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Original article

Intra-articular etanercept treatment in inflammatory arthritis: A randomized double-blind placebo-controlled proof of mechanism clinical trial validating TNF as a potential therapeutic target for local treatment



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ABSTRACT

Objective: There is an increased interest in developing gene therapy approaches for local delivery of therapeutic genes in patients with arthritis. Intra-articular (i.a.) gene delivery, using an adeno-associated virus encoding a TNF soluble receptor, resulted in reduced paw swelling in an arthritis animal model, but i.a. treatment with a similar vector did not induce robust clinical improvement in patients. It is unclear whether this can be explained by for instance insufficient transduction efficiency or the fact that TNF is not a good therapeutic target for i.a. treatment. The objective of this study was to explore the effects of i.a. TNF blockade.

Methods: Thirty-one patients with rheumatoid or psoriatic arthritis were assigned to a single i.a. injection of 25 mg etanercept or placebo in a double-blind randomised controlled clinical trial. The primary end point was target joint improvement, determined by a composite change index.

Results: Twenty-two patients received etanercept and 9 received placebo. Treatment was generally well tolerated. Treatment with etanercept resulted in a prompt and statistically significant improvement of the index ($P < 0.001$) in comparison with placebo. As expected in light of the half-life of etanercept, the beneficial effect was transient and only statistically significant at week 1 and 2 after i.a. injection.

Conclusion: The results support the development of novel approaches for long-term inhibition of TNF at the site of inflammation, such as gene therapy.

Trial registration: The Netherlands National Trial Register (NTR), www.trialregister.nl, NTR-1210.

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Abbreviations: AMC-UvA, Academic Medical Center/University of Amsterdam; ACR, American College of Rheumatology; AS, Ankylosing spondylitis; Anti-CCP, Anti-citrullinated cyclic peptide; CASPAR, Classification criteria for Psoriatic ARthritis; CCI, Composite change index; CRP, C-reactive protein; DMARD, Disease-modifying antirheumatic drugs; ESR, Erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MUMC, Maastricht University Medical Center; MCP, Metacarpophalangeal; NTR, Netherlands National Trial Register; PsA, Psoriatic arthritis; RCT, Randomized controlled trials; RA, Rheumatoid arthritis; TJC, Tender joint count; UMGCG, University Medical Center Groningen; VAS, Visual analogue scale.

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1. Introduction

The clinical experience with intra-articular corticosteroid injections highlights the potential of local treatment of inflammatory arthritis [1]. Tumour necrosis factor (TNF) has been validated as an important therapeutic target, in among other indications, rheumatoid arthritis (RA) and spondyloarthritis (SpA), but it is at present unclear whether the beneficial effect of systemic anti-TNF therapy could also be achieved by local treatment.

Over the last decade, there has been an increased interest in developing gene therapy approaches for delivery of therapeutic genes at the site of inflammation in patients with arthritis. In animal models of arthritis, intra-articular administration of recombinant adeno-associated virus (rAAV) vectors (both serotype 2 and 5) expressing soluble TNF receptors has resulted in reduced paw swelling and a decrease of spontaneous synovial pathology, including decreased inflammatory cell infiltration, pannus formation and cartilage and bone destruction [2–4]. However, intra-articular treatment, with rAAV2 encoding the human TNF-immunoglobulin Fc fusion gene, did not induce robust clinical improvement in patients with inflammatory arthritis (RA, psoriatic arthritis [PsA] and ankylosing spondylitis [AS]) [5]. It is currently unclear whether this can be explained by for instance insufficient expression of etanercept, selection of patients who were less likely to respond to anti-TNF therapy (anti-TNF inadequate responders were treated with AAV-etanercept) or by the fact that TNF is not a good therapeutic target for intra-articular treatment. Beside this gene therapy trial, several clinical studies have investigated the use of intra-articular TNF inhibitors, revealing conflicting results: case-reports suggested improvement after single or repeated injections in different types of inflammatory arthritis [6–16]. Uncontrolled studies confirmed these findings and demonstrated efficacy using different imaging techniques [17–19]. Intra-articular anti-TNF treatment ameliorated histological and cytological markers of inflammation in samples obtained from the site of inflammation [6,8,16,20,21]. Randomized controlled trials (RCTs), in patients with RA comparing intra-articular etanercept treatment to intra-articular treatment with corticosteroids, have shown comparable efficacy [22,23]. However, there was no clear-cut decrease of synovial inflammation after local TNF blockade, as shown by ultra-sound examination or MRI [24]. Intra-articular administration of 100 mg of infliximab resulted in an insufficient response, with a relapse of arthritis in all patients, while intra-articular injection of 80 mg of methylprednisolone resulted in sustained remission in almost 40% of patients during a follow-up period of six months [25]. More recently, an uncontrolled study, investigating repeated intra-articular etanercept injections in SpA patients, showed early improvement in both local and systemic clinical scores, a decrease in synovial thickness measured by ultra-sound examination and MRI, as well as synovial biomarker expression [26].

In spite of the major improvement in the treatment of patients with RA and spondyloarthritis [27], a significant proportion of the patients still suffer from disease activity in at least one joint. Local treatment with corticosteroids is widely used, but not all patients respond and there may be side effects when patients receive intra-articular treatment > 4 times/year. Thus, it is important to identify new therapeutic targets for local intervention.

Based on the conflicting results of these prior studies, we decided to perform a proof of mechanism study to further validate TNF as a therapeutic target for local inhibition in the inflamed joint. Therefore, the objective of this study was to explore the effects of intra-articular TNF blockade, using etanercept as a tool compound. Both efficacy and safety of a single intra-articular etanercept injection compared to placebo were investigated in patients with inflammatory arthritis, and related to serum levels of the compound. The hypothesis was that TNF blockade

might also be effective when administered locally at the site of inflammation. The study demonstrated that a single intra-articular etanercept injection is feasible and safe and results in transient improvement of disease activity in the target joint. These results support the development of novel approaches for long-term inhibition of TNF at the site of inflammation, such as gene therapy.

2. Patients and methods

2.1. Ethics statement

The study was conducted according to the principles outlined in the Guideline for Good Clinical Practice ICH Tripartite Guideline (January 1997). The study was conducted with the approval of the Academic Medical Center/University of Amsterdam (AMC-UvA) medical research ethics committee. From the boards of directors of the Maastricht University Medical Center (MUMC) and the University Medical Center Groningen (UMCG), a local feasibility declaration was obtained. The trial was registered in the Dutch Trial Register (NTR), www.trialregister.nl, NTRcode 1210. All participants gave written informed consent (according to the Declaration of Helsinki) prior to the study.

2.2. Study population

Patients from the rheumatology outpatient clinic of the AMC-UvA, Amsterdam, the MUMC, Maastricht and the UMCG, Groningen, The Netherlands, were included.

Inclusion criteria were age between 18–85 years; a diagnosis of RA according to the revised 1987 American College of Rheumatology (ACR) criteria, PsA according to the CASPAR (Classification criteria for Psoriatic Arthritis) criteria or AS according to the modified New York criteria; and arthritis of a knee, ankle, wrist, elbow or metacarpophalangeal (MCP) joint despite a stable dose (at least 4 weeks) of methotrexate and/or prednisone (maximum of 10 mg/day). Concomitant stable non-steroidal anti-inflammatory drugs were permitted.

Exclusion criteria were the current use of disease-modifying antirheumatic drugs (DMARDs) (conventional other than methotrexate or biological), intra-articular or intramuscular treatment with corticosteroids within 3 months of inclusion, a history of or current chronic infectious diseases, a history of cancer in the past 10 years, or severe cardiac, pulmonary or renal co-morbidity. Tuberculosis screening was performed prior to administration of the study medication.

During the course of the trial, the following amendments were made to the protocol to improve patient inclusion: patients could be included with a diagnosis of RA, PsA or AS existing for a minimum of 3 instead of 6 months, if they had endured an adequate wash out period after previous biological therapy and in case of a history of cancer, if this had been more than 10 years ago. The trial primarily aimed at patients with knee arthritis, but later also included patients with ankle, wrist, elbow and MCP joint arthritis. Patients who had undergone an arthroscopy within 2 weeks of inclusion were excluded.

2.3. Procedures and assessments

This trial was designed as an exploratory proof of mechanism clinical trial and intended to include a total of 60 patients (20 patients per disease). Patients were randomized to receive either etanercept (1 mL containing 25 mg; Pfizer, New York City, USA) or placebo (1 mL 0.9% NaCl) administered by intra-articular injection in a 2:1 ratio in a double-blinded fashion. For MCP joints a volume of

0.5 mL was injected. Randomization and preparation of study medication was performed by an independent investigator or research nurse. Dissolved etanercept and NaCl have the same appearance in the syringe. The syringe was blinded for the patient with an etiquette. An online accessible randomization program (ALEA) was generated by the AMC Clinical Research Unit and stratified per disease.

Patients were evaluated at baseline, weekly up until 4 weeks and at 6 weeks after injection. The primary endpoint, target joint improvement, was determined by a composite change index (CCI), consisting of a visual analogue scale (VAS) for target joint pain (0–100 mm), clinical assessments of the target joint (joint tenderness at palpation, joint swelling and functional disability, range: 0–3) and both patient’s and doctor’s global assessment of the effect of treatment on the target joint (range: 0–3) [28]. Calculation of the CCI was based on changes of the first four variables from baseline. The last two variables were evaluated at each time point. The total CCI ranged from 0 (no effect or deterioration) to 10 (maximal effect). Successful treatment was defined as CCI ≥ 5 [28].

Next to the target joint evaluation, safety and general disease activity parameters were monitored, including a disease activity score based on 28 joints (DAS28) calculated with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), tender and swollen joint count (66–68 joints) and Ritchie Articular Index (RAI), as well as acute phase reactants CRP (mg/L) and ESR (mm/h). The Health Assessment Questionnaire-Disability Index (HAQ-DI) was used to evaluate physical function. Health status was assessed through the SF-36 questionnaire. Etanercept levels and anti-etanercept antibodies were determined in serum by ELISA, as previously described [29,30].

2.4. Statistical analysis

All analyses were performed using Graphpad Prism (La Jolla, CA), and SPSS® version 19 for Windows® (IBM, Armonk, NY). Data are shown as mean (SD or SEM where appropriate), median (IQR) or percentages. To evaluate the effect of treatment on the CCI as a dependent variable, generalised estimating equations was used with age, gender, disease duration, anti-citrullinated cyclic peptide (CCP) positivity, CRP at baseline and tender joint count (TJC) at baseline as covariates, and an exchangeable working correlation structure was chosen. This statistical model takes the different time points and the effect over time into account. To evaluate the effects of treatment on separate dependent variables, a linear mixed model analysis was chosen, with age, gender, and anti-CCP positivity as independent variables. Differences between treatment groups in single comparisons and for etanercept levels were assessed using an independent *t*-test. The CCI-response rate (CCI ≥ 5) was calculated per group for each time point by X-square test; similarly the adverse event rate was calculated for the overall follow-up period. Values less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Overall, 32 patients were randomised between February 2008 and January 2012. Last patient follow-up was ended on February 1st, 2012. The trial was set up to include a total of 60 patients (20 patients per disease), but stopped earlier due to low patient inclusion rates. The trial profile is depicted in Fig. 1. One patient

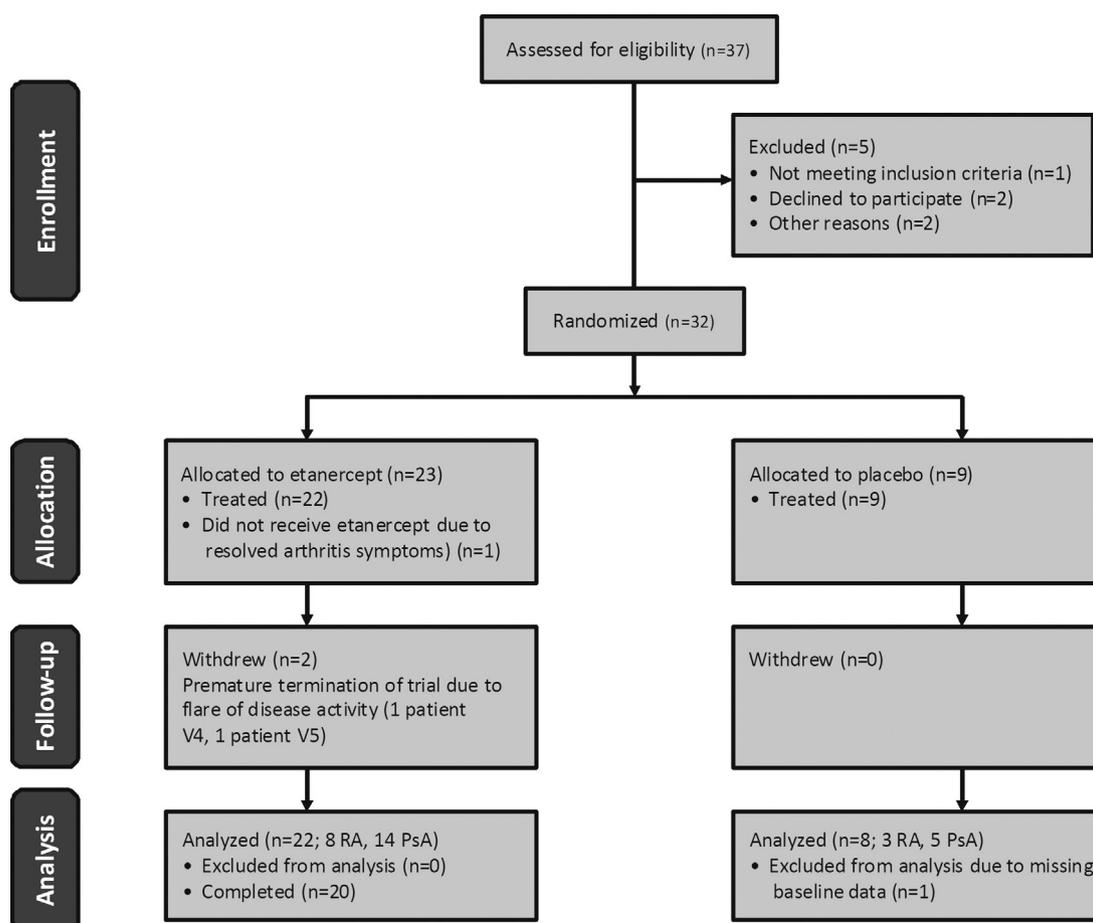


Fig. 1. Trial profile. Patients are grouped according to treatment received. V: visit.

Table 1
Baseline demographic and disease characteristics.

	Etanercept (n=22)	Placebo (n=8)
Age (years)	50.9 (14.6)	52.1 (12.4)
Female	10 (45%)	4 (50%)
Disease		
PsA	14 (64%)	5 (62%)
Rheumatoid factor positivity	0 (0%)	0 (0%)
Anti-CCP positivity	1 (7%)	0 (0%)
RA	8 (36%)	3 (38%)
Rheumatoid factor positivity	6 (75%)	1 (33%)
Anti-CCP positivity	5 (63%)	1 (33%)
Disease duration (years)	3.7 (0.9–9.3)	2.4 (1.6–4.9)
Receiving concomitant medication		
MTX	17 (77.3%)	7 (87.5%)
Prednisone	2 (9.1%)	1 (12.5%)
NSAIDs	11 (50%)	2 (25%)
Injected joint		
Knee	20 (91%)	6 (75%)
Ankle	0 (0%)	1 (12.5%)
Wrist	0 (0%)	0 (0%)
Elbow	0 (0%)	0 (0%)
MCP	2 (9%)	1 (12.5%)
Disease activity parameters		
VAS pain target joint	50.6 (27.6)	45.8 (24.8)
Target joint swelling (range: 0–3)	2.1 (0.7)	1.75 (0.5)
Target joint tenderness (range: 0–3)	1.3 (0.8)	1.1 (1.0)
Target joint function (range: 0–3)	1.6 (1.2)	1.0 (1.1)
CRP (mg/L)	8.1 (4.1–23.6)	3.8 (1.7–14.6)
ESR (mm/hr)	9.0 (5.8–23.5)	10.5 (5.5–27.0)
Tender joint count (0–68 possible joints)	7.5 (2.0–24.0)	3.0 (1.0–8.0)
Swollen joint count (0–66 possible joints)	2.5 (1.0–4.5)	2.0 (1.0–2.8)
DAS28 (CRP)	4.2 (1.2)	3.5 (1.0)
DAS28 (BSE)	4.1 (1.4)	3.6 (1.2)
Health Assessment	0.6 (0.2–1.8)	0.2 (0.0–1.2)
Questionnaire (range: 0–3)		

CRP: C-reactive protein; DAS28: Disease activity Score in 28 joints; ESR: erythrocyte sedimentation rate; MTX: methotrexate. Categorical data are presented as numbers (%) and continuous data are presented as mean (SD) if normally distributed and as median (IQR) if not normally distributed.

discontinued prior to study medication injection due to the resolution of arthritis symptoms, and was excluded from the analysis. Two patients left the study prior to completion because of worsening of disease symptoms, which required a treatment adjustment in the opinion of the rheumatologist (at visit 4 and at visit 5). Their data before the treatment adjustment are included in the analysis. One patient (placebo) was excluded from the analysis because of missing baseline data. A total of 30 patients were included in the analysis, 19 patients with PsA (17 knee joints and 2 MCP joints) and 11 patients with RA (9 knee joints, 1 ankle joint and 1 MCP joint). Baseline demographic and disease characteristics were similar between treatment groups (Table 1).

3.2. Clinical response

Treatment with etanercept resulted in a prompt and statistically significant improvement of the CCI ($P < 0.001$) in comparison with placebo. As expected in light of the half-life of etanercept, when analysed over time, this beneficial effect was transient and only statistically significant at week 1 and 2 after IA injection (Fig. 2). This effect was transient for most CCI components (VAS pain, swelling and functionality) except for joint tenderness, which remained decreased compared to baseline up to week 6 ($P < 0.01$). Placebo treatment did not improve local disease activity parameters. The CCI-response rate ($CCI \geq 5$) after 1 week was 55% for

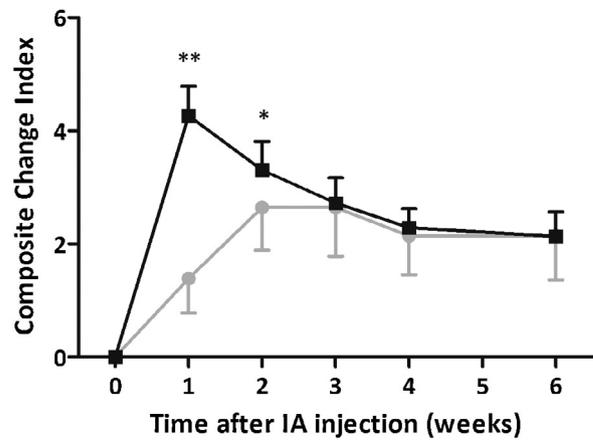


Fig. 2. Effect of treatment over time on the composite change index (CCI). The CCI is calculated relative to the baseline visit. Etanercept has a significant effect on the CCI at 1 and 2 weeks after intra-articular injection. Data were evaluated through a generalised estimating equations model and shown as mean ± SEM, the group treated with etanercept is depicted in black, the placebo group is shown in grey; * $P < 0.05$; ** $P < 0.01$.

patients treated with etanercept versus 0% for patients treated with placebo ($P = 0.03$). A sustained effect over a period of 6 weeks was seen in only 2 PsA patients receiving etanercept treatment (9.1%).

The effect of etanercept on general disease activity parameters was analysed per parameter. In general, baseline disease activity turned out to be higher for patients treated with etanercept versus placebo. Over time, these parameters remained unchanged, regardless of treatment with etanercept or placebo (Appendix B, Table S1; see the supplementary material associated with this article online).

3.3. Safety outcomes

Mild transient adverse events, such as flu-like symptoms and gastrointestinal complaints, were reported for 9 patients, 7 (32%) of patients treated with etanercept and 2 (25%) with placebo ($P = 0.55$) (Table 2). Intra-articular administration of 25 mg etanercept did not result in serious adverse events. Adverse events leading to early withdrawal included exacerbation of RA in 2 patients after intra-articular etanercept treatment as mentioned earlier.

3.4. Analysis of serum etanercept levels

Serum etanercept levels measured after a single intra-articular injection were 1.39 ± 0.46 mg/L (mean ± SD) after 1 week and subsequently declined to baseline levels 4 weeks after injection (Fig. 3A). Increased CRP baseline levels (>5) did not have an effect on the maximum serum level of etanercept ($P = 0.67$) (Fig. 3B). Levels were comparable between CCI good and non-responders (data not shown). Anti-etanercept antibodies were observed in none of the sera.

Table 2
Summary of safety data over 6 weeks.

	Etanercept (n=22)	Placebo (n=8)
AE incidence: No. of patients (%)		
Any AE	7 (32%)	2 (25%)
Any serious AE	0 (0%)	0 (0%)
AE subtypes		
Infection	4 (18%)	0 (0%)
Neurological	0 (0%)	1 (13%)
AE leading to early withdrawal	2 (9%)	0 (0%)
Other	1 (5%)	1 (13%)

AE: adverse event.

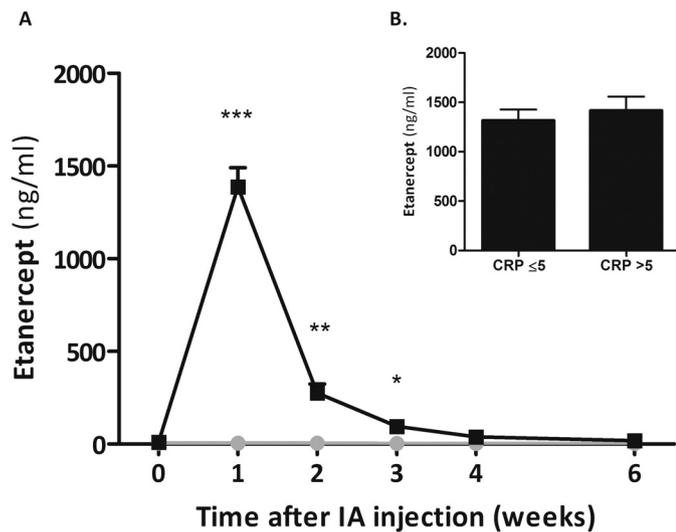


Fig. 3. A. Etanercept levels measured in serum over time. B. Etanercept levels 1 week after injection for patients with a high versus low CRP at baseline ($n=14$ and 6 respectively). Data shown are mean \pm SEM, the group treated with etanercept is depicted in black, the placebo group is shown in grey; * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

4. Discussion

The objective of this clinical trial was to explore whether local TNF inhibition at the site of inflammation could improve clinical signs and symptoms of inflammatory arthritis in conditions where TNF has previously been validated as a therapeutic target for systemic treatment. Systemic anti-TNF treatment exerts its effects at least in part by deactivation of vascular endothelium and decreased migration of inflammatory cells towards the inflamed compartment [31], and perhaps a direct effect on the central nervous system [32]. It is unclear whether improvement can also be achieved by local injection where these mechanisms may not be operative. We found that a single intra-articular etanercept injection is safe and results in transient improvement of disease activity in the target joint, with similar trends in RA compared to PsA patients. No differences were observed in general disease activity parameters at baseline and safety outcomes between etanercept and placebo treated patients. Thus, this study supports the notion that local TNF blockade may be sufficient to improve clinical signs and symptoms of patients with inflammatory monoarthritis in both RA and PsA, providing the rationale for future research on approaches that could lead to more prolonged TNF inhibition at the site of inflammation. This may have advantages for patients with persistent mono- or oligoarthritis who do not necessarily need to be exposed to systemic anti-TNF treatment and its inherent effects on host defence.

While the effect of local TNF blockade compared to intra-articular corticosteroids has been explored before [22,23], we studied for the first time the effects of intra-articular etanercept treatment compared to placebo, in a randomized, controlled study design. Efficacy and safety were assessed frequently during the follow-up period of 6 weeks. Furthermore, the efficacy of etanercept was related in this study to the serum levels of etanercept. Also, our study evaluated a combination of both validated single joint patient reported and physician assessed outcomes, combined to a composite single joint assessment score, as well as general disease activity parameters.

The need for validated single joint assessments has been recognized long ago, and in 2004 an OMERACT special interest group was established to assess and further develop single joint outcome measures. However, until now this has proven to be a difficult endeavour [33]. Single joint patient reported outcomes

have been shown to demonstrate construct validity and responsiveness in patients with inflammatory arthritis, while physician clinical assessments showed very high interobserver agreement, yet a relative lack of sensitivity in detecting changes over time [34]. Despite the lack of a gold standard in establishing effectiveness of a single joint intervention, the relevance of both patient reported outcomes as well as physical assessment has been acknowledged. The CCI used in this study combines both aspects. Of importance, the CCI did not include acute phase reactants, thereby excluding the possible influence of persistent arthritis in other joints in patients with oligoarthritis [1]. Furthermore, clinical efficacy as measured by the CCI has been shown to be associated with ultrasonographic changes (decrease in synovial thickness) [35]. This study can provide a contribution to the validation of the CCI and supports the use of the CCI as a single joint assessment in future studies.

The safety data obtained from this study are in line with previous safety data on subcutaneously administered etanercept. Previously reported adverse events after intra-articular etanercept treatment, including a subcutaneous injection site reaction [36], were not observed during this trial. Common side effects seen with longer-term systemic administration of etanercept (25 mg twice weekly of 50 mg once weekly), including (upper respiratory tract) infections, were not observed.

Fewer patients were included in the trial than originally planned, which is a limitation. Still, the effect was markedly stronger than anticipated and the difference between active treatment and placebo was highly statistically significant ($P<0.001$). In the planned analysis, data of RA and PsA patients were combined to achieve sufficient statistical power. A formal subgroup analysis had not been planned based on the assumption that the response to intra-articular etanercept would be the same for both groups. It should be noted however that the trends were similar for RA and PsA (data not shown). For missing data, a sensitivity analysis with last observation carried forward (LOCF) imputation was performed, which gave similar results. The slow recruitment rates reflect improved disease control in The Netherlands where treatment can be initiated during an early stage of the disease in early arthritis clinics and where patients are treated according to the treat to target principle [37]. Another limitation was that we used standard intra-articular injection techniques as used in routine clinical practice rather than ultra-sound guided injections, which could have resulted in peri-articular injection in some cases.

We also performed pharmacokinetic analysis. Previous work has shown that a single dose of 25 mg etanercept subcutaneously (s.c.) in healthy volunteers has a half-life of 2.8 days, with a maximum concentration of 1.46 ± 0.72 mg/L (mean \pm SD) and range 0.37–3.47 reached after 2.1 days (51 hours) and a concentration of approximately 0.6 mg/L after 1 week [38]. The maximum concentration measured in RA patients after a single dose is 1.10 mg/L ± 0.6 , which is reached after an average of 69 hours. The average steady state concentration in RA patients with 25 mg s.c. biweekly is 1.88 ± 0.8 mg/L, reached after 62 hours [39]. In our study, serum etanercept levels were 1.39 ± 0.46 mg/L 1 week after intra-articular injection. Presumably, higher serum levels of etanercept were reached at an earlier time point possibly due to increased resorption of the drug from the inflamed and highly vascularised joint. Alternatively, higher etanercept levels remained locally and resorption was delayed, reaching its peak after approximately 1 week. Up to now, anti-etanercept antibodies have not been detected in several clinical studies. Possible explanations could be the less immunogenic structure of etanercept or drug interference, leading to an underestimation of anti-etanercept production [29,30].

This study was not designed to evaluate intra-articular administration of etanercept to treat persistent monoarthritis as a new

approach for clinical practice, and it appears unlikely that chronic intra-articular treatment with a biologic would be a cost-effective therapeutic strategy. However, this study does support the rationale for research on new modalities aimed at TNF inhibition in the synovial compartment of patients with persistent monoarthritis or oligoarthritis. One modality would be gene therapy, if sufficient expression levels can be reached and patients are selected who have TNF-dependent disease. Proof of concept has already been demonstrated in pre-clinical studies: gene therapy with AAV expressing TNF receptor has been shown to be a successful approach in animal models of arthritis [2]. Furthermore, expression could be regulated by an inflammation inducible promoter, resulting in transient and therapeutically relevant expression when needed [4]. More recently, it was shown that rAAV5-mediated RNAi-based gene therapy targeting TNF effectively blocked experimental arthritis [40].

In conclusion, this study shows that intra-articular administration of a single dose of etanercept is feasible and safe and results in transient improvement of disease activity in the target joint. This work provides the rationale for novel approaches that could result in long-term inhibition of TNF at the site of inflammation, for example by local, prolonged and regulated overexpression of an anti-TNF antibody, a soluble TNF receptor or short hairpin small interfering RNA (shRNA) against TNF.

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Appendix A. Supplementary data

Supplementary data (Table S1) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jbspin.2015.03.002>.

Disclosure of interest

C.J.A. is affiliated with ArthroGen BV, a company developing adeno-associated virus based gene therapy for rheumatoid arthritis. This study was sponsored by ArthroGen.

M.J.V. is affiliated with ArthroGen BV.

P.P.T. is affiliated with ArthroGen BV. He became an employee and stakeholder of GlaxoSmithKline (GSK) after completion of this study; GSK is not involved in this work.

R.B.L. has received consultancy fees from Abbott, Amgen, Centocor, BMS, Johnson&Johnson, Merck, Pfizer and Roche.

D.G. and K.V. declare that they have no conflicts of interest concerning this article.

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