Efficacy of Etanercept in the Treatment of Acute and Severe Sciatica. A Pilot Study.

Stephane Genevay, Sibylle Stingelin, and Cem Gabay

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Efficacy of Etanercept in the Treatment of Acute, Severe Sciatica
A pilot study

S. Genevay, S. Stingelin, C. Gabay

Division of Rheumatology, University Hospital of Geneva,
26 avenue. Beau-Séjour, 1211 Geneva 14, Switzerland

Corresponding author: Dr S. Genevay
Tel: 0041 22 382 26 73
Fax: 0041 22 382 35 35
Email: stephane.genevay@hcuge.ch

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ABSTRACT

Objectives: To explore the efficacy of a TNF-α inhibitor (etanercept, Enbrel®) in patients with severe sciatica.

Methods: We conducted a pilot study of etanercept in patients hospitalised for acute severe sciatica. Ten consecutive patients received 3 subcutaneous injections of etanercept (25 mg every 3 days) in addition to standard analgesia. Response was evaluated at day 10 (T1) and week 6 (T2) using a visual analogue scale for leg pain (VASL) and for low back pain (VASB), and two validated functional scores: the Oswestry disability index (ODI) and the Roland Morris disability questionnaire (RMDQ). The control group consisted of 10 patients with severe sciatica, who took part in an observational study on IV methylprednisolone.

Results: In the etanercept group all variables were improved: VASB from 36 to 7; VASL from 74 to 12; RMDQ from 17.8 to 5.8 and ODI from 75.4 to 17.3, all p < 0.001. Compared to the methylprednisolone group, pain (VASL and VASB: p<0.001) and ODI (p<0.05) were significantly better in the etanercept group.

Conclusion: In this open, historical group controlled study, patients with severe sciatica had a sustained improvement after a short treatment with etanercept that was superior to standard care plus a short course of methylprednisolone. These results suggest inhibition of TNF-α is beneficial in the treatment of sciatica and support a pathological role for TNF-α in the pathogenesis of sciatica. These results need to be confirmed by a randomised controlled trial.
Low back pain is a common clinical problem with enormous medical, social and financial implications. A subgroup of these patients may present with pain radiating into the lower limb. This is often called sciatica, when clinical signs of nerve root irritation are present (i.e. positive straight leg raising test) and the pain follows a radicular pattern. At times corresponding neurological deficit can be found. Mixter and Barr where the first to describe the presence of an herniated disc in the vicinity of the involved nerve root (1). Standard pharmacological therapy consists of simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), the role of steroids being more controversial. With this treatment up to 20% of patients may require surgical intervention and 10 to 15% will develop chronic pain and handicap leading to significant direct and indirect costs (2, 3).

Lack of concordance between clinical and surgical findings has been documented since the forties. More recently studies using MRI and CT scanning have revealed that up to 20% of asymptomatic individuals have radiological evidence of intravertebral disc protrusion or herniation (4). More recently, repetition of earlier functional studies confirm that pinching of a normal lumbar nerve root results in paraesthesia rather than pain (5). These observations led to the conclusion that a purely mechanical process is insufficient to explain sciatica.

In the nineties several animal studies suggested that sciatica could be reproduced by applying the nucleus pulposus (NP) (the core of the vertebral disc) to a nerve root, in the absence of nerve root compression (6). This contact was sufficient to produce not only allostomy but also electrical and histological changes of the nerve compatible with acute sciatica (7). In parallel, several authors have reported the presence of inflammatory mediators in human herniated disc tissue (8-11). Among these mediators, tumor necrosis factor alpha (TNF-α) has attracted much attention for, in addition to its detection in herniated discs and its key role in inflammatory cascade, it has a neurotoxic effect when injected into the endoneur (12). The discovery that the application of TNF-α alone, isolated from NP tissue, to nerve roots could reproduce the clinical and histological effects induced by the application of whole NP strongly supports a central role for TNF-α in animal models of sciatica (13). The positive effect of TNF-α inhibitors (infliximab, etanercept) in the treatment of animal models of sciatica (14, 15) has reinforced this theory and opens the way for a new approach to the treatment of this disease leading several editorialists to call for trials of anti-TNF-α agents in human sciatica.

This pilot study was undertaken to test the hypothesis that TNF-α inhibitors could be a potential alternative in the treatment of acute and severe sciatica and that TNF-α may participate in the pathogenesis of human sciatica.

PATIENTS AND METHODS

Study design

This is an open observational cohort study using historical controls.

Patients

After approval by the local ethics committee, 10 consecutive patients hospitalised for acute sciatica were recruited. Patients had to be over 18 years of age, capable of giving full informed consent and have leg pain for less than 8 weeks. Sciatica was defined as unilateral lower limb pain following a dermatoma (L3, L4, L5 or S1) with signs of radicular irritation (reproduction of leg pain with the straight leg raising test (SLR) or femoral nerve stretch test...
in the case of L3 or L4 involvement or with the Valsalva manoeuvre). Severity was defined by a VASL score of greater than 50 (on a scale from 0 to 100) and the need for hospitalisation (a decision that was taken by the admitting physician, not evolved in the study). Exclusion criteria were the need for surgical intervention (patient presenting with progressive or major muscle weakness or with cauda equina syndrome), the presence of concomitant infection, past history of tuberculosis or cancer, signs of latent tuberculosis on chest X-ray, autoimmune disease except rheumatoid arthritis (RA), and pregnancy or lack of efficient contraception.

**Comparison group**

All 10 patients recruited to an earlier study of IV methylprednisolone in acute severe sciatica were used as controls for the present observations. These were 10 consecutive patients hospitalised for acute severe sciatica, fulfilling the same definition as used in the current study. Exclusion criteria were the same as for the current trial, except that evidence of latent pulmonary tuberculosis was not sought.

**Treatments**

The etanercept group was treated with subcutaneous etanercept 25 mg at day 1, 4, and 7. The historical group received IV methylprednisolone 250 mg at day 1, 4 and 7. Both groups received simple analgesics (including opioids if needed), non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants and physical therapy. Steroids were not administered, apart from the study treatment of methylprednisolone. For both groups, the attending physician who was not involved in the study decided hospital discharge. After hospital discharge all patients returned to their family physician who was entirely responsible for future clinical decisions (i.e. surgery). There was no contact with the study team until the final evaluation (T2).

**Evaluation**

For both groups, a thoughtful clinical examination was performed on admission, and at regular interval during hospitalisation. Back and leg pain were recorded by using the VAS every day for the first 10 days and at week 6. Day 10 (T1) and week 6 (T2) were defined as the two time points of evaluation. Functional impairment was evaluated with the Roland Morris disability questionnaire (RMDQ) (16), modified to include the evaluation of leg pain, and Oswestry Disability Index (ODI) (17) at inclusion (T0), T1 and T2. Primary outcome measures was VAS for leg pain (VASL) at T2. Other endpoints were back pain (VASB), raw functional scores (i.e. RMDQ and ODI) at T1 and T2 and percentage of improvement for each of the variables (VASL, VASB, ODI, RMDQ) at T2. Patients achieving either VASL < 30 or ODI < 20 at T2 were defined as having good evolution (12).

**Statistical analyses**

Statistical analyses were performed using SPSS version 11.0 (SPSS corporation, Chicago, IL). Fisher’s exact test was used for dichotomous variables and Mann-Whitney for continuous variables. Statistical significance was defined as a p value <0.05. In order to take into account all patients (i.e. including patients that may have had surgery), analyses were also performed using the percentage of improvement of each variable. Patients who underwent surgery were considered as failure (no improvement = 0%) and LOCF procedure (last observation carried forward) was used for missing data. As this was a pilot study no sample size calculation could be performed.
RESULTS

Patients

Twelve patients hospitalised with acute sciatica between May 2002 and June 2003 fulfilled the inclusion criteria and where offered etanercept therapy. Two refused to participate for personal reasons. The methylprednisolone group included 10 consecutive patients hospitalised for acute, severe sciatica between July 2001 and April 2002. There were no demographic differences between the 2 groups (Table 1).

Table 1 demographic data

<table>
<thead>
<tr>
<th></th>
<th>Etanercept (N=10)</th>
<th>Methylprednisolone (N=10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (SD)</td>
<td>45.0 (11.9)</td>
<td>49.4 (14.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>6/4</td>
<td>4/6</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of sciatica (weeks) (SD)</td>
<td>2.7 (1.8)</td>
<td>3.7 (5.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Disc level:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3 – L4</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>L4 – L5</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>L5 – S1</td>
<td>2°</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>6</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Reflex deficit</td>
<td>5</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Past history of back pain</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Past history of leg pain</td>
<td>3</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

SD: standard deviation

° 1 patient with S1 radiculopathy refused imagery (see text)

All twenty patients had a positive SLR (or positive femoral nerve stretch test when appropriate) and at least one objective sign of nerve root compression (muscle weakness, sensitive disturbances or decreased tendon reflex). There was a good concordance between clinical findings and radiological evidences of disc hernia (either CT Scan or MRI) for the nineteen available exams. One patient in the etanercept group had clinical sign of S1 irritation and refused to have an MRI because she experienced a major clinical improvement before the scheduled appointment. One patient in the methylprednisolone group suffered from leg pain for 16 weeks. Patients in both groups suffered form severe leg pain and a high degree of functional impairment as indicated by the VASL, ODI and RMDQ scores, without any significant difference between the two groups (Table 2).
Table 2 Evolution of pain and functional scores

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etanercept Methyl-prednisolone</td>
<td>Etanercept Methyl-prednisolone</td>
<td>Etanercept Methyl-prednisolone</td>
</tr>
<tr>
<td></td>
<td>(N=10)</td>
<td>(N=10)</td>
<td>(N=10)</td>
</tr>
<tr>
<td>VASL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-100</td>
<td>74.4 (12.9)</td>
<td>20.2 (16.6)</td>
<td>12.4 (13.2)</td>
</tr>
<tr>
<td>(SD)</td>
<td>75.1 (14.2)</td>
<td>25.5 (15.5)</td>
<td>52.9 (25.1)</td>
</tr>
<tr>
<td>VASB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-100</td>
<td>36.4 (39.8)</td>
<td>8.4 (11.9)</td>
<td>7.4 (10.8)</td>
</tr>
<tr>
<td>(SD)</td>
<td>39.8 (29.2)</td>
<td>19.9 (18.4)</td>
<td>47.6 (28.5)</td>
</tr>
<tr>
<td>ODI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-100</td>
<td>75.4 (19.4)</td>
<td>33.9 (25.4)</td>
<td>17.3 (13.1)</td>
</tr>
<tr>
<td>(SD)</td>
<td>62.4 (11.7)</td>
<td>31.6 (15.3)</td>
<td>33.4 (13.0)</td>
</tr>
<tr>
<td>RMDQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24</td>
<td>17.8 (3.3)</td>
<td>9.8 (7.8)</td>
<td>5.8 (5.5)</td>
</tr>
<tr>
<td>(SD)</td>
<td>15.5 (2.9)</td>
<td>10.4 (4.6)</td>
<td>11.1 (4.6)</td>
</tr>
</tbody>
</table>

T0: inclusion. T1: day 10. T2: week 6. SD: standard deviation. VAS: visual analogue scale; VASL: VAS leg pain; VASB: VAS back pain; ODI: Oswestry Disability Index; RMDQ: Roland Morris Disease Questionnaire.

**Etanercept treatment group**

All ten patients showed clinical improvement at T1 that was statistically significant for VASL, ODI and RMDQ. Nine of them continued to improve between to T2 (table 2). At T2, VASL decreased from 74.4 (SD 12.9) to 12.4 (SD 13.2), RMDQ from 17.8 (SD 3.3) to 5.8 (SD 5.5) and ODI from 75.4 (SD 19.4) to 17.3 (SD 13.1), all p<0.001. VASB decreased from 36.4 (SD 39.8) to 7.3(SD 10.8), a difference that was not statistically significant due to the large standard deviation. One patient had a relapse of leg pain three weeks after inclusion and required surgical intervention. He was considered as a treatment failure.

**Historical group**

T2 evaluation was slightly delayed compared with the group etanercept: (9.4 versus 6.2 weeks, p<0.05)) as a result of the observational design of this study and one patient refused to participate.

In this group, all variables (VASL, VASB, ODI RMDQ) were better at T1 compared to inclusion (T0) (Table 2). These differences were statistically significant for VASL, ODI, and RMDQ (all p<0.01) but not for VASB. Between T1 and T2 most of the patients suffered from increased pain or functional impairment, but at T2 VASL, ODI and RMDQ were still statistically better than at T0 (p<0.05) One patient underwent a surgical procedure a week after enrolment because of persistent severe leg pain.
Comparison between etanercept and methylprednisolone group

At T1, there was no difference between the two groups. But at T2 both pain (VASL and VASB) and functional scores (ODI) were significantly improved in the etanercept group compare to the methylprednisolone group (table 2). The difference in RMDQ score at T2 between the 2 groups was greater than 5 points in favour of the etanercept group. This difference is considered clinically meaningful but did not reach statistical significance.

Data were also analysed regarding the percentage of improvement, a mode of analysis that can encompass all the 20 patients and where those who underwent surgery were considered as having 0% improvement. At T2 leg pain had improved by a mean of 75% in the etanercept group versus 17.6% in the methylprednisolone group (p<0.01). The results of both ODI (67.2% vs. 40.3%) and RMDQ (63.4% vs. 40.3%) were also significantly better in the etanercept group than in steroid group (p<0.05) (Figure 1).

Eight on ten patients in the etanercept group had VASL<30 versus only 2/10 in the steroid group (p<0.05), and 5 achieve an ODI score inferior to 20 in the etanercept group versus 2 in the methylprednisolone group. Thus, 90% of the etanercept group comply with the definition of a good clinical result versus only 30% in the methylprednisolone group (p<0.05). The mean hospitalisation time did not differ between the 2 groups (15 days).

DISCUSSION

Our results show that patients with acute, severe sciatica treated with a short course of TNF-α inhibitor exhibit major clinical improvement at week 6, as assessed by a measure of leg pain and functional scores. This supports the hypothesis that TNF-α could play a central role in human acute sciatica.

Both etanercept and steroid treated patients improved at day 10. Patients in the etanercept group exhibited further improvement after 6 weeks. However this was not the case for patients treated with methylprednisolone, some of whom deteriorated by the time of the last evaluation. This difference could be related to a rebound effect in the corticosteroid group or to a possible direct effect of TNF-α on peripheral nerves besides its role in the inflammatory process. Consistent with this hypothesis, TNF-α has been shown to induce pathogenic changes in peripheral nerves similar to those usually seen in neuropathic pain (13). Thus an anti-TNF-α treatment may be more effective in treating radiculopathy. IV methylprednisolone has been used in our service for more than 20 years, as a result of the hypothesis that inflammation plays a role in sciatica. Although we have empirical evidences of its effectiveness, no controlled trials have ever been published. Zufferey et.al. have recently performed a placebo controlled study with IV methylprednisolone in which only short term effect could be demonstrated (18). This would suggest that our controlled group is close to a placebo group.

Our results are supported by a recent study reporting the efficacy of infliximab in acute sciatica (19). The main difference between the 2 studies is the more rapid improvement in patients treated with infliximab (50% improvement in pain score within one hour). This difference could be due to variations in pharmacokinetics or to the route of administration (intravenous versus subcutaneous).

They were no side effects reported by the ten patients treated in this study. Feared side effects with TNF-α inhibitors are systemic allergic reaction and increased risk of infection, mainly
tuberculosis. As these risks appear to be lower with etanercept than with infliximab (20) we tended to favour the use of the former for pilot studies on sciatica. It should also be remembered that sciatica is a potentially relapsing condition. Data on the use of infliximab in Crohn’s disease showed that in the absence of concomitant use of immunosuppressive drugs, retreating patients after a prolonged time interval increases the risk of infusion reaction and decreases the efficacy of the drug (21).

Although this study supports a potential role for TNF-α inhibitors in the treatment of sciatica, these results should not be generalised. First, the studied population was a highly selected group of patients suffering from severe sciatica requiring hospitalisation. The benefit of this treatment may not be as significant when treating less severe symptoms, which generally have a higher rate of spontaneous favourable evolution. Second, only randomised control trials will provide a definitive answer regarding the role of TNF-α in the pathogenesis of sciatica and the potential of TNF-α inhibitors for its treatment.

Cost of such treatments is a major concern, especially when considering the use of biological agents in a common condition. However the cost of TNF-α inhibitors have to be weighted against direct and indirect costs (length of hospital stay, days lost from employment, potential cost of surgery). The reduction of hospital stay or earlier return to work could justify the cost of this treatment. Further studies should also explore the cost-effectiveness of TNF-α inhibitors in severe sciatica.

ACKNOWLEDGMENT

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REFERENCES

Figure 1 This figure shows the percentage of improvement between T0 and T2. Box plots length represent interquartile range; means and extremes are also given. 0% = no improvement, 100% total recovery. VASL: visual analogue scale for leg pain; ODI: Oswestry Disability Index; RMDQ: Rolland Morris Disease Questionnaire.