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Perispinal TNF-alpha inhibition for discogenic pain

Edward L. Tobinick, Susan Britschgi-Davoodifar

Institute for Neurological Research, Los Angeles, California

Summary

Objective: To examine the potential of etanercept, a biological inhibitor of tumour necrosis factor-alpha (TNF), delivered by perispinal administration, for the treatment of pain associated with intervertebral disc disease.

Methods: Charts from 20 selected patients treated at our private clinic by perispinal delivery of etanercept 25 mg for severe, chronic, treatment-resistant discogenic pain were reviewed. Therapeutic benefit was assessed clinically and was documented by changes in a validated pain instrument, the Oswestry Disability Index. The patients were treated off-label with etanercept as part of our usual practice of medicine. Five detailed case reports are presented, including three additional patients.

Results: Rapid, substantial and sustained clinical pain reduction was documented in this selected group of patients. The cohort of 20 patients had a mean age of 56.5 and mean duration of pain of 116 months. Nine of the patients had undergone previous spinal surgery; 17 had received an epidural steroid injection or injections (mean 3.2). This group of patients received a mean of 1.8 doses (range 1–5, median 1.0) of etanercept during the observation period. The mean length of follow-up was 230 days. Clinical improvement was confirmed by a decrease in the calculated Oswestry Disability Index from a mean of 54.85 ± 12.5 at baseline, improving to 17.2 ± 15.3 ($p < 0.003$) at 24 days and ending at 9.8 ± 13 ($p < 0.003$) at 230 days.

Conclusions: TNF inhibition by etanercept delivered by perispinal administration may offer clinical benefit for patients with chronic, treatment-resistant discogenic pain. Further study of this new treatment modality is warranted.

Key words: tumuor necrosis factor; TNF; etanercept; discogenic pain; cervical radiculopathy; lumbar radiculopathy; failed back syndrome

Introduction

The biological TNF inhibitors, consisting of etanercept, infliximab, adalimumab, CDP 870, onercept and other molecules in clinical development, constitute a new class of therapeutic agents which have proved remarkably effective for a variety of treatment-refractory chronic inflammatory disorders [1–6]. Etanercept, an anti-TNF fusion protein, was the first recombinant TNF inhibitor to be available for subcutaneous use. It functions as a selective and potent inhibitor of the biological action of TNF. Etanercept is currently approved for the treatment of rheumatoid arthritis in children [7] and adults [8] and psoriatic arthritis [9]. It has also been shown to be effective in relieving refractory back and neck pain associated with ankylosing spondylitis [10]. Because of the fundamental involvement of TNF in generating the inflammatory response, etanercept has potential for treating a diverse group of systemic and localised clinical disorders. It is currently being studied with a view to treating Wegener's granulomatosis, dermatomyositis, histiocytosis, psoriasis, cancer cachexia, temporomandibular disorders, pain and swelling after molar extraction, and a number of other inflammatory disorders with documented involvement of TNF.

A central role of TNF in one localised inflammatory disorder, pain associated with intervertebral disc disease, has been suggested by an elegant series of experiments conducted over two decades. It is known that disc herniation can lead to pain by mechanical compression of adjacent nerve roots. However, a subset of patients have pain without demonstrable compression, or continue to have pain despite seemingly successful surgical removal of the offending protruding disc [11]. A chemical component of the pain, independent of structural deformation, was suspected [12, 13]. Subsequent research showed that a component of the intervertebral disc, the nucleus pulposus, was inherently inflammatory and could cause nerve damage without compression [14, 15]. Investigation has confirmed that TNF duplicates nucleus pulposus-induced inflammation and neuropathy [16]. TNF

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was shown to be a direct cause of neuronal damage if injected into a nerve or applied exogenously [17, 18]. TNF inhibition using etanercept or infliximab was found to prevent this nucleus-pulposus induced neuropathy [19]. Subsequent studies have suggested the key involvement of TNF in the development of neuropathic pain [20–22] and have also demonstrated the ability of etanercept and other TNF inhibitors to reduce pain in experimental models [23, 24]. Other recent studies have suggested that intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators [25, 26].

Corticosteroids are widely used for the treatment of patients with discogenic pain who fail to respond to more conservative measures. A standard treatment modality in this setting is perispinal delivery of corticosteroids by epidural route [27]. The availability of etanercept for subcutaneous administration provides the clinician with another possible therapeutic agent for perispinal delivery. The use of etanercept and infliximab off-label has recently been advocated for other chronic, treatment-resistant inflammatory disorders [1]. The anatomic proximity of the intervertebral disc to the overlying subcutaneous space, the central pathogenic role of TNF in nucleus pulposus-induced pain and neuropathy, and the potency of etanercept all combine to provide a rationale for its off-label use for discogenic pain. On the hypothesis that etanercept may be beneficial, and that perispinal delivery may produce an enhanced therapeutic effect, we began treating patients with chronic, treatment-resistant pain thought to be discogenic in origin.

Patients and methods

Methods: We reviewed charts from patients treated at our private clinic by perispinal delivery of etanercept for severe, chronic, treatment-resistant low back or neck discogenic pain between June 2001 and January 2003, and who reported significant and prolonged clinical improvement. Twenty charts of patients meeting the following criteria were found:

1. Severe pain, defined as pain graded by the patient as 7 or greater on a scale of 0–10, daily;
2. Chronic pain, occurring daily, for at least two months, and at least 12 hours per day;
3. Treatment resistance as evidenced by daily pain persisting despite previous epidural steroid injection or spinal surgery,
4. MRI or CT demonstrating anatomical intervertebral disc disease correlating with the patient's symptoms, and
5. Significant and prolonged clinical improvement beginning within 48 hours of etanercept administration.

On the basis of history, physical examination and MRI, the symptoms of all patients were thought to be secondary to intervertebral disc disease. None of the patients had symptoms or signs suggestive of ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis or other forms of autoimmune or collagen-vascular disease. This group of 20 patients with treatment-resistant chronic pain is heterogeneous, and includes fourteen patients with clear-cut lumbar or cervical radiculopathy, five with suspected radiculopathy (low back pain and radiation to the thigh but not below the knee), and one patient with localised low back pain without radiation. In 17 of the 20 patients MRI demonstrated multi-level disc disease. Discography data is available on only one of these patients (patient 9, table 1) and documented annular tears involving all four lumbar intervertebral discs (L1–2, L2–3, L3–4, and L4–5). All 17 patients treated with epidural steroids had failed to obtain lasting clinical benefit: eight derived no benefit whatsoever from steroids; seven experienced up to 50% relief, generally for less than one week, and two experienced more than 50% relief, one for two weeks and the second for six months after epidural steroid injections. All 20 patients were treated off-label with etanercept (source Immunex Corporation, Seattle, Washington), 25 mg in 1 ml. of bacteriostatic water subcutaneously by local administration in either the lumbar or cervical region, after informed consent, as part of our usual practice of medicine. Perispinal administration in these patients consisted of localised subcutaneous injection into the perispinal area in closest proximity to the site of presumed disc protrusion, using a 23 gauge 1.5 cm needle, by administration immediately overlying the spine. The primary outcome measure used was the Oswestry Disability Index [28, 29], a standardised instrument for measurement of low back pain and associated functional disability. The Oswestry questionnaire was completed by the patient immediately prior to treatment. After treatment the patients were observed for twenty minutes to record their response to treatment. They were then asked to prospectively return their treatment results, including follow-up Oswestry questionnaires, by mail or when revisiting the clinic for follow-up. The following information was collected from their charts: age, sex, duration of pain (months), number of previous epidural steroid injections, number of previous spinal surgeries, time to onset of clinical improvement, number of etanercept doses documented over the period of observation, length of observation (being the time from inception of etanercept treatment to the date of the last reported Oswestry score), initial date of treatment, final date of observation, baseline Oswestry score (OW 1, table 1), first available post-treatment Oswestry score (OW2, table 1), and final Oswestry score (OW3). Detailed case reports are presented documenting the clinical response of five patients: the first with chronic cervical and lumbar discogenic pain, who is currently enrolled in an ongoing IRB-approved clinical trial (Biomed IRB, San Diego, California) conducted by the authors and has been treated with perispinal etanercept therapy on a prospective basis; the second patient with acute lumbar radiculopathy, the third with subacute lumbar radiculopathy and two additional patients from the 20-patient cohort.

One of the authors[1] has been awarded US patents for methods discussed in this article.

Statistical methods

The Oswestry values were compared at baseline (OW1) (n = 20), mid-course (OW2) (n = 17) and at conclusion (OW3) (n = 20) for the 20-patient cohort (see table 1).

[1] Tobinick EL. Cytokine antagonists for the treatment of localized disorders. US patent 6, 419,944. 2002 July 16, and others.

Table 1

Targeted etanercept – results for 20-patient cohort.

	age	sex	pain duration (months)	pain location Low back/ cervical	epidural steroids (#)	SX (#)	targeted etanercept doses	Oswestry #1 (OW1) baseline	OW 2* (OW1–OW2) (days)	OW 3** (OW1–OW3) (days)
1	38	M	216	LB	1	0	1	68	0 (20)	0 (288)
2	42	F	24	LB	3	0	1	58	0 (38)	0 (353)
3	43	F	240	LB/C	3	0	1	48	16 (31)	16 (132)
4	47	M	120	LB	2	0	3	56	6 (14)	11 (122)
5	48	F	9	LB	0	2	1	54	0 (89)	0 (310)
6	50	M	4	LB	3	0	1	36		0 (335)
7	53	F	15	LB/C	0	1	4	60	26 (21)	52 (304)
8	53	F	360	LB/Arm	2	0	1	34	25 (3)	14 (111)
9	54	F	8	LB	2	1	2	70	26 (28)	22 (157)
10	55	F	204	LB/C	3	3	1	64	0 (63)	0 (151)
11	55	F	204	LB/C	2	0	5	76	23 (6)	0 (144)
12	57	F	72	LB	0	3	1	62	9 (28)	9 (49)
13	60	F	240	C	1	1	1	54	8.6 (1)	8 (371)
14	61	M	42	LB/C	3	1	1	30		0 (395)
15	62	M	46	LB	1	1	1	62	34 (6)	28 (77)
16	62	F	240	LB	30	3	3	50		8 (124)
17	64	M	132	LB	3	0	1	48	15.5 (31)	0 (504)
18	70	F	4	LB	1	0	1	56	14 (14)	6 (116)
19	78	M	132	LB	2	0	5	42	34 (15)	4.4 (518)
20	79	F	2	LB	2	0	1	69	55.5 (1)	17.5 (49)
Mean	**56.6**		**116**		**3.2**	**0.8**	**1.8**	**54.85**	**17.2 (24)**	**9.8 (230)**
Median	55.0		96		2.0	0.0	1.0	56.00	15.5 (20)	7.0 (154)
Min.	38		2		0	0	1	30	0 (1)	0 (49)
Max.	79		360		30	3	5	76	55.5 (89)	52 (518)

* Oswestry Disability Index [26, 27] score 2, followed (in parentheses) by length in days between OW1 and OW2
** Oswestry Disability Index [26, 27] score 3, followed (in parentheses) by length in days between OW1 and OW3

Variable	N	Median	Mean	Std Dev	Minimum	Maximum
OW1	20	56.0	54.85	12.50	30.0	76.0
OW2	17	15.5	17.21	15.30	0	55.5
OW3	20	7.0	9.80	12.97	0	52.0

A repeated measures analysis of variance was conducted to determine whether the mean Oswestry values differed over the three time periods. A statistically significant difference was found among the three periods, with $F(2,32) = 78.96$, $p < 0.001$. Three pairwise post hoc t-tests were conducted to compare the means at time 1 vs 2, time 1 vs 3, and time 2 vs 3. The criterion level for significance, adjusted for the multiple tests, was 0.003. The resulting t-test values are as follows:
Time 1 vs Time 2: $t(19) = 10.51$, $p < 0.003$ (significant)
Time 1 vs Time 3: $t(19) = 12.54$, $p < 0.003$ (significant)
Time 2 vs Time 3: $t(17) = 1.75$, $p = 0.10$ (not significant)

Results

All patients reported substantial and sustained clinical improvement documented by a reduction in Oswestry score. Additionally, all patients were able to reduce significantly or completely discontinue analgesic medication after etanercept treatment. This included 11 of the 20 patients who had required chronic opioids for pain control, eight of whom were able to discontinue opioids completely. Two patients who had been completely disabled were able to return to work full-time (patients 2 and 9, table 1). 14 of the 20 patients were treated by only a single dose of etanercept; six pa-

tients required multiple doses (range 0 to 5, mean 1.8, median 1.0). The response to treatment was rapid in all patients; 19 of the 20 patients reported substantial pain relief within 24 hours of etanercept administration, in most cases setting in within twenty minutes, while one patient reported delayed onset of pain relief beginning at 48 hours. The mean baseline Oswestry score of this patient cohort was 54.85 ± 12.5. At first report (mean 24 days, range 1–89 days) the mean Oswestry score decreased to 17.2 ± 15.3 ($p < 0.003$). Final Oswestry score at a mean of 230 days (range 49 to 518 days) further decreased to a mean of 9.8 ± 13 ($p < 0.003$) (range 0 to 52). The one patient whose final Oswestry score remained high (patient 7, table 1) reported significant relief of pain lasting for several weeks after each dose of etanercept.

The patient characteristics and treatment results are tabulated individually in table 1.

To illustrate the potential benefit of perispinal etanercept five case reports follow, three of which are not included in the 20-patient cohort.

Case presentations

Case 1. Chronic cervical and lumbar discogenic pain

A 51-year-old woman with a 16-year history of severe low back and neck pain requiring chronic use of oral opiate analgesics presented at our clinic. Her chief complaint was severe neck pain radiating to the left shoulder and left arm to the wrist; and severe low back pain radiating into the left leg down to the left foot. The pain was constant, present throughout the day, and was made worse by walking. She also complained of decreased grip strength in her right hand. Physical exam showed decreased range of motion of the neck in all directions; she was unable to touch her chin to her chest. She had difficulty walking on the toes of her left foot. Deep tendon reflexes were intact and symmetrical. Grip strength of her right hand was diminished. Strength and sensation, except as noted above, were otherwise normal. Straight leg raising was positive on the left at 90 degrees. Lumbar MRI showed degenerative changes in the L4–5 disc with a small bulge at that level. Cervical MRI showed a 2–3 mm central disc protrusion at C4–5 and degenerative changes with a small bulge at C5–6. Six epidural steroid injections, three each in the lumbar and cervical areas, provided only temporary relief, and all symptoms recurred. She entered a clinical trial performed by the authors in August 2002. After informed consent she received a dose of etanercept 25 mg by perispinal subcutaneous delivery in the lower lumbar region and her response to treatment was carefully followed. Her baseline characteristics were pain measured as 100 (100 mm VAS scale) and Oswestry score of 56. Following treatment the patient experienced rapid and nearly complete symptom relief, setting in within 20 minutes, with pain diminishing to 40 at two weeks, 30 at one month, and 18 at three months, with corresponding changes in the calculated Oswestry score (figure 1). After three months the neck pain returned, but the back pain relief continued. At four months a second dose of etanercept 25 mg was delivered by perispinal subcutaneous administration to the cervical region. This again resulted in rapid, substantial and sustained symptom relief (figure 1).

Case 2. Acute lumbar radiculopathy

A 34-year-old man presented with a three-week history of severe low back pain and sciatica, unrelieved by two courses of oral corticosteroids. The pain began suddenly, was constant, and was felt in the right lower back with radiation to the

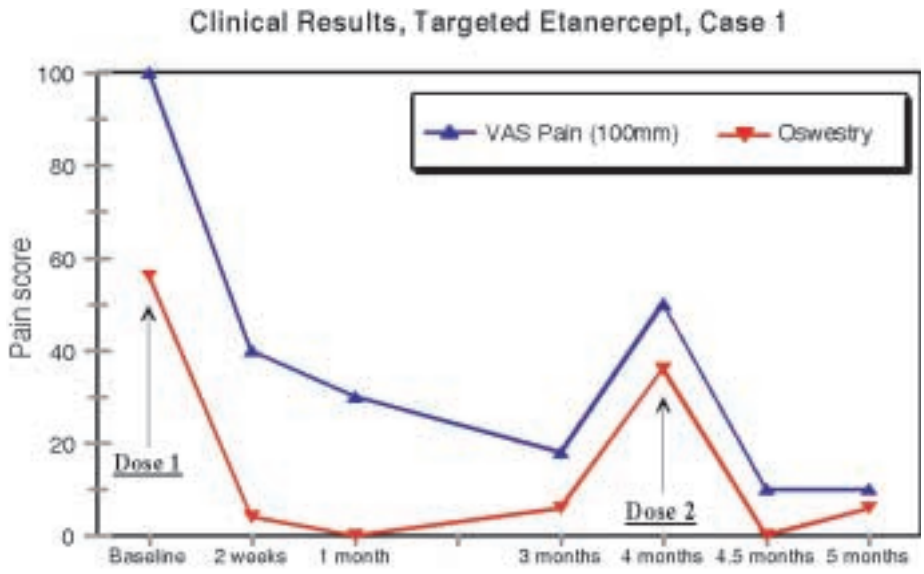

Figure 1
Clinical response to targeted etanercept, case 1.

right leg below the knee. The pain interfered with sleep and was worsened by sneezing. Paresthesia involving the right thigh and right foot and numbness of the right foot were experienced constantly. MRI showed a 1 cm right paracentral and lateral recess extrusion at L5–S1, moderately displacing the right S1 nerve root. Physical examination revealed an absent right achilles reflex and weakness of the right foot extensors; deep tendon reflexes were intact in both knees and the left achilles. The patient walked with an obvious limp. He was unable to walk on the toes of his right foot. There was marked weakness of the right gastrocnemius. Etanercept 25 mg was administered by perispinal subcutaneous injection to the lower lumbar region. Substantial pain relief set in within 20 minutes. At three days he reported 95% pain improvement. Oswestry score prior to treatment was 58. At one month the Oswestry score was 22, at two months 10 and at 4 months 6. At one year he continued to be pain-free.

Case 3. Subacute lumbar radiculopathy

A 39-year-old man with a six-week history of severe low back pain and sciatica was referred by his neurosurgeon for perispinal etanercept treatment. Pain was experienced in the lower back and down the right leg into the right shin. The patient noted that his right great toe was numb and he also experienced numbness in the lateral calf near the dorsum of the right foot. Most notable physical signs were slight weakness of right foot dorsiflexion, positive straight leg raising at 45 degrees on the right, and diminution of sensation with a right L5 distribution. Deep tendon reflexes were unremarkable and symmetrical. MRI showed a 2 cm by 1 cm disc extrusion at L4–5 with compression of the right L5 nerve root (figure 2). Etanercept 25 mg by perispinal subcutaneous injection was administered to the lower lumbar region. Substantial pain relief set in within 20 minutes. The patient became asymptomatic within 24 hours of treatment. The symptoms have not recurred for 16 months and he has resumed normal activity, including basketball.

Figure 2.

Lumbar MRI, case 3, L4–5 disc extrusion.

Case 4. Chronic discogenic pain; failed back surgery syndrome

This 57-year-old woman (patient 12, table 1) with a longstanding history of scoliosis treated by Harrington rod placement twenty years previously, presented for treatment of back pain and sciatica. For six years she had been experiencing constant and severe low back pain and sciatica unrelieved by three lumbar fusion surgeries. CT myelogram had revealed an extruded disk at the right L5–S1 foramen. Pain was present 24 hours per day, and both pain and numbness were experienced in the right lower back, right buttock, right thigh, right lower leg, and right foot. The patient also complained of weakness in the right leg and, to a lesser extent, in the left leg. She was unable to walk for more than ten minutes, stand for more than ten minutes or sit for more than fifteen minutes. Physical examination revealed intact deep tendon reflexes in both knees, but absent achilles deep tendon reflexes bilaterally and decreased sensation in the right lateral foot. Straight leg raising was negative. Heel walking produced pain in the right lower back. Etanercept 25 mg by perispinal subcutaneous injection was administered to the lumbar region. Dramatic diminution in pain ensued within ten minutes. The patient reported 95% pain relief at one day post treatment. The Oswestry pain score prior to treatment was 60; at one month post-treatment it was 9, and at seven weeks continued to be 9.

Case 5. Chronic low back pain and sciatica

This 42-year-old woman (patient 2, table 1) presented with chronic low back pain and sciatica after a motor vehicle accident. The pain had failed to respond to three courses of epidural steroids and required daily use of oral opiates. For two years the patient had been experiencing constant pain 24 hours per day at an intensity of 9–10 on a scale of 1–10, felt in the lower back with radiation to the right buttock and down into the toes of her right foot. Paraesthesia and numbness were experienced in the right posterior thigh. The patient had difficulty in walking, could not stand or sit for longer than 15 minutes and complained of weakness, numbness, and tingling of the right leg extending into her toes. Physical examination revealed a no-

ticeable limp on the right when walking and inability to heel walk or toe walk. Subtle motor weakness was present in knee extensors, foot dorsiflexors and plantiflexors on the right. Deep tendon reflexes were unremarkable; sensation was decreased in the right lateral foot and heel. Ipsilateral straight leg raising was positive; crossed straight leg raising was negative. MRI showed a 3 mm diffuse disk bulge causing mild foraminal impingement at L4–L5 and moderate to severe degenerative disc disease of the L5–S1 disc which was markedly flattened. Etanercept 25 mg by perispinal subcutaneous injection was administered to the lumbar region. Complete pain relief was reported within 20 minutes. Oswestry score prior to treatment was 58; at one day post treatment it was 14. One day post treatment the patient reported that she had 100% pain and sensory improvement and 95% weakness improvement. She walked without a limp, and required no pain medication. At four months the patient reported continued absence of pain and 97% improvement in weakness. Oswestry score decreased to zero at five weeks and was still zero at 353 days.

Discussion

TNF inhibition by perispinal delivery of etanercept resulted in rapid, substantial and sustained clinical improvement in this cohort of selected patients with chronic, treatment-resistant discogenic pain. The baseline Oswestry score (mean 54.85) of the 20-patient cohort with chronic pain denoted severe disability [28]; the reported decline in mean Oswestry score to 17.21 at 24 days and 9.8 at 230 days denotes dramatic clinical improvement [28, 29]. As the additional case reports suggest, perispinal etanercept may also result in clinical improvement in patients with acute and subacute lumbar radiculopathy. In these patients perispinal etanercept seemed effective for discogenic pain of either lumbar or cervical origin.

These results are in direct concordance with those of a recent study [30] in which ten sciatica patients were given a single infusion of infliximab. Both studies document clinical neurological improvement, both rapid and sustained, after TNF antagonist administration in the periphery. A mechanism which may facilitate this has been demonstrated experimentally [31]. In this study it was found that Evans blue-labelled albumin, administered epidurally, crossed the dura and was present one minute later in the intraneural capillaries. A fine venous network linking the epidural space to the endoneurial space was demonstrated. This transport mechanism may provide rapid and direct vascular access from the epidural space to the axons themselves without requiring diffusion through the dura. It is suggested that this is a possible route by which perispinally administered etanercept reaches the neuraxis, and it may be one mechanism accounting for the rapidity of the observed clinical response. This could also explain the anatomically widespread clinical improvement noted in several of the patients; alternatively this may be due to a systemic effect of etanercept. The authors suggest that there may be other mechanisms whereby TNF inhibitors reach the neuraxis rapidly. The dural barrier, for example, may be anatomically disrupted by prior surgery, or the nerve-blood barrier may be functionally disrupted due to cytokines or chemokines [26] from the nucleus pulposus, exposed via either a disc herniation or an annular tear [32].

Another significant factor to consider in these patients with pain due to intervertebral disc disease is the localised nature of the inflammatory process. In contrast to the labelled indications for biological TNF inhibitors, all of which are systemic diseases involving widespread TNF overproduction, disc herniation is anatomically localised. Pathological exposure of the disc nucleus pulposus is thought to produce a local inflammatory reaction at the level of the disc and the adjacent neuronal apparatus (nerve roots, dorsal root ganglia and spinal cord). Because of the localised nature of the inflammation and the lack of a continuing systemic immune stimulus (such as that present in the autoimmune arthritides), there are reasonable grounds for expecting that a shorter course of treatment will be necessary to treat discogenic pain than to treat a systemic autoimmune condition.

A fact of note is that the majority of patients with acute disc herniation have spontaneous resolution of symptoms without definitive treatment of any kind, despite the fact that the anatomical disc herniation persists. Chronic pain is the exception rather than the rule. Administration of a biological TNF antagonist to patients with continuing discogenic pain may initiate down-regulation of this localised TNF-dependent process. Once down-regulation begins inflammation may continue to resolve without further intervention. Prolonged clinical improvement has also been reported with targeted delivery of corticosteroids [33], which, despite their general anti-inflammatory action, do not specifically block TNF. Both etanercept and infliximab have, in fact, been shown to be effective in treating multiple chronic inflammatory diseases whose progression corticosteroids have failed to prevent [1–10]. The biological origin of etanercept, consisting as it does simply of two TNF receptors fused to an immunoglobulin fragment, allows it to function in a more direct and fundamental way than a synthetically derived pharmaceutical, and may allow it to effect pain relief for these patients even in minute concentration.

Our clinical experience has documented a remarkable lack of adverse effects in patients treated

with perispinal etanercept. Most of this must be attributed to the excellent safety record of etanercept when used in a properly screened population. Also, these patients, in contrast to patients with resistant rheumatoid arthritis, have not been subject to previous immunosuppressive therapy or sustained treatment with corticosteroids. Lastly, these patients, in contrast to those with rheumatoid arthritis, received a greatly reduced cumulative dose of etanercept. Nevertheless, it must be noted that etanercept has serious potential toxicity. Its use is contraindicated in the presence of active infection, demyelinating disease and uncontrolled diabetes. Serious infections, some leading to death, have been reported after etanercept use. Other serious adverse reactions, including cytopenia, have been reported. Caution when using etanercept is absolutely necessary, and widespread adoption of this method should await further study.

The clinical improvement in this 20-patient cohort over time compares favourably with the results in a study of the change in Oswestry score experienced by patients after spinal surgery [34]. Although the results document rapid and dramatic improvement in this group of patients with previously chronic, stable pain and severe disability, a limitation of this study is that there was no formal control group. The 20-patient cohort studied represents a selected patient population chosen from among a group of patients who have failed to respond to conventional therapy. Many of these conventionally-treated patients have also failed to respond to etanercept. Other patients have required multiple doses of etanercept because the clinical benefit they derive wanes over time, perhaps due to additional or continuing release of TNF from a damaged disc. Further study will be necessary to determine whether the use of biological TNF inhibitors with a longer half-life, such as adalimumab, will produce more long-lasting benefits for those patients who fail to develop a sustained response to etanercept (which has a measured half-life of 102 hours [package insert, Enbrel®, Amgen]). Epidural administration of etanercept or the other biological TNF inhibitors may be even more effective than perispinal subcutaneous administration, but it remains to be determined whether the potentially greater expense and risk are justified by the potentially greater benefit.

Additional limitations of this study are that since the treatment was open-label the contribution of a placebo response cannot be discounted or quantified. Caution is therefore necessary in generalising from these preliminary results. Documentation of these patient responses is meant to highlight the potential clinical utility of this new treatment modality rather than to precisely define it. Exact characterisation of treatment response rates, duration of response and optimal treatment regimens will require additional investigation. The unmet medical need of the large patient population suffering from chronic disc-related pain, and these promising results, together indicate that further study of this new clinical application of the biological TNF inhibitors is clearly warranted.

Conclusion

Perispinal delivery of etanercept for treatment-resistant discogenic pain may lead to rapid, substantial, and sustained clinical improvement. Further study of this new therapeutic modality is warranted.

Correspondence:
Edward Lewis Tobinick, M.D.
100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90095
E-Mail: etmd@ucla.edu

References

1 Aeberli D, Oertle S, Mauron H, Reichenbach S, Jordi B, Villiger PM. Inhibition of the TNF-pathway: use of infliximab and etanercept as remission-inducing agents in cases of therapy-resistant chronic inflammatory disorders. Swiss Med Wkly 2002;132(29–30):414–22.
2 Lorenz HM, Kalden JR. Perspectives for TNF-alpha-targeting therapies. Arthritis Res 2002;4(Suppl 3):S17–24.
3 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340(18): 1398–1405.
4 Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359: 1187–93.
5 Kalden JR. Emerging role of anti-tumor necrosis factor therapy in rheumatic diseases. Arthritis Res 2002;4(Suppl 2):S34–40.
6 Williams JD, Griffiths CE. Cytokine blocking agents in dermatology. Clin Exp Dermatol 2002;27(7):585–90.
7 Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342(11):763–9.
8 Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130(6):478–86.
9 Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet;356(9227):385–90.
10 Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor-alpha. N Engl J Med 2002;346(18):1349–56.
11 Anderson VC, Israel Z. Failed back surgery syndrome. Curr Rev Pain 2000;4(2):105–11. Review.
12 Marshall LL,Trethewie ER. Chemical irritation of nerve-root in disc prolapse. Lancet 1973;2(7824):320.
13 McCarron RF, Wimpee MW, Hudkins P, Laros GS. The inflammatory effect of nucleus pulposus: a possible element in the pathogenesis of low-back pain. Spine 1987;12(8):760–4.
14 Takahashi H, Suguro T, Okazima Y, Motegi M, Okada Y, Kakiuchi T. Inflammatory cytokines in the herniated disc of the lumbar spine. Spine 1996;21(2):218–24.
15 Otani K, Arai I, Mao GP, Konno S, Olmarker K, Kikuchi S. Nucleus pulposus-induced nerve root injury: relationship between blood flow and motor nerve conduction velocity. Neurosurgery 1999;45(3):614–9; discussion 619–20.

16 Igarashi T, Kikuchi S, Shubayev V, Myers RR. 2000 Volvo Award winner in basic science studies: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathy. Molecular, histologic, and behavioral comparisons in rats. Spine 200F;25(23):2975–80.
17 Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. Neuroreport 1996;7: 2897–01.
18 Aoki Y, Rydevik B, Kikuchi S, Olmarker K. Local application of disc-related cytokines on spinal nerve roots. Spine 2002;27(15): 1614–7.
19 Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica. Spine 2001;26(8):863–9.
20 Onda A, Hamba M, Yabuki S, Kikuchi S. Exogenous tumor necrosis factor-alpha induces abnormal discharges in rat dorsal horn neurons. Spine 2002;27(15):1618–24; discussion 1624.
21 Liu B, Li H, Brull SJ, Zhang JM. Increased sensitivity of sensory neurons to tumor necrosis factor alpha in rats with chronic compression of the lumbar ganglia. J Neurophysiol 2002;88(3): 1393–9.
22 Homma Y, Brull SJ, Zhang JM. A comparison of the chronic pain following local application of tumor necrosis factor alpha to the normal and mechanically injured lumbar ganglion in the rat. Pain 2002;95(3):239–46.
23 Schafers M, Brinkhoff J, Neukirchen S, Marziniak M, Sommer C. Combined epineurial therapy with neutralizing antibodies to tumor necrosis factor-alpha and interleukin-1 receptor has an additive effect in reducing neuropathic pain in mice. Neurosci Lett 2001;310(2–3):113–6.
24 Sommer C, Schafers M, Marziniak M, Toyka KV. Etanercept reduces hyperalgesia in experimental painful neuropathy. J Peripher Nerv Syst 2001;6(2):67–72.
25 Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. J Bone Joint Surg Br 2002;84(2):196–201.
26 Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Spontaneous production of monocyte chemoattractant protein-1 and interleukin-8 by the human lumbar intervertebral disc. Spine 2002;27(13):1402–7.
27 Carette S, LeClaire R, Marcoux S, Morin F, Blaise GA, St-Pierre A, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. N Engl J Med 1997;336(23): 1634–40.
28 Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66(8):271–3.
29 Fairbank JC, Pynsent PB. The Oswestry Disability index. Spine 2000;25(22):2940–53.
30 Karppinen J, Korhonen T, Malmivaara A, Paimela L, Seitsalo S, Hurri H. Treatment of sciatica with infliximab, a monoclonal humanised chimaeric antibody against TNF-alpha. Suomen ortopedia ja traumatologia 2002;25(2):249–52.
31 Byrod G, Olmarker K, Konno S, Larsson K, Takahashi K, Rydevik B. A rapid transport route between the epidural space and the intraneural capillaries of the nerve roots. Spine. 1995; 20(2):138–43.
32 Lipetz JS. Pathophysiology of inflammatory, degenerative, and compressive radiculopathies. Phys Med Rehabil Clin N Am 2002;13(3):439–49.
33 Geurts JW, Kallewaard JW, Richardson J, Groen GJ. Targeted methylprednisolone acetate/hyaluronidase/clonidine injection after diagnostic epiduroscopy for chronic sciatica: a prospective, 1-year follow-up study. Reg Anesth Pain Med 2002;27(4): 343–52.
34 McGregor AH, Hughes SP. The evaluation of the surgical management of nerve root compression in patients with low back pain: Part 1: the assessment of outcome. Spine 2002;27(13): 1465–70.F:138–43.

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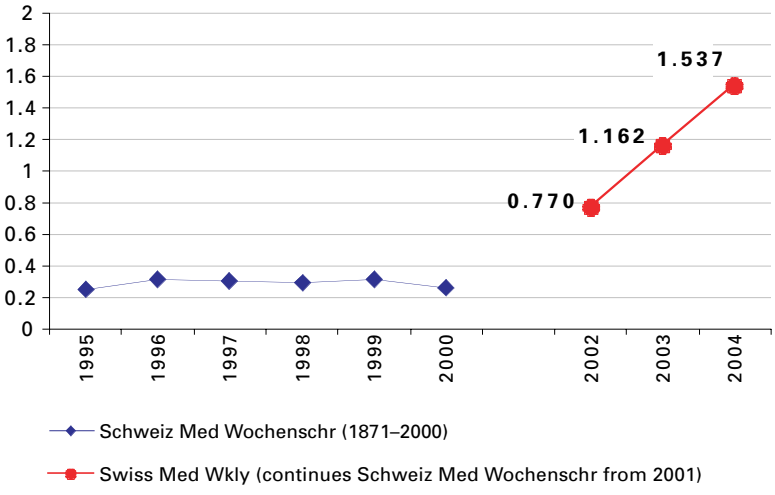

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