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Short Report

How thiopurines are used for the treatment of inflammatory bowel diseases: An Italian survey

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ABSTRACT

Background: The ideal manner of thiopurine use in inflammatory bowel disease has not been defined. We aimed at investigating the attitudes of Italian gastroenterologists on thiopurine use.
Methods: A web-based survey was performed among 295 gastroenterologists.
Results: Overall, 70 surveys were completed. At baseline, thiopurine methyltransferase genotype and phenotype were not assessed by 87.1% and 97.1% of respondents, respectively. At treatment onset, 17.1% adopted full weight-calculated dose while 80.0% preferred escalating the dose. During treatment, 87.1% and 64.3% reduced the dose for myelo- and liver toxicity, respectively; 48.6% for increased pancreatic enzymes, 17.1% for fever, and 5.7% for arthralgia. A systematic shift from one thiopurine to the other was reported by 4.3% of respondents in case of failure, and by 5.7% for adverse effects. Forty-four gastroenterologists (62.9%) stopped thiopurine treatment after 5–7 years.
Conclusions: Several discrepancies regarding the use of thiopurines in clinical practice were found, deviating from available guidelines. A more standardised attitude is needed in clinical practice.

1. Introduction

The thiopurine analogues 6-mercaptopurine (6-MP) and its prodrug, the nitroimidazole derivative azathioprine (AZA), are the most widely used immunosuppressants in inflammatory bowel diseases (IBD) [1,2]. They can be used virtually interchangeably with the exception of dosing [3].

The onset of thiopurines' full activity is slow and may take more than 3 months; also, their use may be complicated by several side effects that are either dose-independent or dose-related [2].

It has been suggested that genetic polymorphism determination, as well as phenotypical activity assessment of enzymes involved in the thiopurine metabolism (e.g. thiopurine methyltransferase, TPMT), may be useful in preventing possible severe side effects on bone marrow function [4–7]. Interaction with concomitant medications, such as 5-aminosalycilic acid (5-ASA) [8] and allopurinol [9], may alter the safety and efficacy profiles of thiopurines. Monitoring of the thiopurine metabolites (i.e. 6-thioguanine nucleotides, 6-TGN, and 6-methylmercaptopurine, 6-MMP) may predict toxicity and can be useful in evaluating treatment intensity and patient's adherence to treatment [10,11]. In addition, switching from one thiopurine to the other in case of intolerance may be useful in re-gaining a therapeutic opportunity [12].

However, since studies provided controversial results [13,14] there is no unanimous agreement on the real effectiveness of these attitudes in clinical practice.

The aim of this study was to evaluate the conducts of Italian gastroenterologists (GEs) treating IBD patients with thiopurines.

2. Methods

The survey consisted of a web-based questionnaire. Questions concerned physicians' behaviour about drug choice, starting dose, toxicity and failure management, therapy duration. Physicians flagged the answers selected, and only in some cases an open answer was required.

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An invitation to complete the survey was sent by e-mail to the 295 members of the Italian Group for Inflammatory Bowel Disease (IG-IBD); a second invitation was sent after two months.

Myelotoxicity and hepatotoxicity were evaluated as previously defined [15].

The GraphPad Instat package software (GraphPad Software Inc., San Diego, CA, USA) was used to analyse data by means of the Fisher's exact test and Chi-square test for independence, as appropriate. The statistical tests were two-tailed and the statistical significance was set at $p = 0.05$.

3. Results

Seventy out of 295 GEs (23.7%) filled the questionnaire comprehensively (Table 1).

3.1. Treatment modalities

Before starting therapy, 61 (87.1%) and 68 (97.1%) GEs did not perform genotype or phenotype testing for TPMT, respectively; 6 (8.6%) and 2 (2.9%) GEs tested them for research purposes.

At therapy onset, 68 (97.1%) GEs chose AZA. Informed consent to treatment was obtained orally by 54 (77.1%) GEs, while signing the case history was obtained by 6 (8.6%) and signing the exhaustive document by 10 (14.3%) GEs.

As far as optimal dose is concerned, for AZA 36 (51.4%) GEs used 2 mg/kg/day, whereas 34 (48.6%) used 2.5 mg/kg/day; for 6-MP, 30 (42.9%) GEs used 1 mg/kg/day, whereas 40 (57.1%) used 1.5 mg/kg/day.

Twelve (17.1%) GEs immediately adopted the full weight-calculated dose, whereas 56 (80.0%) preferred a dose-escalation strategy. Among the latter group, 20 (35.7%) started with AZA 50 mg, increasing by 25 mg every 7–14 days, while the others did not follow any scheduled strategy. Two (2.9%) GEs established dosage according to TPMT genotype.

The concomitant use of 5-ASA was considered "irrelevant" by 55 (78.6%) GEs, "to avoid" by 6 (8.6%) GEs, and "to encourage" by 9 (12.8%).

The duration of thiopurine therapy is shown in Fig. 1.

3.2. During therapy

3.2.1. Treatment monitoring and toxicity management

The parameters assessed by blood tests are shown in Fig. 2.

Table 1
Features of responding physicians.

	n (%)
Age	
<30 years	6 (8.7)
30–39 years	19 (27.1)
40–49 years	19 (27.1)
50–59 years	19 (27.1)
>60 years	7 (10.0)
Affiliated hospitals	
Public, non academic	35 (50.0)
Public, academic	24 (34.3)
Private, non-academic	7 (10.0)
Private, academic	4 (5.7)
Number of IBD patients followed	
<100	5 (7.1)
100–499	36 (51.5)
500–999	10 (14.3)
1.000–1.499	12 (17.1)
>1.500	7 (10.0)

IBD, Inflammatory Bowel Disease

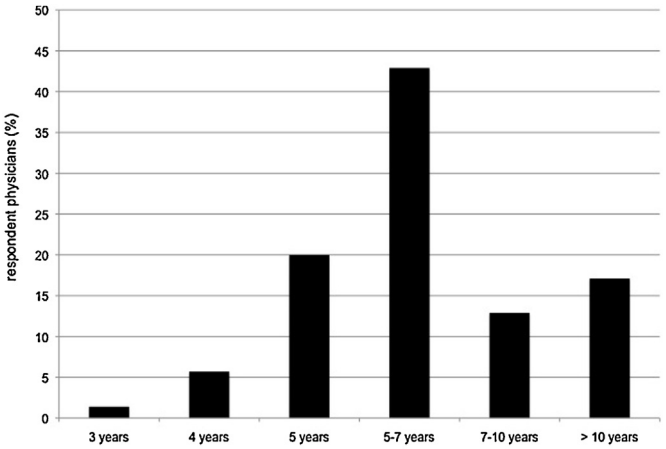

Fig. 1. Duration of thiopurine therapy. Bars represent the percentage of respondent physicians.

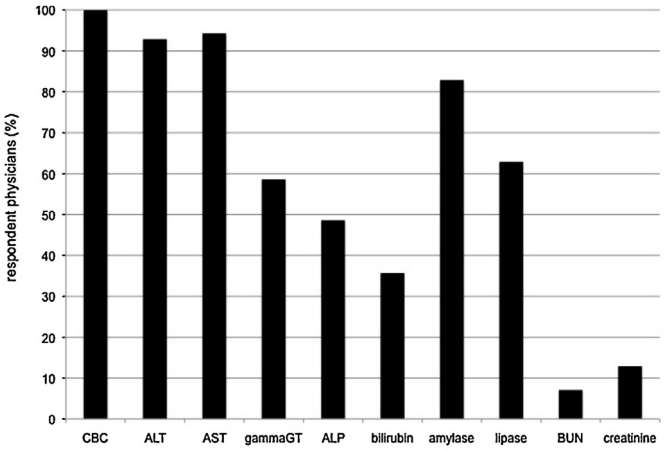

Fig. 2. Blood chemistry for monitoring thiopurine toxicity. Bars represent the percentage of respondent physicians. CBC, complete blood count; ALT, alanine aminotransferase AST, aspartate aminotransferase gammaGT, gamma-glutamil transpeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.

Fifty-five (78.6%) GEs performed tests every 15 days for the first 3 months, monthly for 3 more months, and every 3 months during treatment. Fourteen (20.0%) GEs performed tests every 7–10 days during dose adjustment and then every 2 months; one physician performed complete blood counts (CBC) every 6 months during treatment.

In case of toxicity, 4 (5.7%) GEs systematically shifted from one thiopurine to the other, whereas 9 (12.9%) did not shift.

The side effects leading to dose reduction and thiopurines shifting are listed in Table 2.

Table 2
Management of thiopurine toxicity.

Side effect	Dose reduction *n* (%)	Thiopurine shift *n* (%)[a]
Myelotoxicity	62 (88.6)	5 (8.8)
Hepatotoxicity	47 (67.1)	16 (28.1)
Increase of pancreatic enzymes	36 (51.4)	5 (8.8)
Gastrointestinal symptoms	29 (41.4)	43 (75.4)
Fever	13 (18.6)	15 (26.3)
Arthralgias	12 (17.1)	18 (31.6)
Skin manifestations	–	2 (3.5)

[a] Denominator is 57 instead of 70 (see text).