EXTENDED REPORT

Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial

Margreet Kloppenburg,[1,2] Roberta Ramonda,[3] Klaus Bobacz,[4] Wing-Yee Kwok,[1] Dirk Elewaut,[5,6] Tom W J Huizinga,[1] Féline P B Kroon,[1] Leonardo Punzi,[3] Josef S Smolen,[4] Bert Vander Cruyssen,[5] Ron Wolterbeek,[7] Gust Verbruggen,[5] Ruth Wittoek[5]

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For numbered affiliations see end of article.

Correspondence to
Professor Margreet Kloppenburg, Department of Rheumatology, Leiden University Medical Center, Leiden 2300 RC, The Netherlands; g.kloppenburg@lumc.nl

GV and RW are last authors.

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ABSTRACT

Objective Hand osteoarthritis is a prevalent disease with limited treatment options. Since joint inflammation is often present, we investigated tumour necrosis factor (TNF) as treatment target in patients with proven joint inflammation in a proof-of-concept study.

Methods This 1-year, double-blind, randomised, multicentre trial (NTR1192) enrolled patients with symptomatic erosive inflammatory hand osteoarthritis. Patients flaring after non-steroidal anti-inflammatory drug washout were randomised to etanercept (24 weeks 50 mg/week, thereafter 25 mg/week) or placebo. The primary outcome was Visual Analogue Scale (VAS) pain at 24 weeks. Secondary outcomes included clinical and imaging outcomes (radiographs scored using Ghent University Scoring System (GUSS, n=54) and MRIs (n=20)).

Results Of 90 patients randomised to etanercept (n=45) or placebo (n=45), respectively, 12 and 10 discontinued prematurely. More patients on placebo discontinued due to inefficacy (6 vs 3), but fewer due to adverse effects (1 vs 6). The mean between-group difference (MD) in VAS pain was not statistically significantly different (−5.7 (95% CI −15.9 to 4.5), p=0.27 at 24 weeks; − 8.5 (95% CI −18.6 to 1.6), p=0.10 at 1 year; favouring etanercept). In prespecified per-protocol analyses of completers with pain and inflammation at baseline (n=61), MD was −11.8 (95% CI −23.0 to −0.5) (p=0.04) at 1 year. Etanercept-treated joints showed more radiographic remodelling (delta GUSS: MD 2.9 (95% CI 0.5 to 5.4), p=0.02) and less MRI bone marrow lesions (MD −0.22 (95% CI −0.35 to −0.09), p = 0.001); this was more pronounced in joints with baseline inflammation.

Conclusion Anti-TNF did not relieve pain effectively after 24 weeks in erosive osteoarthritis. Small subgroup analyses showed a signal for effects on subchondral bone in actively inflamed joints, but future studies to confirm this are warranted.

Key messages

What is already known about this subject?
- Hand osteoarthritis (OA) is a prevalent disease with limited treatment options.
- Evidence for an important role of inflammation in hand OA is accumulating.
- Previous studies of different anti-inflammatory trials led to ambiguous results.

What does this study add?
- In this one-year, double-blind, randomised trial, etanercept, a tumor necrosis factor (TNF) inhibitor, did not relieve pain effectively after 24 weeks in patients with erosive hand OA.
- Small subgroup analyses showed a signal for effects on subchondral bone in actively inflamed joints, but future studies to confirm this are warranted.

How might this impact on clinical practice or future developments?
- This trial does not provide evidence for the use of TNF inhibitors in daily treatment of patients with hand osteoarthritis patients.
- Studies investigating treatment strategies specifically targeting inflammation, for example, short-term anti-inflammatory treatment with glucocorticoids or TNF inhibitors during 'flares' of the disease, are warranted.

INTRODUCTION

Osteoarthritis, commonly occurring in knees, hands and hips, is a prevalent cause of disability.[1] Currently, therapeutic options are limited, only moderately addressing symptoms and not preventing or retarding disease progression.[2 3] Despite considerable efforts to find relevant treatment targets, a lack of suitable candidates has hampered the development of disease-modifying therapies in osteoarthritis. Traditionally, osteoarthritis is known as a degenerative disease resulting in bone deformations and cartilage loss, although in the last decades it has become clear that local inflammation is important in its pathophysiology.[4] Especially in erosive hand osteoarthritis, characterised by subchondral erosions and cortical destruction in the interphalangeal joints (IPJs), synovitis is frequently demonstrated.[5–8] Recent MRI and ultrasonography studies show that synovitis is associated with pain and future radiographic damage.[9–11] Proinflammatory cytokines, including tumour necrosis factor (TNF), are produced in the osteoarthritic joints and are

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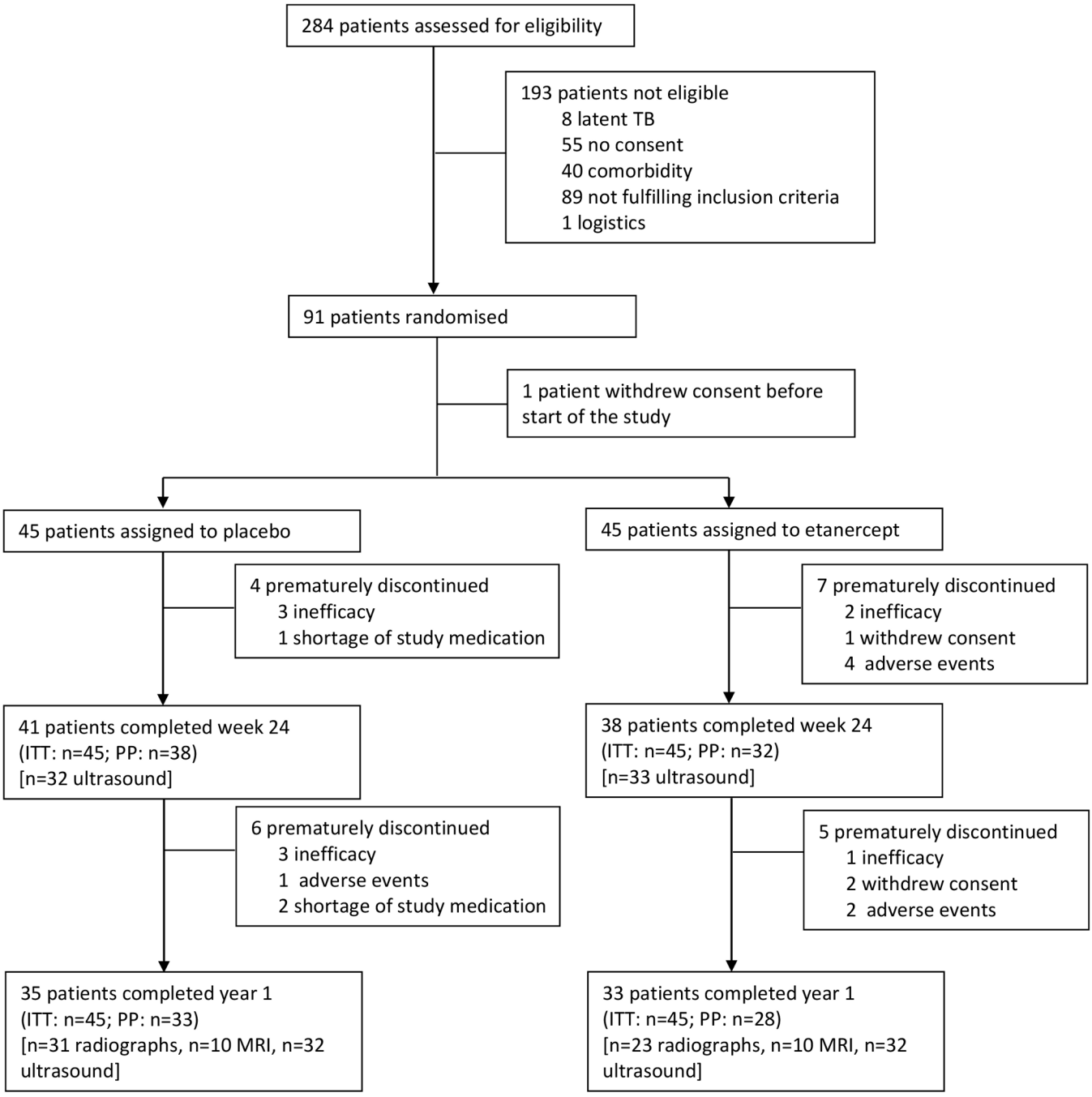

Figure 1 Trial profile. ITT, intention-to-treat; PP, per-protocol; TB, tuberculosis.

thought to play a role in the induction of structural damage. Thus, TNF could serve as a potential treatment target.[12]

Earlier clinical trials in hand osteoarthritis have investigated the efficacy of anti-inflammatory medication, but with ambiguous results.[13–20] Although some studies with (systemic) glucocorticoids and TNF inhibitors showed symptom relief,[14–16 20] most randomised placebo-controlled trials were negative.[13 19] Furthermore, systemic glucocorticoids did not seem to influence osteoarthritic synovitis, as assessed by ultrasound or MRI.[15 19] The lack of efficacy of anti-inflammatory medication in previous studies might partly be explained by inclusion of patients without proven joint inflammation at baseline. Because of the latter, patients most likely to benefit from these drugs may have been missed in previous trials, leading to negative results. Results of a 1-year randomised trial implying that compared with placebo the TNF inhibitor adalimumab may lead to less erosive radiographic progression in finger joints with palpable soft tissue swelling (as a measure of inflammation) support this hypothesis.[18]

The aim of this proof-of-concept study was thus to investigate the efficacy and safety of anti-TNF in patients with erosive hand osteoarthritis with proven joint inflammation.

METHODS

Study design and participants

The EHOA study, an investigator-initiated, 1-year, double-blind, randomised, placebo-controlled, multicentre trial in patients with symptomatic erosive inflammatory hand osteoarthritis was conducted in four European rheumatology outpatient clinics (Austria, Belgium, Italy and the Netherlands), which serve as

Table 1 Baseline characteristics of the intention-to-treat population

	Etanercept (n=45)	Placebo (n=45)	All patients (n=90)
Age (years)	59.4 (6.5)	60.1 (8.7)	59.7 (7.6)
Sex			
Men	8 (18%)	9 (20%)	17 (19%)
Women	37 (82%)	36 (80%)	73 (81%)
BMI (kg/m^2)*	26.3 (3.8)	25.5 (3.8)	25.9 (3.8)
Symptom duration (years)*	8.8 (6.0)	10.7 (8.0)	9.7 (7.1)
Duration after diagnosis (years)*	6.2 (6.2)	7.3 (8.3)	6.8 (7.3)
Inclusion criteria			
Use of NSAIDs	42 (93%)	44 (98%)	86 (96%)
Fulfilling ACR hand OA criteria*	42 (96%)	43 (96%)	85 (96%)
≥4 IPJs with osteoarthritic nodes*	41 (91%)	41 (93%)	82 (92%)
≥1 IPJ with soft tissue swelling	42 (93%)	40 (89%)	82 (91%)
≥1 IPJ with positive power Doppler*	40 (93%)	40 (91%)	80 (92%)
J-phase or E-phase*	38 (93%)	37 (95%)	75 (94%)
VAS pain at screening >30 mm	44 (98%)	45 (100%)	89 (99%)
Flare after NSAID washout ≥20 mm	37 (82%)	39 (87%)	76 (84%)

Data are mean (SD) or n (%).
*Data not available for all randomised patients: BMI n=89, symptom duration n=86, duration after diagnosis n=87, ACR criteria n=85, paid work n=89, IPJs with osteoarthritic nodes n=89, IPJs with power Doppler signal n=87 and J-phase or E-phase n=80.
ACR, American College of Rheumatology; BMI, body mass index; IPJ, interphalangeal joints; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; VAS, Visual Analogue Scale.

secondary and tertiary care clinics for this condition. Patients with ≥4 IPJs with osteoarthritic nodes, ≥1 IPJ with soft tissue swelling or erythema, ≥1 IPJ with positive power Doppler signal on ultrasound, and ≥1 IPJ with radiographic pre-erosive or erosive disease (represented respectively by loss of joint space (J-phase) or by erosions or collapse of the subchondral bone (E-phase) according to the Verbruggen-Veys system) were eligible.[5] Clinical inflammation, ultrasound abnormalities and radiographic erosions did not have to be present in the same joint. Patients had to have finger pain >30 on a 100 mm Visual Analogue Scale (VAS) while using a stable dose of non-steroidal anti-inflammatory drugs (NSAIDs) for ≥5 days/week. Moreover, an insufficient response to at least two NSAIDs was required. Eligible patients discontinued their NSAIDs, and those with a flare, defined as an increase in VAS pain >20 mm (as indication of modifiable pain), were included. Exclusion criteria were contraindications for TNF inhibitors, such as uncontrolled serious comorbidities, active or recurrent infections, malignancy, and drug or substance abuse. Patients with another autoimmune or inflammatory rheumatic disease, or psoriasis, or patients who were using immunomodulating drugs within 90 days before baseline were also excluded. The complete list of exclusion criteria is provided in the online supplementary appendix.

Randomisation and masking

Patients were randomly assigned (1:1) to etanercept or placebo. Randomisation was performed using a random-number list in blocks of four. Randomisation and study medication coding list were supplied to an independent person in each centre, responsible for treatment allocation. The study drug was provided as a phial with powder, containing 25 or 50 mg etanercept or placebo, and a prefilled syringe containing 1 mL of sterile water for subcutaneous injection once weekly. Masking was achieved by the similar appearance of placebo and active drug; patients, healthcare providers and outcome assessors remained masked throughout the study.

Procedures

Etanercept was administered subcutaneously at a dose of 50 mg weekly for the first 24 weeks, followed by 25 mg weekly for the remainder of the study, or placebo. Study visits were after 4, 8, 12, 24, 36 weeks and 1 year. Patients who took analgesics during screening were allowed to continue at the same dose or discontinue if desired. No new analgesics were permitted during the first 12 weeks of the study, except paracetamol (up to 2000 mg/day) as rescue medication, which had to be discontinued 1 day prior to the study visits. A stable dosage for at least 3 months with chondroitin sulfate, glucosamine, bisphosphonate, tetracycline, glucocorticoid and oestrogen was allowed to be continued during the study. No intra-articular steroids or hyaluronic acid type drugs were allowed during the study.

At every study visit tender and soft swollen IPJ counts (0–18), grip strength (in kg; using a hand dynamometer (My-Gripper (Yamasa), SH5001 (Saehan), DYNA Test) or vigorimeter), VAS pain in IPJs, and patient and physician global assessment on VAS were assessed by trained research nurses. Every 4 weeks, patients completed the Functional Index for Hand OsteoArthritis (FIHOA). The Short-Form 36 (SF-36) was completed at baseline and 1 year.

Hand radiographs were taken at baseline, 24 weeks and 1 year, and read paired in chronological order blinded for patient characteristics and treatment applying the Verbruggen-Veys score (GV, RW) and the Ghent University Scoring System (GUSS, GV).[5 21] Progression was defined as (1) transition towards an erosive or remodelling Verbruggen-Veys phase (from normal (N-phase), stationary (S-phase) or J-phase, to E-phase (erosive progression), or from N-phase, S-phase, J-phase or E-phase, to R-phase (remodelling)); or (2) decrease in GUSS score (range 0–300 per joint). Ultrasound of the IPJs was performed at screening, 24 weeks and 1 year by experienced ultrasonographers according to a standardised scoring system.[22] Power Doppler signal and synovial thickening were assessed semiquantitatively (0–3). Contrast-enhanced MRI of the IPJs of one hand was performed in a subset of 20 patients (n=10 in each treatment group) at baseline and 1 year. Images were scored according to the OMERACT hand osteoarthritis MRI score for synovitis and bone marrow lesions (BMLs) (0–3 per joint). Imaging protocols and information on reliability are provided in the online supplementary appendix.

Patients were monitored for clinical and laboratory evidence of adverse events on a routine basis throughout the study.

Outcomes

The primary endpoint was VAS pain at 24 weeks. Secondary clinical endpoints included VAS pain at 1 year, patient and physician global assessment, health-related quality of life (physical component summary (PCS) of SF-36), FIHOA, number of tender or swollen joints, and grip strength (right and left hand averaged), all at 24 weeks and 1 year. Secondary imaging endpoints were the number of joints with synovial thickening and power Doppler signal on ultrasound at 24 weeks and 1 year, and radiographic progression assessed with (1) Verbruggen-Veys scores at 24 weeks and 1 year, and (2) change in GUSS scores over 1 year in the per-protocol population. Change in MRI features over 1 year was defined as post-hoc endpoint.

Table 2 Joint pain at baseline, 24 weeks and 1 year, and between-group differences at 24 weeks and 1 year in intention-to-treat and per-protocol population

	Etanercept			Placebo			Between-group difference			
	Baseline	24 weeks	1 year	Baseline	24 weeks	1 year	24 weeks	P values	1 year	P values
Intention-to-treat										
	n=45			n=45			n=90		n=90	
VAS pain	71.1 (15.7)	39.2 (24.7)	35.7 (25.1)	68.4 (12.8)	46.5 (23.4)	45.4 (25.7)	−5.7 (−15.9 to 4.5)	0.27	−8.5 (−18.6 to 1.6)	0.10
Per-protocol										
	n=32	n=32	n=28	n=38	n=38	n=33	n=70		n=61	
VAS pain	69.2 (13.9)	44.8 (22.8)	35.1 (24.4)	67.0 (13.0)	40.6 (24.7)	45.2 (26.1)	−5.6 (−16.9 to 5.6)	0.32	−11.8 (−23.0 to −0.5)	0.04

Data are mean (SD) and mean difference (95% CI).
VAS, Visual Analogue Scale.

Statistical analysis

A sample size of 45 patients per group was calculated to provide 80% power to detect a between-group difference in mean 10 cm VAS pain of 1.1 per week based on an estimated group SD of 1.9, based on a previous placebo-controlled trial, using mixed-effect models with a two-sided 0.05 significance level.[23]

All outcomes were analysed in two populations as defined in the protocol: the intention-to-treat population including all randomised patients receiving at least one dose of study medication, who underwent at least one outcome assessment, and the per-protocol population including only completers with symptomatic, inflammatory and radiographic erosive disease.

VAS pain was analysed using linear mixed models for repeated measures (at 4, 8, 12, 24, 36, 48 weeks and 1 year), including treatment, study centre, time (categorical), baseline VAS pain and the interaction between treatment and time as independent variables, using a heterogeneous Toeplitz correlation matrix. VAS pain at 24 weeks was the primary outcome. VAS pain at 1 year and patient global assessment were analysed similarly.

The secondary outcomes, that is, VAS physician global assessment, FIHOA, grip strength, SF-36 PCS, tender and swollen joint counts, and number of joints with ultrasound features, were analysed with generalised estimating equations (GEE), specifying the working correlation as first-order autoregressive. Fixed treatment effects were specified in such a way that it excluded a treatment effect on baseline. The SF-36 PCS was calculated using the Medical Outcomes Study (MOS) SF-36 scoring algorithm, applying norm-based scores using age-specific and sex-specific Dutch population-based norm scores (since no such norm values are available for the other countries).[24] Scores were standardised to a scale of 0–100, mean of 50 and SD of 10; lower scores represent worse health. Changes in GUSS scores and MRI features over 1 year were both analysed on joint level using GEE, accounting for within-patient clustering

Table 3 Secondary clinical and imaging outcome measurements at baseline, and between-group differences at 24 weeks and 1 year

	Etanercept	Placebo	Between-group difference			
	Baseline	Baseline	24 weeks	P values	1 year	P values
Intention-to-treat						
Clinical outcomes	n=45	n=45	n=89		n=89*	
VAS patient global	63.7 (18.8)	66.3 (16.2)	−2.5 (−12.6 to 7.6)	0.62	−2.3 (−13.0 to 8.4)	0.67
VAS physician global	58.1 (16.9)	56.1 (13.6)	−4.0 (−14.9 to 6.8)	0.53	−2.8 (−17.4 to 11.6)	0.70
FIHOA	9.9 (5.9)	10.9 (9.9)	0.0 (−1.7 to 1.8)	0.97	0.0 (−2.4 to 2.3)	0.98
Grip strength	15.9 (10.8)	17.3 (11.9)	0.4 (−1.7 to 2.4)	0.74	0.0 (−2.2 to 2.1)	0.97
SF-36 PCS†	42.9 (8.4)	42.9 (9.3)			0.7 (−3.6 to 5.1)	0.11
Tender joint count	8.0 (9.0)	6.5 (4.6)	−0.4 (−1.8 to 1.0)	0.58	0.4 (−1.4 to 2.1)	0.66
Soft swollen joint count	3.0 (2.2)	2.1 (1.8)	−0.03 (−0.8 to 0.8)	0.94	−0.01 (−0.9 to 0.9)	0.99
Ultrasound	n=43	n=44	n=89		n=89	
Joints with power Doppler, median (IQR)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	−0.3 (−1.04 to 0.4)	0.39	−0.01 (−0.7 to 0.7)	0.98
Joints with synovial thickening, median (IQR)	3.0 (1.0–6.0)	2.0 (1.0–5.0)	0.2 (−1.02 to 1.3)	0.07	−0.3 (−1.9 to 1.3)	0.73
Selected patient groups						
Radiographs‡§	n=23	n=31			n=54	
GUSS	287 (36)	288 (34)			2.9 (0.5 to 5.4)	0.02
MRI‡	n=10	n=10			n=20	
Synovitis	1.0 (0.5)	1.4 (0.3)			0.03 (−0.2 to 0.3)	0.81
Bone marrow lesions	0.6 (0.3)	0.7 (0.3)			−0.2 (−0.4 to −0.1)	0.001

Data are mean (SD) and mean difference (95% CI) unless otherwise specified. All analyses are performed in the intention-to-treat population, unless otherwise indicated.
*One patient on etanercept had no baseline or any follow-up assessment.
†Data available from n=32 and n=33 patients in etanercept and placebo groups at baseline.
‡In patients from per-protocol population.
§Data are presented on joint level, between-group difference represents the between-group difference in change over 1 year on joint level.
FIHOA, Functional Index for Hand Osteo Arthritis; GUSS, Ghent University Scoring System; SF-36 PCS, Short-Form 36 physical component scale; VAS, Visual Analogue Scale.

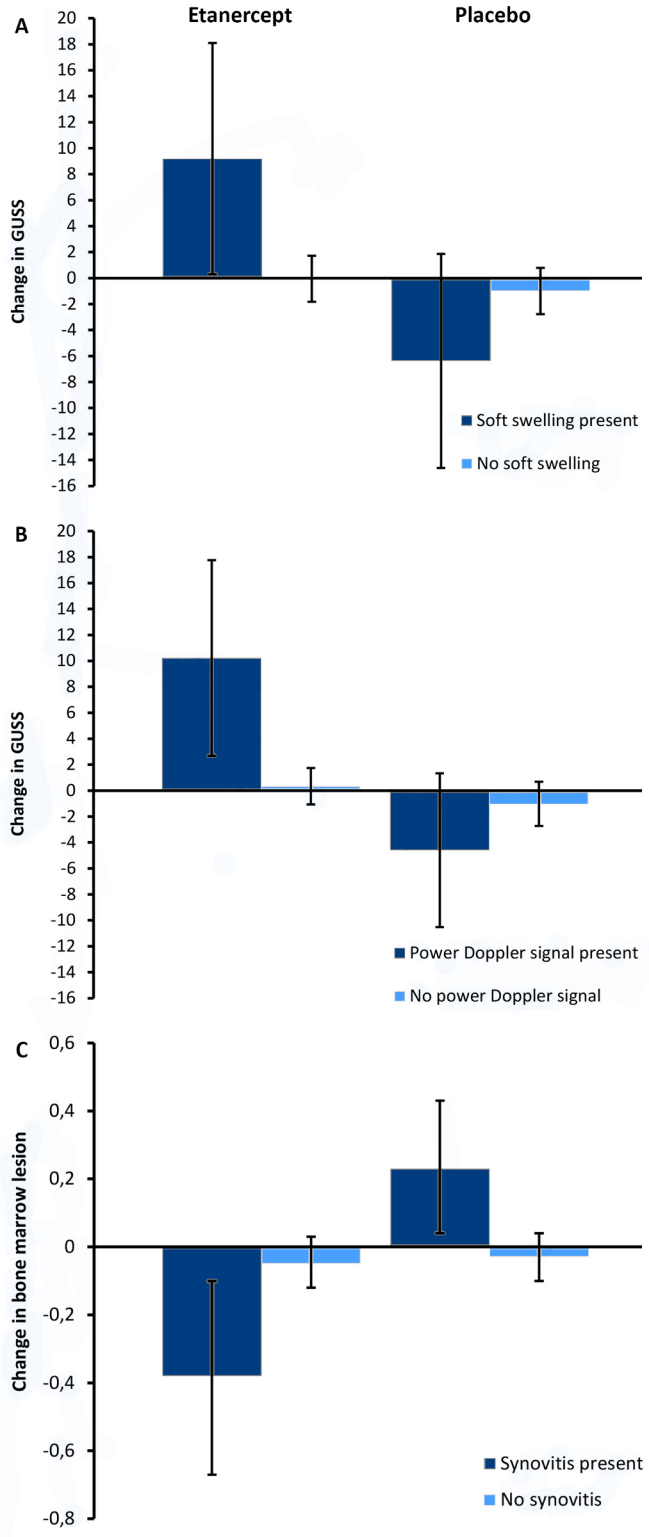

Figure 2 Interaction between etanercept treatment and presence of baseline inflammation in a joint (based on soft swelling (A), power Doppler signal on ultrasound (B) or MRI-detected synovitis (C)) on change in GUSS (A,B) and bone marrow lesions on MRI (C) over 1 year. Error bars represent 95% CIs. GUSS, Ghent University Scoring System.

effects, specifying the working correlation exchangeable (pairwise correlations of repeated measures considered the same). In addition, statistical interaction between the presence of baseline inflammation, reflected by soft swelling, power Doppler signal or MRI-detected synovitis, and treatment effect on change in GUSS scores or BMLs over 1 year was tested. Analyses were performed with SPSS V.23. No data monitoring committee was appointed. This trial was registered at the Netherlands Trial Register, trial registration number NTR1192.

Table 4 List of reported adverse events

	Etanercept (n=45)	Placebo (n=45)
Adverse events (n)		
Total*	28	24
Infectious problems	11	10
Cardiovascular	1	4
Gastrointestinal	2	2
Skin/mucosal	3	1
Exacerbation osteoarthritis	2	0
Pulmonary	0	1
Neurological	1	0
Malignancy	1	0
Other†	7	6
Serious adverse events (n)		
Total	1	1
Development of breast cancer	1	0
Infectious diarrhoea	0	1
Dropouts due to adverse events		
Total‡	6	1
Skin eruptions	2	0
Development of breast cancer	1	0
Infectious diarrhoea	0	1
Progression of polyneuropathy	1	0
Disturbed liver function tests	1	0
Musculoskeletal pain and swelling with submandibular gland swelling	1	0

*P=0.65.
†Including back pain, bursitis, deep venous thrombosis, disturbed kidney function, local reaction after trauma, perineum cyst, pharyngodynia, progression of polyneuropathy, radicular pain (n=2), submandibular gland swelling, tendinitis and traumatic fracture.
‡P=0.11.

RESULTS

Patient population

Patients were recruited between 11 March 2008 and 9 January 2012. There were 284 patients assessed for eligibility, and 91 were randomly assigned to a group, of whom 1 withdrew consent before receiving a study drug, leaving 90 patients in the intention-to-treat population (figure 1). Ten (11%) in the placebo and 12 (13%) in the etanercept group prematurely discontinued the study medication. Baseline characteristics were well balanced between the groups (table 1). The study population was representative of patients with hand osteoarthritis, with 81% women and a mean age of 59.7 years. As shown in table 1, not all patients fulfilled the extensive inclusion criteria. At 24 weeks and 1 year, n=70 and n=61 were eligible for the per-protocol population, respectively.

Primary and secondary clinical outcomes

Between-group differences after 24 weeks and 1 year in the intention-to-treat analysis were −5.7 (95% CI −15.9 to 4.5) and −8.5 (95% CI −18.6 to 1.6), respectively, favouring etanercept, although not being statistically significant (table 2). At 24 weeks, there were no between-group differences in reported analgesic

use. In the per-protocol analysis, between-group differences were −5.6 (95% CI −16.9 to 5.6) and −11.8 (95% CI −23.0 to −0.5, p=0.04) at 24 weeks and 1 year, respectively, in favour of etanercept (table 2). Between-group differences in the other clinical outcome parameters were in favour of etanercept, but not statistically significant (table 3).

Secondary imaging outcomes

Of 54 patients (31 on placebo, 23 on etanercept) in the per-protocol population, radiographs were available for scoring at baseline and 1 year. Their Verbruggen-Veys phases at baseline and the changes during follow-up are provided in online supplementary table S2. Over 1 year, 9 (3.3% of eligible joints) and 14 (3.5%) joints showed erosive progression (p=0.86), and 24 (8.0%) and 22 (5.2%) joints showed remodelling in the etanercept and placebo groups (p=0.13), respectively. The GUSS score was performed in 862 joints. At baseline the mean (SD; range) GUSS score was 287.6 (34.8; 90–300) per joint and similar in both groups (table 3). The between-group difference in change over 1 year was 2.9 (95% CI 0.5 to 5.4, p=0.02) on joint level, indicating more remodelling in the etanercept group. Moreover, a statistical interaction was observed between the presence of soft swelling at baseline in a joint and the effect of etanercept on the GUSS, resulting in a larger improvement in GUSS in those joints (p=0.008; figure 2). We found similar results for joints with positive power Doppler signal on ultrasound at baseline (p=0.005; figure 2).

In the subgroup with MRI available (n=20), no change and no between-group difference could be observed in MRI-detected synovitis over 1 year, whereas BML scores decreased more in the etanercept group (table 3). A similar statistical interaction was found as with GUSS, namely between etanercept treatment and the presence of MRI-detected synovitis (grade 2 or 3) at baseline (p=0.003; figure 2).

On ultrasound, no between-group differences in the number of joints with power Doppler signal or synovial thickening were observed (table 3).

Adverse events

Fifteen of 45 (33%) patients on etanercept and 12 of 45 (27%) on placebo reported at least one adverse event (p=0.65) (table 4). Infectious problems were most often reported: 11 times in the etanercept group and 10 times in the placebo group. Six (13%) patients in the etanercept compared with one (2%) in the placebo group dropped out due to an adverse event (p=0.11). Two serious adverse events occurred (development of breast cancer in the etanercept group and hospital admission for infectious diarrhoea in the placebo group), both not deemed to be related to the study drug.

DISCUSSION

In this proof-of-concept study on patients with erosive hand osteoarthritis, no statistically significant effect of treatment with anti-TNF on the primary prespecified clinical endpoint, VAS pain at 24 weeks, was seen. However, in subgroup analyses of patients with signs of active inflammation, anti-TNF treatment led to limited symptomatic relief, as well as structural effects. Patients with signs of inflammation at baseline showed a statistically significant and clinically relevant improvement in pain after 1 year, based on a minimally clinically important difference in pain of 0.37 SD units as used before by others (corresponding to 9.1 mm on a 100 mm VAS in this study).[25] Moreover, we demonstrated that the possible beneficial effects of TNF inhibition on subchondral bone were especially present at baseline in actively inflamed joints, marking a possible interplay between synovitis and subchondral bone.

Although TNF inhibitors have consistently been shown to be effective in other rheumatic diseases like rheumatoid arthritis,[26] trials in hand osteoarthritis are scarce and have led to conflicting results, some showing symptom relief and others not.[13 14 17 18] The two randomised trials of anti-TNF failed to show beneficial effects on symptom relief after 6 months and 1 year.[13 18] The difference with previous controlled trials may have been the result of selecting different study populations, since none of these studies specifically included patients with proven joint inflammation as in this trial. Also in the current trial, despite our best intentions, some patients were included who had no inflammation at baseline and who indeed appeared to have no benefit of etanercept treatment. In addition, the treatment period in previous studies may have been too short. We found that the reduction in pain was only after 1 year of treatment, at which time we also found an effect on structural damage. Therefore we cannot rule out that the pain reduction could be associated with the observed drug's structural effects.

This is the first-hand osteoarthritis study investigating the effects of anti-TNF on inflammatory signs on ultrasound and MRI. Remarkably, no treatment response on ultrasonographic or MRI-detected synovitis was seen, although this is in line with trials investigating systemic glucocorticoids in hand osteoarthritis.[15 19] However, the severity of BMLs in a joint did decrease on etanercept treatment. Various studies in knee osteoarthritis investigating treatments primarily targeting subchondral bone have also shown that BMLs, but not synovitis, were modified by these interventions.[27–29]

Surprisingly, synovitis in itself did not improve even though we observed that the effect of etanercept on radiographic erosive damage and BMLs was more pronounced in actively inflamed joints. This is indicative that the interrelation between synovitis, subchondral bone marrow inflammation and structural damage is not straightforward and clearly distinct in erosive hand osteoarthritis compared with rheumatoid arthritis. However, ultrasonography was performed in several centres with different equipment, focusing on the presence or absence of synovitis, which might have hampered sensitivity to change. Moreover, MRI was only performed in a small (random) subset of participants. In any case, it suggests that there may not be a direct role for synovitis in the pathophysiology of osteoarthritis, but rather that synovitis may act as an intermediate factor, negatively influencing the subchondral bone or cartilage through production of cytokines like TNF. Alternatively, the observed synovitis is occurring secondary to structural changes, with the primary events occurring in the subchondral bone or cartilaginous tissues. This interplay between synovitis and subchondral bone or cartilage confirms the suspected importance of the entire joint structure that has been emphasised before.[30]

Several pathways have been described by which TNF-alpha, which is known to be produced in the inflamed synovium in osteoarthritis, could induce structural damage, including induction of other proinflammatory cytokines (eg, interleukin (IL)-6 and IL-8), synthesis of matrix metalloproteinases by chondrocytes and synovial cells, an increased synthesis of cyclo-oxygenase-pathway products, and an upregulation of nitric oxide production.[12] Moreover, TNF-alpha has been shown to induce osteoclastic bone resorption in vitro, and in an animal osteoarthritis model treatment with anti-TNF appeared to improve subchondral bone structure.[31 32]

While this study has a number of strengths, such as its randomised, double-blind design, the inclusion of a specific

subset of patients with hand osteoarthritis likely to benefit from treatment, and the inclusion of ultrasound and MRI evaluation, there are also several limitations. The etanercept dose of 50 mg weekly was based on experience in inflammatory rheumatic diseases such as rheumatoid arthritis. With the eye on safety and the uncertainty of clinical efficacy, it was decided to halve the dose after 24 weeks to 25 mg weekly, which may have been too low for the drug to be efficacious. Not all patients fulfilled all the stringent inclusion criteria, but the vast majority fulfilled most criteria. Since this trial was set up as a proof-of-concept study, a prespecified per-protocol analysis was performed including only those who did fulfil all the criteria. Although postrandomisation exclusion may introduce bias, it is known to lead to more informative analyses when applied appropriately.[33] Although no important imbalance between the groups was noted in the number of dropouts, numerically more patients on etanercept dropped out due to adverse events and less due to inefficacy. Also, for the analysis of the radiographic data, a number of data were missing, due to absence of or bad-quality radiographs at one or more time points. The potential influence of missing data on the results is unclear; however, specific (preplanned) statistical methods were chosen to minimise bias. The study sample size, as calculated, resulted in 90 patients, but the sample size of the per-protocol analysis was smaller. Nevertheless a difference between the groups was seen.

Future research is warranted to elucidate the proposed interaction between synovium and subchondral bone. This trial does not provide evidence for the use of TNF inhibitors in daily treatment of patients with hand osteoarthritis in general. Rather it highlights the possible role of targeted treatment of patients or even joints in which inflammation is present. Studies investigating treatment strategies specifically targeting inflammation, for example, short-term anti-inflammatory treatment with glucocorticoids or TNF inhibitors during 'flares' of the disease, are warranted.

Author affiliations
[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[3]Rheumatology Unit, Department of Medicine DIMED, University of Padua, Padua, Italy
[4]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
[5]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
[6]VIB inflammation Research Center, Ghent University, Ghent, Belgium
[7]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

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REFERENCES

1 GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, *et al*. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* 2015;386:2145–91.
2 Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol* 2014;10:242–51.
3 Hochberg MC, Altman RD, April KT, *et al*. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2012;64:465–74.
4 Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum* 2001;44:1237–47.
5 Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308–20.
6 Kortekaas MC, Kwok WY, Reijnierse M, *et al*. In erosive hand osteoarthritis more inflammatory signs on ultrasound are found than in the rest of hand osteoarthritis. *Ann Rheum Dis* 2013;72:930–4.
7 Wittoek R, Carron P, Verbruggen G. Structural and inflammatory sonographic findings in erosive and non-erosive osteoarthritis of the interphalangeal finger joints. *Ann Rheum Dis* 2010;69:2173–6.
8 Punzi L, Frigato M, Frallonardo P, *et al*. Inflammatory osteoarthritis of the hand. *Best Pract Res Clin Rheumatol* 2010;24:301–12.
9 Yusuf E, Kortekaas MC, Watt I, *et al*. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis* 2011;70:60–7.
10 Haugen IK, Bøyesen P, Slatkowsky-Christensen B, *et al*. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899–904.
11 Kortekaas MC, Kwok WY, Reijnierse M, *et al*. Brief report: association of inflammation with development of erosions in patients with hand osteoarthritis: a prospective ultrasonography study. *Arthritis Rheumatol* 2016;68:392–7.
12 Kapoor M, Martel-Pelletier J, Lajeunesse D, *et al*. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011;7:33–42.
13 Chevalier X, Ravaud P, Maheu E, *et al*. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697–705.
14 Fioravanti A, Fabbroni M, Cerase A, *et al*. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. *Rheumatol Int* 2009;29:961–5.
15 Keen HI, Wakefield RJ, Hensor EM, *et al*. Response of symptoms and synovitis to intramuscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. *Rheumatology* 2010;49:1093–100.
16 Kvien TK, Fjeld E, Slatkowsky-Christensen B, *et al*. Efficacy and safety of a novel synergistic drug candidate, CRx-102, in hand osteoarthritis. *Ann Rheum Dis* 2008;67:942–8.
17 Magnano MD, Chakravarty EF, Broudy C, *et al*. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. *J Rheumatol* 2007;34:1323–7.
18 Verbruggen G, Wittoek R, Vander Cruyssen B, *et al*. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891–8.
19 Wenham CY, Hensor EM, Grainger AJ, *et al*. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology* 2012;51:2286–94.
20 Spolidoro Paschoal NO, Natour J, Machado FS, *et al*. Effectiveness of triamcinolone hexacetonide intraarticular injection in interphalangeal joints: a 12-week randomized controlled trial in patients with hand osteoarthritis. *J Rheumatol* 2015;42:1869–77.
21 Verbruggen G, Wittoek R, Vander Cruyssen B, *et al*. Morbid anatomy of 'erosive osteoarthritis' of the interphalangeal finger joints: an optimised scoring system to monitor disease progression in affected joints. *Ann Rheum Dis* 2010;69:862–7.

22 Keen HI, Lavie F, Wakefield RJ, *et al*. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. *Ann Rheum Dis* 2008;67:651–5.
23 Vander Cruyssen B, Moqadam Q, Groeneboer S. Xylosan polysulphate as a symptom modifying osteoarthritis drug in patients with finger joint arthritis. *Scand J Rheumatol* 2008;37.
24 Aaronson NK, Muller M, Cohen PD, *et al*. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055–68.
25 Wandel S, Jüni P, Tendal B, *et al*. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010;341:c4675.
26 Nam JL, Ramiro S, Gaujoux-Viala C, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:516–28.
27 Callaghan MJ, Parkes MJ, Hutchinson CE, *et al*. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Ann Rheum Dis* 2015;74:1164–70.
28 Laslett LL, Doré DA, Quinn SJ, *et al*. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Ann Rheum Dis* 2012;71:1322–8.
29 Pelletier JP, Roubille C, Raynauld JP, *et al*. Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss. *Ann Rheum Dis* 2015;74:422–9.
30 Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115–26.
31 Bertolini DR, Nedwin GE, Bringman TS, *et al*. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986;319:516–8.
32 Ma CH, Lv Q, Yu YX, *et al*. Protective effects of tumor necrosis factor-α blockade by adalimumab on articular cartilage and subchondral bone in a rat model of osteoarthritis. *Braz J Med Biol Res* 2015;48:863–70.
33 Fergusson D, Aaron SD, Guyatt G, *et al*. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4.