ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld.2014.1121.274.tor

Patient-Reported Experiences with a Relicensed Generic: Thioguanine for the Treatment of Inflammatory Bowel Diseases

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Received: 31.10.2018
Accepted: 28.11.2018

ABSTRACT

Background & Aim: Patient-reported outcomes and experiences are indicative of the impact and the quality of care. Thioguanine, a generic drug initially developed for leukemia, has been explored and relicensed as a certified treatment for patients with inflammatory bowel diseases (IBD). The patients' perception of this treatment has not been evaluated before. In this study, we aimed to assess self-reported experiences with thioguanine for IBD.
Methods: Questionnaires were sent out to members of the Dutch National Crohn's and Colitis patient organization. The Treatment Satisfaction with Medicines Questionnaire (SATMED-Q) was used to address questions regarding the satisfaction and impact of thioguanine therapy on the disease and their daily life. Furthermore, data on demographics, disease and (historical) treatment characteristics were collected. Open-ended questions were used for additional comments to the questionnaire.
Results: A total of 173 organization members (73% female) reported to be previous or current users of thioguanine. A total of 74% were satisfied with the effectiveness of thioguanine, whereas 5% were not. Eighty percent of the respondents were satisfied with the quality of care. A good or excellent impact on daily life was reported by 54%. A neutral or bad impact on daily life was reported by 40% and 6%, respectively. Improvement of disease activity was reported by 58%. This remained stable or worsened in 39% and 3%, respectively.
Conclusion: In this self-report survey, among thioguanine treated patients with IBD who had failed with traditional therapies, 80% reported satisfaction with medical care and 74% with the effectiveness of the therapy. In the evaluation of new or rediscovered therapies, patient-reported outcomes and experiences should be considered as a key instrument.

Key words: patient-reported outcomes – patient satisfaction – pharmacology – drug rediscovery – survey data – inflammatory bowel disease – Crohn's disease – ulcerative colitis – thiopurines – thioguanine.

Abbreviations: IBD: inflammatory bowel diseases; NRH: nodular regenerative hyperplasia.

INTRODUCTION

Patient-reported outcomes and experiences are reflections of patients' perception of their quality of life, diseases and associated treatments [1]. These outcomes provide a pivotal insight into the impact and quality of treatments and are important to improve the patient-centered care. Moreover, these measurements have a valuable place in medical product labeling by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [2].

In the past 15 years, thioguanine, a thiopurine-derivative, encountered a remarkable rise, fall and a rise again for the treatment of patients with Crohn's disease and ulcerative colitis, together known as inflammatory bowel diseases (IBD) [3, 4]. This drug was introduced in 1950's for the treatment of hematological malignancies [5]. In the beginning of the 21th century, there was less demand for thioguanine as a cytostatic drug due to newer therapies in the field of oncology. In the same period, there was a growing interest in the rediscovery of thioguanine for the treatment of patients with complicated IBD. In early trials, thioguanine therapy showed promising results, especially in IBD patients who had failed prior treatment with azathioprine or mercaptopurine [6]. The interest in thioguanine, however, was globally restrained by an alarming association with drug-induced liver abnormalities, mainly nodular regenerative hyperplasia (NRH) [7]. Concerned that there might have been a premature judgement on the

benefit-risk profile of this drug, research on thioguanine as an off-label drug for IBD was continued by a limited amount of institutes. In the following studies, it appeared that drug-induced liver injury such as NRH was dose-dependent and occurred rarely during the current established thioguanine dosages (0.2-0.3 mg/kg, not exceeding 25 mg/day) [8, 9]. Following these reassuring results, and to provide a qualified treatment, thioguanine has been conditionally licensed as a certified treatment for IBD in the Netherlands since 2015 [3]. The relicensing of a generic drug for a new indication was a remarkable evolvement and created awareness regarding the relevance of the continuous development of existing drugs [10].

In spite of sufficient research on the rediscovery of thioguanine for IBD, the patients' perceptions of this drug, including their expectations and satisfaction, have not been explored before. These outcomes are valuable for the continuous evaluation of thioguanine for IBD (by physicians and legislative authorities), as well as to improve patient-centered care. In this study, we aimed to survey self-reported patient experiences with thioguanine for the treatment of IBD among the members of the Dutch Crohn's and Colitis patients' organization.

METHODS

The Crohn's and Colitis patients' organization controls a panel represented by patients with IBD who gave consent to participate in surveys about disease and treatment-related topics, which are executed several times a year. In December 2017, an online predefined questionnaire was sent to the panel members of the organization who had mentioned previously that they had been treated with immunomodulating drugs for IBD, and were willing to participate in future surveys (n = 245 patients). In addition, a link to this questionnaire was added to the Facebook group of the organization (n = 7,787 members).

Inclusion criteria were adult patients (≥ 18 years) with a self-reported diagnosis of IBD and previous or current use of thioguanine. The "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q) was used to collect data on patient-reported treatment satisfaction with thioguanine [11]. The SATMED-Q questionnaire is a valid and feasible instrument to explore patients' satisfaction with different aspects of prolonged drug treatment (i.e. side effects, effectiveness, convenience, impact on daily life, general satisfaction and satisfaction with medical care) [11-13]. Due to its generic nature, this instrument can be used in any patient regardless of the type of chronic illness or medication involved.

The questionnaire was structured as follows: questions about disease characteristics, current and historical treatment regimens (e.g. dosage, duration, co-medication), satisfaction with thioguanine (i.e. questions about effectiveness, adverse events, convenience of drug use, impact on daily life, general satisfaction and satisfaction with treatment care) and demographics. The adverse events were classified into gastrointestinal complaints, general malaise, myalgia and/or arthralgia, bone marrow suppression, pancreatitis, liver toxicity, alopecia and skin disorders. Moreover, we asked additional questions regarding treatment concerns and if they would recommend this drug to other patients. Open-ended questions were addressed to offer patients the opportunity to give additional comments to the questionnaire. Data were presented as numbers with percentages and medians with interquartile ranges (IQR).

Ethics approval and consent to participate

All patients in the Dutch Inflammatory Bowel Diseases Organization gave consent to participate in surveys about disease and treatment-related topics which are executed several times a year.

RESULTS

Patient and treatment characteristics

Out of 245 panel members of the IBD organization, 159 (65%) responded to the questionnaire. Another 127 patients (out of 7,787 members, 2%) responded through the Facebook group of the organization. We could not identify the number of Facebook members who noticed the online questionnaire on the Facebook page.

Table I. Self-reported experiences with thioguanine for inflammatory bowel disease of 173 patients.

Female	127 (73%)
Current age, years	42 (35 – 49)
Crohn's disease	109 (63%)
Current use of thioguanine	91%
Dosage of thioguanine, mg/day	20 (15 – 25)
Co-medication	54%
Adverse events	49 (28%)
Gastrointestinal complaints	12%
General malaise	11%
Myalgia and/or arthralgia	9%
Deranged liver enzymes	6%
Alopecia or skin disorders	10%
Satisfaction with effectiveness	
Good or excellent	74%
Neutral	21%
No	5%
Disease activity	
Improved	58%
Stable	39%
Worsened	3%
Satisfaction with treatment	
Good or excellent	82%
Neutral	14%
Unsatisfied	4%
Impact on daily life	
Good or excellent	54%
Neutral	40%
Bad	6%
Recommendation to other patients	
Yes	63%
Neutral	34%
No	3%

Out of 286 respondents, 173 (60%) reported to be previous or current users of thioguanine (Table I). These were 127 Facebook- and 46 panel members of the organization (out of 159 panel members who responded, 29%). Out of 173 thioguanine users, 127 (73%) were female and 109 (63%) patients had Crohn's disease. The median age was 42 years (IQR 35 – 49). Thirty-one patients (18%) had a disease duration of more than 10 years. About 97% (168/173) of the patients reported to have failed previous therapies, including azathioprine (53%), mercaptopurine (22%), methotrexate (5%) and biologicals (20%).

A total of 158 patients (91%) were current users of thioguanine. Fifteen patients (9%) reported that they had discontinued thioguanine therapy. This was due to adverse events in five (5/15, 33%), insufficient response in six (6/15, 40%) and quiescent disease in four patients (4/15, 27%). The median thioguanine dosage was 20 mg/day (IQR 15 – 25). Dosage of more than 25 mg/day was reported by 10 patients (6%). More than half of the patients (52%) used this drug for at least one year. Co-medication was reported in 54% and included corticosteroids in 18%, mesalazine in 20% and biologicals in 35%.

Toxicity and effectiveness of therapy

Adverse events were reported by 28%, including gastrointestinal complaints by 12%, general malaise by 11%, myalgia and/or arthralgia by 9%, deranged liver tests by 6% and alopecia or skin disorders by 10%. Severe or life-threatening adverse events were not reported, as well as bone marrow suppression or pancreatitis, during thioguanine therapy. A total of 59% respondents reported to have had initial concerns about the use of thioguanine. This was mainly due to mentioned adverse events on the product leaflet or the Internet and 6% reported concerns about an increased risk of skin cancer. The mentioned concerns together with the positive comments are depicted in Table II.

A total of 74% reported a good or excellent satisfaction with effectiveness of therapy, whereas 21% were neutral and 5% were not satisfied with the effectiveness. About 58% reported an improvement in disease activity during thioguanine therapy. The disease course remained stable or worsened in 39% and 3%, respectively.

Satisfaction with treatment and impact on daily life

More than 80% of the respondents reported that adequate information was provided about this drug, indicating satisfaction with medical care. Six patients (4%) were unsatisfied with the medical care. About 70% of the patients reported general satisfaction with thioguanine treatment. A total of 127 patients (73%) reported that the drug was convenient to use.

A good or excellent impact on daily life was reported by 82 patients (54%). A neutral or bad impact on daily life was reported by 40% and 6%, respectively. About 60% of the patients would recommend thioguanine as a therapy to other IBD patients, whereas five patients (3%) would discourage its use.

DISCUSSION

In this survey on self-reported experiences with thioguanine treatment for IBD, consisting of patients who failed several previous therapies, we observed that 80% were satisfied with the treatment care, whereas 4% were not. A total of 74% of patients were satisfied with the effectiveness of therapy and 54% reported an improved impact on daily life. In 6%, treatment had a bad impact on everyday life.

Table II. Comments raised by patients regarding their experiences and concerns about thioguanine treatment.

Theme	Quotes
Effectiveness and satisfaction with therapy	„I am happy that it considers one tablet per day and I did not experience any adverse events so far."
	„I failed previous therapies with four other drugs and was prednisone dependent for a long time. Finally, I got thioguanine from my gastroenterologist. I am using it for a short while but it seems to be effective."
	„The adverse events which I experienced with previous drugs did not reoccur during thioguanine therapy."
	"Very positive about the drug!"
	"I tried azathioprine for a long time but did not get in remission. Now my doctor told me for the first time that my disease is inactive."
	"I use this drug since 2006, first in an experimental setting and since 2011 together with an anti-TNF drug. I am satisfied with the efficacy.''
Concerns and/or uncertainties about therapy	„I was worried about the mentioned adverse events in the product leaflet. When I googled this drug, I read about its initial use in leukemia which worried me enormously. Then I understood that it is used in a lower dosage for the treatment of chronic bowel diseases."
	„I wish to conceive but I am afraid about the effects of thioguanine on the pregnancy and child. There is almost no information about this topic."
	„I am worried about the risk for skin cancer and infections and other adverse events such as losing my hair. I would not really recommend this drug to others."
	„I was worried about the effect of thioguanine on my other organs such as my liver and the pancreas. Currently, the therapy is effective and I have less concerns."
	"I discontinued thioguanine therapy due to pain in the joints. The pain did not disappear after cessation of therapy."
	"I developed liver test abnormalities at a higher dosage. After decreasing the dosage, I did not experience adverse events, but it seems less effective."
	"I have pre-cancerous skin lesions. I wonder if the drug had a role in this"

In recent years, there has been an increasing recognition of the importance of involving patients in both clinical and research settings to provide a patient-centered care. Consequently, patient-reported outcomes and experiences are progressively used as quality indicators of the care, also in the management of IBD [14]. Additionally, in the evaluation of new therapies, direct input from patients for whom the therapy is intended, has been considered a "key" in the medical product labeling by the FDA and EMA [2, 15].

For almost two decades, thioguanine, originally a chemotherapeutic agent, was explored and rediscovered as a treatment option for IBD. Especially in IBD patients who failed prior therapy with conventional drugs, thioguanine has been reported to be effective and well tolerated in up to 80% [16]. The wide use of thioguanine for IBD, however, has been limited by previous reports about drug-induced hepatotoxicity, especially NRH [7]. Even though it appeared that thioguanine was safe and effective when administered in precarious but adequate dosing (0.2-0.3 mg/kg, not exceeding 25 mg/day), concerns about its use seem to persist [4]. In this study, 6% of the patients reported deranged liver tests as an adverse event during therapy and 59% reported to have had initial concerns about thioguanine treatment, especially because of worrisome information in the product leaflet or the Internet. On the other hand, 63% of the patients would recommend thioguanine as a therapy to other IBD, whereas only 3% would not. These results, especially regarding concerns and satisfaction with this drug, are essential for physicians to improve the patient-centered care in thioguanine therapy.

The main strength of this study was that the questionnaire was conducted by a patient organization, compared to most surveys which are often performed in an outpatient setting, by treating physicians supervised. Therefore, we could explore 'real' patient-reported outcomes and minimize response and selection bias, which are very likely to be introduced in such surveys [1, 17]. Limitations of this self-report study were its cross-sectional design and small sample size; consequently, further (quantitative) data analysis was not performed. Furthermore, the questionnaire was sent out to a panel of selected patients of the Crohn's and Colitis organization and also added to its Facebook page. This patient organization, mostly consisting of members who voluntary participate in disease-related surveys, may be represented by patients who have more severe diseases and/or are more devoted to report complaints. Therefore prudent generalization to the broader thioguanine treated population is recommended. Moreover, our cohort mainly consisted of difficult-to-treat patients who had failed previous therapies and the half of the group was exposed to co-medication. It remains difficult to attribute the satisfaction with thioguanine solely to this drug, and other supporting co-drugs might have influenced the outcomes as well.

Additionally, self-reported outcomes on disease activity during thioguanine treatment should be interpreted with caution. The natural course of IBD is characterized by alternating periods of flare-ups and remission, reflecting the difficulty of assessing the impact of treatments on disease activity [18]. Last, we used a validated questionnaire measuring satisfaction with chronic drug treatment (SATMED-Q), which was not tested specifically in patients with IBD as a focus group. However, due to the generic nature of this questionnaire, its use by any patient population with chronic treatments has been supported [11].

CONCLUSION

The patients' perceptions of thioguanine for IBD was studied by conducting a self-report survey among the members of the Dutch Crohn's and Colitis patients' organization. Nearly all patients reported to have failed previous traditional therapies. More than half of the patients had initial concerns about thioguanine; 74% were satisfied with its effectiveness and 80% with the treatment care. It is strongly recommended to consider patients' view on their therapies as endpoints in clinical practice and trials for the optimal management of patients with chronic illnesses.

Conflicts of interest: The department of Gastroenterology and Hepatology of the Amsterdam UMC, Vrije Universiteit Amsterdam, received an unrestricted research grant by TEVA Pharma BV for conducting research on thioguanine in inflammatory bowel disease outside of this submitted work.

Authors' contribution: N.dB. was the guarantor of the article. M.S., T.M.dK. and D.vdH. conceived the study, collected and interpreted all data. M.S. drafted the manuscript and developed the tables. C.J.M., T.M.dK., D.vdH. and N.dB. revised the manuscript critically. All authors commented on drafts of the paper and approved the final draft of the manuscript.

Funding: This work did not receive any funding.

REFERENCES

1. Kingsley C, Patel S. Patient-reported outcome measures and patient-reported experience measures. Bja Educ 2017;17:137-144. doi:10.1093/bjaed/mkw060
2. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006;4:79. doi:10.1186/1477-7525-4-79
3. Simsek M, Meijer B, van Bodegraven AA, de Boer NKH, Mulder CJJ. Finding hidden treasures in old drugs: the challenges and importance of licensing generics. Drug Discov Today 2018;23:17-21. doi:10.1016/j.drudis.2017.08.008
4. de Boer NK, Reinisch W, Teml A, et al. 6-Thioguanine treatment in inflammatory bowel disease: a critical appraisal by a European 6-TG working party. Digestion 2006;73:25-31. doi:10.1159/000091662
5. Elion GB. The purine path to chemotherapy. Science 1989;244:41-47. doi:10.1126/science.2649979
6. Meijer B, Mulder CJ, Peters GJ, van Bodegraven AA, de Boer NK. Efficacy of thioguanine treatment in inflammatory bowel disease: A systematic review. World J Gastroenterol 2016;22:9012-9021.doi:10.3748/wjg.v22.i40.9012

7. Dubinsky MC, Vasiliauskas EA, Singh H, et al. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. Gastroenterology 2003;125:298-303. doi:10.1016/S0016-5085(03)00938-7
8. van Asseldonk DP, Jharap B, Verheij J, et al. The Prevalence of Nodular Regenerative Hyperplasia in Inflammatory Bowel Disease Patients Treated with Thioguanine Is Not Associated with Clinically Significant Liver Disease. Inflamm Bowel Dis 2016;22:2112-2120. doi:10.1097/MIB.0000000000000869
9. Simsek M, Meijer B, Ramsoekh D, et al. Clinical Course of Nodular Regenerative Hyperplasia in Thiopurine Treated Inflammatory Bowel Disease Patients. Clin Gastroenterol Hepatol 2018 Jan 1. doi:10.1016/j.cgh.2018.05.009
10. Simsek M, Boer N. Can we make old drugs great again? The relevance of licensing generics. 2018 October 3. Available at: https://sciencetrends.com/can-we-make-old-drugs-great-again-the-relevance-of-licensing-generics/
11. Ruiz MA, Pardo A, Rejas J, Soto J, Villasante F, Aranguren JL. Development and validation of the "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q). Value Health 2008;11:913-926. doi:10.1111/j.1524-4733.2008.00323.x
12. Rejas J, Ruiz MA, Pardo A, Soto J. Minimally important difference of the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q). BMC Med Res Methodol 2011;11:142. doi:10.1186/1471-2288-11-142
13. Rejas J, Ruiz M, Pardo A, Soto J. Detecting changes in patient treatment satisfaction with medicines: the SATMED-Q. Value Health 2013;16:88-96. doi:10.1016/j.jval.2012.08.2224
14. El-Matary W. Patient-reported outcome measures in inflammatory bowel disease. Can J Gastroenterol Hepatol 2014;28:536-542.
15. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health 2007;10 Suppl 2:S125-S137. doi:10.1111/j.1524-4733.2007.00275.x
16. Taylor KM, Ward MG, Blaker PA, Sparrow MP. Is there a role for thioguanine therapy in IBD in 2017 and beyond? Expert Rev Gastroenterol Hepatol 2017;11:473-486. doi:10.1080/17474124.2017.1294062
17. Short ME, Goetzel RZ, Pei X, et al. How accurate are self-reports? Analysis of self-reported health care utilization and absence when compared with administrative data. J Occup Environ Med 2009;51:786-796. doi: 10.1097/JOM.0b013e3181a86671
18. Langholz E. Current trends in inflammatory bowel disease: the natural history. Therap Adv Gastroenterol 2010;3:77-86. doi: 10.1177/1756283X10361304