Joint Bone Spine 82 (2015) 338–344

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

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

Caroline Aalbers[a,b,*], Danielle Gerlag[a], Koen Vos[a,c], Margriet Vervoordeldonk[b], Robert Landewé[a,d], Paul Peter Tak[b,e,f,g]

[a] *Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*
[b] *Arthrogen B.V., Meibergdreef 45, 1105 BA Amsterdam, The Netherlands*
[c] *Department of rheumatology, Flevoziekenhuis, Hospitaalweg 1, 1315 RA Almere, The Netherlands*
[d] *Department of Rheumatology, Atrium Medical Center, Postbus 4446, 6401 CX Heerlen, The Netherlands*
[e] *GlaxoSmithKline, Stevenage, UK*
[f] *University of Cambridge, Cambridge, UK*
[g] *Ghent University, Ghent, Belgium*

ARTICLE INFO

Article history:
Accepted 3 March 2015
Available online 15 July 2015

Keywords:
Intra-articular therapy
Rheumatoid arthritis
Psoriatic arthritis
Etanercept
TNF blockade
Gene therapy

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.

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; UMCG, University Medical Center Groningen; VAS, Visual analogue scale.

* Corresponding author. Arthrogen B.V., Meibergdreef 45, 1105 BA Amsterdam, The Netherlands.
E-mail address: c.j.aalbers@amc.uva.nl (C. Aalbers).

http://dx.doi.org/10.1016/j.jbspin.2015.03.002
1297-319X/

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 (MPC) 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 of 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