TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF ULCERATIVE COLITIS
TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN ÜLSERATİF KOLİT İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

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Can azathioprine/6-mercaptopurine treatment be withdrawn in patients with response in ulcerative colitis: What is the most appropriate time for this?

Tedaviye yanıtlı ülseratif kolit hastalarında azatiopurin/6-merkaptopurin tedavisi kesilebilir mi; bunun için en uygun zaman nedir?

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, inflammatory disease affecting the gastrointestinal system. The disease presents itself typically by remission and relapses, so that in the first year after the diagnosis, 40%-50% of the cases are clinically in remission, whereas only 25% remain in remission 3-7 years later (1). Moreover, 18% of the cases remain continuously active, and 57% of them have a course with intermittent relapses. If the follow-up period is extended up to 25 years, intermittent activation is reported to be seen in 90% of the cases. That is the logic underlying the need for agents maintaining the remission.

Corticosteroids, which play a key role in UC treatment, cause side effects in as frequent as 50% of the cases (2). Some of these side effects are serious and life-threatening, and thus result in treatment discontinuation. The immunomodulatory (IMM) agents like azathioprine (AZA) and 6-mercaptopurine (6MP) are also known as steroid-sparing agents, and can be used for long-term maintenance treatment (Number Needed to Treat [NNT] for steroid sparing is 3.95 [Confidence Interval (CI)=2-8]). Indications of an IMM agent use in UC according to the last European Crohn's and Colitis Organisation (ECCO) management guideline is: severe relapse; frequent (>1/year) relapses; and steroid-dependent cases characterized by relapse below the steroid dose of 15 mg/day and relapse after 3 months of stopping the steroid treatment (3).

In a recent metaanalysis, the effects of AZA and 6MP were compared with placebo, and the results indicated that the effects in the IMM group were superior, not in remission induction, but in the maintenance of remission (4).

The most important concerns for the long-term treatment with these medications are about safety. There is no specific recommendation in the current ECCO guideline about the proper time for discontinuing the AZA/6MP maintenance treatment.

The aim of this study was to find clues regarding the appropriate duration, and whether it is possible to stop the AZA/6MP maintenance treatment.

MATERIALS AND METHODS

The question was rephrased to be suitable for systematic literature research as follows:

"When will there be no significant change in the relapse rate if the medication is withdrawn in patients taking AZA/6MP maintenance treatment?". Afterwards, a literature research was performed among the studies conducted with the most appropriate scenarios.

In the PubMed database, a search was conducted using the keywords ("azathioprine"[Substance Name] OR "6-Mercaptopurine"[Mesh]) AND "Colitis, Ulcerative"[Mesh]. All the randomized controlled studies that were carried out among adults and re-

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ported in English were evaluated. Other studies were also retrieved from the references of the accessed articles. Titles and abstracts of the 199 studies found were evaluated, and most of them were excluded according to suitability. Exclusion criteria were: case reports, therapeutic trials with different agents, and designs: pediatric studies and non–therapeutic trials. As a result, six manuscripts were found, one of which was prospective, and five were retrospective.

Through these studies, withdrawal time of the maintenance treatment, relapse rate, time after withdrawal, risk factors, and expert opinions of the authors, if any, were considered. Moreover, studies implicating the safety and long-term tolerability of the drugs and side effects or long-term complications like lymphoma development were evaluated.

RESULTS

Country of origin, year of the study, design, and relapse rates after defined durations of AZA treatment are seen in Table 1.

According to these studies, withdrawal of maintenance treatment during remission resulted in relapse of an almost constant rate of one-third of the cases in the first year in three of the studies (5, 6, 10). If it is stopped earlier than 1 year, which is mostly due to toxicity, 100% of the cases were found to be at risk of relapse (7). In third year of withdrawal, two-thirds of the cases relapsed, which is similar between two studies, and furthermore, the risk increased to 75% in the 5th year in one study (6, 10).

In the multicenter study conducted in European countries, prolongation of treatment duration showed the additional benefit of decreased rates of flares, which could be treated with lower doses of corticosteroids (8). Among these studies, the longest reported AZA use among UC patients was as long as 16 years without any significant side effect.

The risk factors for relapse among these studies and the comment of the author on treatment withdrawal are seen in Table 2.

Younger age, male gender, early withdrawal due to toxicity, not being on remission, and extensive disease were the risk factors increasing the relapse rate. Older age, sustained remission on AZA treatment without any symptoms or corticosteroid need, and 5–ASA maintenance decreased the risk of relapse.

CONCLUSION

In another study among refractory UC patients by Adler et al. (11), they stopped the 6MP treatment in 29/81 cases in a mean time of 1.8 years, and the mean relapse time was found as 21 months. Patients who have frequent relapse, who do not achieve remission with steroids, who have issues regarding quality of life due to distal colitis, and who do not want to be operated have a chance of prolonged remission with AZA maintenance. In the low-risk patients, treatment can be withdrawn after 4–5 years. Lobel (12) suggested that most patients should take indefinite treatment.

Table 1. Country of origin, year of study, design, and relapse rates after defined durations of AZA treatment

Author	Country	Year	Design	N	Age	Duration of AZA (mo)	Relapse Rate
AB Hawthorne (5)	UK	1992	Prospective	33 vs 34	44	19 vs 21 (placebo)	35% vs 59%/1 y
A Cassinotti (6)	Italy	2008	Retrospective	127	38	47	1 y: 1/3 2 y: 1/2 3 y: 2/3
GC Actis (7)	Italy	2008	Retrospective	39	36	14 (1-201 mo)	100% (early stoppers)
MH Holtmann (8)	Europe	2005	Retrospective	358	34	<3 y vs 3-4 y vs >4 y	2.4 flares/y 1.68 flares/y 1.2 flares/y (Lower CS need)
MH Holtmann* (9)	Europe	2010	Retrospective	358	34	<3 y vs 3-4 y vs >4 y	
AG Fraser (10)	UK	2002	Retrospective	346	31.1	20	1 y: 37% 2 y: 56% 3 y: 65% 5 y: 75%

AZA: Azathioprine. mo: Month. y: Year. CS: Corticosteroids. *: subanalysis of the previous study by Holtmann et al.

Table 2. The risk factors for relapse and the comments of the author on treatment withdrawal

Author	Country	Risk Factor	Suggestion
AB Hawthorne (5)	UK	Sex, duration of remission: no effect Age: HR = 0.95 / 1 year	At least 2 years of maintenance required
A Cassinotti (6)	Italy	Increased Risk: Male (73% vs 64%) Early withdrawal due to toxicity (85% vs 60%) No remission Extensive disease Decreased Risk: Sustained response (59% vs 91%) Long duration of AZA treatment 5-ASA after stopping AZA	Can be stopped in selected cases
GC Actis (7)	Italy	Withdrawal in first 7 month is related to toxicity (22/38); 10: Surgery, 9: re-AZA	Re-AZA-treated 7 cases are on treatment for 10-16 years without side effect
MH Holtmann (8)	Europe	-	It can be stopped in those patients with no symptom or corticosteroid need for 3-4 years.
MH Holtmann* (9)	Europe	BMI has no effect on relapse, or CS need; increase flare incidence	
AG Fraser (10)	UK	Sex, being on remission, duration of AZA has no effect	>5 year treatment can be given with minimal toxicity

HR: Hazard ratio. 5-ASA: 5-Amino salicylic acid. CS: Corticosteroids. *: subanalysis of the previous study by Holtmann et al.

Safety

In the Cochrane database review, the odds ratio for any adverse effect was found as 3.05, but serious adverse effects like acute pancreatitis and bone marrow toxicity were not significantly increased (13). On the other hand, a study conducted in the United Kingdom provides some clues regarding real-life practice, in that 93% of the consultant gastroenterologists reported that they are using AZA, but 46% of them gave it less than 2 years. Treatment duration was directly related to the physician's expertise (14). Many other studies have demonstrated that AZA is used less frequently in UC than in Crohn's disease (15-17).

Actual IMM doses were found to be inappropriately low in 80% of the cases (18). In another study about IMM, indications and protocols were inappropriate in 78% of the cases (19).

Lymphoma risk was found to be increased fourfold in a recent metaanalysis, which is certainly the major drawback for long-term treatment with these drugs for a disease like UC that is potentially curable by surgery (20).

In light of these findings, recommendations for the withdrawal of IMM treatment in UC patients are seen in Box.

Recommendation:

Withdrawal of AZA/6MP maintenance treatment of UC in remission is recommended only for a selected group of patients ***(EL 2b, RG D).***

Long-term treatment with IMM drugs is found to be safe in most studies ***(EL 2b, RG D).***

In the patients with low risk of relapse, treatment duration of 4-5 years should pass before withdrawal ***(EL 2b, RG D).***

In the patients with high risk of relapse, withdrawal of AZA/6MP maintenance treatment is not recommended. On the other hand, the patient should be informed about the possible side effects of long-term treatment ***(EL 5, RG D).***

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