Etanercept Reduces Synovitis as Measured by Magnetic Resonance Imaging in Patients with Active Rheumatoid Arthritis After Only 6 Weeks

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ABSTRACT. ***Objective.*** To demonstrate the efficacy of etanercept to reduce synovitis as measured by magnetic resonance imaging (MRI) as early as 6 weeks after starting treatment in patients with active rheumatoid arthritis (RA).

Methods. Twenty-two patients with active RA despite disease modifying antirheumatic drug (DMARD) treatment were included in this prospective, controlled study. Patients were randomized in 2 groups. In the treatment group, etanercept was added at usual doses during 6 weeks. In the control group, patients continued with prior DMARD therapy. MRI of the dominant wrist and 2nd-5th MCP joints were obtained at baseline and at 6 weeks and evaluated according to OMERACT recommendations. Results of changes in synovitis in the treatment group were compared with changes in the control group.

Results. Changes in synovitis measured by MRI of the hand (OMERACT evaluation) in the etanercept group showed a significant reduction after 6 weeks of treatment compared with no changes in the control group. Reduction of synovitis in the treatment group also showed good correlation with decrease of various clinical and laboratory measures.

Conclusion. In patients with active RA despite DMARD therapy, etanercept, but not placebo, reduced synovitis as measured by MRI after 6 weeks. (First Release Jan 15 2008; J Rheumatol 2008;35:394–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — ETANERCEPT
MAGNETIC RESONANCE IMAGING — SYNOVITIS

The efficacy of etanercept in treating patients with active rheumatoid arthritis (RA) is now well established. In randomized clinical trials (RCT), etanercept added to methotrexate or other disease modifying antirheumatic drug (DMARD) was effective in reducing clinical measures and radiographic progression of joint destruction[1-3].

In clinical trials, results are usually reported after 3–6 months of treatment for clinical data and 1 year for radiographic progression. Nevertheless, from clinical practice and additional data from RCT, improvements seem to occur even earlier in the course of treatment with etanercept, with most responders experiencing improvement 1 month after starting this biologic therapy[1,2].

Magnetic resonance imaging (MRI) has proved to be more sensitive than conventional clinical and radiographic examinations for detection of inflammatory and destructive joint changes in RA[4,5]. MRI can also be used to directly visualize and evaluate changes in synovitis in active RA. Further, synovitis measured by means of MRI is a good marker for evaluation of disease activity and prediction of joint destruction[6].

We investigated the efficacy of etanercept, added to other DMARD in patients with active RA despite these treatments, in reducing synovitis evaluated by means of MRI in a very short period of time (after 6 weeks).

MATERIALS AND METHODS

Patients and design. Twenty-two patients at the Department of Rheumatology, Hospital del Mar, Barcelona, with active disease defined as Disease Activity Score-28 (DAS28) > 3.2 and synovitis in the hands were enrolled in this prospective, randomized, controlled study. They had RA fulfilling American College of Rheumatology (ACR) 1987 criteria[7]. Synovitis was defined as the presence of 1 or more swollen and tender joints in the dominant hand.

Patients [21 women, 1 man; median age 50.5 yrs (range 28–73); mean duration of disease 6.4 yrs (range 2.4–27); among whom 72.7% were positive for rheumatoid factor] were assigned by simple randomization to 2 groups: 8 patients as a control group, and 14 as a treatment group (etanercept). The 14 patients in the treatment group were given etanercept by a conventional regimen (25 mg, twice a week, subcutaneously) added to previous DMARD; the 8 controls continued the previous treatment with DMARD. All patients were taking DMARD (13 patients 1 DMARD: methotrexate 69.2%, leflunomide 23.1%, chloroquine 7.7%; and 9 patients a combination of 2 DMARD). Doses of previous treatment with DMARD, corticosteroids, and nonsteroidal antiin-

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flammatory drugs were kept stable through the study (6 weeks). Treatment with paracetamol (maximum 3 g/day) was allowed for disease flares during this period. All patients gave signed informed consent before inclusion, and the study was approved by the local ethics committee according to the principles of the Declaration of Helsinki.

At baseline and at 6 weeks, complete clinical [DAS28, visual analog scale (VAS) for pain, Health Assessment Questionnaire (HAQ)] and laboratory [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] evaluations were performed by one rheumatologist (JM) blinded to patient's treatment regimen. An MRI of the dominant hand was obtained.

Imaging. MRI of dominant wrist and 2nd-5th metacarpophalangeal (MCP) joint was performed at baseline and after 6 weeks, in a 1.5-Tesla superconductive system (Signa Echo-speed Excite II; General Electric Medical Systems, Milwaukee, WI, USA) equipped with a dedicated wrist coil. Coronal and axial T1-weighted sequences (repetition time 460 ms; echo time 10 ms; slice thickness 3 mm; matrix 256 × 224; field of view 160 mm) and T2-weighted sequences with fat suppression (repetition time 4000 ms; echo time 94 ms; slice thickness 3 mm; matrix 256 × 224; field of view 160 mm) were obtained. After intravenous injection of 0.2 ml/kg of the contrast agent Omniscan (GE Healthcare, Amersham, UK), coronal and axial T1-weighted sequences with fat suppression (repetition time 640 ms; echo time 15 ms; slice thickness 3 mm; matrix 256 × 224; field of view 160 mm) were performed.

MRI were scored for bone erosions, bone edema, and synovitis according to the latest Outcome Measures in Rheumatology Clinical Trials (OMERACT)[8] recommendations by 2 trained readers (radiologist JP and rheumatologist MPL). Intrareader and interreader intraclass correlation coefficients (ICC) were calculated for status and change score. Reading was performed with paired images but without knowledge of the chronological order or the patient identity, clinical or biochemical data, or treatment group.

Statistical analysis. Wilcoxon test was used to evaluate changes in scores of MRI synovitis within patients in each group and for changes in laboratory and clinical variables. Values of the differences between baseline and Week 6 (delta values) were calculated for each group, and Mann-Whitney U-test was used. Correlations of scores for synovitis with DAS28, HAQ, VAS pain, ESR, and CRP between baseline and Week 6 values were calculated by Spearman test. Values of $p < 0.05$ were considered significant.

RESULTS

Results of intrareader ICC were higher than 0.92 for all the variables for status score and were acceptable for change score, with lower results for erosions. Interreader single and average measures were generally acceptable (all ICC > 0.76) for both status and change scores for synovitis, bone edema, and total score (Table 1).

There were no differences between groups for clinical and laboratory measures at baseline. All patients presented with active disease with a median DAS28 of 4.6 (range 3.1–6.7), ESR 25 mm/h (range 4–37), CRP 1.1 mg/dl (range 0.2–7.5), VAS for pain 60 mm (range 10–100), and HAQ 0.88 (range 0–2.8).

A significant statistical reduction of all clinical activity variables (DAS28, VAS pain, HAQ) and laboratory variables (ESR, CRP) was observed after 6 weeks of treatment with etanercept, but not in the control group (Table 2).

MRI measures between groups showed no statistically significant differences at baseline. In the treatment group, a significant decrease in the median synovitis score from 9.5 to 7.5 was observed after 6 weeks of treatment ($p = 0.01$). Nevertheless, delta values of changes between the 2 groups showed no statistically significant differences. A decrease of the scoring of bone edema was also found, but with no significant difference. But if wrist and MCP joints were analyzed separately, a statistically significant decrease ($p = 0.002$) of bone edema score was observed in the MCP joints after 6 weeks of treatment with etanercept. Scoring of erosions did not change during the study in both groups. Global scoring decreased nearly 10 points for all patients in the treatment group. In the control group, no significant change was found in all the MRI variables (Table 3).

In the treatment group, a correlation of the decrease of clinical and laboratory variables with the reduction of synovitis on MRI was found. DAS28, VAS pain, HAQ, and ESR correlated positively, but CRP did not. Decrease in HAQ and ESR also correlated significantly with reduction of global scoring of MRI of the hand (Table 2).

DISCUSSION

The clinical efficacy of tumor necrosis factor-α (TNF-α) blockers in patients with RA has been proven extensively in numerous RCT and studies. Treatment of RA with anti-TNF therapy not only significantly reduces signs and symptoms of disease but also retards or stops radiographic progression of joint damage. Most of these RCT and studies have reported clinical results as improvement in the clinical, biochemical, and composite indices ACR20 and DAS at 12, 30, and 54 weeks.

However, in daily practice, clinical improvement and beneficial effects of TNF blockers seem to occur very rapidly in the majority of patients who are responders to this therapy over time. Moreover, additional data from pilot and RCT studies of etanercept, infliximab[9], and adalimumab[10] reported significant clinical and biochemical responses in a majority of patients as early as 4–8 weeks after start of treatment.

Efficacy of anti-TNF therapy in slowing joint destruction, using different radiographic methods for scoring damage, has been reported usually at 1–2 years after starting treatment, because of the lack of sensitivity to change of those methods in shorter periods of time.

MRI of the hand in patients with RA has been demonstrated to be more sensitive for detection of changes in joint damage than conventional radiographic examination[4,5], and sensitivity to change in different MRI variables using validated methods of scoring (RAMRI-OMERACT) is also very good[11]. Moreover, MRI can directly visualize synovitis and bone edema. MRI measures have been shown to correlate with radiographic progression over time[6,12,13].

Although MRI is used increasingly as an outcome measure to monitor activity and efficacy of treatment for RA, there are few systematic studies investigating changes in MRI measures over time during fixed therapies[14-16], and only one trial comparing anti-TNF therapy with placebo[17]. All the studies reported their results at 3–12 months after start of treatment.

We found a rapid, significant reduction of synovitis meas-

Table 1. Intrareader and interreader agreement on synovitis, bone edema, erosions, and total scores [2-way mixed-effect model, single measure intraclass correlation coefficients (ICC), and average measures ICC].

MRI Variables	Measure		Status Score	Change Score
Synovitis	Intrareader	Sm ICC	0.96–0.98	0.98
		Av ICC	0.98–0.99	0.99
	Interreader	Sm ICC	0.93	0.76
		Av ICC	0.96	0.86
Bone edema	Intrareader	Sm ICC	0.92–0.98	0.94
		Av ICC	0.96–0.99	0.97
	Interreader	Sm ICC	0.90	0.84
		Av ICC	0.95	0.91
Erosion	Intrareader	Sm ICC	0.93–0.97	0.51
		Av ICC	0.96–0.98	0.68
	Interreader	Sm ICC	0.84	0.05
		Av ICC	0.91	0.10
Total score	Intrareader	Sm ICC	0.95–0.98	0.75
		Av ICC	0.97–0.99	0.86
	Interreader	Sm ICC	0.90	0.86
		Av ICC	0.94	0.92

Sm: single-measure; Avm: average-measure.

Table 2. Clinical and laboratory measures at baseline at Week 6 of the control and etanercept groups. There is correlation in etanercept group between changes in variables of clinical activity (DAS28, ESR, VAS pain, CRP) and functional capacity (HAQ) and changes in MRI synovitis. Values are medians (ranges).

Clinical and Laboratory Measures	Control Group			Etanercept Group			Correlation	
	Baseline	Week 6	p	Baseline	Week 6	p	Spearman r	p
DAS	4.3 (3.1–5.3)	3.8 (2.4–6.3)	0.64	4.7 (3.1–6.7)	3.3 (1.8–4.7)	< 0.001	0.61	0.02
HAQ	0.7 (0.2–1.2)	0.5 (0.1–1.8)	0.54	0.9 (0–2.8)	0.4 (0–1.5)	0.003	0.60	0.02
VAS pain (0–100 mm)	54 (10–70)	28 (0–82)	0.17	60 (19–100)	40 (0–90)	0.008	0.55	0.03
ESR, mm/h	17 (5–34)	21.5 (4–32)	0.9	26.5 (4–37)	13 (4–37)	0.002	0.63	0.01
CRP, mg/dl	1.0 (0.3–1.4)	0.9 (0.2–2.6)	0.84	1.4 (0.2–7.5)	0.3 (0.2–1.1)	0.001	0.47	0.07

Table 3. Comparison between baseline and Week 6 MRI measures for each group and between groups. Delta values = baseline to Week 6, for each group and comparison between groups. Values are medians (ranges).

	MRI	Control Group	Etanercept Group	p
Baseline	Synovitis	8 (5–11)	9.5 (1–17)	0.18
	Bone edema	8 (1–36)	16.5 (0–40)	0.68
	Erosion	24 (7–55)	28.5 (2–87)	0.77
	Total score	53 (16–83)	63.5 (3–127)	0.47
Week 6	Synovitis	7.5 (3–11)	7.5 (2–15)	0.73
	Bone edema	10 (0–27)	11 (0–28)	0.68
	Erosion	29.5 (7–50)	28 (4–73)	0.99
	Total Score	54 (10–88)	54 (6–108)	0.96
p	Synovitis	0.31	0.01	
	Bone edema	0.56	0.15	
	Erosion	0.37	0.38	
	Total Score	0.68	0.052	
Delta values of change between groups	Synovitis	–1 (–3 to +2)	–2 (–6 to +2)	0.36
	Bone edema	+1 (–11 to +10)	–1 (–22 to +6)	0.14
	Erosion	+0.5 (–5 to +6)	–0.5 (–19 to +11)	0.30
	Total Score	+1 (–6 to +7)	–5 (–41 to +5)	0.08

ured by MRI in the treatment group (etanercept) compared to baseline values in this group, while the control group showed no change for any of the variables.

Values of the differences between baseline and Week 6 (delta values) for each group did not show any statistically significant difference. We consider that the sample size could be

insufficient to detect this difference when calculating delta values.

We also found a significant correlation between changes (decrease) in clinical and laboratory measures and reduction of synovitis, except for CRP. Although the design of the study was not double-blind and the number of patients was small, this possibly does not account for the lack of correlation with CRP. It could be better explained because of low baseline values (median CRP 1.4 mg/dl).

We found no statistically significant decrease of median bone edema score in our study after 6 weeks of treatment with etanercept. Nevertheless, although not significant, an actual decrease was observed (from 16.5 to 11). There was a slight decrease in 18 patients, while in 3 patients there was a 4-point increase of the median, and in one patient there was no change. Although a significant and rapid decrease in bone edema score was noted in other studies, different clinical characteristics of the patient cohort, duration of disease (early arthritis), higher disease activity, different biologic therapy used, and different joints evaluated (only MCP) could account for this discrepancy[17]. In patients with early arthritis a higher clinical and laboratory response is reported with early treatment. Infliximab is reported to achieve a rapid response after the charge dose. It is also possible that changes in bone edema are also more dramatic in patients with more active disease.

Moreover, in our study if wrist and MCP joints were analyzed separately a statistically significant decrease of bone edema score could be observed in MCP joints ($p = 0.002$) in the etanercept group, in agreement with results of the study by Quinn, *et al*[17].

Our study is the first to demonstrate the efficacy of etanercept added to DMARD therapy in active RA in reducing synovitis as measured by MRI of the hand using a validated method (RAMRI-OMERACT) in a very short period of time (6 weeks). It also showed the possible usefulness of MRI in measuring treatment efficacy in this very short period of time. This could have important implications in using changes in MRI as a proof of concept for new treatments in future clinical trials with RA patients, since this could be done in shorter periods of time and with few patients.

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