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Alimentary Tract

The use of thiopurines for the treatment of inflammatory bowel diseases in clinical practice

S. Saibeni [a,*], T. Virgilio [a], R. D'Incà [b], L. Spina [c], A. Bortoli [d], M. Paccagnella [b], M. Peli [d], R. Sablich [e], G. Meucci [f], E. Colombo [g], G. Benedetti [e], C.M. Girelli [h], G. Casella [i], G. Grasso [j], R. de Franchis [a], M. Vecchi [c]

[a] *IRCCS Policlinico Hospital, Mangiagalli and Regina Elena Foundation Milan, Italy*
[b] *Department of Surgical and Gastroenterological Sciences, University of Padua, Padua, Italy*
[c] *IRCCS Policlinico San Donato, San Donato Milanese, Italy*
[d] *Rho Hospital, Rho, Italy*
[e] *Hospital "S. Maria degli Angeli", Pordenone, Italy*
[f] *Valduce Hospital, Como, Italy*
[g] *Hospital "G. Salvini", Garbagnate, Italy*
[h] *Busto Arsizio Hospital, Busto Arsizio, Italy*
[i] *Desio Hospital, Desio, Italy*
[j] *Angera Hospital, Angera, Italy*

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Abstract

Background. Thiopurines are the most commonly used immunomodulatory drugs in inflammatory bowel diseases.

Aim. To evaluate the use, the therapeutic and safety profiles of thiopurines in a large sample of IBD patients.

Methods. We reviewed 3641 case histories of IBD patients. Thiopurines were prescribed in 582 patients (16.0%); the analysis was performed on the 553 (267 ulcerative colitis, 286 Crohn's disease) with exhaustive clinical data.

Results. The main indications for treatment were steroid-dependence (328/553, 59.3%) and steroid-resistance (113/553, 20.7%). Thiopurines were started when CD were younger than UC patients ($p < 0.001$) but earlier from diagnosis in UC than in CD patients ($p = 0.003$). Efficacy was defined as optimal (258/553, 46.6%), partial (108/553, 19.5%), absent (85/553, 15.4%) and not assessable (102/553, 18.4%). Efficacy was independent of disease type, location/extension or duration and age at starting. Side effects were observed in 151/553 (27.3%) patients, leading to drug discontinuation in 101 (18.3%). 15 out of the 130 (11.5%) patients who took thiopurines for more than 4 years relapsed, more frequently in CD than in UC (OR = 3.67 95% C.I. 0.98–13.69; $p = 0.053$).

Conclusions. Thiopurines confirm their clinical usefulness and acceptable safety profile in managing complicated IBD patients. The majority of patients treated for longer than 4 years maintain response. No clinical and demographic predictive factors for efficacy and side effects were identified.

Keywords: Inflammatory bowel diseases; Therapy; Thiopurines

1. Introduction

The thiopurine analogues mercaptopurine (MP) and its prodrug, the nitroimidazole derivative azathioprine (AZA), are the most widely used immunosuppressive agents in inflammatory bowel diseases (IBDs).

AZA and MP are characterized by a complex metabolism in which the involved enzymes are in constant competition for

* Corresponding author. Present address: Department of Internal Medicine and Hepatology, Fatebenefratelli and Oftalmico Hospital, Corso di Porta Nuova 23, 20121 Milan, Italy. Tel.: +39 0263632489; fax: +39 0263632714.
E-mail address: saibo@tiscali.it (S. Saibeni).

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the substrate [1]; their mechanisms of action are still not fully elucidated. The main immunosuppressive effect appears to be mediated by the active metabolites 6-thioguanine nucleotides (6-TGN) by incorporation into DNA of leukocytes as fraudulent bases [2] and by induction of T-cell apoptosis [3] but additional anti-proliferative effects have been proposed [4,5].

Since the first report in the late 1960s of the past century [6], several papers investigated the role of thiopurines in IBD and the majority of data, with more or less convincing evidence, suggests that AZA is effective both in inducing and maintaining remissions of Crohn's disease (CD) and ulcerative colitis (UC) [7], the two major forms of IBD.

In clinical practice, AZA and MP are used virtually interchangeably with the exception of dosing. The onset of their full activity is slow and may take more than 3 months, and their use is complicated by several side effects which are typically considered as dose-independent or dose-related [7].

The aim of this study was to retrospectively evaluate the use, the therapeutic and the safety profiles of thiopurines in a large sample of IBD patients. Information arising from clinical practice may give a reliable measure of the effectiveness, the toxicity and acceptability of a given therapy, which may significantly differ from the data resulting from the ideal conditions created in clinical trials.

2. Materials and methods

2.1. Patients

We reviewed 3641 case histories of IBD patients that were followed at the 8 participating centres; AZA or MP had been prescribed in 582 of them (16.0%).

The analysis was performed on 553 patients (267 UC, 278 CD, 8 indeterminate colitis (IC)) with complete clinical and demographic data; for patients treated more than once with thiopurines we considered only the first course of therapy. The 8 IC patients were combined with patients with CD, as already suggested by other authors [8] for the purpose of clinical analysis. In most patients, blood chemistry was performed at screening, every 7–14 days for the first 3 months or during dose adjustment and then every 3 months.

CD location and behaviour were defined according to the Vienna classification [9].

2.2. Thiopurines treatment

The time of observation was calculated from the date of therapy initiation until the discontinuation or the last contact with the patient still taking thiopurines.

2.2.1. Indications

Indications to treatment with thiopurines were defined as follows:

- "steroid-dependence": partial or complete clinical response to treatment with prednisone or equivalent and relapse with a dose reduction of prednisone at doses $\leq$15–25 mg/day for at least 6 months or relapse within 30 days of stopping prednisone treatment [10];
- "steroid-resistance": failing to respond within 30 days to prednisone treatment at doses of 40–60 mg/day [10];
- "penetrating disease": presence of fistulas and/or abscesses;
- "post-surgery": after surgically induced remission, as prophylactic treatment;
- "extraintestinal manifestations (EIMs)": when the main indication was represented by an extraintestinal manifestation;
- "infliximab (IFX)": when thiopurines were concomitantly prescribed in association with infliximab treatment.

2.2.2. Efficacy

Efficacy of thiopurines therapy was evaluated as follows:

- "optimal", when steroids were stopped and/or no further treatment was needed over 2 years from the beginning;
- "partial", when steroids were reduced/discontinued and/or additional treatment started within 2 years from the beginning;
- "absent", when no clinical effect was observed over 6 months and/or additional treatment or surgery became necessary within 1 year from the beginning;
- "not assessable", when the available follow-up was too short (less than 6 months) [8] or side effects led to early treatment discontinuation.

2.2.3. Discontinuation

Reasons for thiopurine discontinuation were classified as follows:

- Side effects, long-lasting treatment (patients in remission after at least 3 years of drug), patient's decision, inefficacy, neoplasm, infection, pregnancy.

2.2.4. Toxicity

The main side effects were defined as follows:

- "Myelotoxicity": white blood cells count $<3000\,mm^{-3}$ and/or platelets $<70{,}000\,mm^{-3}$ and/or haemoglobin <10 g/dl.
- "Liver toxicity": transaminases and/or γ-GT and/or ALP > 1.5 upper limit normal in at least two repeated assessments.
- "Pancreatitis": abdominal symptoms accompanied by amylase and/or lipase increase.
- "Systemic toxicity": occurrence of one of the following signs or symptoms: fever, skin rash, arthralgias, asthenia, myalgia, diarrhea, nausea, abdominal pain.
- "Infection": bacterial, viral or fungal (when requiring specific treatment and/or hospitalization and/or drug discontinuation).