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

TJG
The Turkish Journal of Gastroenterology

How long should we treat patients with azathioprine/6-mercaptopurine before deciding that it is refractory to immunomodulatory treatment?

İmmunomodülatör tedaviye refrakter olduğuna karar vermek için hastaların azatiopurin/6-merkaptopurin ile ne kadar süre tedavi edilmesi gereklidir?

Gökhan KABAÇAM, Murat TÖRÜNER

Department of Gastroenterology, Ankara University School of Medicine, Ankara

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the intestines with a continuously active or relapsing, remitting course in most patients (1). The mainstay of the treatment is corticosteroids, especially in severe cases, but they can cause side effects in up to 50% of the cases (2). The so-called "steroid-sparing agents" - the group of immunomodulatory (IMM) agents like azathioprine (AZA) and 6–mercaptopurine (6MP) - are used to alleviate the need for corticosteroid therapy and thus the side effects related to these agents (3).

Due to the pharmacodynamic profiles of these IMM agents, onset of their action is slow. This results in longer exposition to corticosteroids, and thus more side effects related to their use. An additional issue related to this slow action profile is the difficulty in determining their effectiveness, and withdrawal of the steroid treatment, which is administered at baseline in view of its rapid onset of action to induce the clinical remission. In the most recent European Crohn's and Colitis Organisation (ECCO) consensus report on the treatment of UC, there is no specific recommendation on the timing for determining the effectiveness of AZA and 6MP – the IMM agents.

The purpose of this systematic literature review was to demonstrate the scientific evidence regarding the shortest duration of therapy needed to determine whether the disease is refractory to IMM treatment.

MATERIALS AND METHODS

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

"After what duration of treatment with AZA/6MP will there be no change in the number of cases entering remission?". 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 studies that were carried out among adults and reports in English were evaluated. Other studies were also retrieved from the references of the accessed articles. Because of the insufficiency of the identified studies, those in Crohn's disease and the pediatric studies were also taken into consideration. Furthermore, a research among the presentations in the ECCO 2010 Congress was also performed.

The criteria for evaluation and analysis were the timing of the induction of remission in UC patients with AZA/6MP in the studies. Remission criteria were clinical (±endoscopic) improvement, and being able to withdraw the corticosteroid therapy. Our final aim was to draw a Kaplan–Meier curve showing the timing of the patients entering remission, by the raw data eligible from the manuscripts. In this curve, place of the plateau would be determined as time of refractoriness to IMM treatment.

Address for correspondence: Gökhan KABAÇAM
Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey
E-mail: gokhankabacam@yahoo.com

Manuscript received: 14.05.2012 **Accepted:** 24.08.2012

Turk J Gastroenterol 2012; 23 (Suppl. 2): 13-16
doi: 10.4318/tjg.2012.0617

Exclusion criteria for the studies were case reports, studies performed with different agents, and methods (non-therapeutic trials).

Among the 201 studies found, 183 were eliminated by either screening of the abstract (n=152) or the full text of the manuscripts (n=31), resulting in 18 studies having at least some information on the necessary data.

RESULTS

There was no randomized controlled trial evaluating the duration of treatment necessary for determination of refractoriness to IMM agents in UC or Crohn's disease. Instead, the studies showing timing of remission in both diseases were taken into consideration through the scope of opinions of the experts in the field. Nine of the 18 studies were prospective, 5 were retrospective, and 4 were review or meta–analysis (Table 1).

Among the studies performed, AZA doses ranged between 2-2.5 mg/kg, and 6MP dose was 1.5 mg/kg. Global response rate was between 42%-77.8% to IMM therapy. With respect to the onset of responses to the treatment, in the prospective trials, cumulative weighted average of the time of remission was found as 15.5 weeks (n=363, min–max = 4-36 weeks) (4-12). According to the retrospective trials in the literature, onset of response can be seen between 2-36 weeks (17-21).

There was not enough information in the published manuscripts to be able to draw a cumulative Kaplan-Meier curve to determine the time to a plateau for entering remission.

In the meta-analysis by Pearson et al. (16), the odds

Table 1. The studies showing data on design, primary disease, medication, dose, treatment response times, and response rates, if available

Author	Reference	Design	Disease	Tx	Dosage (mg/kg)	Time of Response (wk)	Response rate (%)
Gisbert JP (4)	Aliment Pharmacol Ther 2008	Prospective	UC/CD	AZA	2.2	18 (15.2-20.8)	42
Mantzaris GJ (5)	Am J Gastroenterol 2001	Prospective	UC	AZA	2.2	8 (6-12)	60
Kull E (6)	Gastroenterol Clin Biol 2002	Prospective	UC	AZA	2	Max 24 wks	-
Lopez-Sanroman A (7)	Aliment Pharmacol Ther 2004	Prospective	UC	AZA	2.17	18.4 (4-36)	70.6
Kirk AP (8)	BMJ 1982	Prospective	UC	AZA	2–2.5	12 (Max: 24)	-
Paoluzi OA (9)	Aliment Pharmacol Ther 2002	Prospective	UC	AZA	2	12	69
Chebli LA (10)	Med Sci Monit 2010	Prospective	UC	AZA	-	20	-
Present DH (11)	N Engl J Med 1980	Prospective	CD	6MP	-	32% >12 wks 19% >16 wks	-
Ewe K (12)	Gastroenterology 1993	Prospective	CD	AZA	-	8	-
Leung Y (13)	Dig Dis Sci 2008	Review/ Metaanalysis	UC	AZA	-	12 (Max: 24)	-
Prefontaine E (14)	Cochrane Dbase Sys Rev 2009	Review/ Metaanalysis	UC	AZA	-	17	-
Nielsen OH (15)	Aliment Pharmacol Ther 2001	Review/ Metaanalysis	UC	AZA	-	12-17	-
Pearson DC (16)	Ann Intern Med 1995	Review/ Metaanalysis	CD	AZA/6MP	-	<17 wks OR=1.25 >17 wks OR=19.2	-
Ardizzone S (17)	J Clin Gastroenterol 1997	Retrospective	UC	AZA	2	14 (6-32)	64
Adler DJ (18)	Am J Gastroenterol 1990	Retrospective	UC	6MP	1.5	10	63
Verhave M (19)	J Pediatr 1990	Retrospective	UC/CD	AZA	-	UC: 12 wks CD: 16 wks	77.8
Theodor E (20)	Am J Gastroenterol 1981	Retrospective	UC	AZA	-	Start 2 wks Max: 6.8 wks	62
Escribano MS (21)	ECCO Congress 2010	Retrospective	UC	AZA	2.5	10±6 wks	63

Tx: Treatment. wk: Week. UC: Ulcerative colitis. CH: Crohn disease. AZA: Azathioprine. 6MP: 6-mercaptopurine. OR: Odds ratio.

ratio (OR) for response to AZA/6MP treatment in Crohn's disease increased from 1.25 to 19.2 after 17 weeks of treatment. In other reviews or meta–analyses published to date regarding UC treatment, a range was found between 12-17 weeks (13-15).

In a study comparing the effectiveness of AZA on UC and Crohn's disease by means of remission rate and time in 394 cases, there was no difference between the two diseases (4).

CONCLUSION

Late onset of action is a major problem with IMM drugs like AZA and 6MP. Since they are the main role players for the long-term treatment of inflammatory bowel diseases, it is important to know the time of action of such drugs.

According to studies published in the literature to date, the mean onset of action is 15.5 weeks. It is shown to start from as early as 2 weeks, and can be as late as 36 weeks. Awaiting the action for 9 months by administering corticosteroid treatment is of course not the ideal option, although it may be necessary in some patients who cannot take or tolerate other medications.

Indeed, some studies have been done to decrease the response time, such as by giving an intravenous loading dose of AZA; however, there are other studies showing that this step has no advantage (22, 23).

In light of these findings, recommendations about the duration of IMM treatment to determine refractoriness are seen in Box.

Recommendation:

In the AZA/6MP treatment of patients with UC, one should wait at least until the 4th month of treatment to decide about immunomodulatory refractoriness **(EL 1b, RG D).**

Time to response to immunomodulatory treatment can be as long as 9 months **(EL 2b, RG D).**

REFERENCES

1. Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994; 107: 3-11.
2. Dignass A, Van Assche G, Lindsay JO, et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010; 4: 28-62.
3. Travis SP, Stange EF, Lémann M, et al. for the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: current management. J Crohns Colitis 2008; 2: 24-62.
4. Gisbert JP, Niño P, Cara C, Rodrigo L. Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients. Aliment Pharmacol Ther 2008; 28: 228-38.
5. Mantzaris GJ, Archavlis E, Kourtessas D, et al. Oral azathioprine for steroid refractory severe ulcerative colitis. Am J Gastroenterol 2001; 96: 2797-8.
6. Kull E, Beau P. [Compared azathioprine efficacy in ulcerative colitis and in Crohn's disease]. Gastroenterol Clin Biol 2002; 26: 367-71.
7. Lopez-Sanroman A, Bermejo F, Carrera E, Garcia-Plaza A. Efficacy and safety of thiopurinic immunomodulators (azathioprine and mercaptopurine) in steroid-dependent ulcerative colitis. Aliment Pharmacol Ther 2004; 20: 161-6.
8. Kirk AP, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. Br Med J (Clin Res Ed) 1982; 284: 1291-2.
9. Paoluzi OA, Pica R, Marcheggiano A, et al. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. Aliment Pharmacol Ther 2002; 16: 1751-9.
10. Chebli LA, Felga GG, Chaves LD, et al. Early onset steroid-dependent ulcerative colitis is a predictor of azathioprine response: a longitudinal 12-month follow-up study. Med Sci Monit 2010; 16: PI1-6.
11. Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980; 302: 981-7.
12. Ewe K, Press AG, Singe CC, et al. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. Gastroenterology 1993; 105: 367-72.
13. Leung Y, Panaccione R, Hemmelgarn B, Jones J. Exposing the weaknesses: a systematic review of azathioprine efficacy in ulcerative colitis. Dig Dis Sci 2008; 53: 1455-61.
14. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2009; CD000545.
15. Nielsen OH, Vainer B, Rask-Madsen J. Review article: the treatment of inflammatory bowel disease with 6-mercaptopurine or azathioprine. Aliment Pharmacol Ther 2001; 15: 1699-708. Review. PubMed PMID: 11683683.
16. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med 1995; 123: 132-42.

17. Ardizzone S, Molteni P, Imbesi V, et al. Azathioprine in steroid-resistant and steroid-dependent ulcerative colitis. J Clin Gastroenterol 1997; 25: 330-3.
18. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. Am J Gastroenterol 1990; 85: 717-22.
19. Verhave M, Winter HS, Grand RJ. Azathioprine in the treatment of children with inflammatory bowel disease. J Pediatr 1990; 117: 809-14.
20. Theodor E, Niv Y, Bat L. Imuran in the treatment of ulcerative colitis. Am J Gastroenterol 1981; 76: 262-6.
21. Escribano MS, Sánchez VG, Flores EI, et al. Duration of azathioprine treatment in ulcerative colitis. ECCO Congress Abstract Book, 2010, P168n.
22. Sandborn WJ, Van O EC, Zins BJ, et al. An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. Gastroenterology 1995; 109: 1808-17.
23. Sandborn WJ, Tremaine WJ, Wolf DC, et al. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. Gastroenterology 1999; 117: 527-35.