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ScienceDirect
Joint Bone Spine 73 (2006) 714–717
JOINT BONE SPINE
http://france.elsevier.com/direct/BONSOI/

Original article

Safety of intra-articular injection of etanercept in small-joint arthritis: an uncontrolled, pilot-study with independent imaging assessment

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Received 30 January 2006; accepted 30 May 2006
Available online 20 September 2006

Abstract

This study was conducted to test the safety of intra-articular tumor necrosis factor alpha (TNF-α) antagonists in small joints with arthritis. A dose of 2–8 mg etanercept was given intra-articularly guided by ultrasonography (US) in 26 patients with a flare of arthritis in a particular joint (16 wrists, two elbows, two ankles, six finger joints). Primary end points were imaging analyses by independent investigators: US-Doppler measurements were performed in all patients before and after the injection and MRI before and after were obtained in nine patients. The only adverse event was a case of swelling of the hand lasting 2 days after a wrist injection. Two patients had a supplementary glucocorticoid injection and were excluded from efficacy analysis after 4 days and 3 weeks, respectively. VAS for pain decreased after 1 week in 23 of 25 patients (median 0.62), and after 1 month in 14 of 24 patients (median 0.60). No significant changes were seen in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). On MRI, all nine cases tested had a reduction in synovial thickness ($P = 0.008$) and US Doppler signals diminished after treatment (resistance index (RI) $P = 0.02$, pixels $P = 0.09$). In conclusion, intra-articular injection of etanercept gave no noticeable adverse events.

Keywords: Intra-articular; etanercept; Safety; MRI; Ultrasound Doppler

1. Introduction

Tumor necrosis factor alpha (TNF-α) is found in the synovial tissue and cartilage–pannus junctions in patients with rheumatoid arthritis (RA) [1] and has been associated with levels of pain [2]. In arthritis, systemic anti-TNF-α therapy is seemingly as effective as glucocorticoids and might also be used for injections into joint in parallel to the widespread use of intra-articular injections of corticosteroids [3]. Circumstances warranting the more expensive biological medication would include former adverse events to the corticosteroids or a reduction in steroidal load to the individual patient. The few studies published on anti-TNF medications given intra-articularly have varying results [4–8]. Some of this variation may be due to extra-articular placement of the injections [9], which can be avoided by giving the injection guided by ultrasound [10].

The aim of this study was to test the safety of TNF-α antagonists by etanercept (Enbrel®) administered intra-articularly in patients with a flare of RA in single joints. The treatment was restricted to small joints in which a limited dose was expected to have a local impact on the arthritis.

2. Methods

2.1. Patients

Patients aged over 18 years with RA were recruited from the outpatient clinic at the Department of Rheumatology, Frederiksberg Hospital, Denmark. Patients were eligible irrespective of DMARD treatment; however, none received anti-TNF-α therapy. Intra-articular therapy was indicated because of flare

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doi:10.1016/j.jbspin.2006.05.004

of arthritis activity in single joint(s). Patients were excluded if they had received intra-articular injection of steroids in the joint in the preceding 3 months, or had an increased risk of infection or bleeding after injection.

Twenty-six participants (mean age 58.6 years, range 25–82 years, IgM rheumafactor positive $N = 16$) were injected with etanercept: 16 wrists, two elbows, two ankles, and six finger or toe joints.

2.2. Design

The first 12 participants were randomized to three different doses of etanercept (2, 4, or 8 mg). As no adverse events occurred, the remaining 14 participants were given 8 mg. All participants were followed both clinically and by ultrasonography (US) measurements of the target joint; images were stored and evaluated by investigators blinded to all clinical information.

In cases of non-response, participants in the study were offered supplementary injections with steroids, preferably first after the 1-month follow-up. A further injection of etanercept in another joint was also offered after a minimum of 1 month.

2.3. Injection technique

Before injection, the skin and subcutaneous tissue above the joint cavity were anaesthetized with 1 ml of 1% lidocaine and the joint cavity was aspirated. US was used to determine the placement of aspiration and injection into the joint cavity.

2.4. Safety

After injection of etanercept, the first 12 participants were examined both clinically and with ultrasound daily for 3 days. All participants were seen weekly during the first month after receiving etanercept and again after the second and third month. Participants were questioned about adverse events at all visits.

2.5. Pain and blood tests

Self-reported pain was registered and blood samples were obtained for analysis of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

2.6. Joint score

Participants were tested by an independent clinician, who evaluated swelling and tenderness of the joint treated on a scale 0–3 [11] and filled in a joint score.

2.7. MRI imaging

MRI was performed using a 1.5 T MR-system (Gyroscan ACS-NT, Philips, Best, The Netherlands) as previously described in detail [12]. Coronal T1-weighted fast-field-echo (FFE) images were obtained before and after Gadodiamid (Gd, Nycomed Amersham A/S). The thickness of the enhanced synovial membrane was outlined on the slice (post Gd images).

2.8. Ultrasound

A Sequoia® (Acuson, Mountain View, CA, USA) was used with an 8–13 MHz linear array transducer and color Doppler and spectral Doppler applied. A computerized estimate of the relative pixel area with perfusion in the synovial tissue was calculated at each examination along with measurements of resistance index (RI) for synovial blood flow measured by spectral Doppler technique [13,14].

2.9. Ethical considerations

The local Ethical Committee and the Danish Medicines Agency approved the study (KF 02-003/01) and all patients signed an informed consent form.

2.10. Statistical analysis

No significant difference between different joints or doses was found and for the final calculations all data were pooled because of the limited material. Non-parametric statistical analyses were chosen: the Wilcoxon matched-pairs signed rank test for the comparison of baseline with 1-month data of imaging. Level of significance was chosen at 0.05.

3. Results

3.1. Safety

Only one participant reported an adverse event during the study. This participant had received etanercept 4 mg in the wrist and developed a slight, diffuse swelling on the back of the hand the day after the aspiration/injection. No redness or induration of the tissue was present and the swelling subsided 2 days later. This participant responded well to therapy and had no other noticeable effects. The remaining participants had no adverse events, apart from temporary local soreness. No symptom flare, local skin reaction, or signs of infection or any other reactions at the joints or their surroundings were seen on the clinical or ultrasound examinations. Six participants with a very good response received a second injection of etanercept in another joint a minimum of 1 month after the first injection. These joints responded equally well and no adverse events were seen.

3.2. Clinical evaluation

Two of the initial participants were not included all through this analysis due to an intra-articular steroid injection (one within the first week, the other after 3 weeks) before the 1-