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An Observational Study on the Use of Etanercept in Indian Rheumatoid Arthritis Patients

KEYWORDS: Etanercept, rheumatoid arthritis, Methotrexate, ACR50, DAS-28

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ABSTRACT ***Objective:*** *To determine the effectiveness and safety of Etanercept (ETN) in Indian patients of rheumatoid arthritis (RA) who are inadequately controlled with combination therapy of two or more disease modifying anti-rheumatic drugs (DMARDs) and oral low dose glucocorticoids (GC).*

Method: *This is a 52-weeks observational study of 35 RA patients with inadequate response to combination DMARDs, who were shifted to subcutaneous ETN 50 mg weekly along with MTX. The clinical response of therapy was measured through the American College of Rheumatology criteria (ACR) for ACR20 & ACR50 improvement and Disease Activity Score (DAS-28). The other response assessment criteria were Health Assessment Questionnaire Disability Index (HAQ-DI), visual analogue scale (VAS) and erythrocytic sedimentation rate (ESR). Safety of ETN treatment was assessed by recording any adverse event that occurred during the 52 weeks of study duration.*

Results: *ETN in combination with MTX resulted in achievement of ACR20 response in 68.5% and ACR50 response in 45.7% patients at 24 weeks. At 52 weeks, 51% of the patients attained both the DAS-28 remission (DAS-28 score less than 2.6) as well as ACR50 response. Significant outcomes ($p<0.001$) of VAS score, HAQ-DI and ESR values were achieved after 24 weeks. Five patients (14.2%) had no improvement in disease activity and were withdrawn from the treatment. Two patients were discontinued due to development of injection site reaction after 4 weeks of initiation of ETN. One patient reported transient cough during the course of study which spontaneously resolved in a week without any treatment and one patient developed herpes zoster during ETN treatment.*

Conclusion: *RA patients, who were inadequate responders to two or more combination DMARDs including MTX and oral GC therapy, responded well when switched to ETN with continued MTX therapy. Significant clinical improvement was seen as early as 4th week of treatment and there was further improvement at 12 and 24 weeks of treatment. Beneficial response to ETN was sustained during the 1-year duration of study. This study supports the therapeutic benefits of switching over to ETN therapy while continuing MTX in RA patients who were partial responders to combination DMARD therapy.*

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that clinically manifests as joint pain, stiffness, and swelling and if left untreated, persistent synovial inflammation can progress to cartilage and bone destruction and ultimately to major long-term disability and mortality. The Indian prevalence rate is 0.9% which is almost similar to 1% prevalence worldwide [1-2]. Total disease burden of RA globally is 1.3 million patients with predominance in women [3]. A recent epidemiological study from Sweden reported that 0.77% of the population has been diagnosed with RA[4], while a survey from UK found the prevalence to be 0.82% [5].The disease affects people of all ages but is more common in women between 40-70 years of age [1]. Both genetic and environmental factors play a role in pathogenesis of disease [6].

Conventional DMARDs such as MTX are the mainstay of treatment for patients with moderate to severe RA [7]. Failure to achieve adequate disease control in many patients, even with combination therapy of two or more DMARDs, has now necessitated the use of other biological agents that target various immune mediators involved in the disease process.

Recently, the 2012 update of 2008 American college of Rheumatology recommendations advocate the treatment of RA with synthetic disease modifying anti-rheumatic drugs (DMARDs) in combination with biological agents in patients with advanced disease or patients who are inadequate responders to conventional therapy [8]. Several anti-TNF biologics like ETN, infliximab, adalimumab, golimumab and certolizumab and non-TNF biologics like abatacept, rituximab and tocilizumab have been developed and are in clinical use [8].

ETN, a soluble TNF receptor is approved as monotherapy or in combination with MTX for the treatment of moderate

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to severe, progressive active RA in adults when DMARDs including MTX have shown inadequate response. Though there is adequate international data, but there are scarce Asian [9] and Indian trials [10] on the efficacy of ETN in RA. Therefore the aim of the present study was to evaluate the effectiveness and safety of ETN in the treatment of inadequately controlled RA patients previously on combination therapy of two or more DMARDs therapy including MTX and oral GC under routine clinical practice conditions in the Indian population.

Study design & Methodology

This was a 52-weeks observational study at Rheumatology OPD of Army Hospital (Research and Referral), New Delhi, between April 2011 to March 2012. We evaluated 35 adult RA patients who were inadequate responders to two or more DMARDs agents including MTX and GC, and were now switched to ETN therapy with continuation of MTX. These patients were also classified as per the American College of Rheumatology (ACR) global functional status at the time of participation in the study [11]. The following data was recorded in the study corresponding to specific and clinically relevant parameters at regular time intervals (i.e. at baseline and at week 4, week 8, week 12, week 24 & week 52). At baseline, patients' demography (age, gender etc), duration of disease, VAS score, Rheumatoid factor, ESR, functional class, swollen/tender joint count, and medication history were recorded. All the patients in the study were receiving ETN at the dose of 50 mg subcutaneous injection once weekly and simultaneously the dose of GC was tapered and completely stopped within 4 weeks of initiation of ETN treatment. DMARDs other than MTX were discontinued before the initiation of ETN administration. In addition, the measures of disease activity, clinical response of therapy through ACR20 and ACR50, evaluation of DAS-28, physician's global assessment of disease status, patient's assessment of disability as indicated by responses to the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI),[12] patient's assessment of pain according to a VAS(0-10),[11] the ESR (as measured by the Westergren method),[13] were recorded at baseline and at various time intervals till 52 weeks. Safety assessments were performed at baseline and at week 4, week 8, week 12, week 24 & week 52 and consisted of recording of all adverse events (AEs). Patients were followed up for a period of 52 weeks; however the patients who failed to report during this period were considered lost to follow up.

Statistical analyses

Descriptive statistical methods were used to summarize the demographic and disease characteristics. Measurement data was expressed as mean with standard deviation (S.D.). Discrete data of gender distribution & response rates was expressed as numbers & percentages. Data for DAS-28, VAS and HAQ-DI were analyzed by one-way ANOVA. All statistical analyses were performed using the SAS System, version 9.2 and p value of <0.05 was considered significant and $p<0.001$ was considered as highly significant.

RESULTS:

Patients' disposition

Of the 35 patients initially included in the study, data of 28 (80.0%) patients was available for analysis at the end of 52 weeks, since 7 (20.0%) patients had been discontinued from the study out of which 5 were lost to follow-up, and 2 were withdrawn due to adverse events of injection site reaction (table 1).

Table 1: Patients completion status at the end of the study (N=35)

	ETN Treatment
Patient Disposition	
Total patient included	35
Total patient completed the total study period	28
Total patient discontinued before completion of study	7
Details of discontinuation	
Lost to follow-up	5
Adverse events of study medication	2

In addition, ETN treatment of 5 (14.2%) patients was stopped at 4 weeks because of inadequate efficacy and these patients were considered as non-responders and were included in the analysis.

Study population & disease characteristics

The mean age of 35 patients evaluated in the study was 34.7 ± 5.1 years, ranging from 26 to 47 years with mean duration of disease being 6.02 ± 2.22 years (range 3–12 yrs). Majority of the patients were female (68.5%). The detailed demographic description and baseline characteristics of patients evaluated in the study are given in table 2.

Table 2: Demographic summary and baseline characteristics of the enrolled patients

Characteristics		N=35
Age (years)	Mean ± SD	34.77 ± 5.13
	Range	26 -47
Age Group N (%)	20-30	7 (20%)
	31-40	23 (65.7%)
	41-50	5 (14.2%)
Gender N (%)	Male	11(31.4%)
	Female	24(68.5%)
Duration of disease (years)	Mean ± SD	6.02 ± 2.22
	Range	3 -12
Duration of morning stiffness (minutes)	Mean ± SD	84 ± 39.38
	Range	30 -180
Tender joint counts (TJC-28)	Mean ± SD	7.14 ± 2.93
	Range	3 -14
Swollen joint counts (SJC-28)	Mean ± SD	5.43 ± 2.17
	Range	2 -10
VAS score	Mean ± SD	5.11 ± 0.99
	Range	4-7
Rheumatoid factor	Present	28
	Absent	7
ACR functional classification	I	0
	II	6
	III	18
	IV	11

The average duration of morning stiffness time of patients was 84.0 ± 39.3 minutes ranging from 30 to 180 minutes. Majority of these patients (88.5%) belonged to the revised ACR functional class III and IV and remaining belonged to class II. Twenty-eight patients were positive for rheumatoid factor (table 2). All the patients were on MTX (12.5 to 20 mg/week) (table 3) in combination with other DMARDs in optimal dosage for at least six months. Twenty seven (77%) patients were receiving oral GC (prednisolone 5 mg/day or 7.5 mg/day or 10mg/day) before ETN therapy was started (table 3).

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Table 3: Dose of MTX and GC therapy

MTX Dose (mg/kg/ day)	No. of patients N= 35	Oral GC dose (mg/kg/day)	No. of patients N= 27
12.5	2 (5.7%)	5.0	17(48.5%)
15	7 (20.0%)	7.5	7 (20.0%)
17.5	5 (14.3%)	10.0	3 (8.5%)
20	21 (60.0%)	-	-

ACR20, ACR50 and DAS-28 responses

After 12 weeks of ETN treatment, 62.8% of the patients attained ACR20 responses and this response was further increased to 68.5% patients after 24 and 52 weeks of treatment (table 4).

Table 4: ACR20, ACR50 and DAS-28 responses at various time period of treatment

Response	Week 12	Week 24	Week 52
	Number (%) of patients		
ACR20	22 (62.8%)	24 (68.5%)	24 (68.5%)
ACR50	12 (34.2%)	16 (45.7%)	18 (51.4%)
DAS 28 remission (score < 2.6)	10 (28.5%)	16 (45.7%)	18 (51.4%)

ACR20: American College of Rheumatology 20% improvement, ACR50: American College of Rheumatology 50% improvement, DAS: Disease activity score

Detailed analysis shows that ACR50 responses were 34.2%, 45.7% and 51.4% at 12, 24 and 52 weeks respectively. DAS-28 scores showed a persistent decrease in the disease activity with a significant reduction appearing as early as 4 weeks (mean at 0 vs. 4 weeks: 4.97 ± 0.54 vs. 4.42 ± 1.09, p<0.001). DAS remission with a score < 2.6 was seen in 28.5% patients at 12 weeks and showed further improvement to 45.7% and 51.4% at 24 and 52 weeks respectively (figure 1).

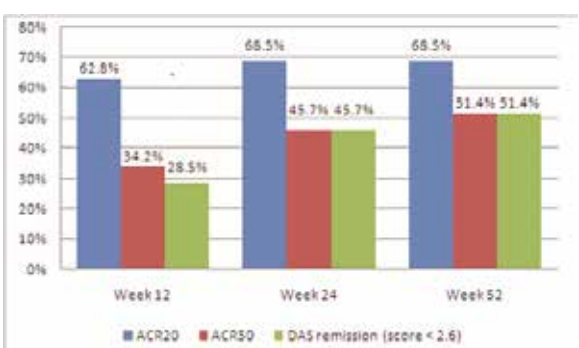

Figure 1: ACR20, ACR50 and DAS-28 responses at 12, 24 and 52 weeks

However, five (14.2%) patients had no improvement in disease activity (non responder) and ETN treatment in these patients was stopped after 4 weeks. All these five patients were of ACR functional class IV and were receiving MTX (15 or 20 mg/week), hydroxychloroquine (200 or 400 mg/day) and prednisolone (5 or 7.5 mg/day) therapy for more than 6 months. The duration of disease in the non responders was between 5–8 years. Four out of five non responder patients were positive for rheumatoid factor.

ESR, HAQ-DI and VAS pain scale (0-10) responses

ESR showed a decreasing trend with ETN treatment with a significant reduction from baseline was observed at 8 weeks (40.48 ± 17.72, p<0.001) and reached nadir (29.08 ± 14.94, p<0.001) at 24 weeks (table 5). HAQ-DI and VAS were evaluated at 0, 24 and 52 weeks. There was a significant reduction in the disability after 24 weeks (1.76 ± 0.28; p<0.001) of treatment as evident by decrease in HAQ-DI scores which were reduced further at 52 weeks (1.63 ± 0.46; p<0.001). VAS pain score also showed a significant decrease (2.90 ± 1.06: p<0.001) at 24 weeks as compared to 0 week.

Table 5: Mean values of ESR, DAS-28, HAQ-DI and VAS 10 at baseline and at various time period of treatment

	Week 0	Week 4	Week 8	Week 12	Week 24	Week 52
ESR (mm/ hr) (Mean ± SD)	56.11 ± 19.76	49.38 ± 17.82	40.48 ± 17.72*	30.60 ± 13.44*#	29.08 ± 14.94*#	30.26 ± 20.32*#
DAS-28	4.97 ±0.54	4.42 ± 1.09*	3.67 ± 1.12*†	3.12 ± 1.04*†	2.80 ± 1.21*†#	2.45 ± 1.43*†#
HAQ-DI	2.17 ±.34	(-)	(-)	(-)	1.76 ± 0.28*	1.63 ± 0.46*
VAS	5.11 ± 0.99	(-)	(-)	(-)	2.90 ± 1.06*	2.72 ± 1.24*

*P<0.001 versus week 0; † P<0.001 versus week 4; # P<0.001 versus week 8; (-) data not evaluated at these time points

ESR: Erythrocyte sedimentation rate, DAS: Disease activity score,

HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analogue Scale

Safety

A total of 4 adverse events were observed in 4 (11.4%) patients; 2 patients developed injection site reaction at 4th week and further treatment with ETN in these patients was stopped and patients were discontinued from the study. One patient developed transient cough and another patient developed herpes simplex. They were managed conservatively and ETN and MTX treatment was continued in these patients.

DISCUSSION

Progression of RA is quite variable, ranging from very mild to rapidly progressing and debilitating forms. Persistent inflammatory activity in RA characterized by symptoms such as constant pain and synovitis in continuation of treatment with DMARDs is suggestive of refractory or inadequately controlled disease [13]. Earlier RA disease activity was evaluated through symptoms such as duration of morning stiffness, number of painful and edematous joints and laboratory measurements to detect inflammatory activity, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [14]. Currently, a broader evaluation of disease activity by composite measures such as the American College of Rheumatology (ACR) response criteria [15], the index of disease activity based on evaluation of 28 joints (DAS-28) [16], etc are used. According to EULAR recommendations [17], MTX is the standard treatment at initial diagnosis, preferably combined with low dose GC. Combination DMARD therapy

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should be considered in MTX inadequate responders and in patients with poor prognostic factors like erosive disease and seropositivity. Biologicals should be initiated in patients with persistent high activity after 6 months of conventional treatment and still earlier in patients with early destruction or unfavorable prognosis. A switch to another biological is indicated after 3-6 months of ineffective therapy [17]. Previously, clinical studies have evaluated the efficacy and safety of ETN in RA patients given as mono-therapeutic agent [18-20] or in combination with MTX [18-23] or as substitution therapy for MTX or infliximab [24-25]. In two monotherapy trials, ETN (16 mg/m2 BSA twice weekly) treatment in refractory RA patients had resulted into an ACR20 response in 75% of patients, compared to 14% of those receiving placebo with no serious toxic effects [18], and an ACR20 response among 62% of the ETN-treated patients (25 mg weekly) as compared to 23% of the patients receiving placebo [19].

Combination therapy of ETN with MTX has shown good results with rapid and sustained improvement [21,23]. In a 24-week, double-blind trial (TEMPO trial), combination therapy of ETN with MTX in persistently active RA patients produced statistically significant ACR20 and ACR50 responses in 71% and 39% of the patients respectively compared to 27% and 3% of patients those received placebo with MTX, respectively ($p<0.001$) [19]. Additionally, significantly better outcome ($p<0.01$) according to all measures of disease activity were seen with ETN plus MTX therapy. Adverse events of only mild injection-site reactions were seen in these patients and no patient was withdrawn from the study because of ETN associated adverse events [21]. The efficacy of ETN as substitution therapy for DMARDs was compared in TEMPO trial [20]. Treatment with ETN in combination of MTX was compared with monotherapy of either agent in 686 patients with active disease of over six months duration who had responded inadequately to at least one DMARD, but not received MTX. The study observed that the combination of MTX and ETN was more efficacious than MTX or ETN alone. Follow-up analysis of TEMPO trial reported that clinical response was sustained during year 1 to year 2 [21]. The ACR20, ACR50, and ACR70 responses achieved were more with combination therapy than with either monotherapy. The COMET study also compared the remission and radiographic non-progression rate in active early RA patients treated with MTX plus ETN versus MTX monotherapy [23]. In the COMET study 50% patients attained clinical remission with combination therapy compared to 28% patients taking MTX alone ($p<0{\cdot}0001$) [23]. Haraoui et al, (2004) [24] and Buch et al, (2007) [25] showed the clinical benefits of ETN in patients' primarily not responding to infliximab and in patients inadequately controlled with infliximab and MTX combination. Treatment of 'infliximab non-responder' patients with ETN resulted into ACR20 response in 64% of the patients and an improvement in Health Assessment Questionnaire (HAQ) score were seen among 59% of the patients [24]. In another observational study, substitution of infliximab and MTX by ETN had resulted in ACR20, ACR50 and ACR70 responses in 38%, 24% and 15% of the treated patients, respectively. After 12 weeks of treatment, reduction in DAS-28 (low index) as well as moderate or good EULAR score was attained in 67% of primary and 56% of secondary infliximab failures [25].

In a retrospective study at Apollo Hospitals India, significant positive outcomes were achieved with anti-TNF biologic agents in three patients of active rheumatoid arthritis[10]. Besides, there were no serious side effects and infectious complications noted. Our study further substantiates the fact that anti-TNF biologic agents are safe and effective in treating refractory RA patients in an Indian setting.

In the present study, combination therapy of ETN and MTX resulted in low disease activity (i.e. both ACR50 response and DAS remission, score less than 2.6) in 45.7% patients by 24 weeks and 51.4% patients at 52 weeks of therapy (table 4). The study also resulted into significant ($p<0.001$) reduction of ESR, HAQ-DI and VAS score (table 5). ETN therapy was found largely safe in the present study as it did not cause any serious adverse events and is in accordance with the previous reports. The most commonly reported adverse events in RA as documented in other trials of ETN were, injection site reaction, infection, and headache.

One of the limitations of the study was that the patients were not evaluated for radiological changes. Also a study with larger number of subjects should be carried in future to further confirm the findings.

Key messages

The findings of this 52 weeks study in patients with active RA provides further evidence that ETN as a combination to MTX therapy, has a favorable long-term safety and efficacy profile in Indian population. The results of the current study also strongly suggest the clinical benefits of ETN in DMARD non- responder patients which is in conformity of previous reports on ETN use in RA patients.

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Conflicts of interest

None

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