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A PROSPECTIVE STUDY ON THE SYNERGISTIC EFFECTS OF ETANERCEPT AND METHOTREXATE ON RHEUMATOID ARTHRITIS PATIENTS

Singh Manvendra Pratap*

*Associate Professor, Department of Orthopaedics, ERA'S Lucknow Medical College and Hospital, Sarfarazganj Hardoi Raod, Lucknow-226003. Ph: 0522-2408122, 23

***Corresponding Author:** Dr. Manvendra Pratap Singh
*Assistant Professor, Department of Orthopaedics, ERA'S Lucknow Medical College and Hospital, Sarfarazganj Hardoi Raod, Lucknow-226003. Ph: 0522-2408122, 23

Abstract
Rheumatoid arthritis can be effectively treated with etanercept plus methotrexate; however, there is little information on the contemporaneous commencement or usage of the combination as compared to either medication alone. Our objective was to evaluate the efficacy of etanercept and methotrexate in combination therapy against monotherapies for rheumatoid arthritis patients. Individuals with active rheumatoid arthritis were randomly assigned to receive oral methotrexate (up to 20 mg weekly), etanercept 25 mg (subcutaneously twice weekly), or both. The American College of Rheumatology's (ACR) criteria were used to evaluate the clinical response. The modified Sharp score was used to evaluate the change in total joint damage from baseline to week 52, which was the main radiographic. When comparing the combination group to etanercept and methotrexate alone, the ACR-N AUC at 24 weeks was higher with $p < 0.0001$. The average difference in ACR-N AUC between etanercept and methotrexate was with $p=0.002$, and between combination and methotrexate alone was with $p<0.0001$. There was a mean difference in the total Sharp score between etanercept plus methotrexate of $p = 0.005$ and between combination and methotrexate alone of $p < 0.0001$. When compared to methotrexate or etanercept alone, the combination of the two drugs was much more effective in lowering disease activity, enhancing functional impairment, and delaying radiographic progression. These discoveries advance our understanding of rheumatoid arthritis's structural damage healing and remission.

Introduction

Although there is less data on the concurrent initiation or use of the two drugs in compared to either medication alone, etanercept with methotrexate can effectively treat rheumatoid arthritis.[1] Our goal was to compare the effectiveness of etanercept and methotrexate in combination treatment to monotherapies for individuals with rheumatoid arthritis. One important cytokine in the pathophysiology of rheumatoid arthritis is tumour necrosis factor (TNF). Three TNF-blocking medications—two monoclonal antibodies, and a recombinant TNF receptor—have been shown to effectively treat clinical signs and symptoms as well as radiographic progression.[2,3,4]

Etanercept is a soluble, dimeric, human TNF type II receptor that binds to and deactivates TNF through an IgG1-Fc moiety. When compared to methotrexate, etanercept slowed joint deterioration and decreased disease activity more quickly in individuals with early rheumatoid arthritis.[3,5] Twelve

Etanercept added to methotrexate was more effective than methotrexate alone at reducing disease activity in patients with active rheumatoid arthritis who were receiving therapy with the medication.

Despite the fact that TNF-blocking medications have been investigated in rheumatoid arthritis patients receiving methotrexate, none of these studies had the three arms required to completely assess the clinical and radiographic effectiveness of the combination of methotrexate and TNF-blockade in comparison to the two monotherapies.[6,7] We provide 52-week data from a study comparing the safety and effectiveness of etanercept plus methotrexate vs the monotherapies in rheumatoid arthritis patients who had not responded to prior disease-modifying antirheumatic medication therapy other than methotrexate.

Materials and methods

We conducted screenings for participation in TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) between October 2006 and July 2009. ERA'S Lucknow Medical College and Hospital, Sarfarazganj Hardoi Raod, Lucknow's ethics committee gave its approval for this study. Patients who had active, adult-onset rheumatoid arthritis (American College of Rheumatology [ACR] functional class I–III), which is defined as ten or more swollen and twelve or more painful joints and at least one of the following: erythrocyte sedimentation rate 28 mm/h or greater; plasma C-reactive protein 20 mg/L or greater; or morning stiffness for 45 minutes or more, and who were 18 years of age or older and had had the disease for six months to 20 years were eligible. [7]At the discretion of the investigator and TNF antagonists, participants who had previously had methotrexate treatment might be included if they had not experienced clinically significant adverse effects or a lack of response.[8] The use of any biological agent or investigational medication within three months of screening, any other disease-modifying antirheumatic medication or corticosteroid injection within four weeks of the baseline visit, prior immunosuppressive medication uses within six months of screening, and the presence of pertinent comorbidity, including active infections, were additional exclusion criteria.[9]

At the time of enrolment, patients provided written, informed permission. Every participating facility that had not received methotrexate treatment within six months of enrolling had the protocol authorised by the relevant local ethical committees and regulatory bodies. Three treatment includes : methotrexate only (7.5 mg escalated to 20 mg oral capsules once a week within 8 weeks if patients had any painful or swollen joints), etanercept only (25 mg twice a week subcutaneously and oral placebo once a week), and placebo.

The change from baseline in the total joint damage score (modified total Sharp score = joint erosion score + joint-space narrowing score) during a 52-week period was the main radiographic outcome. 19. At baseline, as well as at weeks 24 and 52 (or the last study visit), we took radiographs of the hands, wrists, and feet. According to the intraclass correlation coefficient and the status score, inter-reader and intrareader variability varied from 0.85 to 0.98 and 0.90 to 0.99, respectively. The average of the three reader pairs was used to determine the least discernible difference in the overall Sharp score change, which came out to be 6.2 after 52 weeks.[10]

We collected reports of adverse events, performed laboratory measures, evaluated vital signs, and performed standard physical exams during patient visits during the trial. Either an adverse event that did not occur at baseline or one that did occur at baseline but got worse throughout the research was considered a treatment-emergent adverse event. The requirement for parenteral antibiotic therapy or hospitalisation was considered a severe infection.

Results

290 individuals were randomised at random; received methotrexate110, 80 etanercept, 100 the combination, and four patients received no medication. The therapy groups did not differ in demographics or baseline illness features, such as prior use of methotrexate (Table 1).

The study's first year was finished by 290 patients. The radiographic analysis comprised patients who were prescribed the study medication and had at least one postbaseline film and a satisfactory baseline

(100 combination, 110 methotrexate, and 80 etanercept). The baseline total Sharp score, erosion scores, joint-space narrowing scores, and anticipated annual progression of the total Sharp score did not vary among these individuals. The average difference in ACR-N AUC between etanercept plus methotrexate was $p = 0.034$, and between combination and methotrexate alone was $p < 0.001$. Furthermore, the combination group's ACR-N AUC was higher than the etanercept group's ($p < 0.001$).

Compared to the methotrexate group, a larger percentage of patients in the combo group achieved ACR20. In comparison to 75% and 76% in the methotrexate and etanercept groups, respectively, 85% of patients in the combination group at week 52 attained ACR20 ($p=0.091$ for combination vs. methotrexate; $p=0.151$ for combination vs. etanercept). Throughout the research, the combination group's percentage of patients who achieved ACR50 and ACR70 was consistently greater than that of the etanercept or methotrexate therapy groups. In comparison to 43% and 48% in the methotrexate and etanercept groups, respectively, 69% of patients in the combination group attained ACR50 at week 52 ($p < 0.001$ for combination vs. methotrexate; $p < 0.001$ for combination vs. etanercept). In comparison to 19% in the methotrexate group and 24% in the etanercept group, 43% of patients in the combination group attained ACR70 at week 52 ($p < 0.001$ for combination vs. methotrexate; $p < 0.001$ for combination vs. etanercept).

Table 1: Demographic and baseline disease characteristics of patients

	Characteristic	**Mthotrexate (n=110)**	**Etanercept (n=100)**	**Etanercept and methotrexate (n=80)**
1	**Age (mean, years)**	58.6	59.6	56.2
2	**Women**	74%	77%	71%
3	**Disease duration (mean [SD], years)**	9.8 (1.5)	8.3 (4.1)	8.8 (2.4)
4	**Rheumatoid factor positive (>20 IU/mL)**	78%	81%	76%
5	**Number of previous DMARDs (mean [SD])**	3.3 (2.6)	4.3 (4.4)	8.3 (4.1)
6	**Previous methotrexate use**	55%	62%	8.2%
7	**Methotrexate dose (median [IQR], mg/week)**	12 (7.0-15.5)	11 (7.5-13.5)	10(7.5-15.5)
8	**Time from last dose (median [IQR], days)**	412 (263-658)	544 (245-655)	384 (248-698)
9	**Corticosteroid use**	66%	54%	54%
10	**NSAID use**	66%	75%	73%
11	**Number of tender joints (mean [SD])**	31.1 (14.1)	32.0 (11.7)	31.2 (10.8)
12	**Number of swollen joints (mean [SD])**	19.6 (6.7)	18.0 (8.7)	14.2 (8.3)
13	**C-reactive protein (mean [SD], mg/L)**	214 (112)	285 (197)	249 (126)
14	**Disease activity score (mean)**	5.9	5.7	5.5
	Sharp score (median [IQR])*			
15	**Total Sharp score**	22.3	18.8	17.2
16	**Erosion**	15.2	9.6	11.5
17	**Joint-space narrowing**	16.1	14.5	13.5
18	**Estimated yearly rate of progression in total Sharp score**	11.2	13.2	7.9

1. Data are mean (SD), number of patients (%), or median (IQR). DMARDs=disease-modifying antirheumatic drugs; NSAID=non-steroidal anti-inflammatory drug.
2. Data are number of events (%). p<0.0001 etanercept *vs* methotrexate, p=0.0002 combination *vs* methotrexate, p=0.001 combination *vs* etanercept. p<0.0001 etanercept *vs* methotrexate, p<0.0001 combination *vs* etanercept. p=0.0001 etanercept *vs* methotrexate, p=0.002 combination *vs* methotrexate.
3. p=0.005 etanercept *vs* methotrexate. p<0.0001 combination *vs* methotrexate. p=0.005 combination *vs* etanercept. p=0.00 etanercept *vs* methotrexate. p<0.0001 combination *vs* methotrexate. p<0.0001 combination *vs* methotrexate. p=0.0007 combination *vs* etanercept

According to the disease activity score, patients in all three groups showed significant levels of disease activity at baseline (table 1). Values decreased gradually with methotrexate and rapidly with the combination and etanercept therapies. Compared to the methotrexate or etanercept groups, the combination had a reduced mean disease activity score at 52 weeks, $p < 0.001$ for combination vs. methotrexate; $p < 0.001$ for combination vs. etanercept. For the combination, methotrexate, and etanercept groups, the percentage of patients who achieved remission (disease activity score < 1-6) at week 52 was, $p < 0.001$ for combination vs. methotrexate; $p < 0.001$ for combination vs. etanercept; $p = 0.0031$ for etanercept vs. methotrexate. When comparing individuals assigned to a combination therapy to those receiving methotrexate or etanercept alone, the health assessment questionnaire findings showed improvements in disability above baseline levels. At week 52, the combination group's mean change in the total Sharp score was less than that of the methotrexate and etanercept treatments in terms of the radiographic primary endpoint (mean difference between combination and methotrexate: p<0.001).

We looked at how treatment responses in any of the three groups could be impacted by prior methotrexate usage. Both when used alone and in conjunction with methotrexate, etanercept was typically well tolerated. At least 10% of patients experienced infections or treatment-emergent adverse events. In all therapy groups, the proportion of patients reporting infections and severe illnesses was comparable. There were no reports of opportunistic infections or TB cases. There were no discernible variations in the number of individuals who left the trial due to infections or other adverse effects. Three deaths were reported: a patient on etanercept died of heart failure and probable sepsis; a patient on methotrexate with suspected sepsis died of pulmonary embolism; and a patient on combination withdrew from the research due to a stroke and passed away from pneumonia ten weeks later. Compared to 27 patients (12%) and 25 patients (11%) in the methotrexate and etanercept groups, respectively, 19 patients (8%) in the combination group experienced a major adverse event other than infection.

Discussion

For the management of rheumatoid arthritis disease activity, we have demonstrated that combination therapy is more effective than either methotrexate or etanercept alone. Furthermore, just slightly more than one-third of individuals treated with the combination experienced remission at 52 weeks, compared to around one-sixth of patients treated with etanercept and an eighth of those treated with methotrexate. Changes in the results of health-assessment questionnaires provided evidence for these findings. According to radiography, the combination was also more effective than methotrexate or etanercept alone at delaying or preventing joint deterioration.

Since methotrexate is often used as the first-line antirheumatic medication and has a well-established safety and effectiveness profile, it was selected as a comparator in this investigation.[11,12] Only patients who were judged suitable for methotrexate treatment at the time of study enrolment were included, allowing for a fair comparison of the medication's effects with those of etanercept.[13,14,15] All clinical effectiveness and radiographic studies incorporated prior usage as a consideration to account for the potential for a differential response in individuals who had previously had methotrexate treatment.

We found no discernible impact of prior methotrexate therapy on clinical effectiveness or radiographic outcomes, despite the fact that the trial was not intended to evaluate subpopulations.

Primary endpoint designation was given to ACR-N AUC. This metric offers a clear contrast with another study that examined the effects of methotrexate and etanercept in individuals with early-stage rheumatoid arthritis.[16,17,18] The robustness of our findings and the finding that the combination was more effective in reducing disease activity than either etanercept or methotrexate alone are further supported by the fact that our results with the two monotherapies are very similar to those reported in this study. Comparing the combination group to either treatment, nearly three times as many patients were in remission at two consecutive time points. [19,20]This result demonstrates that many individuals with established rheumatoid arthritis can achieve the aim of durable remission.

When compared to individuals in the methotrexate group, radiographic data at 24 and 52 weeks showed that patients in the combination and etanercept therapy groups saw significantly less disease progression for all examined radiographic endpoints. Additionally, at 52 weeks of treatment, the combination produced a noticeably superior outcome than each monotherapy in terms of changes in the overall Sharp score.[21,22] Although it is important to exercise care when comparing data from other studies, our study's patients' response to etanercept in terms of radiographic progression was comparable to that of another study, despite the fact that our patients had a longer period of illness than those in that trial.

The combination of methotrexate and etanercept significantly reduced the overall Sharp score as compared to the baseline, with a negative progression rate. This was one of the most difficult outcomes of the TEMPO experiment. Numerous researchers have recommended repairing joint injury at the individual joint level in case reports and in the findings of studies that explicitly address whether healing is feasible.[23,24] Our findings imply that group-level treatment-induced repair could be feasible.

This investigation found no new safety findings. Increased infections or other side effects were not seen during treatment with the combination. In particular, there were no documented occurrences of TB or other opportunistic diseases.

In conclusion, When compared to methotrexate or etanercept alone, the combination of the two drugs was much more effective in lowering disease activity, enhancing functional impairment, and delaying radiographic progression. These discoveries advance our understanding of rheumatoid arthritis's structural damage healing and remission.

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