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TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF CROHN'S DISEASE

TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN CROHN HASTALIĞI İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

What is the importance of anti-TNF agents in the treatment of luminal (inflammatory type) Crohn's disease?

Luminal (inflamatuar tip) Crohn hastalığının tedavisinde anti-TNF ajanlarının rolü nedir?

Key words: Crohn's disease, luminal Crohn's disease, anti-TNF therapy

Anahtar kelimeler: Crohn hastalığı, luminal Crohn hastalığı, anti TNF tedavi

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INTRODUCTION

Crohn's disease (CD) is an inflammatory chronic disease of the gastrointestinal tract. Although primary treatment for the majority of patients with an active disease has been reported as corticosteroids (CS), many patients can develop serious complications such as unresponsiveness to these drugs, addiction, or Cushing's syndrome (1, 2). Immunomodulators (IMM) such as azathioprine (AZA), mercaptopurine and methotrexate (MTX) and anti-tumor necrosis factor (TNF) agents such as infliximab (IFX) and adalimumab (ADA) are being used as steroid-sparing treatments at an increasing rate.

Recent recommendations published by the European Crohn's and Colitis Organization indicate that treatment with these anti-TNF agents should be considered at the earlier stages (3). This study was performed in order to evaluate all the relevant literature and to create recommendations because, after the above-mentioned guideline was published, important studies have been conducted assessing the importance of anti-TNF agents in the treatment.

METHODS

Using the systematic literature review method, a search was conducted in Medline using the keywords "Crohn's Disease" [Mesh] AND "infliximab" [Mesh] OR "Adalimumab" [Mesh]. 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. One-year results of the SONIC study, although not readily published, were accessed and included in the analysis (4).

Studies related with certolizumab pegol, which is not used in our country and has a limited use worldwide, were not evaluated. Study results concerning the fistulizing disease were excluded except for the safety data, because there is no major debate related to this topic.

Studies concerning remission induction and maintenance were evaluated separately. If the remission induction studies included a maintenance arm, this was evaluated as a separate maintenance study. The evaluation criteria comparing the treatment efficacy were specified as: "Clinical remission": decrease in Crohn's Disease Activity Index (CDAI) to under 150 and "Clinical response": reduction in CDAI of more than 70 points and endoscopic mucosal healing. The safety evaluation crite-

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ria were accepted as withdrawal due to toxicity and serious adverse event rate.

Endpoints and Statistical Analysis: using the means and standard deviations of the continuous variables, "effect size" was calculated (a calculation method resulting in an increase in the rate from <0.2 to >1.2 as the effect increases). For categorical variables, calculation of NNT (Number Needed to Treat) with the number of recovered patients in both the active and placebo groups and calculation of NNH (Number Needed to Harm) with the number of withdrawn patients in both the active and placebo groups were conducted.

RESULTS

Twenty studies were retrieved from the review. Sub-group analysis (i.e., Quality of Life studies) of the identical studies were evaluated together in order to avoid duplications.

Remission induction studies

Eight studies fitting the criteria were included in the analysis. All the studies were conducted among patients having moderate-severe active CD. Patient study groups, dosage, duration, and results of the administrated treatments are presented in Tables 1-4.

Both IFX and ADA were found to be superior compared to the placebo in the terms of the remission induction and the treatment response. With an increased dose of ADA, a better remission rate was achieved; however, this association was not reflected in the clinical response at the same rate (5, 10). IFX (5 mg/kg) was found to be superior to the placebo in the steroid treatment of refractory CD,

Table 1. The rates of clinical remission upon induction therapy

Author - year	Treatment vs control	Dosage	Interval	Period (week)	Number of patients	Patient characteristics	Clinical remission-NNT
SB Hanauer – 2006 (5)	ADA vs placebo	40/20 80/40 160/80	0 – 2 .w	4	74 75 vs 74 76	Refractory	18.5 8.33 4.34
SR Targan – 1997 (6)	IFX vs placebo	5/10/20	Single dose	12	27 28 vs 25 28	Refractory	4.76 11.1 5.88
O Schroder – 2006 (7)	IFX + MTX vs IFX	5	0-2 .w	2	11 vs 8	Refractory	5.55
G D'Haens – 2008 (8)	Top – down vs Step – up	5	0 – 2 – 6 .w	10	67 vs 66	Treatment naïve	5.26
WJ Sandborn – 2009 (4)	IFX+AZA vs IFX vs AZA	5	0 – 2 – 6 – 14 – 22 .w	54	167 vs 166 166	CS dependent	4.54 10
WJ Sandborn – 2007 (9)	ADA vs placebo	induction: 160, maintenance: 80	0 – 2 .w	4	159 vs 156	Patients non-responder to IFX	7.14

NNT: Number needed to treat.

Table 2. The rates of clinical response upon induction therapy

Author - year	Treatment vs control	Dosage	Interval	Period (w)	Number of patients	Patient characteristics	Clinical responce-NNT
SB Hanauer – 2006 (5)	ADA vs placebo	40/20 80/40 160/80	0-2 .w	4	74 75 vs 74 76	Refractory	3.36 2.94 2.85
SR Targan – 1997 (6)	IFX vs placebo	5 10 20	Single dose	12	27 28 vs 25 28	Refractory	1.53 2.94 2.08
WJ Sandborn – 2001 (10)	ADA vs placebo	10 20	Single dose	2	54 vs 56 57	Refractory	3.7 10
O Schroder – 2006 (7)	IFX + MTX vs IFX	5	0-2 .w	2	11 vs 8	Refractory	5.26
WJ Sandborn – 2007 (9)	ADA vs placebo	induction: 160, maintenance: 80	0-2 .w	4	159 vs 156	Patients non-responder to IFX	5.55

NNT: Number needed to treat.

Table 3. The rates of mucosal recovery upon induction therapy

Author - year	Treatment vs control	Dosage	Interval	Period (w)	Number of patients	Patient characteristics	Mucosal recovery-NNT
FJ Baert – 1999 (11)	IFX vs placebo	5, 10, 20	Single dose	4	13 vs 5	CS refractory	3.33
G D'Haens – 2008 (8)	Top – down vs Step – up	5	0 – 2 – 6 .w	10	67 vs 66	Treatment naïve	2.32

NNT: Number needed to treat.

Table 4. Safety data for induction therapy

Author - year	Treatment vs control	Dosage	Interval	Period (w)	Number of patients	Drop - out - NNH	SAE - NNH
SB Hanauer – 2006 (5)	ADA vs placebo	40/20 80/40 160/80	0 – 2 .w	4	74 75 vs 74 76	16.6 50 16.6	24.6 33.3 NA
SR Targan – 1997 (6)	IFX vs placebo	5/10/20	Single dose	12	27 28 vs 25 28	- -	25 25 100
O Schroder – 2006 (7)	IFX + MTX vs IFX	5	0-2 .w	2	11 vs 8	9.09	8.3
G D'Haens – 2008 (8)	Top – down vs Step – up	5	0 – 2 – 6 .w	10	67 vs 66	20	100
WJ Sandborn – 2009 (4)	IFX+AZA vs IFX vs AZA	5	0 – 2 – 6 – 14 – 22 .w	54	167 vs 166 166	- -	9.09 33.3
WJ Sandborn – 2007 (9)	ADA vs placebo	induction: 160, maintenance: 80	0 – 2 .w	4	159 vs 156	25	33.3

NNH: Number needed to harm. NA: Not applicable.

but higher dose administrations did not increase the clinical remission and the response compared to a 5 mg/kg dose (6). The combination of IFX with IMM agents such as MTX and AZA was found to be superior to its single use, in terms of the remission and treatment rates of the induction treatment (4, 7, 8). While mucosal healing was observed more frequently in IFX fields compared with the placebo, it was also more common in patients that were given early stage combination (top-down) treatment rather than conventional treatment (step-up) (8, 11). Considering the side effects, anti-TNF treatments were found to be safe (4-9). In combination fields of IFX+AZA, side effects were observed more frequently compared with the single use of these two agents (4).

Maintenance studies

Twelve studies fitting the criteria were included in the analysis. All the studies were conducted among patients having moderate-severe active CD. Patient study groups, dosage, duration, and results of administrated treatment are presented in Tables 5-8.

In all the studies, the use of anti-TNF as the maintenance therapy was determined to be superior compared to the placebo in terms of clinical remission, treatment response and mucosal healing (4, 12-18). During combination treatment, discontinuation of one of the immunosuppressive drugs at the sixth month did not affect the remission rate or the mucosal healing rate at the end of the treatment (12). In the maintenance treatment, anti-TNF treatments were also found to be safe regarding the side effects (12-17, 19-22).

In a recently published study that aimed to compare the treatment strategies, "step-up" (classic gradual treatment - the primary care was CS, followed by immunosuppressive treatments and anti-TNF treatments for non-responsive patients) and "top–down" (anti-TNF/immunosuppressive combinations in early stages) in naive patients, the results were as follows: 39 of the 65 patients (60%) in the early stage combination treatment group achieved remission in the 26th week, without the need of steroid use and surgical treatments, while this rate was determined as 23/64 (35.9%) in the classical treatment group (p=0.0062) (8). At the end of the 52 weeks, this difference was maintained: 40/65 (61.5%) vs. 27/64 (42.2%) (p=0·0278). No difference was detected in the side effect rates of these two treatment arms.

In the SONIC study, which was conducted to determine the efficacy of the early combination treatment among steroid-dependent patients, the efficacy determined as steroid-free remission rate at

Table 5. The rates of clinical remission determined in the maintenance trials

Author - year	Treatment vs control	Dosage	Interval (w)	Period (w)	Number of patients	Patient - characteristics	Clinical remission-NNT (ES*)
G Van Assche, 2008 (12)	IFX+Immuno-suppression (IS) vs IFX-IS	5	8	104	40 vs 40	Possible to discontinue the IS at 6th month?	*ES=0.12
J-F Colombel, 2007 (13)	ADA vs placebo	40 40	2 1	56	260 vs 261 257	Randomized responder (4w)	4.34 5.88
J-F Colombel, 2009 (14)	ADA vs ADA induct/reinit	40 40	2 1	56	260 vs 261 257	Open label +	8.33 9.09
SB Hanauer, 2002 (15)	IFX vs single induct - placebo	5 10	0-2-4-8	54	113 vs 110 112		5.55 4.34
W J Sandborn, 2007 (16)	ADA vs placebo	40 40	2 1	56	19 vs 18 18	Open label +	2.94 2.56
P Rutgeerts, 1999 (17)	IFX vs placebo	10	8	48	37 vs 36		3.12

* ES: Effect size. IS: Immunosuppression.

Table 6. The rates of clinical response in the maintenance trials

Author - year	Treatment vs control	Dosage	Interval (w)	Period (w)	Number of patients	Patient - characteristics	Clinical response-NNT
J-F Colombel, 2007 (13)	ADA vs placebo	40 40	2 1	56	260 vs 261 257	Randomized responder (4w)	2.77 2
W J Sandborn, 2007 (16)	ADA vs placebo	40 40	2 1	56	19 vs 18 18	Open label +	14.28 6.25
P Rutgeerts, 1999 (17)	IFX vs placebo	10	8	48	37 vs 36		4.16

NNT: Number needed to treat.

Table 7. The rates of mucosal response with maintenance therapy

Author - year	Treatment vs control	Dosage	Interval (w)	Period (w)	Number of patients	Patient - characteristics	Mucosal response-NNT
G Van Assche, 2008 (12)	IFX+Immuno-suppression (IS) vs IFX-IS	5	8	104	40 vs 40	Possible to discontinue the IS at 6th month?	25
P Rutgeerts, 2006 (18)	IFX vs single induct – placebo	5 10	0-2-4-8	54	11 vs 14 15		2.63 2.17
WJ Sandborn – 2009 (4)	IFX+AZA vs IFX vs AZA	5	0 – 2 – 6 – 14 – 22 .w	54	167 vs 166 166	CS dependent	3.57 3.33

IS: Immunosuppression.

the 26th week was determined as significantly superior in the IFX+AZA group compared to the IFX+placebo group, and the results of these two groups were found significantly superior compared to the AZA+placebo group (4). Furthermore, the mucosal healing rates at the 26th week were higher in the IFX+AZA group compared to both the IFX+placebo and the AZA+placebo groups; the mucosal healing rate of the IFX+placebo group was also detected as higher than the rate of the AZA+placebo group. Side effect profiles of all three groups were determined as similar.

DISCUSSION

For the induction and the maintenance of remission in luminal CD with moderate-severe activity, anti-TNF agents are superior compared to placebo among patients who are refractory or intolerant to steroid and/or IMM treatments.

For the induction and the maintenance of remission in CD with moderate-severe activity, anti-TNF+IMM combination therapy is superior compared to the single use of anti-TNF and the single use of an IMM.

Table 8. Safety data for maintenance therapy

Author - year	Treatment vs control	Dosage	Interval (w)	Period (w)	Number of patients	Droup - out - NNH	SAE - NNH
G Van Assche, 2008 (12)	IFX+Immuno-suppression (IS) vs IFX-IS	5	8	104	40 vs 40	20	NA
J-F Colombel, 2007 (13)	ADA vs placebo	40 40	2 1	56	260 vs 261 257	14.2 11.1	16.6 20
J-F Colombel, 2009 (19)	ADA vs placebo	40 40	2 1	60	30 40	-	50
J-F Colombel, 2009 (14)	ADA vs ADA induct/reinit	40 40	2 1	56	260 257	9.09 6.66	11.1 11.1
SB Hanauer, 2002 (15)	IFX vs placebo	5 10	0-2-6-8	54	113 112	11.1 100	50 14.2
BE Sands, 2004 (20)	IFX vs single induct	5, if not responded 10	0-2-6-8	54	96	25	11.1
BE Sands, 2004 (21)	IFX vs placebo	5	0-2-6	54	14	-	5
W J Sandborn, 2007 (16)	ADA vs placebo	40 40	2 1	56	19 18	8.33 6.25	16.6 11.1
P Rutgeerts, 1999 (17)	IFX vs placebo	10	8	48	37	9.09	7.14
BG Feagan, 2005 (22)	ADA vs placebo	20 10	0-8	16	39	9.09	100

IS: Immunosuppression.

Anti-TNF agents increase the mucosal healing rates compared to the placebo in CD with moderate-severe activity among IMM/CS refractory or intolerant patients.

Anti-TNF+IMM combinations provide a higher rate of mucosal healing compared to both anti-TNF treatment alone and IMM treatment alone in IMM-naive patient groups of CD with moderate-severe activity. Because only one randomized, placebo controlled study has been conducted, this issue will be clarified with the results of forthcoming studies.

Anti-TNF agents appear to be safe in the use of induction and maintenance of remission in CD with moderate-severe activity.

Anti-TNF+IMM combination treatment causes more side effects than use of either treatment alone.

When anti-TNF+IMM combination treatment is used for the induction and maintenance of remission in CD with moderate-severe activity, discontinuation of IMM treatment in the 6th month does not affect the mucosal healing or the clinical response. There are only a limited number of studies on this issue.

In light of these findings, recommendations related to the use of anti-TNF agents for the treatment of luminal (inflammatory type) CD are presented in the box.

Recommendation:

Anti-TNF treatment can be considered among the CS/IMM non-responsive or intolerant patients for remission induction and remission maintenance treatment in Crohn's disease with moderate-severe activity ***(EL 1a, RG B).***

Anti-TNF+IMM combination treatment can be considered instead of IMM alone among the CS-dependent or corticosteroid-refractory Crohn's disease with IMM-naive moderate-severe activity with poor prognostic factors ***(EL 1b, RG B).***

If anti-TNF+IMM combination is used for the maintenance of remission in the luminal Crohn's disease with moderate-severe activity, IMM treatment can be discontinued in the 6th month and the treatment with anti-TNF can be continued considering the clinical condition of the patient ***(EL 1b, RG D).*** *Sufficient evidence is not available concerning the duration of treatment.*

For all of the above-mentioned three items, the decision should be made after discussing with the patient the potential side effects and the probable results of the treatment and also thoroughly considering the international recommendations.

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