OPEN-LABEL EVALUATION OF THE EFFICACY AND SAFETY OF ETANERCEPT IN RHEUMATOID ARTHRITIS

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ABSTRACT:
OBJECTIVE: In this open label Phase IIIb study, the safety and efficacy of Etanercept in Indian patients with Rheumatoid arthritis was assessed in 4 centres across the country.
PATIENTS AND METHODS: Forty patients who fulfilled the ACR criteria of RA and had active disease despite at least one disease modifying anti rheumatic drug (DMARD) therapy were administered Etanercept (Wyeth) 25 mg subcutaneously twice a week for a 16 week period. The primary outcome measures were proportion of patients achieving ACR 20 response at 16 weeks. Secondary outcome measures were proportion of patients achieving ACR 50 and 70 response, improvement of morning stiffness, tender and swollen joint score at 4, 8,12 and 16 weeks. Quality of life assessed by the Health Assessment Questionnaire and Short-Form Health Survey. Intent to treat analysis was done and adverse events were noted.
RESULTS: Seventy percent achieved ACR 20 response at the end of 16 weeks. This was statistically significant as compared to baseline and improvement at 4 and 8 weeks of 25% and 57.5% respectively. The proportion of patients achieving 50% and 70% improvement were 42.5% and 17.5% at 16 weeks respectively. The HAQ decreased from 1.89 ± at baseline to 1.00 (± 0.673) at week 16. The Short Form-36 Health Survey assessment found that the mean scores of all aspects of this measure of patient physical and mental functioning improved from baseline. The domains most affected by Etanercept treatment were role function as limited by physical problems (mean change from baseline at week 16, 46.9 ± 46.75) and role function as limited by emotional problems (mean change from baseline at week 16, 47.5 ± 51.69).
CONCLUSION: The data from this study population have shown Etanercept to be efficacious and well tolerated drug in Indian patients with RA.

Key words: Biologicals, anti tumor necrosis factor, India, soluble treatment receptors.

Introduction

Rheumatoid arthritis (RA) is a chronic and disabling arthritis leading to occupational disability and/or unemployment and associated with lower life expectancy by 4-10 years compared to the general population. Despite treatment, over 50% of subjects experience substantial functional loss within five years. Only a small percentage of subjects continue various drug therapies for longer than three years due to adverse reactions or lack of efficacy.

Tumor Necrosis Factor (TNF) plays an important role in the inflammatory process of RA and the resulting joint pathology. Elevated levels of TNF have been reported in the synovial fluid of patients with RA. TNF mediates its action through 2 cell bound TNF receptors (TNFR), p55 and p75, which also exists in soluble forms. Etanercept is a dimeric fusion protein consisting of the p75 TNFR linked to the fragment crystalline (Fc) portion of human Immunoglobulin G (IgG1), capable of binding two TNF molecules. Etanercept inhibits binding of both TNF-a and TNF-b to cell surface TNFR rendering them biologically inactive.

The clinical safety and efficacy of Etanercept has been demonstrated in clinical trials in patients with active RA. A six-month Phase III, double-blind, randomized, multi-centre study was conducted in 158 patients with active RA showed significant improvement by Etanercept (n=78) as compared to placebo (n=80). At three months, 62% of patients receiving Etanercept had an ACR20 response compared with 23% of the placebo-treated patients. At six months, 40% of patients receiving Etanercept had an ACR50 response as compared to 5% in the placebo group. Seventy-six percent of patients receiving Etanercept completed six months of treatment compared to 33% in the placebo group. No dose-limiting toxicity was observed. The most frequent adverse events (AEs) were mild and consisted of injection-site reactions and respiratory infections.

A six-month Phase II/III trial with concurrent methotrexate evaluated 89 patients who had received methotrexate for at least six months with a stable dose of 12.5 to 25 mg/week. At
six months, 71% of patients receiving Etanercept plus methotrexate had an ACR20 response compared with 23% of the Etanercept placebo plus methotrexate treated patients. At three months, 42% of patients receiving Etanercept plus methotrexate had an ACR50 response compared with 0% in the Etanercept placebo plus methotrexate group.

The current study was a Phase IIIb, open-label, non-comparative, multicentre, outpatient study to assess the efficacy, quality of life and safety of Etanercept in Indian patients with active RA for whom classical anti-rheumatic therapy was insufficient or inappropriate. The total duration of the study was approximately seven months.

Patients and study design

Patients, who fulfilled ACR 1987 criteria of RA, above the age of 18 years and consented for the study, were included in the study if they had active disease despite use of at least one DMARD agent. Active RA was defined by the presence of at least six swollen joints and at least six tender or painful joints and at least one of the following: C-reactive protein (CRP) > 20 mg/L and morning stiffness > 45 minutes. The primary outcome, was assessed by proportion of patients achieving ACR20 response at 16 weeks. Other outcomes measures were ACR50 and ACR70 response, improvement in duration of morning stiffness, quality of life assessed by the health assessment questionnaire (HAQ) and short-form health survey (SF-36), evaluated at 4, 8, 12 and 16 weeks. Patients were evaluated clinically for adverse events at each visit.

Patients were excluded if they had concurrent medical disease including: cancer, congestive heart failure, myocardial infarction within 12 months of the screening visit, uncontrolled angina pectoris, active infection, sepsis or at risk of sepsis, severe pulmonary disease, known HIV infection, liver disease, renal disease (creatinine level > 175 mmol/L), leukopenia (white blood cells < 3.5 x 10^9/L), thrombocytopenia (platelets < 125 x 10^9/L), hemoglobin < 8.5 g/dL, females who were pregnant, breast feeding, or at risk of pregnancy and not using a medically acceptable form of contraception, previous unsuccessful treatment with Etanercept, anti-TNF monoclonal antibodies or a soluble TNF receptor, patients who were planning to undergo elective surgery during the study period and receipt of any live attenuated vaccine within four weeks before the screening visit.

Each patient received twice weekly subcutaneous injections of Etanercept 25 mg for a period of 16 weeks. As per the protocol, Etanercept was continued beyond this period in patients who had shown a beneficial effect as the drug was not available for sale in the country.

Stable doses (four weeks prior to baseline) of oral corticosteroids (prednisolone ≤ 10 mg/day, or equivalent) and methotrexate (up to 20 mg orally or 30 mg by injection per week) were permitted. Only one Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was permitted at any given time. Folic acid was permitted throughout the trial.

Statistical analysis. The ACR 20,50 response at 4, 8, 12, 16 weeks was analysed using and individual variables were compared with baseline data using chi square and students t test respectively.

Results

A total of 45 patients were screened for entry into the study, of which five were screening failures. All 40 patients

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Table 1: Improvement of Disease activity variables in 40 patients on Etanercept therapy at 4 weekly visit as compared to baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk</th>
<th>16 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain VAS</td>
<td>64.5 ± 19.67</td>
<td>46.2 ± 21.42*</td>
<td>39.5 ± 18.58*</td>
<td>35.4 ± 22.20*</td>
<td>33.7 ± 22.35*</td>
</tr>
<tr>
<td>EMS (mts)</td>
<td>186.4 ± 131.69</td>
<td>99.5 ± 101*</td>
<td>71.6 ± 104.82*</td>
<td>68.9 ± 118.77*</td>
<td>40.62.7 ± 129.87*</td>
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<tr>
<td>SJ</td>
<td>16.1 ± 7.28</td>
<td>9.0 ± 5.06*</td>
<td>6.8 ± 4.17*</td>
<td>5.5 ± 6.98*</td>
<td>4.3 ± 3.90*</td>
</tr>
<tr>
<td>TJ</td>
<td>22.0 ± 6.26</td>
<td>15.0 ± 8.20*</td>
<td>13.7 ± 8.72*</td>
<td>10.4 ± 8.61*</td>
<td>7.9 ± 6.18*</td>
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<tr>
<td>PGA</td>
<td>6.6 ± 1.88</td>
<td>5.0 ± 1.67*</td>
<td>4.2 ± 1.57*</td>
<td>3.8 ± 1.88*</td>
<td>3.7 ± 2.03*</td>
</tr>
<tr>
<td>PhysGA</td>
<td>6.6 ± 1.53</td>
<td>4.8 ± 1.59*</td>
<td>4.0 ± 1.44*</td>
<td>3.6 ± 1.82*</td>
<td>3.4 ± 1.98*</td>
</tr>
<tr>
<td>CRP</td>
<td>28.8 ± 36.46</td>
<td>24.1 ± 61.84</td>
<td>20.1 ± 35.34</td>
<td>12.9 ± 17.92**</td>
<td>18.2 ± 25.65</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.9 ± 0.53</td>
<td>1.5 ± 0.61</td>
<td>1.3 ± 0.67</td>
<td>1.1 ± 0.71</td>
<td>1.0 ± 0.67</td>
</tr>
</tbody>
</table>

VAS – Visual analog score in a scale of 0-100. EMS – early morning stiffness in minutes, SJ- No of swollen joint, TJ- Number of tender joints, P/PhysGA- Patient’s/Physician’s Global assessment in a scale of 0-10, CRP – C Reactive Protein , HAQ- Health assessment questionnaire. *p<0.001, **p <0.01
completed the treatment phase of the study. There were six males and the mean age was 45.8 ± 11.57 years, range 19 to 69 years). The duration of illness varied from 1 to 28 years with a median of 7 years. Previous DMARD agents that patients had received were Methotrexate (98%), hydroxychloroquine (58%), Sulfasalazine (50%), Gold (33%), D'penicillamine (20%) and Azathioprine (5%). Ninety eight percent of patients received concomitant NSAIDs and 55% oral prednisolone. The proportion of patients who achieved ACR 20 response increased from 4 through 16 weeks and 70% achieved a ACR20 response at 16 weeks. This was statistically significant when compared with baseline, 4, 8 and 12 weeks. (Fig. 1). The proportion of patients showing ACR50 response at 4, 8, 12 and 16 weeks were 2, 10, 40 and 42.5% respectively. The proportion of patients showing ACR70 response was 2, 5 and 7 at 8, 12 and 16 weeks respectively. The median time taken to achieve ACR-20 response was 57 days, and the median time taken to achieve a ACR50 improvement was 113 days. The median time taken to achieve ACR70 could not be estimated due to insufficient patients achieving this level of improvement. There was also a statistically significant improvement of individual variables of disease activity as shown in Table 1. The percent change from baseline in adjusted HAQ score showed steady improvement at each visit; 24.18 at 4 wk, 31.92 at 8 wk, 41.78 at 12 wk and 48.37 at 16 weeks. All domains of the SF-36 health survey showed improvement at 16 weeks. (Table 2).

Etanercept was well tolerated. A total of 33 mild events occurred in 16 patients were reported during the 16 week period. Skin rash in 5, rhinitis in 4, injection site reactions and eczema in 3, each, fever, gastroenteritis, tonsillitis, leucopenia, giddiness, swelling of feet in 2 each and otalgia, oral ulcer, thrombocytopenia in 1 each patient were observed. Two patients developed serious adverse events.

A 54 year male developed diabetes after 60 days which was not related to the biological agent. On the other hand, a 33 year old female developed leucopenia 52 days after initiation of Etanercept which was attributed to development of Systemic lupus erythematosus as her ANA was positive. Her ANA was positive 10 years prior to the present study and she had classical deformities of RA.

<table>
<thead>
<tr>
<th>Table 2. Mean Change from baseline various domain of SF-36 Assessments at 4 weekly intervals</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>4wk</strong></td>
</tr>
<tr>
<td>Physical Function</td>
</tr>
<tr>
<td>Role functions limited by physical problems</td>
</tr>
<tr>
<td>General Health Perceptions</td>
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<tr>
<td>Bodily Pain</td>
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<tr>
<td>Vitality</td>
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<tr>
<td>Social functions</td>
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<tr>
<td>Role funct. limited by Emotional Problems</td>
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<tr>
<td>Mental Health</td>
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</table>
female developed a posterior cervical tubercular lymphadenitis after 1 year of therapy. Another 48 year old lady developed lumbar spine tuberculosis with cold abscess 2 years after Etanercept. Both the patients responded well to antitubercular therapy. A 62 year old female, after 16 months of therapy, developed left 4th toe wound which rapidly progressed to extensive cellulitis extending to lower 2/3rd leg which led to septicemia and multiorgan failure leading to death.

Discussion

This study on a small sample size was carried out to assess the short term safety and efficacy of Etanercept in Indian patients with RA. As Etanercept was new to our country, this trial was essential for approval of the drug regulatory authority.

The proportion of patients achieving ACR20 response at 16 weeks is higher than response rate in earlier trials with Etanercept 25 mg\textsuperscript{15,16}. The response at 16 weeks is comparable to response at 6 months in previous trials where 59% of patients showed ACR20 response with Etanercept alone (compared to 11% for placebo) and 71% responded in Etanercept plus methotrexate group (compared to 27% for placebo plus methotrexate). The rate of response is comparable with earlier trials where the benefit occurred as early as within two weeks after initiation of therapy\textsuperscript{15,16}. Similarly, the proportion of patients achieving ACR 50 and 70 response is comparable with reports at 16 weeks\textsuperscript{15,16}.

Etanercept 25 mg subcutaneously twice weekly was very well tolerated in this patient population. There was one SAE, diabetes mellitus that was severe in severity and probably related to Etanercept. There were fewer reports of injection site reaction in this study as compared to the Austrian study (5% [two patients/three events] and 31% respectively). Overall these were consistent in terms of incidence, severity, and duration, with those reported for previous trials\textsuperscript{15-17}. The type and incidence of AEs was similar to previous trials\textsuperscript{15-17}. The incidence of SAEs (one patient, 3%) was similar to that previously reported (4 – 6%), however, the sample size was much smaller in the present study and results should be interpreted accordingly\textsuperscript{17}.

References


