Short Report

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

Simone Saibeni a,*, Anna Kohn b, Gianmichele Meucci c, Claudio Papi d, on behalf of the Italian Group for Inflammatory Bowel Disease (IG-IBD)

a Azienda Ospedaliera Guido Salvini, Ospedale di Rho, Rho, Italy
b Azienda Ospedaliera San Camillo Forlanini, Rome, Italy
c Ospedale San Giuseppe, Milan, Italy
d Azienda Ospedaliera San Filippo Neri, Rome, Italy

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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.

Conclusion: 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.

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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-aminosalicylic 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 conduct 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.
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%) 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>
<thead>
<tr>
<th>Table 1</th>
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| **Table 1**  
Features of responding physicians. |

<table>
<thead>
<tr>
<th>Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>19 (27.1)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>19 (27.1)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>19 (27.1)</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td><strong>Affiliated hospitals</strong></td>
<td></td>
</tr>
<tr>
<td>Public, non academic</td>
<td>35 (50.0)</td>
</tr>
<tr>
<td>Public, academic</td>
<td>24 (34.3)</td>
</tr>
<tr>
<td>Private, non-academic</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Private, academic</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td><strong>Number of IBD patients followed</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>100–499</td>
<td>36 (51.5)</td>
</tr>
<tr>
<td>500–999</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>1,000–1,499</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>&gt;1,500</td>
<td>7 (10.0)</td>
</tr>
</tbody>
</table>

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-glutamyl 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%) 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>
<thead>
<tr>
<th>Table 2</th>
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| **Table 2**  
Management of thiopurine toxicity. |

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Dose reduction n (%)</th>
<th>Thiopurine shift n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelotoxicity</td>
<td>62 (88.6)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>47 (67.1)</td>
<td>16 (28.1)</td>
</tr>
<tr>
<td>Increase of pancreatic enzymes</td>
<td>36 (51.4)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>29 (41.4)</td>
<td>43 (75.4)</td>
</tr>
<tr>
<td>Fever</td>
<td>13 (18.6)</td>
<td>15 (26.3)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>12 (17.1)</td>
<td>18 (31.6)</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>–</td>
<td>2 (3.5)</td>
</tr>
</tbody>
</table>

* Denominator is 57 instead of 70 (see text).
3.2.2. Management of thiopurine failure

In the absence of clinical benefit, 2 (2.9%) GEs stopped thiopurines after 3 months, 8 (11.4%) 4 months, 46 (65.7%) 6 months, 12 (17.1%) 9 months, and 2 (2.9%) after 12 months.

In case of failure, 3 (4.3%) GEs systematically shifted from one thiopurine to the other, whereas 49 (70.0%) GEs never shifted, and 18 (25.7%) decided case-by-case.

Finally, no significant associations between the attitudes towards thiopurines use and specific physicians’ features were observed (data not shown).

4. Discussion

The percentage of GEs that responded to the questionnaire (1 out of 4) is similar to other comparable surveys [16,17].

As already shown [15], in Italy AZA is largely preferred to 6-MP. All physicians aimed at the recommended doses [3]: 1–1.5 mg/kg/day for 6-MP and 2–2.5 mg/kg/day for AZA; in a previous study [17], respectively 5% and 6% of the GEs used a target dose above these thresholds.

Before starting therapy, very few physicians performed geno-
type (12.9%) or phenotype (2.9%) testing for TPMT; this differs from other surveys in which the percentage was around 30–40% [16,17]. None of the physicians we surveyed routinely assessed 6-TGN and 6-MMP erythrocytes concentrations during therapy, in contrast to 45–55% reported by other authors [16,17].

Despite the suggested usefulness of pharmacogenetics and therapeutic drug monitoring (TDM) in optimizing thiopurine therapy [18,19], the most recent guidelines do not mention their routine use [20,21]. In fact, there is no consensus on their real benefit, and they are not widely adopted in clinical practice. Other factors possibly limiting their application in Italy may be non-reimbursement, limited accessibility, and length of time to obtain the test results.

Regarding concomitant therapy with 5-ASA, the Italian GE sur-
veyed appear to be in agreement both with authors stating the minimal clinical significance of the putative interaction between 5-ASA and TPMT [22], and with those continuing 5-ASA therapy in patients in whom thiopurines have been started [23].

Thiopurine therapy was started at the full weight-calculated dose by 17% of the physicians, slightly less than reported by another survey (23% for 6-MP, and 28% for AZA) [16]. Among physicians that used a dose-escalation strategy, only one third followed a previously suggested scheme [24]. Despite larger evidence from a tertiary-centre supporting the dose-escalation method [25], there is still no agreement on how to start thiopurine therapy. Due to the inverse relationship between TPMT enzyme activity and myelotox-
icity, a previous study [19] suggested to start with the full dose in patients with normal genotype or activity level, to reduce it by half in patients with heterozygous genotype or intermediate activity level, and to strongly limit (or even avoid) the use of these drugs in patients with absent or homozygous-deficient TPMT activity. How-
ever, starting with low doses only delays, but does not prevent, dose-dependent toxicity and dose-independent reactions. On the other hand, starting with the full dose could avoid further delaying the slow onset of action of these drugs. Again, the available guidelines do not provide clear and unequivocal recommendations [20,21].

Four out of five physicians performed blood tests with timing modalities in agreement with the previous recommendations [24–26]. All physicians performed CBC; a proportion essentially far from the much lower percentages (57%) previously reported [27]. Importantly, no unanimous recommendations exist on the type and frequency of the blood testing that needs to be performed [28,29]. CBC and liver tests empirically appear to be the parameters to assess [18,25], but no indication exists about pancreas and nephrotoxi-
city monitoring. To the best of our knowledge, these are the first exhaustive data about the real-life laboratory monitoring during thiopurine therapy.

Dose reduction was performed in case of dose-dependent side effects but, quite surprisingly, also in case of dose-independent side effects, such as increased pancreatic enzymes, fever, and arthralgia. It has been suggested that the absence of the nitroimidazole derivative could account for a possible better tolerability of 6-MP. In recent years, a number of case series and, more recently, a larger study have shown that, in patients intolerant to AZA, a potential treatment strategy consists in switching them to 6-MP [12]. However, the rates of the reported tolerances are widely variable and no clear and reliable recommendations are available [20,21]. In our survey, in case of toxicity around 5% of the GEs systematically shifted from one thiopurine to the other, whereas 13% did not. The switch was more frequent in case of gastrointestinal symptoms (75.4%). In case of failure 5% of the GEs systematically shifted from one thiopurine to the other, whereas 70% did not.

In case of unsatisfactory clinical improvement thiopurine with-
drawal was unevenly performed. It is known that the peak of response is reached after 17 weeks of treatment [30], but several physicians prolonged therapy, despite inefficacy, up to 9 (17%) or 12 (3%) months.

In case of efficacy 20% of the GEs stopped thiopurine therapy after 5 years and approximately 40% after 5–7 years; of interest, around 17% of the GEs systematically stopped thiopurines after 10 years. Despite the fact that the available guidelines do not provide a definite duration of therapy [20,21,28–31], on basis of the avail-
able evidence one can affirm that thiopurines therapy should last at least 4–5 years. The possibility of a longer duration (e.g. more than 10 years) is also contemplated [32]; when prolonged therapy is needed, benefits and risks, such as increased rate of lymphopro-
liferative disorders and non-melanoma skin cancers [33,34], should be discussed with the individual patients.

Our survey provides interesting, exhaustive, and reliable data. Possible limitations may be represented by its nature (i.e. asking physicians what they do, does not necessarily reflect their actual clinical practice) and by the low percentage of responders, despite the latter being similar to that of previous, comparable studies.

Overall, our findings demonstrate the scarce confidence of Italian IBD specialists with thiopurines and the persisting discrepancies in their use. The available American, British, and European guidelines are lacking the relevant practical information and, in some cases, thiopurines are even disregarded as in other IBD fields [35–37].

Unequivocal indications regarding the persisting “grey zones” in the use of thiopurines in IBD are strongly needed in order to consolidate and improve the quality of patient care. This could be done also at a national level by considering the differences of health systems and resources availability in the different countries.

Conflict of interest
None declared.

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References


