were mild, solving within a few days with suspension of AZA and alimentary pause. For patients intolerant to AZA, anti-TNF treatment was generally the next step, and in fact, in our cohort, most of the thiopurine intolerant patients (n = 39) started anti-TNF therapy (26 – IFX; 8 – ADA) and all of them avoided surgery at the end of follow-up. Sixty-two percent of those on IFX were able to achieve clinical remission.

For those submitted to bowel resection, post-operative recurrence remains a hot topic. In fact, endoscopic recurrence occurs in the neo-terminal ileum in 73% of patients within one year, and clinical recurrence rates exceed 30% within one year and 80% twenty years after resection.7,29,30 In our study, when we analyzed the outcome of patients before and after starting AZA in the post-operative group, we were comparing patients before and after being submitted to surgery. We found that the addition of AZA modifies the natural history of the disease in the post-operative setting, changing the recurrence rates reported by others.7,29,30 Efficacy of thiopurines in the prevention of postoperative recurrence was evaluated in four controlled trials.31–35 In the meta-analysis from Peyrin-Biroulet et al., patients with CD have a significantly lower risk of postoperative endoscopic recurrence at 1 year and clinical recurrence at 1 and 2 years when treated with thiopurines when compared with placebo with or without antibiotic induction therapy, or mesalamine.6 In our patients, 61% of patients on AZA for postoperative recurrence were in clinical remission at the end of follow-up.

The retrospective nature of our study is a limitation but we believe that the three goals chosen were easily and confidently identifiable in a database, namely corticosteroid-sparing effect, hospitalizations and surgeries; indeed they constitute surrogates markers of disease control. In the 21-year period of follow-up, the therapy of CD evolved, but the major changes were probably the way we prescribed anti-TNF agents; regarding the use of AZA, we think that the indications remained similar during this period, and therefore we believe that the criteria for beginning AZA treatment were very similar throughout the follow-up. There are, however, several strengths: 1) it is a real-life study with one of the largest number of patients and 2) all patients were followed by the same gastroenterologist, turning the decisions more homogenous and the results more reliable.

In conclusion, herein we confirm the efficacy of AZA in achieving corticosteroid sparing effect and in the ability to decrease hospitalizations over a long period of time in a real life cohort. It was unable to decrease surgery rates and in one sixth of the patients the side effects precluded its use. Nevertheless, we emphasize that the median time to beginning AZA or IFX since diagnosis was very long (median 2 years) and this could definitely affect AZA effect in CD outcome and, in some way, reflects inefficacy of step-up therapeutic approach.

Conflict of Interest

The authors do not have conflicts of interest to declare.
References


