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

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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

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person per year ($p < 0.001$), but had no effect in the surgery rates per person per year. Sixty patients (23%) experienced adverse effects with AZA, 39 requiring discontinuation of the drug.
Conclusions: In this real-life study, azathioprine had a long-term steroid sparing effect and reduced hospitalizations. Combination with infliximab reduced hospitalizations but did not decrease the surgery rate.

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 post-operative 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