

May Etanercept and PTH (1-34) association heal erosions in early rheumatoid arthritis? A pilot study

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Abstract. – Introduction: Rheumatoid arthritis (RA) is characterized by the formation in the joints of an inflammatory tissue, which causes the appearance of localized erosions on the margins of the joints. The molecular mechanism that causes the bone erosion is multifactorial. Inflammatory cytokines imbalance and OPG-RANK-L system are involved.

Objective of the Study: The aim of the study is to evaluate the possibility of inducing healing or reduction in the number of erosions in Rheumatoid Arthritis patients treated with anti-TNF-alpha adding Teriparatide (PTH1-34) to standard treatment with anti-TNF.

Patients and Methods: Twenty adult patients with active RA diagnosed according to American Rheumatism Association (ARA) criteria at least 6 months before study begin were enrolled. Only patients affected by established RA (6 to 18 months from symptoms beginning) were recruited. Eligible patients were randomized to receive a standard dosage of etanercept (50 mg/week) or etanercept at same dosage with an addition of teriparatide (20 mg). Evaluation of eventual healing of arthritic erosions by magnetic resonance imaging was performed at time zero and then at twelve months. The following evaluation was assessed at baseline and after 12 months according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions: number of erosion and presence or absence of synovitis, effusion and bone oedema. A comparative examination of quantitative and qualitative assessment of each parameter was applied. Plain radiographs of the hands were obtained at baseline and 52 weeks. Radiographs were scored blindly

using the van der Heijde modification of the Sharp method. Safety of each treatment was evaluated by means of the adverse events (AES) evaluation and report.

Results: There were no significant differences in baseline characteristics between the groups. The study did not achieve its primary endpoint of healing erosions. In the active arm no healing of erosions was found. At 52 weeks, there were no new MRI erosions in two arms. Bone oedema scores were significantly improved at 52 weeks in favour of both treatments versus baseline scores, without inter-groups differences.

X-ray patterns were unchanged in all patients of both groups. No new erosions or previous erosions' healing were observed. No AEs were reported. Patients from both groups demonstrated a significant reduction in the DAS 28 scores at 52 weeks ($p < 0.005$) if compared with baseline values.

Conclusions: These data confirm rapid control of inflammation and MRI damage benefits after Etanercept administration without a significant improvement in MRI findings after concomitant addition of teriparatide. Even though these results could seem to suggest to avoid the simultaneous use of these two drugs to treat RA erosions, further studies might be suggested to assess if sequential administration of an anabolic agent such as Teriparatide, after achieving clinical remission, may be able to improve bone damage.

Key Words:

Anti-TNF, Rheumatoid Arthritis, Erosions, Etanercept, Teriparatide.

Introduction

Rheumatoid arthritis (RA) is characterized by the formation in the joints of an inflammatory tissue, called pannus, which, through a cytokine network, characterized mainly by interleukin 1 (IL-1) and tumor necrosis factor alpha (anti-TNF alpha), recruits and differentiates active and pre-osteoclastic cells, giving rise to the appearance of localized erosions on the margins of the joints^{1,2}.

The ultimate molecular mechanism that causes the bone erosion is related to the interaction between osteoblasts and osteoclasts RANK system³⁻⁵. OPG-RANK-L regulates the activity of osteoclastic cells and osteoblasts normally involved in the physiological remodeling of bone. The imbalance of the network in favor of RANK-L results in an excessive activation of the resorptive phase at the expense of osteoformation. For several years, products known as “biologics” showed to be able to selectively inhibit TNF-alpha⁶⁻¹⁰. These drugs are characterized, among other effects, by a drastic reduction in the number of erosions in patients affected by RA and treated with such drugs. Such results, in terms of reduction of bone erosions, are significantly superior to the ones obtained by other common immunosuppressive treatments, such as methotrexate or cyclosporine, used in the treatment of RA. Such superiority also demonstrated to be statistically significant. Etanercept¹¹ is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNF-R) linked to the Fc portion of human IgG.

A combined inhibition of pro-resorptive stimulus of TNF could theoretically be associated with a stimulation of bone formation using an anabolic drug that can stimulate osteoblast activity. Teriparatide, which acts as an analogue of the active portion of human parathyroid hormone (PTH), is able to stimulate osteoblastic activity and to induce bone formation.

This drug is administered daily subcutaneously, for a period of 18 months¹²⁻¹⁶; it demonstrated in multicenter randomized trials to be able to induce a sharp recovery in terms of bone mass, bone quality and to reduce appearance of osteoporotic fractures. There is initial evidence that PTH¹⁻³⁴ may promote fracture healing. Systemic PTH administration seems to stimulate bone formation in the fracture healing process. According to preclinical experimental studies, once-daily administration of PTH enhances the morphomet-

ric and mechanical properties of fracture calluses and may accelerate the normal fracture healing. Animal studies have demonstrated accelerated callus formation and remodeling with enhanced biomechanical properties of the healing fracture, also in humans, it is under investigation¹⁷⁻¹⁹.

There are currently no data in the literature to assess the effects of adding Teriparatide to standard treatment with anti-TNF in patients with RA. The aim of the study is to evaluate the possibility of inducing healing or reduction in the number of erosions in Rheumatoid Arthritis patients treated with anti-TNF-alpha.

Objective of the Study

The primary end point of this investigation was to evaluate joint's damage by the comparison of magnetic resonance imaging (MRI), according to the Omeract score (measured erosion scores, synovitis and bone oedema) at baseline and after 52 weeks of treatment, between two groups of patients affected by established (6 to 18 months from symptoms beginning) RA undergoing respectively to anti-TNF- α therapy and anti-TNF- α therapy associated to teriparatide. Secondary outcome measures included safety report of drugs association, conventional radiographs scored according to the van der Heijde modification of the total Sharp score, and clinical disease activity measures, such as Disease Activity Score in 28 joints (DAS28), at 52 weeks.

Patients and Methods

Twenty adult patients with active RA diagnosed according to American Rheumatism Association (ARA) criteria at least 6 months before study begin were enrolled. Patients were required to have had an inadequate response to current or previous disease modifying anti rheumatic drugs (DMARDs). Only patients affected by established RA (6 to 18 months from symptoms beginning) were recruited. Patients were excluded if: they had evidence of latent or active TBC, had chronic or clinically significant infection, malignancy, or congestive heart failure; they used TNF- α inhibitors previously; aged < 18 years. Other exclusion criteria were concomitant use of other therapies such as bisphosphonates, selective estrogen receptor modulators (SERMs) or strontium ranelate, a known allergy to teriparatide or etanercept, and increased serum lev-

els of PTH or alkaline phosphatase. All patients were recruited among those attending our Outpatient Clinic, in concordance with the Ethical Guidelines of the 1975 Declaration of Helsinki.

Treatment Protocol

Eligible patients were randomized to receive a standard dosage of etanercept (50 mg/week) or etanercept at same dosage with an addition of teriparatide (20 mg). All patients also assumed methotrexate (MTX) (15 mg/week) and folic acid (5 mg once a week). The use of oral corticosteroid, other DMARDs than MTX or intra-articular corticosteroids was prohibited within 4 weeks before and after the first injection of etanercept or etanercept and teriparatide and during all the course of the trial.

This study was conducted in 3 different centres in Italy. Local Ethical Committee at the participating sites approved the study, and written informed consent was obtained from all patients before any protocol-specific procedures were performed. This was a phase IV, controlled, randomised, parallel group study, in which patients were randomly assigned in a 1:1 ratio to receive subcutaneous injection of weekly etanercept or weekly etanercept plus daily subcutaneous teriparatide for 12 months. Randomisation was stratified by investigational site and baseline. Teriparatide addition was performed using a dynamic patient allocation algorithm.

Images of hands and wrists were carried out using a whole body high-field MRI 1.5-T superconductive magnet equipped with a 20 cm circular surface coil. Patients were placed in prone position with the arm extended and the hand in the centre of the coil. Coronal, axial and sagittal images were obtained by using fat suppressed T1-weighted spin-echo sequences, before and after i.v. injection of 0.1 mmol/kg gadopentate dimeglumine, with a gradient echo and stir technique. Evaluation of imaging healing of arthritic erosion by magnetic resonance imaging was performed at time zero and then at twelve months by 4 experienced readers who were blinded to the identity of the patient as well as the clinical findings or treatment allocation.

The following evaluation were assessed at baseline and after 12 months according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions²⁰⁻²⁶: number of erosion and presence or absence of synovitis, effusion and bone oedema. A comparative examination of quantitative and qualitative assessment of each parameter was applied.

The visits are carried out at baseline and every three months by assessing the overall index of disease activity (DAS 28) and the following laboratory tests: PTH, TSH, FT3, FT4, serum calcium, phosphorus, calciuria 24 hours, alkaline phosphatase, gamma GT, serum aminotransferases (ALT and AST), creatinine, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), complete blood count (CBC), protein electrophoresis.

Plain radiographs of the hands were obtained at baseline and 52 weeks. Radiographs were scored blindly using the van der Heijde modification of the Sharp method²⁷. Such data were analyzed by 4 radiologists with regards to chronological consecution in order to establish if treatment eventually led to healing or to an arrest of radiological progressions in RA.

Safety of each treatment was evaluated by means of the adverse events (AEs) evaluation and report. The investigators were asked to record into the case report forms (CRFs) all the adverse events that were eventually referred by patients during the study visits every 3 months after the first treatment session for 12 months. Adverse events (AEs) are defined as any illness, sign or symptom or unfavourable change in patient's condition (both clinical or laboratory findings were evaluated and counted) reported by the patient at any time during the study. The investigator rates the intensity of AEs as mild, moderate or severe and establishes the relationship to the trial medication as sure, probable, possible, unlikely and unknown. All untoward events are documented in the subject's medical records and on the CRFs with details on duration, intensity, relationship to test drug, and administration of any other therapy.

Statistics

The sample size in this pilot study was estimated at 10 patients per treatment arm based on previous work in our Department using MRI outcome measures. Statistical analyses were carried out by Stata software 11.0 (Stata Corp, College Station, TX, USA). Baseline variables were analyzed using Student's *t*-test (parametric) or Wilcoxon's rank sum test (non-parametric) as appropriate. MRI outcomes were analyzed using Wilcoxon's 2-sample rank sum test (equivalent to the Mann-Whitney U test). Other variables were analyzed using parametric (2-sample *t*-test) and nonparametric tests as appropriate.

Results

The baseline characteristics of the 2 treatment groups are presented in Table I. There were no significant differences in baseline characteristics between the groups.

MRI Findings. The study did not achieved its primary endpoint of healing erosions. In the active arm no healing of erosions was found.

At 52 weeks, there were no new MRI erosions in two arms. Reductions in synovitis and bone oedema were observed in both groups after 12 months, but there was not a statistical significant difference between two groups.

Bone oedema scores were significantly improved at 52 weeks in favour of both treatments versus baseline scores, without inter-groups differences.

Radiographic Findings. X-ray patterns were unchanged in all patients of both groups. No new erosions or previous erosions' healing were observed.

Adverse Events. No AEs of any kind were reported in the whole study population.

DAS28 Scores. Patients from both groups demonstrated a significant reduction in the DAS 28 scores at 52 weeks ($p < 0.005$) if compared with baseline values, but no statistically significant differences were observed when comparing results obtained in two groups after 52 weeks of treatment, with a convergence of disease activity over time.

Discussion

This randomized controlled pilot study evaluated the possibility of healing erosions using a concomitant association of etanercept, a TNF- α soluble receptor, in addition to teriparatide, an

osteo-anabolic agent, in patients with post-early RA (6-18 months after symptoms beginning). This is the first study to evaluate the association of Etanercept and teriparatide in the control of bone damage progress. The study used MRI to assess damage outcomes in a randomized design for 52 weeks. The study results did not achieve primary endpoint of demonstrating healing of erosions by the association of the osteo-anabolic agent (teriparatide) to the standard treatment of TNFa blockers (etanercept) associated to MTX. However no new erosions were detected in both groups and, moreover, synovitis and bone oedema decreased in both arms without a statistically significant inter-group difference.

An explanation for this lack of efficacy may be that firstly the association has been undertaken too fast in the stage of disease and before achieving remission; if teriparatide was added after arresting inflammatory process its anabolic effect could work better than if administered before remission. Despite evidences of bone healing under teriparatide treatment in post-traumatic subjects, this result could suggest an decreased anabolic effect during active inflammatory status. A second hypothesis is that teriparatide has different anabolic effects in the distinct bone and joint sites, for instance in a non-weight bearing site. Data from literature show that main anabolic effect is exerted in trabecular vertebral bone. Clinical trials have shown that teriparatide increases bone mineral density (BMD) at the lumbar spine and total hip, while BMD at the forearm decreases after 20 months of therapy²⁸. Whether this decrease of BMD at the forearm suggests a higher risk of wrist fracture or a change in bone structure is unclear. Bone biopsies of the pelvis done on people taking teriparatide²⁹ showed improvement of bone geometry (i.e. bone thickness and increased trabeculae (small interconnecting rods of bone), suggesting that a change in bone geometry at the wrist may be occurring as well. It is

Table I. Baseline demographics of the treatment groups.

	Etanercept (n. 10)	Etanercept plus teriparatide (n. 10)
Age, mean $\pm$ SD (years)	51.3 $\pm$ 9.5	53.1 $\pm$ 13.7
Symptom duration, mean $\pm$ SD months	7.4 $\pm$ 4.6	6.9 $\pm$ 4.8
29.8RF positive	90%	90%
DAS 28	5.85 $\pm$ 1.38	5.70 $\pm$ 1.59
CRP, mean $\pm$ SD mg/liter	5.8 $\pm$ 1.88	6.21 $\pm$ 4.80
ESR mm/hr, mean $\pm$ SD	38.2 $\pm$ 18	43.6 $\pm$ 11

Table II. Clinical values.

	Etanercept plus teriparatide group (n. = 10)	
	Baseline values	
DAS2, mean $\pm$ SD	5.85 $\pm$ 1.38	5.70 $\pm$ 1.59
vdH-Sharp test, mean $\pm$ SD	79.9 $\pm$ 29.8	84.2 $\pm$ 28.8
MRI assessment		
Synovitis 0-9	5.0 $\pm$ 2.0	5.5 $\pm$ 2.0
Bone marrow oedema 0-45	12.8 $\pm$ 10.0	13.3 $\pm$ 9.0
Erosions 0-150	27.7 $\pm$ 17.8	31.1 $\pm$ 19.9
	52 weeks values	
DAS28, mean $\pm$ SD	2.34 $\pm$ 0.87	2.38 $\pm$ 0.99
vdH-Sharp test, mean $\pm$ SD	84.2 $\pm$ 31.2	86.3 $\pm$ 34.4
MRI assessment		
Synovitis 0-9	2.7 $\pm$ 2.2	2.9 $\pm$ 2.3
Bone marrow oedema 0-45	10.8 $\pm$ 9.8	9.8 $\pm$ 8.9
Erosions 0-150	29.9 $\pm$ 19.0	32.0 $\pm$ 20.9

unclear whether the decline in BMD at the distal radius observed during PTH therapy is indicative of decreases in bone strength, or is a result of increases in the width of the radius. As no data to date has been published on changes in bone geometry at the radius either by bone biopsy or high resolution peripheral quantitative computer tomography (HR-pQCT) in patients receiving PTH therapy. Angela MW Cheung (<http://clinicaltrials.gov/ct2/show/NCT01155245>) is performing a trial to fill this gap in knowledge with

regard to how PTH affects BMD and bone structure at the radius and tibia in postmenopausal women with severe osteoporosis.

In addition, the treatment period was 12 month while it may be prolonged long 24 months in osteoporotic women, although bone healing by teriparatide seems to be short and fast in non inflammatory diseases ranging from 3 to 6 months.

Even though the implications of this study could seem to avoid the combination use of these two drugs to treat RA erosions, these data must

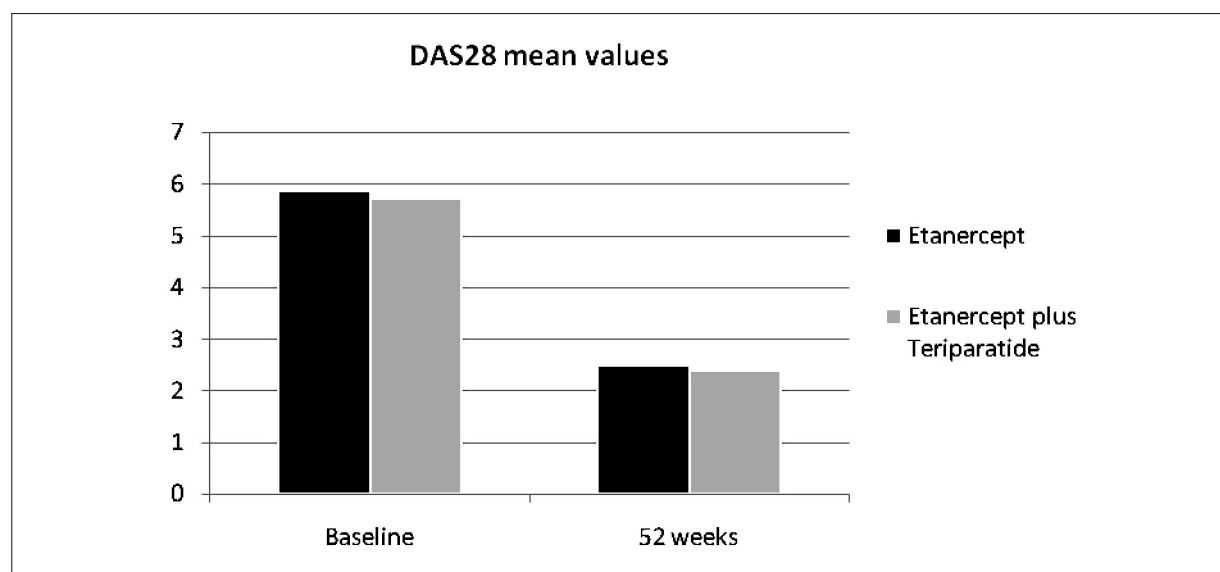


Figure 1. DAS 28 mean values at baseline and after 52 weeks. No statistical significant differences were observed for two groups at baseline and at 52 weeks ($p = 0.552$ at baseline, $p = 0.67$ at 52 weeks).

be interpreted within the limits of the pilot study design. Whatever the process, these results don't exclude further studies to explore new "window of opportunity" for the hypothesis of healing erosions in RA.

The absence of AEs of this work shows the safety of simultaneous administering of a TNF- α blocker (etanercept) and an anabolic agent (teriparatide) confirming our previous data in patients affected by both severe osteoporosis and RA and treated with the same drugs³⁰.

From a clinical point of view, both arm demonstrated improvement of the systemic acute-phase response (CRP), with corresponding suppression of inflammatory joint disease (joint counts and DAS 28), it confirms literature data about etanercept clinical efficacy in RA³¹⁻³⁵.

Conclusions

These data confirm rapid control of inflammation and MRI damage benefits, findings consistent with published data, after Etanercept administration without a significant improvement in MRI findings after concomitant addition of teriparatide. Further studies are suggested to establish if delayed association of anabolic agent after achieving remission is able to improve moreover bone damage.

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