AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Etanercept – A Review on its drug delivery

Varun Mali[1]

1.UCL School of Pharmacy, University College London, U.K.

ABSTRACT

Etanercept is a fusion protein, prescribed primarily for moderate to severe rheumatoid arthritis and psoriatic arthritis. It is being marketed under the brand name of Enbrel. The mechanism of action of this drug includes its ability to bind competitively to Tumor Necrosis Factor TNF alpha and thus prevents interactions with its cell surface receptors leading to inhibition of TNF alpha. Enbrel is available for subcutaneous administration in three dosage forms, a multiple use vial, a prefilled syringe and an auto-injector pen. The latter forms elicit better patient compatibility along with dose accuracy. Studies on other routes of administration of this Etanercept along with innovation in the drug delivery are discussed in the essay. A study discusses the feasibility of conjugating TNF antagonist pharmaceutical preparations with gold nanorods and preservation of the mechanism of action of anti-rheumatic drugs along with preliminary evaluation of novel PAT (Photoacoustic tomography) technology in imaging optical contrast agents conjugated with etanercept. Secondly an investigation of pharmacokinetics and safety of intravitreal delivery of etanercept is done. Lastly Epidural drug delivery of entanercept in treatment for lumbosacral radiculopathy is evaluated. Thus this second generation biopharmaceutical not only holds a promise for a wide range of therapeutics but also proves to be compatible with different approaches in drug delivery.

Keywords: etanercept, enbrel, biopharmaceutical, TNF

*Corresponding Author Email: varunmali004@gmail.com

Received 26 June 2013, Accepted 08 July 2013

Please cite this article in press as: Mali V. Etanercept – A Review on its drug delivery. American Journal of PharmTech Research 2013.

INTRODUCTION

Etanercept is a second generation biopharmaceutical developed for the treatment of autoimmune disease like rheumatoid arthritis and ankylosing spondylitis[1]. It can be classified as a recombinant fusion protein consisting of the extracellular, ligand binding portion of the human tumour necrosis factor (TNF) receptor (p75), linked to the F_c portion of a human IgG antibody [2] It is the first recombinant human protein which has been approved by Food and Drug administration (FDA) for the treatment of psoriatic arthritis [3]. Etanercept (Enbrel®) is marketed by Pfizer and Amgen.

Protein structure:

Etanercept, is a recombinant human TNFR (Tumor Necrosis Factor Receptor) p75-Fc fusion protein (TNFR:Fc), intended for therapeutic neutralization of TNF-alpha. TNFR:Fc is hence a recombinant form of the human p75 sTNFR fused to the Fc fragment of human immunoglobulin Gl (IgG1) (shown in figure.1). This results in a molecule, TNFR:Fc, which is a dimer consisting of two sTNFR molecules per Fc molecule expressed in mammalian cells. The Fc domain contains the C_{H2} and C_{H3} regions but not the C_{H1} region. Etanercept is made up of totally 934 amino acids, with a molecular weight of approximately 150 kd, It is synthesized by recombinant technology in a Chinese hamster ovary mammalian expression system. Each molecule of this fusion protein can bind two molecules of TNF-alpha, thereby removing TNF-alpha from the circulation. Etanercept can thus be categorised broadly as a TNF-alpha antagonist [4].

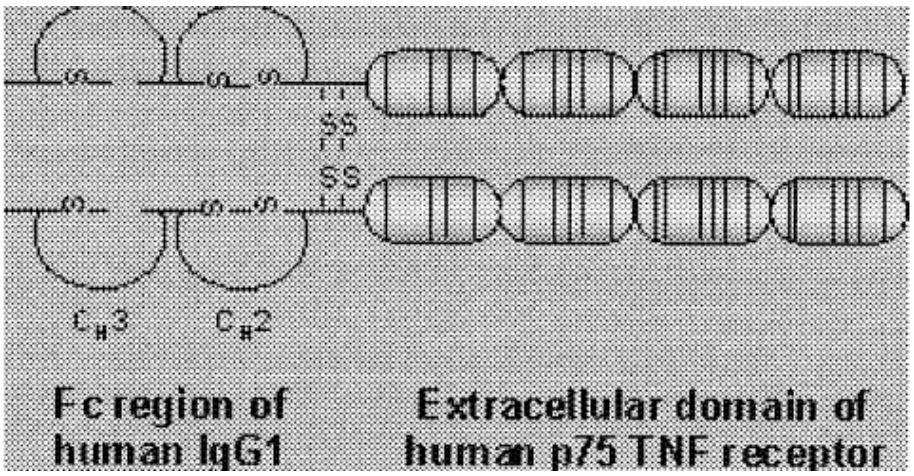


Figure.1 Structure of recombinant form of the human p75 sTNFR fused to the Fc [4]fragment of human immunoglobulin Gl (IgG1)

Mechanism of action:

TNF alpha–mediated event are progressed by the binding of TNF alpha homotrimers to cell surface receptors, followed by multimerization of these receptors and subsequent signal

transduction through the receptor's intracellular domains. These events are shown schematically in Figure 2. Naturally occurring soluble forms of the TNF alpha receptors act as competitive inhibitors for binding of TNF alpha to cell surface receptors. Since natural antagonists do not suffice the blocking action of elevated TNF alpha protein levels as in the case of most inflammatory disorders. Etanercept binds competitively to this pro-inflammatory cytokine and thus prevents interactions with its cell surface receptors leading to inhibition action of TNF alpha. Dimeric etanercept helps in binding of the protein to two free, or receptor bound molecules of TNF alpha with more affinity around 50 to 1000 times than soluble monomeric forms of the TNF alpha receptor. The increased binding affinity of etanercept enhances the TNF alpha-inhibitory activity observed with dimeric forms of the recombinant receptor compared to naturally occurring monovalent forms [3].

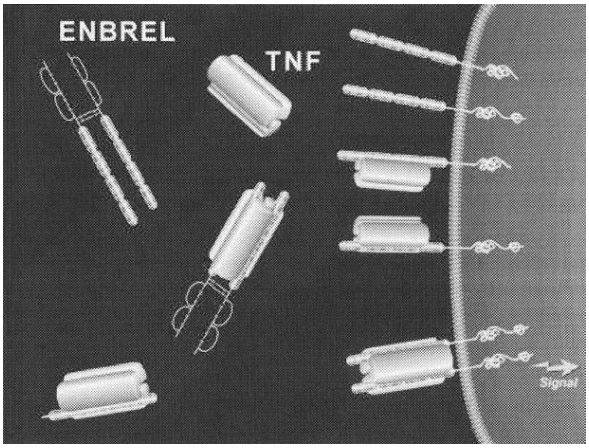


Figure.2 Mechanism of action of Etanercept [3]

Clinical use:

Table 1: EMEA 2004 report on indications and dosing for Enbrel:

Rheumatoid arthritis	Psoriatic arthritis and ankylosing spondylitis	Plaque psoriasis
25 mg Enbrel administered twice weekly is the recommended dose, alternatively, 50 mg administered.	25 mg Enbrel administered twice weekly is the recommended dose. Doses other than 25 mg administered twice weekly have not been studied.	The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

Pharmacology:

In rheumatoid arthritis ENBREL is prescribed as a 25 mg single subcutaneous (SC) injection,

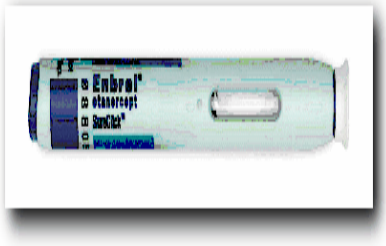
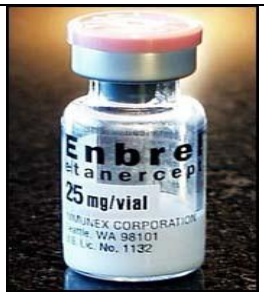
studies elicit a half-life of 102 ± 30 hours with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (Cmax) of 1.1 ± 0.6 mcg/mL and time to Cmax of 69 ± 34 hours is also reported in patients following a single 25 mg dose.

Side-effects:

The major side-effects of the drug reported in a few instances include relapse of tuberculosis and hepatitis B, allergic reactions like skin rash and breathing problems, lymphoma was also reported in certain cases due to suppression of the immune system and blood disorders like reduction in blood cells is also seen.

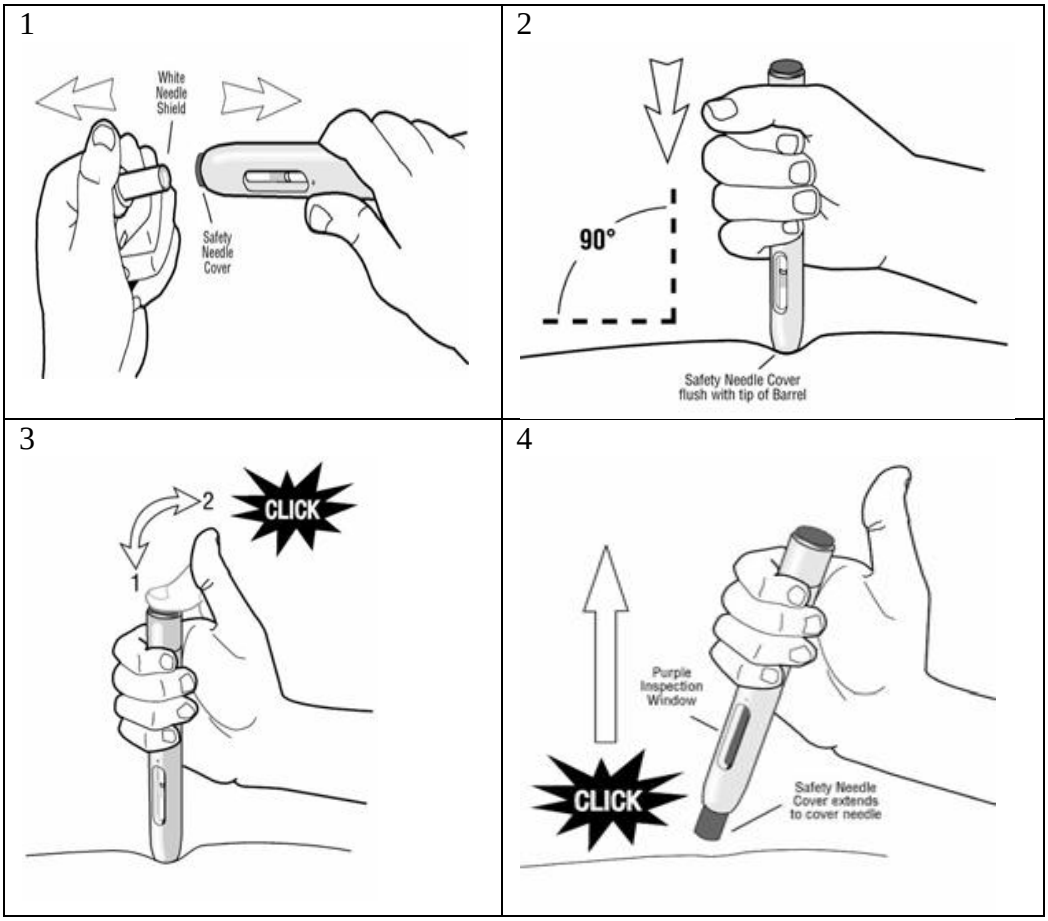
Drug delivery:

Table 2: Dosage forms for Enbrel

ENBREL® single-use prefilled syringes	**ENBREL® SureClick™ autoinjectors**	**ENBREL® multiple-use vial**
		
Available in 50 mg (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.94 mL) dosage strength. Prefilled syringes and autoinjectors are intended for subcutaneous injection.		ENBREL® multiple-use vial is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge ½ inch needle, one vial adapter, and one plunger. Each carton contains four "Mixing Date:" stickers. A single dose replacement tray is available, if needed. contains sterile, white, preservative-free lyophilized powder. Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection (BWFI), USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colourless solution with a pH of 7.4 ± 0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.
The solution of ENBREL® is clear and colourless, sterile, preservative free, and is formulated at pH 6.3 ± 0.2. Each ENBREL® single-use prefilled syringe and SureClick™ autoinjector contains 50 mg/mL solution of etanercept with 1% sucrose, 100 mM sodium chloride, 25 mM L-arginine hydrochloride and 25 mM sodium phosphate. ENBREL® 50 mg single-use prefilled syringes and ENBREL® 50 mg single-use prefilled SureClick™ autoinjectors are supplied in cartons containing four syringes or autoinjectors with 27-gauge, ½ inch needles. A single syringe or autoinjector replacement carton is available if needed.		

The auto-injectors are preferred due to high patient compatibility and also dose accuracy. It is administered in the following steps:

Table 3: Steps for administration of Enbrel:



A recent finding suggests the decrease in the dosing frequency from 50 mg per week to 25 mg per week which induced important biological and clinical relief in some patients with rheumatoid arthritis or spondylarthropathy [1].

Intra-articular drug delivery of etanercept- conjugated with gold nanoparticles:

An interesting innovation in drug delivery system uses Photoacoustic tomography (PAT) of joints aided by an Etanercept-conjugated gold nanoparticle contrast agent with an ex *vivo* preliminary rat study. The study explores the potential of an emerging hybrid imaging technology—photoacoustic tomography—in noninvasive monitoring of Etanercept drug delivery. Etanercept was conjugated with gold nanorods acting as contrast agent, followed by ELISA experiments to confirm the conjugation and to prove that the conjugated anti-TNF-α drug was biologically active. PAT of *ex vivo* rat tail joints with the joint connective tissue enhanced by intra-articularly injected contrast agent was conducted to examine the performance of PAT in visualizing the distribution of the gold-nanorod-conjugated drug in articular tissues (Figure.3). By using the described system, gold nanorods with a concentration down to 1 pM in phantoms or 10 pM in biological tissues can be imaged with good signal-to-noise ratio and high spatial

resolution (figure 4). Thus the feasibility of conjugating TNF antagonist pharmaceutical preparations with gold nanorods, preservation of the mechanism of action of anti-rheumatic drugs along with preliminary evaluation of novel PAT technology in imaging optical contrast agents conjugated with etanercept is studied [5].

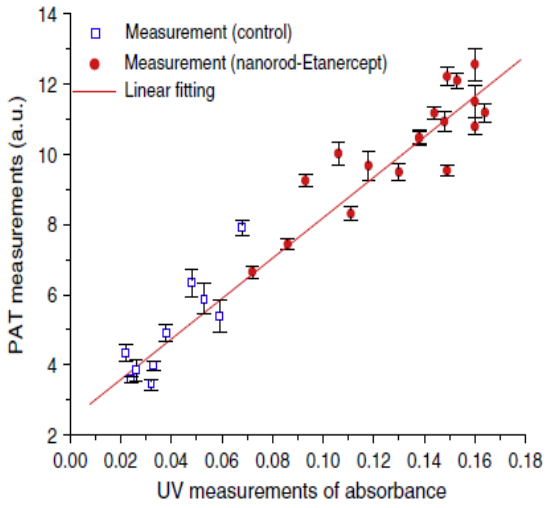


Figure 3. Photoacoustic measurements of the optical absorbance of ELISA wells in comparison with the UV/vis readouts.

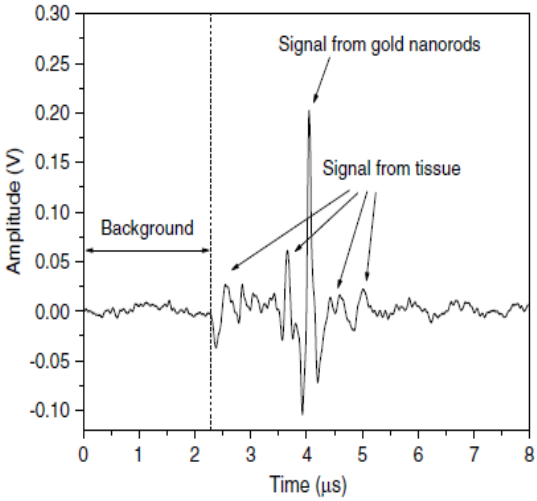


Figure 4. A-line photoacoustic signal from the imaged rat tail joint with the contrast enhanced by the gold nanorods.

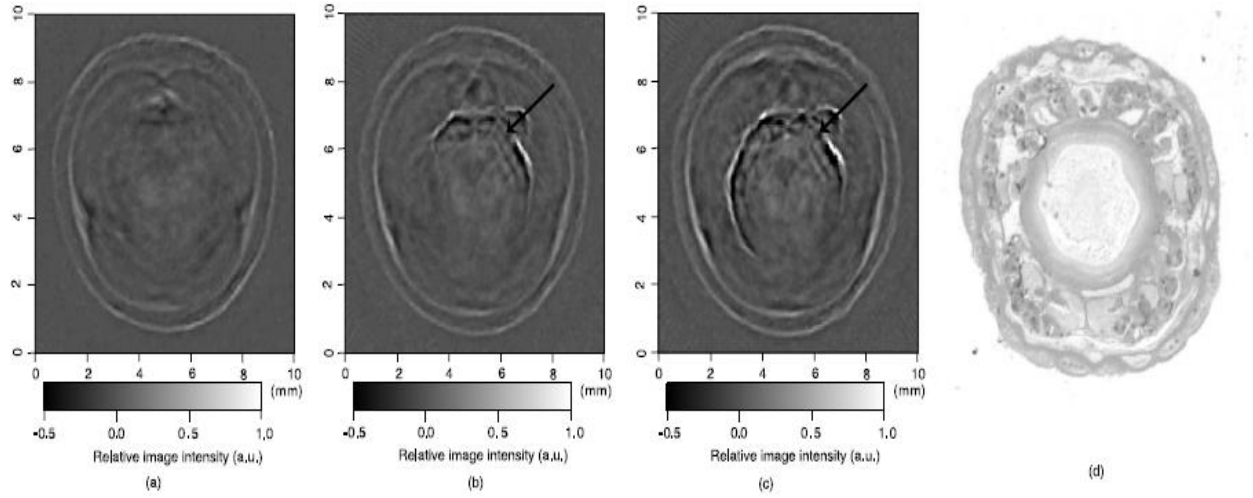


Figure 5. 2D cross-sectional PAT of a rat tail joint. (A) Image based on intrinsic contrast, which was taken before the administration of the contrast agent. Images taken after (B) the first and (C) the second administration of Etanercept-conjugated gold nanorods. For each administration, 0.025 ml agent with a 10 pM concentration was injected intra-articularly through the arrows in the images. (D) Histological photograph of a similar cross section in a rat tail joint showing the morphological features including intra-articular tissue, vessels and muscle.

Drug Delivery Of Etanercept Intravitreally

Apart from the main indication in rheumatoid arthritis, experiments conducted with etanercept in a rat model of diabetic retinopathy demonstrated that the drug reduces leukocyte adhesion, blood–retina barrier breakdown and endothelial injury. The intravitreal route of administration is beneficial in minimizing systemic side effects and also aids in delivering the drug locally.

The study thus involves investigation of pharmacokinetics and safety of this route of administration. After intravitreal injection of high doses of etanercept (100 g per eye), no signs of toxicity were found on evaluation of data from clinical examination, histology, ERG, and VEP. Also after an observation time of up to 8 weeks etanercept did not induce any pathological changes. Function and structure were the same as in control eyes. The vitreous showed no opacities or bands formation. Such signs of toxicity can be found, for example, with intravitreal amphotericin B injections. With increasing doses (10–50 g), retinal ganglion cell loss and focal necrosis of the nerve fiber layer became also apparent.

Fluorescence-labelled etanercept was injected in two doses (5 g and 50 g) intravitreally and the amount of the protein was determined in vitreous, retina, and choroid at 0, 2, 4, and 8 weeks after injection. By using gel filtration, only the amount of intact etanercept was determined. Therefore, a decrease in biological activity by decay of etanercept can be ruled out. In the vitreous, the amount of etanercept gradually declined up to the 8th week after injection. In both the retina and the choroid, a slow accumulation was found with a peak at 4 weeks. After 8 weeks, etanercept was still clearly detectable (figure 6). The pharmacokinetics of etanercept after intravitreal delivery ensure high concentrations of the drug in the target tissue over several weeks and offer the chance of a successful therapy. The relatively high molecular size of etanercept results in slower clearance than, for example, with triamcinolone. After injection of 400 g triamcinolone acetonide, the half-life as determined by HPLC was 1.6 days. Dexamethasone, another glucocorticoid, has a half-life of only 2.5 h in physiologic saline. In summary, the results show that intravitreally delivered etanercept is safe and leads to high concentrations in the retina and choroid over several weeks [6].

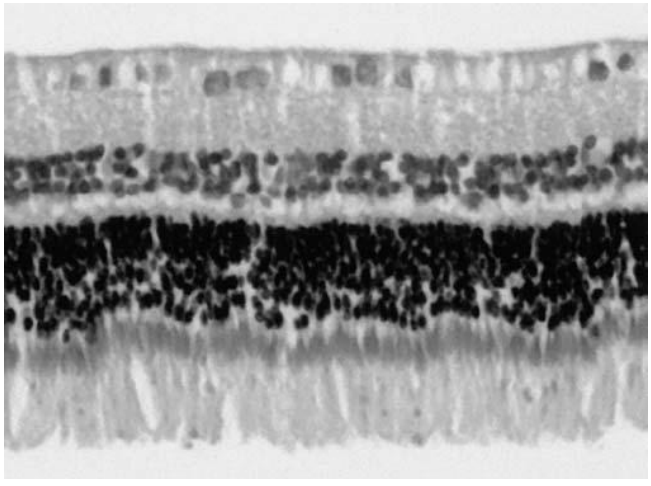


Figure. 6: Section of a rabbit retina 8 weeks after injection of 100 g etanercept into the vitreous. No signs of toxicity are found. The Retina shows normal tissue structures. [6]

TRANSFORAMINAL EPIDURAL DRUG DELIVERY OF ETANERCEPT:

Recent evidence implicates the inflammatory cytokine tumor necrosis factor as a major cause of radiculopathy. Yet, whereas open-label studies with systemically delivered tumor necrosis factor inhibitors have yielded positive results, a placebo-controlled study failed to demonstrate efficacy. One variable that may have contributed to poor outcomes is low drug levels at the site of nerve inflammation. Till date, no studies have been conducted which evaluate the efficacy and safety of epidurally administered anti–tumor necrosis factor agents. This study involves a double-blind, placebo-controlled, dose-response to evaluate an epidural tumor necrosis factor inhibitor. Twenty-four patients with subacute lumbosacral radiculopathy were randomly assigned to receive two transforaminal epidural injections of 2, 4, or 6 mg of entanercept 2 weeks apart in successive groups of eight. In each group, two patients received epidural saline. A parallel epidural canine safety study was conducted using the same injection doses and paradigm as in the clinical study. The animal and human safety studies revealed no behavioral, neurologic, or histologic evidence of drug-related toxicity. In the clinical arm, significant improvements in leg and back pain were collectively noted for the etanercept-treated patients, but not for the saline group, one month after treatment. One patient in the saline group (17%), six patients in the 2-mg group (100%), and four patients each in the 4-mg and 6-mg groups (67%) reported at least 50% reduction in leg pain and a positive global perceived effect one month after treatment. Six months after treatment, the beneficial effects persisted in all but one patient. Thus Epidural drug delivery of entanercept holds promise as a treatment for lumbosacral radiculopathy [7].

CONCLUSION:

Although development and delivery of biopharmaceuticals has always been challenging but a lot of research for exploring the therapeutic range of Etanercept is being carried out. A novel approach involving therapeutic delivery of etanercept across the dura via the cerebrospinal venous system was reviewed, since excess TNF is centrally involved in the pathogenesis of various neuro-inflammatory disorders, like Alzheimer's disease and related disorders. Upon administration of etanercept, peri-spinally may involve clinical effects related to modulation of synaptic dysregulation produced by excess TNF [8]. On similar lines a study involving targeted drug delivery of etanercept subcutaneously in anatomic proximity to the site of disc was useful in patients with resistant pain associated with cervical disc disease [9]. Thus etanercept serves as a subject for further innovation in drug delivery for two major advantages firstly being its long term data portraying excellent safety profile and secondly and its tolerability in both adult and

paediatric population [3].

REFERENCES:

1. Berthelot J, Varin S, Cormier G, Tortellier L, Guillot P, Glemarec J, Maugars Y. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy; Joint Bone Spine2007; (74):144-147.
2. Chin R, Sherman W, Sander H, Hays A, Latov N. Etanercept (Enbrel) therapy for chronic inflammatory demyelinating polyneuropathy; J Neurological Sciences 2003; 210:19– 21
3. Goffe B, Cather J. Etanercept: An overview. J Am Acad Dermatol 2003; (49.2):S105-S111
4. Goldenberg M. Etanercept, a Novel Drug for the Treatment of Patients with Severe, Active Rheumatoid Arthritis. Clinical Therapeutics 1999; (21. 1):75-87
5. Chamberland D, Agarwal A, Kotov N, Fowlkes J, Carson P, Wang X. Photoacoustic tomography of joints aided by an Etanercept-conjugated gold nanoparticle contrast agent—an ex vivo preliminary rat study. Nanotechnology 2008; 19 (095101):1-7.
6. Fauser S, Kalbacher H, Alteheld N, Koizumi K, Krohne T, Joussen A. Pharmacokinetics and safety of intravitreally delivered etanercept. Graefe's Arch Clin Exp Ophthalmol 2004;242:582–586
7. Cohen S, Bogduk N, Dragovich A, Buckenmaier C, Griffith S, Kurihara C, Raymond J, Richter P, Williams N, Yaksh T. Randomized, Double-blind, Placebo-controlled, Dose response and Preclinical Safety Study of Transforaminal Epidural Etanercept for the Treatment of Sciatica; Anesthesiology 2009;110:1116–1126.
8. Tobinick E. Perispinal etanercept for neuro-inflammatory disorders. Drug Discovery Today 2009;14, 3/4:168-177.
9. Tobinick E. Targeted Etanercept for discogenic neck pain: Uncontrolled open label in two adults. Clinical therapeutics 2003; 0149:1211-1218.