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□ Original Article □

Safety and Efficacy Evaluation for the Addition of Either Etanercept or Leflunomide in Korean Rheumatoid Arthritis Patients Inadequately Responding to Methotrexate

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Objective. **To compare the safety and efficacy associated with the addition of etanercept (ETN) with that of leflunomide (LEF) in Korean rheumatoid arthritis (RA) patients, who inadequately respond to methotrexate (MTX) in a randomized, open-label study.**

Methods. **Twenty-nine subjects suffering moderate to severe RA, despite MTX treatment were randomly assigned to a combination therapy with either ETN or LEF. The primary end-point was the proportion of subjects achieving American College of Rheumatology (ACR20) criteria at week 16.**

Results. **Ninety percent (n=18) of the ETN+MTX group (n=20) and 22.2% (n=2) of the LEF+MTX group (n=9) achieved an ACR20 response (p=0.001). All patients (n=20) in the ETN+MTX group showed moderate or good EULAR response as compared with 55.6% (n=5) in the LEF+MTX group (p=0.012). All of the ETN+MTX subjects completed the study without adverse events. Adverse events occurred in 77.8% (n=7) of cases in the LEF+MTX group; significantly elevated serum AST/ALT levels in 6 subjects and mild neutropenia (ANC < 1,500/μL) in 1 subject.**

Conclusion. **The ETN+MTX combination therapy was effective and safe, whereas the LEF+MTX combination therapy resulted in moderate efficacy in only half of the cases, and was accompanied by a high rate of adverse events. Elevated AST/ALT was the most common adverse event causing dose adjustment or discontinuation of therapeutic agent in the LEF+MTX group.**

Key Words. **Etanercept, Leflunomide, Liver function tests, Methotrexate, Rheumatoid arthritis**

Introduction

Rheumatoid arthritis (RA) is a systemic disease characterized by chronic persistent inflammation and juxta-articular bone destruction. Prompt initiation of therapy after diagnosis using disease modifying anti-rheumatic drugs (DMARDs) is crucial because delay in treatment results in substantial damage, as evidenced by radiographic examination (1-3). Methotrexate (MTX) is one of the most widely used DMARDs in RA treatment and is often the drug of choice. However, MTX does not always fully control disease activity and another DMARD, such as leflunomide (LEF) or anti-TNFα inhibitor, must be enlisted. Etanercept (ETN), a fully human TNF soluble receptor, is approved for the treatment of RA and has been shown to be highly effective in achieving clinical remission of disease, radiographic non-progression and normalization of function (4). LEF is an isoxazol derivative used as DMARD in the treatment of RA. Previous randomized controlled trials have reported that MTX and LEF are associated with significantly increased serum elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (5). We investigated the efficacy and safety of combination therapy by adding either LEF or ETN to MTX therapy in the treatment of RA patients who inadequately responded to the full, tolerable dose of MTX.

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Materials and Methods

Study design

This was a 16 week, randomized, open-label, single center study. We compared the efficacy and safety of combination therapies using ETN+MTX or LEF+MTX in patients with moderate to severe RA. They were randomly assigned by central pharmacy to one of two treatment groups consisting of either twice weekly injections of 25 mg of ETN, or 10 to 20 mg/day of LEF in a 2 : 1 allocation, respectively. The dose of LEF was decided according to the disease activity of the patient. There was no loading dose of LEF. All patients continued MTX treatment for the duration of the study at a fixed dose unless dose reduction was indicated for safety reasons. Informed consent was obtained from all the patients.

Patients

The study consisted of 29 patients that met the 1987 American College of Rheumatology (ACR) diagnostic criteria for RA (6). Patients with moderate to severe RA were enrolled in the study as defined by the following; disease activity score based on a 28-joint count (DAS28) $\geq$3.2, and either erythrocyte sedimentation rate (ESR) $\geq$28 mm/hr or morning stiffness $\geq$45 minutes. The patients must have been treated with MTX (at least 7.5 mg/week and no more than 25 mg/week) for a minimum of 3 months. The main exclusion criteria were previous or concurrent treatment with anti-TNFα inhibitor and previous treatment using any DMRAD other than MTX within 3 months prior the initiation of ETN or LEF. Subjects were ineligible to participate in the study if they had active or recent (within 2 years) tuberculosis infection; Korean guidelines were followed for the screening and prophylaxis approach for latent tuberculosis. Positive test results indicating the presence of hepatitis B surface antigen or hepatitis C virus antibody were also criteria for study exclusion.

Efficacy assessment

Primary end-point was the proportion of subjects achieving American College of Rheumatology (ACR20) criteria at week 16 (7). Secondary end-point was the proportion of subjects achieving moderate or good European League Against Rheumatism (EULAR) response at week 16 (8). Safety measures for adverse events at each visit (baseline and weeks 2, 4, 8, 12 and 16), including laboratory data such as hematology and chemistry profiles, were captured in our study data.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (version 19.0; SPSS, Inc., Chicago, IL, USA). The numerical data are shown as mean and standard deviation (SD). The Mann-Whitney U test was used to compare the variables between the 2 groups. Fisher's exact test was used to compare the ACR20 and EULAR response criteria between the 2 groups. A value of $p<0.05$ was considered significant.

Ethics statement

This study was approved by the institutional review board of Inha University Hospital (No. 07-13).

Results

Patient characteristics

Twenty subjects were allocated to the ETN+MTX treatment group and 9 subjects were allocated to the LEF+MTX treatment group (Figure 1). All 29 patients were included in the intention to treat population and were eligible for efficacy and safety analyses. Three subjects in the LEF+MTX group discontinued the study: 2 due to liver function test (LFT) abnormalities which occurred after 8 and 12 weeks into the study and 1 upon the patient's request. None of the subjects in the ETN+MTX group discontinued their participation in the study. The baseline demographic and clinical characteristics were similar between the 2 treatment groups (Table 1). The only significant difference was disease duration; 20.8 years in the LEF+MTX treatment group and 8.4 years in the ETN+MTX treatment group (p=0.018).

Efficacy and safety

A higher percentage of subjects receiving ETN+MTX combi-

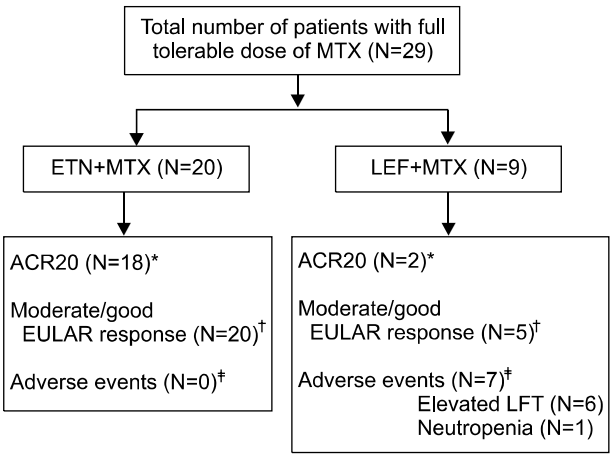

Figure 1. Patient disposition. LEF: lefunomide, MTX: methotrexate, ETN: etanercept, LFT: liver function test, ACR: American College of Rheumatology, EULAR: European League Against Rheumatism. *p=0.001, †p=0.012, ‡p<0.001. Fisher's exact test.

Table 1. Baseline demographics and characteristics of both patient groups.

	LEF+MTX (n=9)	ETN+MTX (n=20)	
Age (years)	54.6±6.6	50.0±10.6	p=0.229
Female, n (%)	9 (100)	18 (90)	p=1.000
Duration of disease (years)	20.8±13.7	8.4±4.8	p=0.018
BMI	23.3±3.7	21.8±2.6	p=0.555
Height (cm)	153.9±5.9	157.8±8.7	p=0.239
Weight (kg)	54.1±8.9	55.1±7.4	p=0.588
DM (%)	2 (22.2)	0	p=0.089
Liver disorder, n (%)	0	0	
Use of NSAIDS, n (%)	6 (66.7)	16 (80)	p=0.642
Use of INH, n (%)	3 (33.3)	13 (65)	p=0.226
Drinking alcohol, n (%)	4 (44.4)	5 (25.0)	p=0.295
Daily prednisolone (mg)	3.9±1.8	3.8±2.4	p=0.782
Weekly methotrexate (mg)	16.4±4.5	14.3±3.6	p=0.219
DAS28-ESR	6.85±1.10	6.41±0.97	p=0.346

All values are mean±SD unless otherwise specified. LEF: lefunomide, MTX: methotrexate, ETN: etanercept, BMI: body mass index, DM: diabetes mellitus, NSAIDS: nonsteroidal anti-inflammatory drugs, INH: isoniazid, DAS28: disease activity score based on a 28-joint count, ESR: erythrocyte sedimentation rate. The Mann-Whitney U test was used to compare the variables

nation therapy achieved the ACR20 response as compared to those taking LEF+MTX (90% [n=18] vs. 22.2% [n=2)]; p=0.001) (Figure 2). All subjects in the ETN+MTX group (n=20) showed moderate or good EULAR response as compared to 55.6% (n=5) of the LEF+MTX group (p=0.012).

All subjects in the ETN+MTX group completed the 16 weeks of treatment without any adverse events while adverse events occurred in 7 out of 9 subjects in the LEF+MTX group (0% vs. 77.8%, respectively; $p<0.001$). Elevated liver transaminases (above the upper normal limit for AST/ALT) were observed in 6 subjects and mild neutropenia (absolute neutrophil count $<1,500/\mu L$) occurred in 1 subject (Table 2). One subject discontinued the study due to continuous elevation of AST/ALT which persisted despite the withdrawal of LEF for 1 week. The AST/ALT levels for this patient normalized after 3 weeks. Another subject discontinued the study due to recurrent elevation of AST/ALT levels upon restarting MTX therapy after their AST/ALT levels normalized 2 weeks after discontinuing MTX+LEF combination therapy; in this case, the AST/ALT levels normalized 4 weeks after study withdrawal. Two subjects recovered from AST/ALT elevation after discontinuing LEF for 1 and 2 weeks, respectively, and they were able to restart LEF at the same dose. In one subject, their elevated AST/ALT levels normalized one week after discontinuing MTX+LEF combination therapy. MTX at half the initial dose was resumed and dosing with LEF was restarted after 6 weeks. One subject showed elevated AST/ALT levels at 16 weeks; this subject completed the study with elevated LFT and their AST/ALT levels normalized 2 weeks after completion of the study. The subject with neutropenia discontinued the study and recovered from neutropenia 4 weeks after withdrawal of MTX.

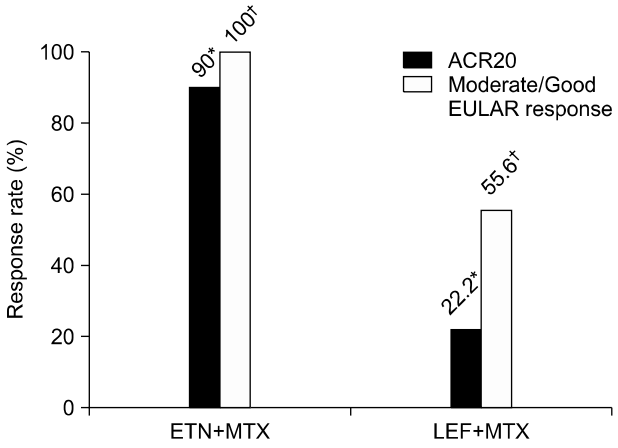

Figure 2. ACR20 and EULAR response rate at 16 weeks (*p=0.001, †p=0.012. Fisher's exact test).

Discussion

A concern that arises upon addition of a second DMARD to a treatment regimen after the failure of MTX therapy is the occurrence of adverse events. Previous randomized controlled trials have reported that MTX and LEF are associated with significantly increased incidence of ALT and/or AST elevations (5). Curtis et al. (9) found LEF+MTX combination therapy to be associated with greater incidence of AST/ALT elevation as compared to either MTX or LEF, and this risk is greater in those taking higher MTX doses. Our study also showed more frequent elevation of LFT in LEF+MTX combination therapy as compared to ETN+MTX combination

Table 2. Characteristics of patients in the LEF+MTX treatment group

Patient number	Age (years)	Disease duration (years)	PD daily dose (mg)	MTX weekly dose (mg)	LEF daily dose (mg)	Adverse event
1	56	12	5	12.5	20	AST/ALT 256/402
2	63	45	5	20	20	AST/ALT 61/70
3	47	8	5	20	10	AST/ALT 53/52
4	64	13	5	10	10	No adverse event
5	46	6	5	20	10	AST/ALT 28/48
6	50	13	0	20	10	Neutropenia (ANC 1,443/μL)
7	53	26	2.5	10	10	AST/ALT 58/35
8	52	37	5	20	10	AST/ALT 75/81
9	60	27	2.5	15	10	No adverse event

PD: prednisolone, MTX: methotrexate, LEF: leflunomide, ANC: absolute neutrophil count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AST upper normal limit 38 IU/L, ALT upper normal limit 43 IU/L

therapy. No case of elevated AST/ALT was observed in the ETN+MTX group.

Lee et al. (10) reported LEF+MTX therapy to be safe when it is used in conjunction with careful LFT monitoring, but their study utilized relatively low doses of LEF of 10 mg or less and MTX was started at 7.5 mg/week initially, increased to 10 mg/week at 4 weeks from baseline, and to 15 mg/week at 8 weeks from baseline, depending on the response and tolerability. Sixteen patients (21.6%) experienced LFT abnormalities, which was lower than our study of 6 patients (67%). Our study included 2 subjects receiving 20 mg of LEF and one of these discontinued the study because of continuous elevation of AST/ALT levels despite the withdrawal of LEF treatment for 1 week. Six out of 7 subjects experiencing adverse events were either on a full tolerable dose of MTX (up to 20 mg/week) or a full, tolerable dose of LEF (20 mg/day), which was a cause for the high rate of LFT abnormalities.

Alves et al. (11) compared LFT levels in MTX therapy to LEF+MTX combination therapy and concluded that LEF+MTX is safe at the full dose of MTX (20～25 mg/week) and full dose of LEF (20 mg/day). However, in that study the LFT elevation was defined as higher than twice the upper normal limit of AST and ALT. In this study we were concerned about the safety of even mild elevation of AST/ALT in the long term course of RA treatment. When the LFT results were abnormal, LEF or MTX, or both were withdrawn or the dose reduced, correcting the elevation of LFT.

There are no known previous reports whereby the efficacy of ETN+MTX and LEF+MTX combination therapies were directly compared. The APPEAL study compared ETN+MTX therapy with MTX+DMARDs, which is one of sulfasalazine, hydroxychloroquine or LEF (12). It is generally accepted that biologic therapies, such as ETN, provide clinical advantages for use in the treatment of RA. COMET study results have indicated that ETN+MTX combination therapy for the treatment of moderate to severe RA provides superior clinical remission outcomes as compared to MTX therapy (4). Our study showed that a higher percentage of patients in the ETN+MTX group achieved ACR20 and moderate or good EULAR response as compared to the LEF+MTX treatment group. Thus, we suggest that when MTX therapy fails, adding ETN to the treatment regimen is more effective than adding LEF or other DMARDs. Lee et al. (10) reported combination of LEF and MTX to be effective with 71.6% of patients being ACR20 responders, which was higher than our study of 22.2%. However, in that study ACR20 was evaluated at week 20 while our study evaluated ACR20 at week 16. Also, due to LFT abnormalities, the dose of LEF was decreased or LEF discontinued in the LEF+MTX treatment group which influenced the efficacy results.

The duration of disease was longer in the LEF+MTX treatment group compared to the ETN+MTX treatment group (p=0.018). This might have influenced the analysis of treatment efficacy between the 2 treatment groups. There was no difference in age between the 2 groups (p=0.229) which would not have influenced the safety analysis.

According to the literature, hematologic toxicities including leukopenia, thrombocytopenia, megaloblastic anemia and pancytopenia occur in approximately 3% of MTX treated patients. Of these, pancytopenia occurs in about 1.4% of cases (13). Some patients treated using LEF experience transient reductions in white blood cell count which do not evolve into sustained leukopenia, as well as transient thrombocytopenia (14). McEwen et al. reported that the use of MTX together with

LEF increases the risk of pancytopenia as compared to the use of LEF alone (15). One subject from our study showed mild neutropenia (absolute neutrophil count $<1,500/\mu L$) who recovered after the MTX treatment was discontinued.

Conclusion

This is the first study whereby the efficacy and safety of ETN+MTX and LEF+MTX combination therapies were directly compared. The ETN+MTX combination therapy was more effective and better tolerated without the occurrence of any adverse events in a short term study, whereas LEF+MTX combination therapy resulted in moderate efficacy in only half of the subjects and was accompanied by a high rate of adverse events. Elevated serum AST/ALT levels were the most common adverse events in the LEF+MTX group which led to dose reduction or discontinuation of therapy. Careful monitoring of LFT levels and hematology test are necessary when LEF is added to a full, tolerable dose of a preexisting MTX therapy.

A limitation of our study was that the number of subjects in the LEF+MTX treatment group was too small to provide meaningful data for the frequency of adverse events in relation to the different MTX and LEF dose. Interim assessment showed most of the patients in the LEF+MTX group with adverse events and further enrollment of patients was thought unethical. Statistical analysis, however, showed meaningful difference in the efficacy and safety between the 2 treatment groups. It is possible that further follow up may show different results, but this was not the scope of this study. Further study with larger number of patients is needed to better understand the effect of LEF combined with MTX in RA patients.

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The authors have no conflicts of interest associated with this study. Won Park was an investigator for this study. Otherwise there's no disclosure for other authors.

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