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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What is the importance of infliximab and cyclosporine in the treatment of corticosteroid-refractory severe ulcerative colitis?

Kortikosteroid refrakter şiddetli ülseratif kolit tedavisinde siklosporin ve infliksimabın önemi nedir?

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory disease involving the large bowel and is characterized by a lifelong chronic course with remissions and exacerbations (1). The etiopathogenesis of the disease is still unknown. The main intestinal manifestations of the disease are abdominal pain and bloody diarrhea, whereas there are also extraintestinal manifestations involving the joints, skin, eyes, and liver.

Approximately 15% of patients have a severe attack requiring hospitalization at some time during their illness. These patients are traditionally treated with intravenous corticosteroids, with a response rate of approximately 60% (2). The introduction of steroid therapy in 1955 reduced the mortality of severe UC to 7%, compared with 24% in the placebo group (3), and it is now <1% in specialized centers (4). Nevertheless, the response of severe UC to steroids has remained unchanged for 50 years (4), and therefore severe to moderately severe attacks of UC still have a high colectomy rate (5). On the other hand, a significant proportion of patients will become resistant to steroids (6).

The remaining treatment options in patients with severe UC include cyclosporine (Cyc), anti- tumor necrosis factor–α (TNF-α blockers), or surgery. The surgical procedure (proctocolectomy or colectomy with an anal pouch) essentially cures the patient from this disease but is associated with some complications such as pouchitis and infection (7). Cyc mainly acts by inhibiting T lymphocyte function, which is essential for the propagation of inflammation. Although Cyc can be effective in a relatively high proportion of these steroid-resistant patients, most of those who do respond initially will eventually need a colectomy. Unlike most other immunosuppressive (or immunomodulator) agents, Cyc does not suppress the activity of other stem cells, does not cause bone marrow suppression, and has a rapid onset of action (8). Furthermore, Cyc requires initial continuous parenteral administration and close monitoring to maintain therapeutic blood levels and has well recognized important side effects (9).

TNF-α, a pro-inflammatory cytokine, is known to play an important role in the pathogenesis of Crohn's disease (CD). The efficacy of the chimeric monoclonal anti-TNF immunoglobulin (Ig) G1 antibody and the genetically engineered humanized monoclonal antibody to TNF-α has been demonstrated in moderate to severe CD. Anti-TNF-α can induce mucosal healing and has been shown to have a high steroid–sparing efficacy in active CD (10). Unlike CD, UC has long been considered to be a Th_2-type disease with a less prominent role of TNF-α (11). However, it has been shown that TNF-α may also play a role in the pathogenesis of UC. Recent studies also support the use of infliximab (IFX) for the management of moderately active corticosteroid-resistant UC. The blockade of

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TNF-α may be associated with the development of serious adverse events including the reactivation of latent tuberculosis, infusion reactions, acute and delayed hypersensitivity reactions, development of lymphoma, and formation of anti-double-stranded DNA antibodies (12). However, only a few studies – most of them including a low number of patients – have evaluated the efficacy of IFX for the treatment of UC, and the results are sometimes controversial.

Recent recommendations published by the European Crohn's and Colitis Organisation (ECCO) indicate that in steroid-refractory UC, second-line therapy with either Cyc or IFX or tacrolimus will often be appropriate. In the framework of ECCO, we discuss which agent has been shown to be best for the therapy of steroid-refractory severe UC.

MATERIALS AND METHODS

Using the systematic literature review method, a search was conducted in Medline using the keywords "Colitis, Ulcerative" [Mesh] AND "Cyclosporine" [Mesh] OR "infliximab" [Substance Name]. All the randomized controlled studies that were carried out among adults were evaluated. Other studies were also retrieved from the references of the accessed articles.

As a result of the systematic literature search, five randomized controlled studies and three meta-analyses were found on IFX and Cyc treatment in corticosteroid-refractory severe UC. No studies were found that directly compared IFX and Cyc. Studies that were repetitive, including less than five cases, including both pediatric and adolescent patients, editor evaluations, shared publications including different keywords, studies on CD and patients with undefined colitis, studies in languages other than English, and studies with insufficient statistical data were not considered during this study.

Studies concerning remission induction and maintenance were evaluated separately.

Although evaluation criteria for activity differ in every study, colectomy, clinical activity index, Mayo score, and modified Truelove-Witt's criteria were considered in clinical remission or response, whereas Mayo sub-score and Blackstone classification were considered in endoscopic mucosal healing. The safety evaluation criteria were accepted as withdrawal due to toxicity and serious adverse event rate.

End points and Statistical Analysis: For categorical variables, calculations of the number needed to treat (NNT) with the number of recovered patients in both the active and placebo groups and calculation of number needed to harm (NNH) with the number of withdrawn patients in both the active and placebo groups were conducted.

RESULTS

Remission Induction Studies

Four studies fitting the criteria were included in the analysis, but two of them were conducted among patients having moderate to severe active UC.

Data of patients who were steroid-refractory were evaluated. In the studies, homogenization of previous immunosuppressive usage was not observed. IFX infusion schemes and infusion numbers were not standard.

Patient study groups, dosage, duration, and results of the administrated treatments are presented in Tables 1-4.

Lichtiger 1997 (13)

Lichtiger et al. (13) enrolled 20 steroid-refractory UC patients (11 Cyc and 9 placebo). Response was defined as a decline in the clinical activity index score to less than 10 according to the modified Truelove and Witt's criteria. Nine of the 11 patients (82%) in the intravenous Cyc group had a response to the therapy in comparison with none of 9 patients in the placebo group. The colectomy rate was 3/11 (27%) for the intervention group and 4/9 (44%) for the placebo group with relative risk (RR) of 0.60 (95% confidence interval [CI]: 0.18-2.06). The main adverse events were hypertension, paresthesias and vomiting. No patient in this study developed nephrotoxicity. This can probably be attributed to the short-term therapy (8-14 days) and the fact that Cyc levels were monitored frequently. There were no infectious complications.

Rutgeerts 2005 ACT 1 and ACT 2 (14)

Two randomized, double-blind, placebo-controlled studies -- the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively) -- evaluated the efficacy of IFX for induction and maintenance therapy in patients with UC. All participants had active UC with a Mayo clinic score of 6-12 points with moderate to severe active disease on sigmoidoscopy. In each study, patients received placebo or IFX (5 mg or 10 mg/kg) intravenously at weeks 0, 2 and 6,

Table 1. The rates of clinical response upon induction therapy

Author-year	Treatment vs control	Dosage	Interval	Period (week)	Number of patients	Patient characteristics	Clinical response–NNT
Lichtiger-1994 (13)	Cyc vs plc	4 mg/kg/d	Daily	1	11 vs 9	Cs refractory	**1.22**
Rutgeerts-2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0-2-6 w	8	121 vs 121 122	Refractory Non-refractory	**3.57** **(2.85)***
Rutgeerts-2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0-2-6 w	8	121 vs 123 120	Refractory Non-refractory	**2.70** **(3.70)***
Sands-2001 (15)	IFX vs plc	5-10-20 mg	Single dose	2	8 vs 3	Refractory	**2.00**

NNT: Number needed to treat. Cyc: Cyclosporine. plc: Placebo. Cs: Corticosteroid. IFX: Infliximab. w: Weeks. * These NNT values were obtained only from Cs-refractory patients.

Table 2. The rates of clinical remission upon induction therapy

Author-year	Treatment vs control	Dosage	Interval	Period (week)	Number of patients	Patient characteristics	Clinic remission-NNT
Lichtiger-1994 (13)	Cyc vs plc	4 mg/kg/d	Daily	1	11 vs 9	Cs refractory	1.22
Rutgeerts- 2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0-2-6 weeks	30	121 vs 121 122	Cs refractory Non-refractory	4.76
Rutgeerts- 2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0-2-6 weeks	30	121 vs 123 120	Cs refractory Non-refractory	4.00

NNT: Number needed to treat. Cyc: Cyclosporine. plc: Placebo. Cs: Corticosteroid. IFX: Infliximab.

Table 3. The rates of mucosal healing upon induction therapy

Author-year	Treatment vs control	Dosage	Interval	Period (week)	Number of patients	Patient characteristics	Mucosal recovery-NNT
Rutgeerts- 2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0–2–6 weeks	8	121 vs 121 122	CS refractory Non-refractory	**3.75**
Rutgeerts- 2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0–2–6 weeks	8	121 vs 123 120	Cs refractory Non-refractory	**3.32**

NNT: Number needed to treat. IFX: Infliximab. plc: Placebo. Cs: Corticosteroid.

Table 4. Safety data for induction therapy

Author-year	Treatment vs control	Dosage	Interval	Period (week)	Number of patients	Drop-out –NNH	SAE – NNH
Lichtiger-1994 (13)	Cyc vs plc	4 mg/kg/d	Daily	1	11 vs 9	50	**11.11**
Rutgeerts- 2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0-2-6 weeks	8	121 vs 121 122	4.44	**33.33**
Rutgeerts-2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0-2-6 weeks	8	121 vs 123 120	4.03	**10.00**
Sands-2001 (15)	IFX vs plc	5-10-20 mg	Single dose	2	8 vs 3	---	**12.50**

NNH: Number needed to harm. SAE: Severe adverse events. Cyc: Cyclosporine. plc: Placebo. IFX: Infliximab.

and then every eight weeks through week 46 (in ACT 1) or week 22 (in ACT 2). Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2.

The primary end point was clinical response at week 8, which was defined as a decrease from baseline in the total Mayo score by at least 3 points and by at least 30% and accompanied by a decrease in the rectal bleeding sub-score by at least 1 point or an absolute rectal bleeding sub- score of 0 or 1. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing was defined as an absolute endoscopy sub-score of 0 or 1. Two studies were quite large (n= 364 and 364),

and both showed a statistically significant benefit for IFX. The rates of clinical response were similar between the subpopulations of patients who were corticosteroid-refractory and those who were not refractory.

Sands 2001 (15)

The researchers originally planned to recruit 60 patients, but the study was terminated early because of slow enrollment. All patients had severe active UC as defined by a modified Truelove and Witt's classification score. The primary end point of the study was treatment failure at two weeks after infusion of the trial medication IFX. Treatment failure was defined as one or more of the following criteria: failure to achieve a clinical response within two weeks, requiring >60 mg/kg/day corticosteroid or requiring Cyc, undergoing a non-elective colectomy, or dying as a result of UC. In this small study, there was no statistically significant difference between IFX and placebo (RR: 4.0, 95% CI: 0.28 to 57.98).

Maintenance Studies

Four studies fitting the criteria were included in the analysis. Three of them were conducted among patients having moderate to severe active UC. Patient study groups, dosage, duration, and results of the administrated treatments are presented in Tables 5-8.

Table 5. The rates of clinical response in the maintenance trials

Author-year	Treatment vs control	Dosage	Interval	Period (month)	Number of patients	Patient characteristics	Clinical response–NNT
Sands-2001 (15)	IFX vs plc	5-10-20 mg	Single dose	1.7	8 vs 3	Cs-refractory	**2.00**
Jarnerot 2005 (16)	IFX vs plc	5 mg	Single dose	3	24 vs 21	Cs-refractory	**2.63**
Rutgeerts- 2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0-2-6-14-22-30-38-46 weeks	13.5	121 vs 121 122	Cs-refractory Non-refractory	**3.22**
Rutgeerts- 2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0-2-6-14-22 weeks	7.5	121 vs 123 120	Cs-refractory Non-refractory	**3.57**

NNT: Number needed to treat. IFX: Infliximab. plc: Placebo. Cs: Corticosteroid.

Table 6. The rates of clinical remission determined in the maintenance trials

Author-year	Treatment vs control	Dosage	Interval	Period (month)	Number of patients	Patient characteristics	Clinic remission-NNT
Rutgeerts- 2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0-2-6-14-22-30-38-46 week	13.5	121 vs 121 122	Cs-refractory Non-refractory	**5.26**
Rutgeerts- 2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0-2-6-14-22 week	7.5	121 vs 123 120	Cs-refractory Non-refractory	**4.16**

NNT: Number needed to treat. IFX: Infliximab. plc: Placebo. Cs: Corticosteroid.

Table 7. The rate of mucosal healing with maintenance therapy

Author-year	Treatment vs control	Dosage	Interval	Period (month)	Number of patients	Patient characteristics	Mucosal response-NNT
Jarnerot-2005 (16)	IFX vs plc	5 mg	Single dose	3	24 vs 21	Cs refractory	**6.45**

NNT: Number needed to treat. IFX: Infliximab. plc: Placebo. Cs: Corticosteroid.

Table 8. Safety data for maintenance therapy

Author-year	Treatment vs control	Dosage	Interval	Period (month)	Number of patients	Drop-out –NNH	SAE – NNH
Rutgeerts- 2005 (ACT1) (14)	IFX vs plc	5 mg 10 mg	0–2-6-14-22-30-38-46 weeks	13.5	121 vs 121 122	**6.62**	**33.30**
Rutgeerts-2005 (ACT2) (14)	IFX vs plc	5 mg 10 mg	0-2-6-14-22 weeks	7.5	121 vs 123 120	**4.83**	**10.00**
Jarnerot- 2005 (16)	IFX vs plc	5 mg	Single dose	3	24 vs 21	------	**166.60**

SAE: Severe adverse events. NNT: Number needed to harm. IFX: Infliximab. plc: Placebo.

In all the studies, the use of IFX as the maintenance therapy was determined to be superior compared to the placebo in terms of clinical remission, treatment response and mucosal healing (14-17). In the maintenance treatment, IFX treatment was also found to be safe regarding the side effects.

Rutgeerts 2005 ACT 1 and ACT 2 (14)

In both studies, the proportions of patients with adverse events were similar in the placebo group and the two IFX groups. Serious adverse events were most commonly related to the gastrointestinal system.

Jarnerot 2005 (16)

Significantly more patients in the placebo group (14/21) than in the IFX group (7/24) had a colectomy. This difference was statistically significant (p=0.017 with odds ratio (OR) of 4.9 (95% CI: 1.4-17) in favor of IFX. No death occurred.

CONCLUSION

Both IFX and Cyc were found to be superior compared to the placebo in the terms of the remission induction and treatment response. For the induction and maintenance of remission, mucosal healing and colectomy rate in severe UC, IFX is superior compared to placebo among patients who are refractory to corticosteroid treatment. IFX treatment response rates are similar in patients with steroid-refractory or steroid-dependent UC. With regard to IFX treatment, 5-10 mg/kg dosage provides more significant response than placebo. Therefore, it may be suggested that the preferred initial dose of IFX in patients with UC is 5 mg/kg.

Controlled studies with Cyc are rare, and there are a limited number of evidences showing that Cyc monotherapy is more efficient than standard treatment for severe UC. Cyc is an effective alternative to corticosteroid, but also demonstrates that Cyc, like steroids, acts as a 'bridge therapy' to azathioprine (AZA), which typically starts its delayed action after 3-4 months. The strategy to add AZA after successful induction of remission with Cyc has already been shown to be effective (17). It remains debatable whether Cyc treatment should be given to a patient who has proven AZA resistance or intolerance (18).

Response time to IFX treatment in steroid-refractory UC patients is 48-72 hours, while it is 5.2-7.1 days for Cyc (13).

There are no studies providing a direct comparison of Cyc and IFX treatments for steroid- refractory UC patients.

After the approval of IFX for the treatment of UC, the potential usefulness and mainly the safety profile of sequential treatment with these two drugs (because of the hypothetical high risk of infectious complications) raised great concerns, considering that IFX serum levels remain increased for at least 8 weeks, whereas the serum half-life of intravenous Cyc is around 6 hours. It seems reasonable that IFX use after Cyc should be safer than starting Cyc in those patients who received IFX some days or weeks before. Data on the safety profile of concomitant or sequential IFX and Cyc therapy are still lacking. In the meantime, all available measures to prevent infectious complications such as the assessment of latent infections (tuberculosis or hepatitis B) or active prevention of *Pneumocystis jiroveci* with cotrimoxazole are strongly advised and must be anticipated in all patients treated for severe UC attacks; sequential therapy should be considered individually (19).

Although serious side effects related to IFX are not encountered in these studies often, one should be cautious regarding anaphylactic reaction and infection in clinical use. Side effects related to IFX are mostly mild, yet the side effects of Cyc are more severe and develop depending on the dosage. Hypertension, paresthesia or tremor, and headache are the most common side effects of Cyc use. Half of the patients show hypomagnesemia, renal failure or gastrointestinal symptoms. Opportunistic infections are the main concerns.

However, data on the long-term efficacy of IFX and Cyc are still lacking, underlying the fact that many unanswered questions remain, which can only be answered by further investigation. More studies are necessary to evaluate the cost-benefit ratio of IFX use, especially when compared with Cyc, in corticosteroid-refractory UC patients.

In light of these findings, recommendations related to the use of IFX and Cyc for the treatment of corticosteroid-refractory severe UC are presented in the box.

Recommendation:

When deciding second-line medical treatment for patients with steroid-refractory severe ulcerative colitis, the side effect profile should be considered primarily. ***(EL 1b, RG A)***

Cyclosporine can be applied in centers experienced in this treatment and where blood levels can be measured. ***(EL 1b, RG A)***

Infliximab treatment in these patients is a good alternative for cyclosporine treatment and surgery with regards to minimum frequency of side effects and easy application. ***(EL 1b, RG A)***

Infliximab can be applied as a transitory treatment in patients with severe ulcerative colitis until the efficiency of immunosuppressive treatments appears. ***(EL 5, RG D)***

Studies including a high number of patients are needed showing the cost efficacy of infliximab use and its comparison with cyclosporine and monitoring the long-term effects. ***(EL 5, RG D)***

It is not suggested to use infliximab and cyclosporine together and/or contiguously due to high risk of side effects. ***(EL 1b, RG A)***

Cyclosporine treatment should not be started in patients (allergic/intolerant/contradicted) who cannot take azathioprine in continuation. ***(EL 5, RG D)***

REFERENCES

1. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347: 417-29.
2. Blomberg D, Jarnerot G. Clinical evaluation and management of acute severe colitis. Inflamm Bowel Dis 2000; 6: 214-27.
3. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955; 4947: 1041-8.
4. Travis SP. Review article: the management of mild to severe acute ulcerative colitis. Aliment Pharmacol Ther 2004; 20(Suppl 4): 88-92.
5. Crabonnel F, Gargouri D, Lemann M, et al. Predictive factors of outcome of intensive intravenous treatment for attacks of ulcerative colitis. Aliment Pharmacol Ther 2000; 14: 273-9.
6. Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001; 121: 255-60.
7. Shibolet O, Regushevskaya E, Brezis M, et al. Cyclosporine A for induction of remission in severe ulcerative colitis. Cochrane Database Syst Rev 2005; 22: 907-16.
8. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. Am J Gastroenterol 1999; 94: 1587-92.
9. Garcia S, Gisbert JP, Gomollon F. Cyclosporine in the treatment of severe attack of ulcerative colitis: a systematic review. Gastroenterol Hepatol 2005; 28: 607-14.
10. Hommes DW, Van de Heisteeg BH, Van der Spek M, et al. Infliximab treatment for Crohn's disease: one year experience in a Dutch academic hospital. Inflamm Bowel Dis 2002; 8: 81-6.
11. D'Haens G. Infliximab for ulcerative colitis: finally some answers. Gastroenterology 2005; 128: 2161-4.
12. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis (review). Cochrane Database Syst Rev 2006; 3: 1-30.
13. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994; 330: 1841-5.
14. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005; 353: 2462-76.
15. Sands BE, Treamine WJ, Sandborn WJ, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. Inflamm Bowel Dis 2001; 7: 83-8.
16. Jarnerot G, Hertervig E, Friis- Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005; 128: 1805-11.
17. Fernandez-Banares F, Bertran X, Esteve-Comas E, et al. Azathioprine is useful in maintaining long-term remission induced by intravenous cyclosporin in steroid-refractory severe ulcerative colitis. Am J Gastroenterol 1996; 91: 2498-9.
18. D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001; 120: 1323-9.
19. Manosa M, San Roman AL, Planella EG, et al. Infliximab rescue therapy after cyclosporin failure in steroid-refractory ulcerative colitis. Digestion 2009; 80: 30-5.