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ORIGINAL ARTICLE

Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients

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SUMMARY

Objective: Documentation of the clinical results obtained utilizing perispinal etanercept off-label for treatment-refractory back and neck pain in a clinical practice setting.

Research design and methods: The medical charts of all patients who were treated with etanercept for back or neck pain at a single private medical clinic in 2003 were reviewed retrospectively. Patients were treated if they had disc-related pain which was chronic, treatment-refractory, present every day for at least 8 h, and of moderate or severe intensity. Patients with active infection, demyelinating disease, uncontrolled diabetes, lymphoma or immunosuppression were excluded from treatment with etanercept. Etanercept 25 mg was administered by subcutaneous injection directly overlying the spine. Visual Analogue Scales (VAS, 0–10 cm) for intensity of pain, sensory disturbance, and weakness prior to and 20 min, 1 day, 1 week, 2 weeks, and 1 month after treatment were completed. Inclusion criteria for analysis required baseline and treatment VAS data.

Main outcome measures: Before and after treatment VAS comparisons for intensity of pain, sensory disturbance, and weakness.

Results: 143 charts out of 204 met the inclusion VAS criteria. The 143 patients had a mean age of 55.8 ± 14, duration of pain of 9.8 ± 11 years, and an initial Oswestry Disability Index of 42.8 ± 18, with 83% having back pain, 61% sciatica, and 33% neck pain. 30% had previous spinal surgery, and 69% had previously received epidural steroid injections (mean 3.0 ± 3). The patients received a mean of 2.3 ± 0.7 doses of perispinal etanercept separated by a mean interval of 13.6 ± 16.3 days. The mean VAS intensity of pain, sensory disturbance, and weakness were significantly reduced after perispinal etanercept at 20 min, 1 day, 1 week, 2 weeks, and 1 month with a $p < 0.0001$ at each time interval for the first dose in this patient population.

Conclusions: Perispinal etanercept is a new treatment modality which can lead to significant clinical improvement in selected patients with chronic, treatment-refractory disc-related pain. Generalizability of the present study results is limited by the open-label, uncontrolled methodology employed. Based on this and other accumulating recent studies, etanercept may be useful for both acute and chronic disc-related pain. Further study of this new treatment modality utilizing double-blind placebo controlled methodology is indicated.

Note: This treatment method is protected by multiple patents awarded to Edward Tobinick MD, including U.S. patents 6 015 557; 6 177 077; 6 419 944; 6 537 549 and Australian patent 758 523.

Introduction

Intervertebral disc disease has long been known to be a cause of back and neck pain, and related lumbar and cervical radiculopathy[1]. Despite years of research and many existing therapeutic approaches, large numbers of patients with chronic intervertebral disc-related pain are unable to find a satisfactory solution[2–4]. Several decades ago it was first surmised that chemical irritation of the nerve root could be involved in the pathogenesis of pain after disc protrusion, which might help explain the failure of surgical decompression to provide pain relief for some patients[5]. Experimental evidence suggested that the source of this chemical irritation was the core of the ruptured disc, the nucleus pulposus, which contained a substance which was highly inflammatory to the nerve root[6–8]. Subsequently the inflammatory substance present in the nucleus pulposus was specifically identified as tumor necrosis factor-alpha (TNF), a pro-inflammatory cytokine[9]. Experimental models provided evidence that TNF was the key mediator of the pain and neuronal dysfunction which is caused by this disc-related inflammation, and that etanercept, an anti-TNF fusion protein, and infliximab, an anti-TNF monoclonal antibody, could interrupt this process in animals[10–12].

The authors first reported in 2003 the successful use of etanercept for the treatment of disc-related pain in humans[13,14]. Rapid and sustained reduction in pain and disability following perispinal administration of etanercept was observed. Delivery of etanercept by perispinal injection was hypothesized to enhance therapeutic efficacy through several theoretical mechanisms: achievement of an increased local concentration of etanercept at the site of TNF-mediated pathology; bypass of both the systemic and hepatic circulation, at least initially, thereby delivering unmetabolized etanercept directly to the nerve root; establishment of a depot of etanercept in the tissue surrounding the nerve root, potentially prolonging the local therapeutic effect; and delivery of an increased concentration of etanercept to the endoneurial space via a direct vascular route across the dura[13–17]. Animal data subsequently provided evidence that an increased local concentration of etanercept could theoretically enhance its action in reducing neuropathic pain, a mechanism which provides a potential basis for the increased efficacy of perispinal etanercept[18]. It is theoretically attractive to treat an anatomically localized process (disc herniation) with an anatomically localized injection (perispinal etanercept). This is in contrast to the use of etanercept for a systemic disease, such as rheumatoid arthritis, which requires systemic delivery of etanercept because of the diffuse involvement of multiple joints which are widely anatomically separated.

Several published articles have now documented the effective treatment of patients with disc-related pain utilizing biologic TNF inhibitors, but all of these studies have small sample sizes[13,14,19,20]. This is the first report of the use of etanercept, delivered by perispinal administration, for a large group of patients with treatment-refractory chronic back and/or neck disc-related pain.

Patients and methods

The medical charts of all patients who were treated with etanercept for back or neck pain at a single private medical clinic in 2003 were reviewed retrospectively. Patients were treated if they had disc-related pain which was chronic, treatment-refractory, present every day for at least 8 h, and of moderate or severe intensity. Patients with active infection, demyelinating disease, uncontrolled diabetes, lymphoma or immunosuppression were excluded from treatment with etanercept.

Etanercept (Enbrel, Immunex Corporation, Thousand Oaks, CA) was given by perispinal administration as follows: etanercept 25 mg was delivered to the soft tissue in anatomic proximity to the spine by subcutaneous administration utilizing a 23 gauge 1.5 cm needle directly overlying the midline of the back or neck, in accordance with the main area of symptomatology reported by the patient. The rationale and proposed mechanism of action of perispinal delivery of etanercept has been previously discussed[13–16].

To measure clinical improvement, patients completed Visual Analogue Scales (VAS, 0–10 cm) for intensity of pain, sensory disturbance, and weakness prior to treatment and were given VAS forms to take home and asked to complete them after 20 min, 1 day, 1 week, 2 weeks, and 1 month. If a patient returned for a second dose at an unscheduled time, the same VAS measurements were requested.

Each patient also completed an Oswestry Disability Questionnaire immediately prior to their first dose of etanercept[21]. The Oswestry Disability Index (ODI) was calculated as described by the published algorithm[22]. Inclusion criteria for analysis required baseline and treatment VAS data and excluded patients who had participated in previous studies treating with etanercept. The same physician (S.D.) treated all of the entered patients.

Study Design

Medical charts for all patients who met the inclusion criteria were analyzed. The charts contained VAS results, as well as the results of MRI and other imaging studies and other clinical data, including medication used in

Table 1. *Patient characteristics in means ± standard deviations (SD) (unless otherwise noted) for n = 143 completing visual analog scales before and after perispinal etanercept treatment*

Patient characteristic	*N*	Mean ± SD	Range
Age (years)	143	55.8 ± 14.3	16, 87
Female (*n*,%)	143	69 (48.3%)	–
Pain duration prior to treatment (years)	140	9.8 ± 11.3	0.13, 60
Oswestry Disability Index (0–100)	143	42.8 ± 17.9	0, 95.6
Previous treatment			–
Spinal surgery (*n*,%)	136	41 (30.1%)	
Epidural steroids (*n*,%)	137	95 (69.3%)	
Number of epidural steroid doses	92	3.0 ± 3.0	
Pain distribution	141		–
Back pain (*n*,%)		117 (83.0%)	
Sciatica (*n*,%)		86 (61.0%)	
Neck pain (*n*,%)		46 (32.6%)	
Signs and symptoms suggestive of radiculopathy	141		–
Lumbar radiculopathy (*n*,%)		86 (61.0%)	
Cervical radiculopathy (*n*,%)		28 (19.9%)	
MRI results	141		–
Disc bulge, protrusion, extrusion, herniation (*n*,%)		94 (66.7%)	
Annular tear (*n*,%)		8 (5.7%)	
Degenerative disc disease (*n*,%)		72 (51.1%)	
Central spinal stenosis and DDD (*n*,%)		19 (13.5%)	
Spondylolisthesis and DDD (*n*,%)		18 (12.8%)	
Other diagnostic studies	141		–
EMGs showing radiculopathy (*n*,%)		4 (2.8%)	
Discograms showing annular tears (*n*,%)		2 (1.4%)	
Doses of perispinal etanercept	143	2.3 ± 0.7	1, 6
Number of days between doses	136	13.6 ± 16.3	1.5, 129

addition to etanercept. The main outcome measures were before and after treatment VAS comparisons for intensity of pain, sensory disturbance, and weakness.

Prior to treatment all patients were screened for medical contraindications to treatment with etanercept. Medical history, physical examination, and review of previous medical records, including imaging studies were performed. All patients were informed of the treatment alternatives, possible risks and benefits of treatment, and that this use of etanercept was off-label[23]. Laboratory testing was not routinely performed prior to treatment, as per current consensus recommendations for the use of etanercept[24]. All patients gave written informed consent for treatment and the same physician followed them throughout their treatment course. Adverse events were assessed from the patients' medical charts and the clinical experience of the treating physician.

Statistical Analyses

Pain intensity, sensory disturbance, and weakness VAS scores were compared between time points before and after treatment by paired, two-sided *t*-tests for continuous parametric data. For continuous nonparametric data, Wilcoxon matched-pair signed-rank tests were used to test that the median change of VAS scores is 0. Categorical variables were tested using the chi-squared test of association. When appropriate, 95% confidence intervals (CI) about the mean were calculated. *p*-values < 0.05 were considered to be statistically significant, and significance levels were adjusted for multiple testing in all comparisons. For all statistical analyses, statistical software SAS Release 8.2 (SAS Institute, Inc., Cary, NC) was used.

Results

Characteristics of the Study Population

With three patients excluded due to inclusion in previous studies, 143 charts out of 204 met the inclusion VAS criteria (presence of before and after VAS

Table 2. *Changes in pain intensity VAS (cm) before and after perispinal etanercept treatment at each available time point of 20 min, 1 day, 1 week, 2 weeks, and 1 month post-treatment for the first treatment dose per patient*

Time after treatment	*N*	VAS before mean ± SD*	VAS after mean ± SD	Mean change in VAS (95% CI†)	Mean % change	*p*-value‡
20 min	138	7.08 ± 1.96	4.99 ± 2.38	–2.09 (–2.53, –1.65)	–29.5%	< 0.0001
1 day	140	7.09 ± 1.94	4.87 ± 2.30	–2.22 (–2.65, –1.79)	–31.3%	< 0.0001
1 week	123	7.08 ± 2.02	5.12 ± 2.55	–1.96 (–2.45, –1.48)	–27.7%	< 0.0001
2 weeks	100	7.06 ± 2.03	5.14 ± 2.71	–1.93 (–2.48, –1.37)	–27.3%	< 0.0001
1 month	27	7.47 ± 1.89	4.75 ± 2.78	–2.72 (–3.78, –1.66)	–36.4%	< 0.0001

*SD: standard deviation

†95% CI: 95% confidence interval for the mean difference in VAS before and after treatment

‡*p*-value for paired differences of VAS before and after treatment; statistical tests by paired 2-sided *t*-tests for parametric data (at 1 month) and by Wilcoxon matched-pair signed-rank tests for nonparametric data (at 20 min, 1 day, 1 week, 2 weeks)

Table 3. *Changes in sensory disturbance VAS (cm) before and after perispinal etanercept treatment at each available time point of 20 min, 1 day, 1 week, 2 weeks, and 1 month post-treatment for the first treatment dose per patient*

Time after treatment	*N*	VAS before mean ± SD*	VAS after mean ± SD	Mean change in VAS (95% CI†)	Mean % change	*p*-value‡
20 min	127	5.56 ± 2.77	4.05 ± 2.68	–1.51 (–1.91, –1.10)	–27.2%	< 0.0001
1 day	124	5.58 ± 2.74	4.24 ± 2.74	–1.34 (–1.76, –0.92)	–24.0%	< 0.0001
1 week	115	5.43 ± 2.82	4.01 ± 2.58	–1.42 (–1.87, –0.98)	–26.2%	< 0.0001
2 weeks	93	5.58 ± 2.80	4.44 ± 2.75	–1.14 (–1.66, –0.62)	–20.4%	< 0.0001
1 month	24	5.59 ± 3.20	3.80 ± 2.85	–1.79 (–2.76, –0.82)	–32.0%	< 0.0001

*SD: Standard deviation

†95% CI: 95% confidence interval for the mean difference in VAS before and after treatment

‡*p*-value for paired differences of VAS before and after treatment; statistical tests by paired 2-sided *t*-tests for parametric data (at 1 month) and by Wilcoxon matched-pair signed-rank tests for nonparametric data (at 20 min, 1 day, 1 week, 2 weeks)

data). The VAS data after the first dose of etanercept in 2003 in the 143 medical charts were analyzed. The characteristics of the 143 patients whose charts met the inclusion criteria for study are presented in Table 1. The mean age at entry was 55.8 years, with 48% female and mean duration of pain prior to etanercept was 9.8 years. Prior to treatment, 83% had back pain, 61% had sciatica, 33% had neck pain, 67% had MRI evidence of disc protrusion, 51% had MRI evidence of degenerative disc disease, and 30% had previous spinal surgery. In addition, 69% had received epidural steroid injections in the past. On average, patients received 2.3 doses of etanercept separated by a mean interval of 13.6 days.

The 143 patients completing the VAS measurements had marginally lower ODI scores before treatment on average than the 61 patients who did not complete a VAS (42.8 ± 17.0 vs. 48.1 ± 16.2, $p = 0.0505$), more treatment doses (2.3 ± 0.7 vs. 1.6 ± 1.0, $p < 0.0001$), and fewer number of days between treatments (13.6 ± 16.3 vs. 28.6 ± 31.2, $p = 0.0232$). There were no other statistical differences between the two patient populations (in age, gender, previous treatment, pain distribution, signs and symptoms suggestive of radiculopathy, MRI results and other diagnostic studies).

Treatment Results

Before and after VAS data were available for 143 patients, with a variable number of patients giving VAS data at each time interval. Comparisons of pain intensity, sensory disturbance, and weakness VAS measurements at each time point of 20 min, 1 day, 1 week, 2 weeks, and 1 month are given for patient responses following the first dose only (see Tables 2–4). Figure 1 shows a graphical representation of the change in pain intensity VAS following the first dose. The mean VAS scores for intensity of pain, sensory disturbance, and weakness improved significantly following treatment with perispinal etanercept at each time interval studied, 20 min, 1 day, 1 week, 2 weeks, and 1 month, with a $p < 0.0001$ at each time interval reported (see Tables 2–4).

Table 4. *Changes in weakness VAS (cm) before and after perispinal etanercept treatment at each available time point of 20 min, 1 day, 1 week, 2 weeks, and 1 month post-treatment for the first treatment dose per patient*

Time after treatment	*N*	VAS before mean ± SD*	VAS after mean ± SD	Mean change in VAS (95% CI†)	Mean % change	*p*-value‡
20 min	122	5.39 ± 2.82	4.32 ± 2.61	–1.07 (–1.46, –0.68)	–19.9%	< 0.0001
1 day	121	5.50 ± 2.81	4.22 ± 2.56	–1.27 (–1.70, –0.84)	–23.1%	< 0.0001
1 week	110	5.54 ± 2.78	4.11 ± 2.55	–1.43 (–1.90, –0.95)	–25.8%	< 0.0001
2 weeks	87	5.75 ± 2.66	4.43 ± 2.73	–1.32 (–1.86, –0.78)	–23.0%	< 0.0001
1 month	22	6.78 ± 2.64	4.17 ± 3.00	–2.61 (–3.90, –1.32)	–38.5%	< 0.0001

*SD: standard deviation

†95% CI: 95% confidence interval for the mean difference in VAS before and after treatment

‡*p*-value for paired differences of VAS before and after treatment; statistical tests by paired 2-sided *t*-tests for parametric data (at 1 month) and by Wilcoxon matched-pair signed-rank tests for nonparametric data (at 20 min, 1 day, 1 week, 2 weeks)

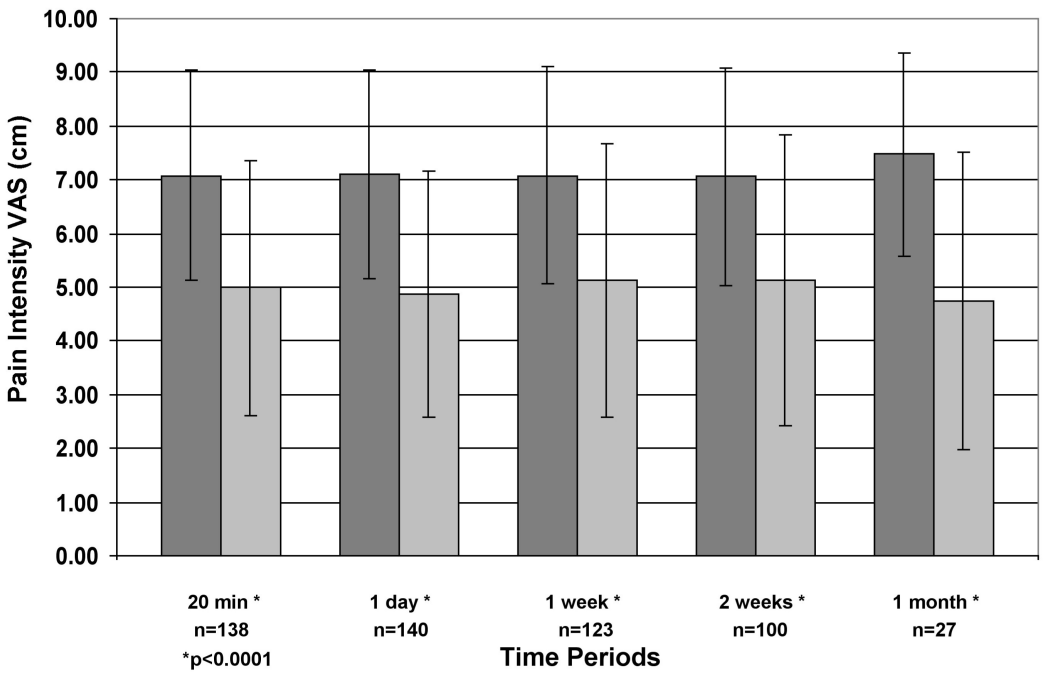

Figure 1. *Pain intensity VAS (cm) before and after perispinal etanercept at each time interval ($p < 0.0001$). Standard deviations are indicated by error bars*

With clinical improvement defined as a decrease of ≥ 1.90 cm[47], the VAS scores for the 143 patients were examined to determine the number and proportion of patients whose scores improved ≥ 1.90 cm following the first treatment dose. At 1 week after the first dose 59 out of the 123 patients who provided data at this time interval reported ≥ 1.90 cm improvement in pain intensity following treatment with etanercept. Similar improvement in pain intensity was reported at each of the other time intervals studied. The results with respect to number and proportion of patients clinically improving after the first dose as shown by each of the three VAS measurements of pain intensity, sensory disturbance, and weakness at each time point are reported in Table 5.

Proportions of patients clinically improving at each time point range from 48.0% to 66.7% for pain, 24.7% to 41.7% for sensory disturbance, and 27.1% to 54.6% for weakness. After 20 min of treatment, for example, 67 out of 138 patients (48.6%) experienced clinical improvement in their pain intensity as measured by the VAS.

After 1 week, 59 out of 123 patients (48.0%) clinically improved, whereas 45 patients (36.6%) had little or no improvement, and 19 (15.5%) reported worsening as measured by the pain intensity VAS. The average VAS

Table 5. *Number and proportion of patients with clinical improvement (≥ 1.90 cm) in pain intensity, sensory disturbance, and weakness VAS after the first treatment dose per patient*

Time after treatment dose	Pain intensity VAS *n/N* (%)*	Sensory disturbance VAS *n/N* (%)	Weakness VAS *n/N* (%)
20 min	67/138 (48.6%)	44/127 (34.7%)	33/122 (27.1%)
1 day	76/140 (54.3%)	40/124 (32.3%)	37/121 (30.6%)
1 week	59/123 (48.0%)	38/115 (33.0%)	37/110 (33.6%)
2 weeks	49/100 (49.1%)	23/93 (24.7%)	27/87 (31.0%)
1 month	18/27 (66.7%)	10/24 (41.7%)	12/22 (54.6%)

**n/N* (%) is the number of patients improving out of the total number of analyzable patients at each time period (%)

pain improvement for this group of 59 patients was 4.16 ± 2.04, improving from an initial VAS of 7.74 ± 1.50 to a VAS of 3.93 ± 2.06 at one week following a single etanercept dose, which corresponds to a decrease of 53.7%.

Review of the 143 patient charts by the treating physician (S.D.) revealed a qualitative decrease in pain medication utilized in 55% of the 143 patients following treatment with perispinal etanercept.

No serious adverse reactions were observed. Patients complained of the following adverse effects after receiving etanercept, which may have been related to treatment: headaches (5), increased pain (5), fatigue (4), or nausea (2), all of which resolved. There were no documented cases of infection, demyelinating disease, hospitalization, or malignancy in any of the treated patients.

Case report

A 40-year-old woman presented to the clinic with a 1-year history of neck pain. The pain was constant and radiated to the left shoulder blade and down the left arm to the left hand. The patient complained of weakness of the grip of her left hand and numbness of the middle and index fingers of the left hand. The pain did not respond adequately to tramadol 1–4 (average 2) per day, methocarbomol 2 per day, and ibuprofen bid. The patient denied fever, infection, tuberculosis, HIV, diabetes mellitus, congestive heart failure, lymphoma or history of lymphoma, multiple sclerosis, optic neuritis, or other demyelinating disease. Cervical MRI 3 weeks prior to her presentation showed a large left paracentral disc extrusion at C6–C7, 10 mm in transverse dimension, causing compression of the lateral aspect of the cord and severe central canal narrowing with severe left lateral recess narrowing; and a 3 mm moderate central and left paracentral focal disc protrusion at C5–C6. The patient consulted three surgeons, two of whom recommended surgery.

On examination the patient was in obvious discomfort. The left paraspinous area of the neck was tender. Decreased grip strength of the left hand was noted, along with decreased strength of finger abduction on the left. Reflexes were intact. Prior to treatment VAS for pain intensity was 8.6, for sensory disturbance 6.1, and for weakness 1.9. After informed consent etanercept 25 mg was administered directly over the lower cervical spine by subcutaneous injection utilizing a 23 gauge 1.5 cm needle. The patient experienced rapid improvement in symptoms. At 5 min post-etanercept there was 70% pain relief. At 20 min post etanercept the VAS for intensity of pain was 6.2; sensory disturbance 4.6 and weakness 1.5. At 1 day VAS for intensity of pain was 4, sensation 1.8 and weakness was not reported. At 1 week VAS for pain was 3.2, and sensation 1.2. At 2 weeks VAS for pain was 2.6, and sensation 0.7. At 3 weeks the patient still reported some pain but had discontinued all pain medication. She requested and received a second dose of perispinal etanercept 25 mg. Two weeks after the second injection all neurological symptoms, including pain, completely resolved and have not recurred for 8 months.

Discussion

Chronic back pain, defined as back pain present for more than 2–3 months, presents a therapeutic challenge[25]. Despite recognition of its health and economic burden no evidence-based guidelines for the treatment of chronic low back pain have achieved widespread acceptance[26]. In the US fusion surgery has been increasingly used, but has come under criticism[27–29]. Anatomically localized (epidural) delivery of corticosteroids adjacent to the nerve root is commonly attempted to reduce disc-related inflammation, but has

been shown to provide little long-term clinical benefit[30,31]. A more effective non-surgical therapeutic modality is needed.

This study provides evidence of rapid improvement of pain, sensory disturbance, and weakness in a large group of patients with chronic pain treated with perispinal etanercept who had failed to respond adequately to previous therapy. These results are consistent with the results of other recent studies which have also documented clinical improvement in a small series of patients with disc-related pain[13,14,19,20]. In addition these results are consistent with basic science studies in animals which have established a central role for TNF in the pathogenesis of neuropathic pain and neuronal injury[12,18,32–37].

Rapid pain reduction after perispinal administration of etanercept, first reported for disc-related pain[13,14] has also been documented in two patients with intractable pain due to cancer metastasis to the spine[38]. The authors have previously speculated on the mechanisms responsible for this rapid pain relief, which they attribute to the central role played by TNF, the recombinant DNA origin of etanercept, and the delivery of etanercept in anatomic proximity to the epidural space, which may allow it to reach the endoneurial space[13,14,17]. Experimental research has demonstrated that TNF may be axonally transported[34,39], that application of TNF to the nerve root may result in inflammation in the corresponding dorsal root ganglion and physiologic effects in the dorsal horn of the spinal cord[40], and that application of anti-TNF antibodies to the nerve root may reduce nucleus pulposus-induced abnormal nociresponses in rat dorsal horn neurons[41]. In 1965 Melzack and Wall proposed the gate control theory of pain, hypothesizing that the perception of pain could be altered by afferent neuronal input at the level of the substantia gelatinosa, in the dorsal horn of the spinal cord[42]. It has been hypothesized that the reduction in sciatic pain observed in patients treated with etanercept may be due to a direct effect of TNF on the peripheral nerves[13,14,20]. Based on the clinical effects observed following perispinal etanercept in patients with pain due to diverse clinical disorders, both benign and malignant, and the above cited experimental evidence, one of the authors (E.T.) theorizes that TNF directly modulates the Melzack–Wall pain gate. It is hypothesized that perispinal etanercept exerts its therapeutic effect not only at the nerve root, but also at the level of the dorsal root ganglion and the substantia gelatinosa in the dorsal horn of the spinal cord. Additionally it is theorized that TNF modulates not only the perception of pain but also sensation. The clinical results observed suggest the existence of TNF-mediated neural mechanisms producing pain, sensory disturbance, and motor weakness which may not have been previously recognized and which may be rapidly reversed (within minutes) utilizing perispinal etanercept. Further clinical and basic science research is indicated to attempt to more precisely define these important fundamental pain mechanisms.

The results reported here utilizing perispinal etanercept may be compared with those from a recent study from University Hospital Geneva which also demonstrated effectiveness of etanercept for disc-related pain[20]. In this study etanercept was found to have sustained effectiveness at 6 weeks which was significantly superior to the effect of high dose IV methylprednisolone given to an historical control group. Pain relief was reported as occurring less rapidly than that seen after IV infliximab (50% improvement in pain score within 1 h)[19,20]. This is in contrast to the rapid pain relief often seen following perispinal etanercept which is documented here (59/123 patients reporting ≥ 1.90 VAS pain intensity improvement 20 min after their first dose of perispinal etanercept). These differences in time to pain relief may be accounted for by the different methodologies of these studies. Although the Geneva authors did not specify the sites of injection it is assumed that etanercept was administered in the manner in which it is routinely given for its labeled indications i.e. in the abdominal area, upper thighs, or arms. We hypothesize that the less rapid improvement in pain in the Geneva patients was due to the fact that etanercept was not delivered by the perispinal route. This hypothesis is supported by the clinical experience of the authors who have observed several patients treated successfully with perispinal etanercept after treatment with etanercept administered at anatomic sites remote from the spine had failed.

This patient population had an initial average VAS pain score of 7 and an average ODI of 42.8, both of which are consistent with severe pain[21,43]. The Visual Analogue Scale was selected as the primary outcome measure because of its widespread use in the field of pain studies, its standardization, and validation[43–46]. In addition, the VAS for pain has been specifically studied with respect to treatment of chronic low back pain[47].

The results described in this large cohort of patients document rapid (within minutes), substantial and sustained reduction of pain in a significant number of the patients treated with perispinal etanercept, all of whom had failed conventional treatment. The reported improvement, at each treatment interval examined, including 20 min, 1 day, 1 week, 2 weeks, and 1 month, is highly statistically significant, with a $p < 0.0001$ (Figure 1 and Tables 2, 5, and 6). Concomitant improvement in related radicular neurological symptoms, including disturbance in sensation (numbness, tingling) and motor weakness is documented, and is also statistically significant (see Tables 3, 4, and 5). Decreased use of

Table 6. *Patient data for pain intensity VAS before and 1 month after perispinal etanercept (n = 27). Clinical improvement in VAS of ≥ 1.90 cm is indicated*

Before treatment VAS	After treatment VAS	Change in VAS	% Change in VAS	Clinical improvement ≥ 1.90 cm
9.6	0.7	–8.9	–92.7%	Yes
10	2.6	–7.4	–74.0%	Yes
9.8	3.1	–6.7	–68.4%	Yes
6.4	0.2	–6.2	–96.9%	Yes
9.9	4.9	–5	–50.5%	Yes
8	3.1	–4.9	–61.3%	Yes
9	5	–4	–44.4%	Yes
5.5	1.8	–3.7	–67.3%	Yes
8.1	4.9	–3.2	–39.5%	Yes
6.7	3.6	–3.1	–46.3%	Yes
4.5	1.5	–3	–66.7%	Yes
8	5	–3	–37.5%	Yes
6.5	3.5	–3	–46.2%	Yes
9	6	–3	–33.3%	Yes
8.1	5.5	–2.6	–32.1%	Yes
4.5	2	–2.5	–55.6%	Yes
3.3	1	–2.3	–69.7%	Yes
7	5	–2	–28.6%	Yes
6.1	5	–1.1	–18.0%	No
5.5	4.5	–1	–18.2%	No
9	8	–1	–11.1%	No
6	6	0	0.0%	No
9.5	9.5	0	0.0%	No
8	8	0	0.0%	No
9.8	9.9	0.1	1.0%	No
7.9	9	1.1	13.9%	No
6	9	3	50.0%	No
Mean: 7.47	Mean: 4.75	Mean: –2.72	Mean: –36.8%*	18 ≥ 1.90 cm
SD†: 1.89	SD: 2.78	SD: 2.69		9 < 1.90 cm

*$p < 0.0001$

†SD: standard deviation

pain medication following etanercept treatment was documented in more than half (55%) of the 143 patient charts studied.

Many of the patients in this study have experienced marked improvement, although there were nearly an equal number of patients who might be characterized as 'non-responders'. It is not precisely known why some patients do not respond. In part this is due to the fact that it is impossible to make a definite diagnosis of the cause of back pain in many patients[48]. If we separate the patients into two populations, one characterized as 'non-responders' and the other as 'responders' then the efficacy of perispinal etanercept is thrown into greater relief. For example, there were 123 patients who provided 1 week VAS pain data following their first etanercept dose. Fifty-nine of these patients reported pain improvement of 1.9 cm or more on a 10 cm VAS scale (see Table 5), a degree of change which has been suggested as indicative of significant clinical improvement (although other studies have suggested 9, 10, or 12 mm)[44–47]. The average VAS pain improvement for this group was 4.16 which corresponded to a 53.7% reduction in pain. Patients reported a similar degree of improvement at 2 weeks and at 1 month (Table 5). The present data and the accumulating medical literature on TNF-inhibition for disc-related pain document that treatment with etanercept may be followed by sustained relief of pain for weeks or months for selected patients. During their more than 3 year clinical experience utilizing perispinal etanercept for patients with severe, chronic, treatment-refractory disc-related pain the authors are aware of a substantial number of patients who have reported more than 6 months of pain relief, but many other patients seem to benefit from

additional dosing, and some patients seem to require frequent maintenance therapy. The present study does not address the question of when to re-dose the patient with perispinal etanercept. In our practice we consider additional doses of etanercept if pain recurs. Further study will be helpful to facilitate the formulation of clinical guidelines in this regard.

Certain precautions are in order. Active infection, demyelinating disease, lymphoma or a history of lymphoma, immunosuppression, and uncontrolled diabetes are absolute or relative contraindications for the use of etanercept[49]. All patients must be advised that serious adverse effects, although uncommon, may be associated with etanercept treatment. These include infection, re-activation of dormant tuberculosis, blood disorders, and exacerbation of demyelinating disease. Overall, however, etanercept has demonstrated an excellent record of safety and tolerability when used for a variety of clinical disorders[49–53]. Safety has now been documented with 5 years of continuous dosing of etanercept 25 mg twice per week for the treatment of rheumatoid arthritis[54]. Recent data have even shown etanercept to be safe when given at twice the usual dosage (50 mg twice per week) for 12 weeks for the treatment of psoriasis, a dosage level that has now been FDA approved for psoriasis[55].

Despite etanercept's safety record the treatment regimen used was designed with caution and patient safety as paramount considerations. Patients were therefore dosed less frequently than for etanercept's labeled indications (which is twice per week for a period of months to years). In fact, the average patient treated in this study received only an average of 2.3 doses of etanercept, with an average interval between doses of 13.6 days. It is possible that a more aggressive initial and follow-up dosing regimen might lead to higher response rates. Further study will be necessary to determine if a more accelerated treatment regimen would be cost-effective.

A limitation of this study is that there is no formal control group. An argument could be made that the results seen merely represent regression to the mean, i.e. that the patients presented for treatment when their pain was worse, and that they would have improved by chance with time alone. Another argument could be made that the results observed are due to a placebo response. The authors agree that a placebo-controlled study would add valuable data regarding the contribution of a placebo response to the degree of pain relief reported. However, the clinical results documented here were highly statistically significant and cannot reasonably be ascribed to either regression to the mean or a placebo response when one examines the patient population and the details of their response to treatment, and considers that this was a cohort of patients who had been refractory to previous treatment. The patients were selected with criteria which included the chronicity and daily presence of their pain, which tended to be constant on a day-to-day basis. This day-to-day constancy, as well as the rapidity of pain relief observed (within minutes) argue strongly against regression to the mean as a significant confounding factor here.

The authors are unaware of any studies which demonstrate the ability of placebo to produce improvement in the non-pain neurological components of radiculopathy (paresthesia/anesthesia and/or motor weakness in a nerve root distribution) which in this study was documented to occur to a significant degree following treatment. A recent review has refuted several commonly held beliefs regarding placebo, concluding there was 'little evidence in general that placebos had powerful effects'[56,57]. In examining 27 trials involving the treatment of pain (including a total of 1602 patients) only a slight effect of placebo, corresponding to a reduction in the mean intensity of pain of 0.65 cm (95% confidence interval, 0.36–0.96) on a 10 cm visual analogue scale, was found[56]. The degree of pain relief documented in this patient population exceeds the 0.65 cm pain relief attributed to placebo in the above review, and corresponds with a highly clinically significant degree of change in VAS as reported by several studies[44–47].

Other limitations are inherent in the study design, that being that follow-up data is not available for all patients at all time intervals after treatment, and that patients who responded to treatment could return for additional dosing. This reflects the realities of clinical practice and limits the ability to extrapolate from the reported data to obtain exact overall rates of response. Because of these limitations it can only be inferred from these data that there was a highly statistically significant treatment effect observed in this group of patients, but the percentage of patients responding to treatment cannot be generalized. Although concurrent use of medications other than etanercept was not precisely quantitated, and could theoretically bias the results, chart review confirmed that the treated patients appeared to be using less pain medication following perispinal etanercept use.

Double-blind, placebo-controlled trials will be necessary to develop further knowledge of this new treatment modality.

Conclusion

Perispinal etanercept is a new treatment modality which can lead to significant clinical improvement in selected patients with chronic, treatment-refractory disc-related

pain. Generalizability of the present study results is limited by the open-label, uncontrolled methodology employed. Based on this and other accumulating recent studies, etanercept may be useful for both acute and chronic disc-related pain. Further study of this new treatment modality utilizing randomized, double-blind, placebo-controlled methodology is indicated.

Acknowledgments

The use of etanercept, infliximab, and other TNF inhibitors, for the treatment of pain due to disc herniation, and related disorders, and for pain due to bone metastases, is the subject of issued claims included in multiple patents awarded to Edward Tobinick, MD, including US patents 6 015 557; 6 177 077; 6 419 944; 6 537 549 and Australian patent 758 523.

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