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Patients’ beliefs about medicine are associated with early thiopurine discontinuation in patients with inflammatory bowel diseases


Introduction

Thiopurines are seen as the cornerstone in the maintenance treatment of inflammatory bowel disease (IBD). Although thiopurines are effective in the treatment of ulcerative colitis (UC) and Crohn’s disease (CD), up to 40% of patients discontinue treatment within 1 year [1,2]. Several factors may result in early treatment discontinuation, such as occurrence of side effects or lack of effectiveness. Apart from the actual occurrence of side effects or the lack of effectiveness, patients’ beliefs about the necessity for the treatment (e.g. the personal need for the prescribed drug) and concerns regarding potential drawbacks of treatment (e.g. side effects, long-term effects, or dependence) may influence the motivation to start and continue medication [3,4].

Patients with IBD have relatively high levels of necessity, which suggests a high need for medical treatment [3,5]. Nevertheless, nonadherence to medication is reported in 30–60% of patients [3,6]. This results in an increased flare risk and a lower quality of life [6]. Nonadherence to thiopurines might seduce the attending physician to an unjustified switch to expensive biologic drugs in an effort to control disease, thereby placing an increased burden on healthcare resources. In IBD, as in other diseases, nonadherence is more frequently encountered in patients with stronger concerns or lower perceived necessity of treatment [7–10].

Evaluation of treatment adherence is a challenge. Objective methods to assess treatment adherence such as drug tests in blood or urine are cumbersome and not available for all drugs; therefore, adherence is frequently assessed by indirect methods to assess treatment adherence such as drug tests in blood or urine are cumbersome and not available for all drugs; therefore, adherence is frequently assessed by indirect methods to assess treatment adherence such as drug tests in blood or urine are cumbersome and not available for all drugs; therefore, adherence is frequently assessed by indirect
and subjective methods [11,12]. Unfortunately, significant discrepancies exist between self-reported adherence and objective assays [13]. In thiopurine treatment, assessment of the thiopurine metabolites 6-methylmercaptopurine ribonucleotides (6-MMPR) and 6-thioguanine nucleotide (6-TGN) levels is becoming increasingly available in daily clinic for optimization and evaluation of thiopurine treatment. The presence of low levels of 6-MMPR and 6-TGN may suggest noncompliance and can therefore be used as a tool to assess treatment adherence [14]. Manipulation of adherence by taking pills just before a hospital visit is less relevant with thiopurines because it takes several weeks to achieve steady-state metabolite levels.

Identification of patients at risk for nonadherence or early treatment discontinuation would be useful in designing a targeted approach to improve adherence. Apart from the influence of personal beliefs on self-reported treatment adherence and factors associated with adherence, little is known on the effect of beliefs about medicine on steady-state thiopurine metabolite levels and, more importantly, how these beliefs may foresee treatment discontinuation [5,12]. To this end, we explored whether beliefs about IBD drugs could be associated with metabolite levels or premature treatment discontinuation of thiopurines.

**Patients and methods**

**Patients**

The current study is a post-hoc analysis of the Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics (TOPIC) trial. In the TOPIC trial, thiopurine-naive patients with IBD were randomized for standard-of-care thiopurine dosing versus a targeted approach to improve adherence. Apart from previous use of thiopurines, laboratory test abnormalities, or mercaptopurine. The main exclusion criteria were known thiopurine S-methyltransferase enzyme activity, or previous use of thiopurines. The study protocol of the TOPIC trial was approved by the Institutional review board of the Radboud University Medical Center. All patients provided written informed consent. The TOPIC trial was registered at clinicaltrials.gov, NCT00521950. The TOPIC trial complies with the Declaration of Helsinki. For a detailed description of the study design, patient selection, and patient data, we refer to Coenen et al. [15].

**Beliefs about Medicine Questionnaire**

Patients participating in the TOPIC trial were asked to complete the Beliefs about Medicine Questionnaire (BMQ) and the Medication Adherence Report Scale (MARS) 4 weeks after thiopurine initiation. Personal needs and concerns regarding a treatment can be quantified with the BMQ [16]. The BMQ is validated in patients with various chronic diseases such as asthma, rheumatoid arthritis, diabetic, renal dialysis, chronic heart disease, IBD, and psychiatric diseases [16,17].

For this study, the BMQ included statements about IBD medication and concerns (six questions; e.g. The use of these IBD drugs disrupt my life). Statements are scored on a Likert-type scale (ranging from 1 = strongly disagree to 5 = strongly agree). The sum of answers for the five statements about necessity leads to a score between 5 and 25. For concern statements, the sum of answers was divided by 6 (the number of statements) and multiplied by 5 to generate a score between 5 and 25. Plotting the necessity score at the y-axis and the concerns score at the x-axis, with a split at the midpoint, enables a classification into four belief subgroups (Table 1) [7].

**Self-reported adherence**

Self-reported adherence was assessed using the five-item MARS questionnaire [16]. Questions are related to several statements concerning adherence (e.g. I forget to take my medication or I take fewer pills than prescribed). Answers were provided on a five-point Likert scale. The sum of answers was used as a subjective marker of adherence, with a maximum score of 25, which can be considered full (self-reported) adherence.

**6-Methylmercaptopurine ribonucleotides and 6-thioguanine nucleotide metabolite measurements**

By protocol, 6-TGN and 6-MMPR levels at week 8 were assessed at a routine check-up in the first 301 patients included in the TOPIC trial. 6-TGN and 6-MMPR levels were determined in red blood cells (RBCs) by high-performance liquid chromatography according to the Lennard method [15]. Thiopurine metabolite concentrations are presented in pmol/8 × 10^8 RBCs. For analyses with metabolite levels, we used data from patients without dose adjustments in the first 8 weeks. Subtherapeutic levels were defined as 6-TGN levels below 230 pmol/8 × 10^8 RBCs, whereas therapeutic levels were defined as 6-TGN levels between 230 and 490 pmol/8 × 10^8 RBCs [18].

**Clinical response**

Clinical response was evaluated using the Harvey–Bradshaw Index in patients with CD and the partial Mayo score in patients with UC. Disease activity was measured at baseline, week 0, and at the end of the clinical trial, week 20 [19]. Treatment response was defined as a reduction of three or more points at week 20 compared with week 0 on either the Harvey–Bradshaw Index or the partial Mayo score.

**Data analysis**

For this study, all patients who completed the BMQ were included. One missing answer per subscale (necessity, concerns, or self-reported adherence part) was accepted; in that case, the

<table>
<thead>
<tr>
<th>Belief subgroup</th>
<th>Necessity score</th>
<th>Concern score</th>
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</thead>
<tbody>
<tr>
<td>Accepting</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ambivalent</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Indifferent</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Skeptical</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

A high score on both the necessity and the concern subscale is defined as a score of more than 15 points and a low score is defined as 15 points or lower.
missing value was replaced by the mean of the other answers on that subscale. Patients were excluded from this study if more than one answer per subscale was missing. Scores are presented as mean±SD, unless mentioned otherwise. Differences between respondents and nonrespondents were compared using a parametric and a nonparametric test, where appropriate. Necessity and concerns scores were compared for CD and UC using an independent-samples t-test. In the same way, necessity and concerns scores were compared between patients who continued and discontinued their thiopurine during the 5 months after treatment initiation. Treatment discontinuation was defined as a patient who stopped the initial prescribed thiopurine within 5 months. Dose reductions and temporary interruptions were accepted, provided that the interruption was not longer than 1 month [20]. Kaplan–Meier curves were plotted to illustrate the time to discontinuation for the four belief subgroups and the log-rank test was used to compare discontinuation rates. Self-reported adherence rates were compared between the different belief subgroups using the Kruskal–Wallis test. The Kruskal–Wallis test was used to compare 6-MMPR and 6-TGN levels between the different belief subgroups and the χ²-test was used to compare the number of patients with 6-TGN levels within the therapeutic range. The degree of correlation between self-reported adherence scores and metabolite levels was examined by Spearman’s correlation coefficient. Differences in treatment response for the belief subgroups were compared using the chi-squared test. A P-value of less than 0.05 was considered significant. All analyses were carried out in SPSS, version 22.0.0.1 (SPSS Inc., Chicago, Illinois, USA).

Results

Patients

Of the 796 randomized patients in the TOPIC trial, 767 patients actually started with thiopurines and 601 (78%) returned the BMQ. A total of 25 returned questionnaires were excluded because of more than one missing answer in one of the three subscales, leaving 576 (75%) patients, the respondents who successfully completed the questionnaires for further analysis. Patients who did not return the questionnaire (n=166) or who were excluded because of missing answers (n=25) were classified as nonrespondents. The characteristics of respondents and nonrespondents are shown in Table 2.

Beliefs about medicine

Patients with IBD scored (17.1±4.2) on the necessity subscale. Necessity scores were higher in patients with UC (17.8±4.2) than CD (16.6±4.1) (P<0.01). Concern scores were not different between UC (15.6±3.4) and CD (15.1±3.4) (P=0.07). Categorization of patients according to the combination of necessity and concerns score showed that 34% of the patients could be defined as accepting, 34% as ambivalent, 17% as indifferent, and 15% as skeptical (Fig. 1).

Thiopurine discontinuation rates

Of the 576 respondents, 197 (34%) discontinued the initial prescribed thiopurine within the first 5 months. Patients who discontinued treatment had higher concerns (16.3±3.6 vs. 14.8±3.2, P<0.01) and lower necessity scores (16.1±4.9 vs. 17.7±3.6, P<0.01) than patients who continued thiopurine treatment. Compared with patients in the accepting group (discontinuation rate 22%), patients classified as either indifferent (discontinuation rate 35%; P=0.02), ambivalent (discontinuation rate 37%; P<0.01), or skeptical (discontinuation rate 54%; P<0.01) all had higher discontinuation rates (Fig. 2). Moreover, discontinuation rates of patients with a skeptical profile were also higher compared with patients classified as either indifferent or ambivalent (P<0.01).

Self-reported adherence

Self-reported adherence scores, measured with the MARS questionnaire, were very high, with a median score (interquartile range) of 25.0 (24.0–25.0). Self-reported adherence scores were not different between the belief subgroups (P=0.88), 6-MMPR metabolite levels (P=0.29) and 6-TGN metabolite levels (P=0.34) were not correlated with the self-reported adherence.

Thiopurine metabolite levels

Overall, 196 (65%) of the 301 patients in whom the week eight 6-MMPR and 6-TGN levels were assessed were considered as steady state (i.e. had no dose adjustments during the first 8 weeks) and were included for further analyses [21]. The number of patients per belief subgroup with 6-TGN levels within the therapeutic range varied between 43 and 48%. 6-MMPR (P=0.99), 6-TGN (P=0.97) levels and the percentage of patients within the therapeutic range (P=0.97) were not different between the four belief subgroups (Table 3).

Clinical response

Clinical response was known for 338 (58.7%) of the 576 respondents. Categorization of these 388 patients in belief subgroups showed that 35% of the patients could be classified as accepting, 35% as ambivalent, 16% as indifferent, and 14% as skeptical, which is in line with the numbers of the entire group (Fig. 1). Treatment response rates per belief subgroup were 26% (30 out of 117) for accepting patients, 26% (31 out of 121) in ambivalent patients, 17% (nine out of 54) in indifferent patients, and 34% (16 of 47) in skeptical patients (Fig. 3). Treatment response was not different between the four belief subgroups (P=0.26).

Discussion

The present study shows that patients with IBD who perceive a low necessity or high concerns for IBD treatment were more likely to discontinue thiopurine treatment prematurely. Categorization into four belief subgroups showed that most patients could be classified as accepting or ambivalent. We found no association between belief subgroups and 6-MMPR and 6-TGN metabolite levels.

The proportion of patients per belief subgroup corroborates with those found in previous studies in IBD patients [3,22]. The relatively high scores of patients toward the necessity for treatment probably follow from a high level of disease burden in patients with IBD [23,24]. Application of the BMQ in diseases with a lower disease burden may result in higher necessity scores and consequently lower discontinuation rates.
burden, such as atrial fibrillation, indeed results in lower necessity scores than thrombosis, which has more impact [25]. The higher necessity scores of UC patients compared with patients with CD might be explained by the fact that UC exacerbations with frequent bloody diarrhea may be perceived as more severe compared with CD, which can be more subtle in presentation [26]. The fact that a third of the patients with IBD scored low on necessity for treatment may have resulted from the cyclical disease manifestation with episodes of no or only minimal disease symptoms [12].

A novel aspect of this study is that we correlated BMQ scores with treatment discontinuation rates. To date, studies using the BMQ in patients with IBD mainly focused on the exploration of factors associated with drug adherence [12,27]. Knowledge of who discontinues treatment is of high relevance, given the limited alternative options in the treatment of IBD. We showed that IBD patients with high concerns or low needs are at risk for premature discontinuation of thiopurines in the first months of treatment. Moreover, the combination of both even further increases this risk. Our findings corroborate studies in patients with IBD that showed a positive relation between the patients’ necessity and medication adherence and a negative relation in case of high concerns [12]. In the current study, the BMQ was collected 4 weeks after thiopurine initiation, which is in line with comparable study designs [25,28]. Although studies showed that patients’ beliefs are considered stable over time, the occurrence of side effects within the first weeks may have resulted in increased concern feelings at the time that the questionnaire was completed [29]. Identification of patients at risk for treatment discontinuation in an early stage might help in the design of strategies to prevent them from discontinuing treatment. Special attention should be paid to patients with high concerns as within the spectrum of IBD drugs, patients consider thiopurines as drugs with the highest risks as a result of fear of side effects and long-term drug-induced comorbidities [30]. This leads to significantly lower adherence rates for thiopurine use [31]. A comprehensive education at start and follow-up phone calls by an IBD nurse or pharmacist seem to be a promising approach to evaluate and anticipate the negative perceptions and expectations toward thiopurine treatment [6,32–34].

This study is unique as thiopurine metabolite levels were used as an indicator for treatment adherence in conjunction with self-reported adherence scores. Most studies only used self-reported adherence or pill count as a proxy for treatment adherence [3,9]. In our study, patients scored very high on self-reported adherence, whereas the number of patients in the therapeutic range varied around 45%. Previous studies reported lower self-reported adherence scores, suggesting that self-reported adherence scores in this study might be biased because of the setting of a clinical trial [3,7,9,24]. Only a few studies have compared self-reported adherence with thiopurine metabolite levels measured in blood. In one
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Table 3. Steady-state week eight 6-methylmercaptopurine ribonucleotides, 6-thioguanine nucleotide levels, and percentage of patients within the therapeutic range per belief subgroup

<table>
<thead>
<tr>
<th>Belief subgroup</th>
<th>6-MMPR (pmol/8 × 10⁶ RBCs)</th>
<th>6-TGN (pmol/8 × 10⁶ RBCs)</th>
<th>Patients within the therapeutic range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accepting (n = 76; 38%)</td>
<td>3068 (918–7352)</td>
<td>259 (204–381)</td>
<td>47</td>
</tr>
<tr>
<td>Ambivalent (n = 63; 32%)</td>
<td>3141 (681–7363)</td>
<td>271 (196–343)</td>
<td>48</td>
</tr>
<tr>
<td>Indifferent (n = 36; 18%)</td>
<td>3639 (867–6219)</td>
<td>271 (195–378)</td>
<td>44</td>
</tr>
<tr>
<td>Skeptical (n = 21; 11%)</td>
<td>4101 (813–8024)</td>
<td>264 (171–508)</td>
<td>43</td>
</tr>
</tbody>
</table>

Week 8 metabolite levels were presented as median (interquartile range). Therapeutic range was defined as 6-TGN levels between 230 and 490 pmol/8 × 10⁶ RBCs. 6-MMPR (P = 0.99), 6-TGN levels (P = 0.97), and therapeutic range (P = 0.97) were not different between the different belief subgroups.

Fig. 3. Percentage of patients with a reduction of three or more points on the Harvey–Bradshaw Index or partial Mayo score after 20 weeks for the four belief subgroups. Treatment response was not different between subgroups (P = 0.26).

of these studies, self-reported nonadherence was limited to 10% of thiopurine users, whereas in practice, only 14% had 6-TGN levels within the therapeutic range [13]. It must be stressed that many genetic and environmental factors influence thiopurine metabolism, which limits analyses between necessity or concern scores and metabolite levels [35]. This underscores the relevance, but also the difficulty, of more objective outcome measures. We found no association between the four belief subgroups and 6-MMPR and 6-TGN metabolite levels at week 8. Furthermore, there were no differences in treatment response between the belief subgroups, which seems logical, given the similar 6-MMPR and 6-TGN levels across the belief subgroups. This indicates that, at least in the short term, the BMQ does not allow to predict adherence or treatment response in patients with IBD, but only who will discontinue treatment.

A limitation of our study is that obtaining metabolite levels at week 8 might be too early in the follow-up to identify differences in levels between the belief subgroups. Nonadherence risk increases with length of treatment, whereas in this study, patients just started treatment and might still be motivated to take their pills [36]. This is supported by a study in 65 patients with IBD with an average thiopurine usage of almost 3 years, in which metabolite levels were significantly lower in patients with a low self-reported adherence [37]. Furthermore, we only used data from patients with steady-state week 8 metabolite levels. Patients with dose adjustments, frequently because of side effects, were excluded. Importantly, proportions of the four belief subgroups of patients with steady-state metabolite levels merely corresponded with numbers of the entire study group, which makes selection bias unlikely. Another limitation is that selection bias occurred, given the differences between respondents and nonrespondents in age, disease duration, and discontinuation rates. The latter can partially be explained by patients who discontinued treatment before week 4 and subsequently did not return the questionnaire [38,39]. Finally, questions in the BMQ and MARS questionnaire contained the term ‘IBD treatment’ rather than ‘thiopurine treatment’ to avoid confusion with complicated chemical drug names (azathioprine or mercaptopurine) or brand names. Therefore, it might be that patients did not answer the questions with reference to thiopurine use. However, we foresee that this influence is minimal as patients were asked to participate in a trial that focused on the initiation of thiopurines.

Conclusion

The use of the BMQ helps to identify IBD patients who are likely to discontinue thiopurines in the first months of treatment. Attention and education in the consulting room or by telephone should be given to patients with low needs and high concerns toward IBD treatment to prevent premature discontinuation.

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M.B., O.K., M.C., M.L.B., D.J. contributed to the study design; M.B., C.M., M.C., D.W., P.H., D.J., G.W. carried out data collection; M.B., W.K., M.L.B. carried out data analysis; M.B., W.K., D.J., G.W., M.L.B. carried out interpretation of data; M.B., G.W., D.J., M.C., M.L.B. contributed in writing of the manuscript; H.G., A.V., H.S., L.D., O.K., W.K. carried out critical revision of the manuscript for important intellectual content; and D.J., M.C. supervised the study.

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Conflicts of interest

There are no conflicts of interest.

References


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