Adalimumab for the Treatment of Refractory Sciatica Induced by Disc Prolapse

Abu Dhabi Experience

*Al Izzi M.,**Hussein I.,**Mahmoud N.

*Division of Rheumatology, Department of Internal Medicine, Zayed Military Hospital, Abu Dhabi, UAE

**Division of Rheumatology, Department of Internal Medicine, Mafraq Hospital, Abu Dhabi, UAE

Abstract:

Ten patients with back pain and sciatica were selected according to certain inclusion criteria for a study to assess the efficacy of the Anti TNF agent Adalimumab in the treatment of refractory sciatica pain induced by a lumbar disc prolapse in patients who failed to improve following lumbar epidural steroid or disc surgery. Each was given a subcutaneous injection of 40mg Adalimumab repeated after two weeks. Patients were assessed regularly on weeks 0, 2, 4 and 8 employing the Visual Analogue Score (VAS) for leg pain and back pain and the Straight Leg Raising (SLR) test. The median improvement of the leg pain VAS was 55. Median improvements of back pain VAS was 37. Median improvement of the SLR was 45. The study demonstrated the beneficial effect of adalimumab therapy in reducing the back and leg pain associated with sciatica in this difficult to treat group of patients. The improvement of leg pain was more significant than that of back pain. The response was better in patients with symptoms of shorter duration and with less SLR restriction at base line.

Key words: Adalimumab, Anti TNF, Sciatica

Introduction:

The presence of a herniated lumbar disc is generally considered as the leading cause of sciatica but recent knowledge indicates that inflammatory mechanisms including expression of IL-1 beta and TNF-alpha might also contribute to the pathophysiology of sciatica.[1]

The fundamental involvement of the Tumor Necrosis Factor (TNF) alpha in generating the inflammatory response in a large number of acute and chronic systemic inflammatory disorders is well established. The favorable therapeutic outcomes of TNF alpha inhibition in the treatment of such disorders as rheumatoid arthritis, spondyloarthropathies and other systemic connective tissue diseases has now been extended into conditions in which the inflammatory process is localized such as that found in discogenic radiculopathy.[2]

Herniated discs contain large amounts of (TNF-alpha) which can induce acute and chronic inflammation and pain, it has been demonstrated recently that TNF-alpha inhibitors are able to prevent the occurrence of pain in an experimental model of sciatica.[3,4]

The purpose of this study was to evaluate the efficacy of adalimumab, a TNF-alpha inhibitor, for patients with severe sciatica who were resistant to other forms of treatment including lumbar epidural steroids and disc surgery.

Methods:

Ten patients older than 18 years attending the rheumatology clinic with back pain and sciatica were selected for the study. All patients signed a written informed consent. NSAID doses were kept stable throughout the study. No corticosteroid therapy was permitted during the study period.

Inclusion Criteria

1. Patients presenting a characteristic leg pain in the L4, L5, or S1 territories.
2. Positive straight-leg-raising test with an elevation of less than 70°
3. Severe radicular type of pain grade 70 or over on VAS scale.
4. Chronic pain, occurring daily for at least 3 months and over.
5. Treatment resistance as evidenced by lack or partial response following disc surgery or epidural steroid injections.
6. A confirmed herniated disc on usual imaging techniques (CT scan or MRI) in the vicinity of the clinically involved nerve root.

Address for correspondence:
Mustafa Al Izzi, MD, MRCP(UK), FRCP(Edin)
Consultant Rheumatologist, Zayed Military Hospital
P. O. Box 61775, Abu Dhabi, UAE
E-mail: **musizi@hotmail.com**

Exclusion Criteria

1. The presence of recent (<48 hours) severe motor weakness (<3/5) or clinical signs of cauda equina compression, requiring immediate surgery
2. Co-morbidities such as:
   - Co-existing infections or a past history of tuberculosis
   - Autoimmune disease
   - History of cancer or malignant lymphoproliferative disorders (unless the patient has been declared in remission for more than 5 years)
   - History of demyelinating disorders
3. Pregnancy

Assessment Parameters

- Radicular leg pain using the VAS from (0–100 mm).
- Low back pain using the VAS from (0–100 mm).
- Sciatic irritation using SLR angle measurement (0-90).

Assessments were done on weeks 0, 2, 4, and week 8.

Drug Administration

Each of the 10 patients was given a subcutaneous injection of Adalimumab 40 mg which was repeated after two weeks.

Statistical Analysis

Baseline values were compared using two sample t-tests, within group changes from baseline to the 2, 4, and 8 weeks assessments were examined by paired samples t tests, and group differences were assessed using analysis of variance (ANOVA). A p value < 0.05 was considered to be significant.

Results:

Ten patients were recruited into the study, seven males and three females. Mean age was 47 years, with a mean duration of symptoms of 17 weeks.

We found a significant difference in leg pain starting from week 2, 4, and week 8 when compared with the pain at base line ($p < 0.05$). The decrease of pain was gradual during the study period **(Table 1)**.The median reduction in VAS score leg pain was 55. Also there was significant difference ($p<0.05$) in leg pain in week 2 when compared with weeks 4 and 8 **(Figure 1)**.

Back pain showed a statistical significant decrease ($p<0.05$) in all weeks (2,4 & 8) when compared with baseline. The median VAS score reduction in back pain was 37. This improvement was gradual and was maintained all through the study period **(Table 1 and Figiure 2)**.

Table 1: Assessment Variables at Baseline 2,4,& 8 weeks

Variable	Baseline	2 weeks	4 weeks	8 weeks	P=value
Leg Pain	83.67	62.68	43.10	29.54	< 0.001
Back Pain	72.02	49.70	36.11	28.01	< 0.001
S L R	24.81	45.66	58.85	71.80	< 0.001

Values are presented as mean VAS, SLR, P-value for week 8 compared to baseline

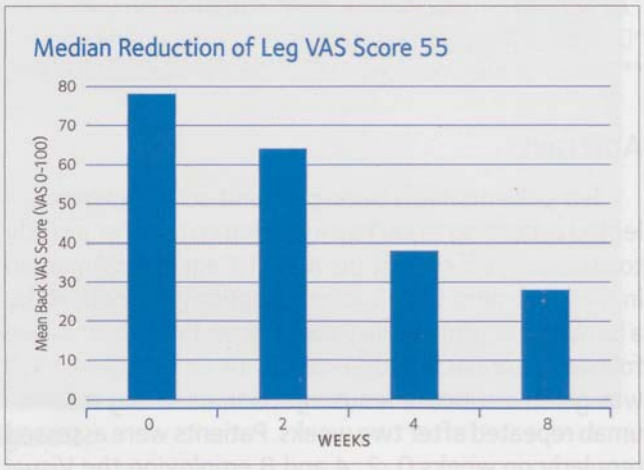

Figure 1: Median VAS score of leg pain in week 2, 4, & 8

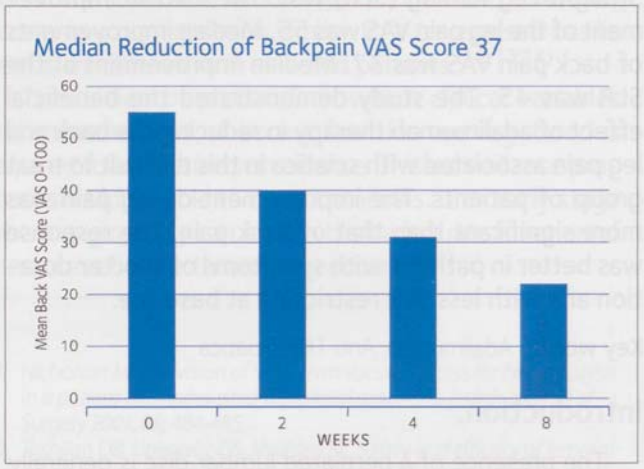

Figure 2: Median VAS score of back pain in week 2,4,& 8

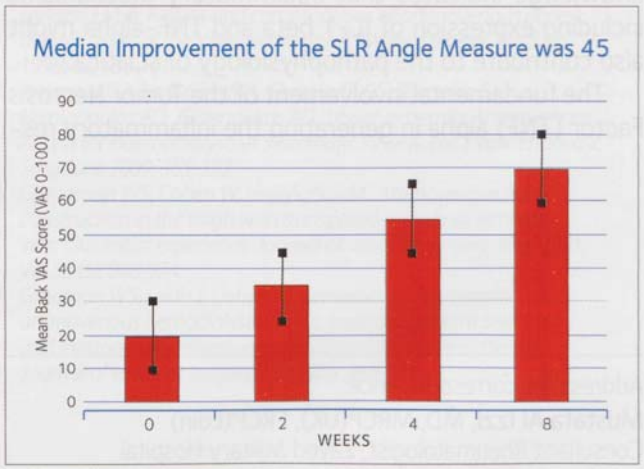

Figure 3: Median Improvement of SLR in week 2, 4, & 8

The sciatic roots irritation was measured using the SLR angle, a significant gradual decrease ($p<0.05$) at week 2, 4, and 8 when compared to baseline. The median SLR angle improvement was 45 **(Figure 3)**.

Discussion:

The therapeutic potentials of Anti TNF agents has been shown in a large variety of immune-mediated inflammatory disorders such as ankylosing spondylitis, psoriasis, and psoriatic arthritis in addition to its proven role in rheumatoid arthritis and Crohn's disease.[5]

Since 1934, a link was demonstrated between disc herniation and sciatica and it was accepted that compression of the nerve root by the herniated disc explained the sciatica. Surgical treatment became a standard after failure of conservative therapy. This has been known as the mechanical theory.[6]

There has been good evidence from a number of studies that the exposed herniated nucleus pulposus can initiate a local inflammatory reaction at the level of the disc and adjacent nerve roots in which the secretion of TNF is abundant aggravating the radiculitis component of the sciatic pain even in the absence of demonstrable compression of the roots as evident by Magnetic Resonance Imaging (MRI) studies.[7] That is supported by the fact that laminectomy is sometimes ineffective, a considerable amount of severe sciatica patients have no visible root compression on MRI imaging, a large proportion of visible root compression on MRI are asymptomatic, and that there is a poor correlation between the severity of the sciatic pain and the extent of disc herniation.[2]

TNF-a has been established as an important mediator in intervertebral disc herniation-induced sciatica in animal models in a number of studies.[3,8,9] As steroids can be effective in acute disease anti-TNF agents seem to make some sense in acute disease as well.

Among the factors that suggested a potential benefit from use of TNF inhibitors in disc herniation-associated radiculopathy are that the "Chemical" effects of a herniated nucleus pulposus (NP) material can resemble the effects of TNF-a locally applied; also blocking of these effects by doxycycline and partial blocking by anti-TNF monoclonals; sensitization by TNF-a of nerve roots that have been subjected to mechanical stress; and the presence of TNF-a in neurons and Schwann cells.[10]

It seems that both the mechanical and chemical components each play a part, acting synergistically, with the chemical component having a dominating effect at an initial stage, it thus appears that even in the absence of mechanical compression , substances secreted by the nucleus pulposus can provoke functional and structural abnormalities of the nerve root.[11] Hence, TNF-a appears to be able to sensitize the nerve root to pain when the latter has previously been subjected to mechanical stress, a hypothesis that is compatible with current understanding of the physiopathology of disc-induced sciatica.[12]

One of the first anti-TNF alpha therapies used was infliximab. The results of one uncontrolled study showed a beneficial effect of a single infusion of infliximab 3 mg/kg for disc herniation-induced sciatica over a 1-year follow-up period.[13]

Following good results in two open-label studies of infliximab in patients with sciatica the first randomized, controlled, double-blind trial comparing infliximab (5 mg/kg) with placebo was undertaken by Korhonen et al in 2005.This trial, dubbed the Finnish Infliximab Related Study (FIRST II), was meant to confirm the efficacy of a single infusion of infliximab for sciatic pain. Forty patients with unilateral moderate to severe sciatic pain and MRI-verified disc herniation were randomized to a single infusion of either infliximab or placebo. The primary end point was a reduction in leg pain from baseline to 12 weeks. The investigators found significant reductions in leg pain in both groups. Seven patients in each group required surgery. The researchers concluded that the results of this trial do not support the use of infliximab for lumbar radicular pain in patients with disc herniation induced sciatica.[14]

In another study by Brennan, et. al. nine subjects with sciatica received a single 40mg subcutaneous injection of adalimumab. The study showed a significant improvement in leg pain ($p=0.000$) but there was no difference in global back pain ($p=0.883$). Their results were consistent with our results as far the improvement of leg pain but the back pain improvement probably needed a second dose of adalimumab. They concluded that this preliminary work suggested a possible benefit from adalimumab in reducing the leg pain and back-related disability associated with sciatica.[15]

In an open study by Genevay, which used the anti-TNF alpha drug etanercept, 25 mg subcutaneous injection were given on days 1, 4 and 7 to 10 patients with sciatica of less than eight weeks duration. The results showed improvement at day 10 for all patients; 9/10 patients continued to improve between day 10 and week 6.[16]

Our results demonstrated that adalimumab therapy produced a rapid improvement in leg, and back pain among patients with sciatica. Two weeks after injection, leg and back pain decreased significantly when compared with base line. This improvement was sustained over the period of the study. The SLR angle showed a significant improvement when compared with baseline. The improvement started at week 2 and then continued all through the weeks of the study.

In conclusion, this uncontrolled prospective study has demonstrated a beneficial effect of, adalimumab therapy in reducing the back and leg pain associated with refractory sciatica. The improvement of leg pain was more significant than that of back pain. The response was better with symptoms of shorter duration and with less SLR restriction at the baseline.

Limitations of this study are the rather small number

of patients in the sample and the lack of a formal control group in which a placebo response could have been elicited. Nevertheless, the results do highlight the potential therapeutic use of this form of therapy.

References:

1. *Le Maitre CL, Hoyland JA, Freemont AJ. Catabolic Cytokine expression in degenerated and herniated human intervertebral discs: IL-1beta and TNF-alpha expression profile. Arthritis Res Ther 2007; 9(4): R77*
2. *Podichetty VK. The aging spine: The role of inflammatory mediators in intervertebral disc degeneration. Cell Mol Biol 2007; 53(5): 4-18.*
3. *Igarashi T, Kikuchi S, Shubayev V. Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology: molecular, histologic, and behavioral comparisons in rats. Spine 2000; 25: 2975-80.*
4. *Modic MT, Ross JS. Lumbar degenerative disc disease. Radiology 2007; 245(1): 43- 61.*
5. *Taylor PC, Williams RO, Feldmann F. Tumor necrosis factor as a therapeutic target for immune mediated inflammatory diseases. Curr Op Biotech 2004; 15(6): 557-583.*
6. *Mixter W. Rupture of the intervertebral disc with involvement of the spinal canal. NEJM 1934; 211: 210-115.*
7. *Peng B, et al. Chemical radiculitis. Pain 2007; 127(1-2): 11-16.*
8. *Aoki Y, Rydevik B, Kikuchi S. Local application of disc-related cytokines on spinal nerve roots. Spine 2002; 27: 1614-1617.*
9. *Onda A, Yabuki S, Kikuchi S. Effects of neutralizing antibodies to tumor necrosis factor-alpha on nucleus pulposus-induced abnormal nociresponses in rat dorsal horn neurons. Spine 2003; 28: 967-972.*
10. *Seguin CA, Pilliar RM, Roughley PJ. Tumor necrosis factor-alpha modulates matrix production and catabolism in nucleus pulposus tissue. Spine 2005; 30(17): 1940-1948.*
11. *Mulleman D. Pathophysiology of disc related low back pain and sciatica. Evidence supporting treatment with TNF-alpha antagonists. Joint Bone Spine 2006; 73(3): 270-277.*
12. *Goupille P, Mulleman D, Valat JP. Radiculopathy associated with disc herniation. Ann Rheum Dis 2006; 65:141-143.*
13. *Korhonen T, Karppinen J, Malmivaara A. Efficacy of infliximab for disc herniation-induced sciatica: One-year follow-up. Spine 2004; 29: 2115-2119.*
14. *Korhonen T, Karppinen J, Paimela L. The treatment of disc herniation-induced sciatica with infliximab: results of a randomized, controlled, 3-month follow-up study. Spine 2005; 30: 2742-2748.*
15. *Brennan S, Vanharanta H, Keenan A, et al. Treating sciatica with adalimumab: a pilot study. EULAR 2004; Berlin, Germany. Abstract SAT 0146.*
16. *Genevay S, Stingelin S, Gabay C. Efficacy of etanercept in the treatment of acute and severe sciatica: a pilot study. Ann Rheum Dis 2004; 63: 1120-1123.*