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Etanercept for the Treatment of Psoriasis

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ABSTRACT

Etanercept has recently been approved for the treatment of moderate-to-severe plaque psoriasis at a dose of 50mg twice per week for 12 weeks followed by a maintenance dose of 50mg once weekly thereafter. Clinical studies have shown excellent efficacy and a good safety profile in patients with psoriasis. Extensive information on etanercept safety is available as this biological agent has been used for many years for other indications such as rheumatoid arthritis, and psoriatic arthritis.

Key Words: *etanercept, plaque psoriasis, Enbrel®, psoriatic arthritis*

Etanercept (Enbrel®, Amgen/Wyeth Pharmaceuticals) is a fusion protein with affinity for soluble tumor necrosis factor alpha (TNF-α) and has been US FDA approved for the treatment of rheumatoid arthritis (RA) since 1998. This biologic treatment is currently approved in several countries, including recent approval in Canada, for the treatment of moderate-to-severe plaque psoriasis. The approved dosage for treatment of psoriasis is 50mg subcutaneous (SC) twice per week for 3 months followed by 50mg once per week thereafter. This dosage regimen is different from the dose commonly used to treat RA, which is 25mg SC twice weekly.

Current Therapies for Psoriasis

Current treatment options for mild psoriasis include topical treatments such as calcipotriol, corticosteroids, and tar. For patients with more severe or extensive disease, phototherapy, including narrow band UVB and PUVA, has been shown to be very effective. Patients with severe and/or extensive disease, disease unresponsive to topical treatment and phototherapy, or disease that has a severe impact on quality of life, such as hand or foot involvement, are usually candidates for systemic therapy.

The three most frequently used oral medications for psoriasis in North America are methotrexate, acitretin, and cyclosporine. Biologics are a new therapeutics class for the treatment of psoriasis, and three agents are currently approved in the US and Canada for the treatment of psoriasis: alefacept (Amevive®, Biogen Idec), efalizumab (Raptiva®, Serono and Genentech/Xoma), and etanercept (Enbrel®, Amgen/Wyeth Pharaceuticals). This article will review safety and efficacy of etanercept in the treatment of moderate-to-severe plaque psoriasis.

Efficacy of Etanercept in the Treatment of Psoriasis

PASI (Psoriasis area severity index) is the primary endpoint used in studies assessing the efficacy of biologics for the treatment of psoriasis. PASI takes into account the extent of the disease, as well as the severity of erythema, scaling, and thickness in different body areas affected by psoriasis. Clinical improvement in biologics trials

for psoriasis is usually reported as PASI-50 or PASI-75. A PASI-75 represents an improvement in the PASI score of at least 75% as compared with baseline (i.e., before the biologic was administered). Etanercept at a dose of 50mg SC twice per week has been shown to induce a PASI-75 response in 49% of patients after 12 weeks.[1,2] Papp, et al. reduced the dose to 25mg twice per week for an additional 12 weeks and found that the percentage of patients exhibiting a PASI-75 response increased to 54%.[2] In this study, 23% of patients lost their PASI-75 response when the etanercept dose was lowered to 25mg twice weekly; however, only 3% of these patients lost their PASI-50 response.[2] Despite lowering the dose after 12 weeks, 32% of patients who did not reached PASI-75 at week 12 reached PASI-75 at week 24.[2] Studies conducted with 25mg of etanercept twice weekly for 6 months (the last 3 months being open-label) demonstrated that 42%-44% of patients reached PASI-75 at week 24.[1,2]

Studies were also conducted where etanercept was stopped after 3 months of continuous treatment to determine if this would lead to a rebound phenomenon, as this can be seen with other systemic agents used to treat psoriasis. Rebound was defined as an increase in PASI of at least 25% compared with baseline, or an erythrodermic, pustular, or severe inflammatory flare within 12 weeks of treatment cessation. Of the 409 patients studied, only one etanercept treated patient presented with an increase of PASI of more than 25% above baseline.[3] This patient received a lower starting dose of etanercept (i.e., 25 mg weekly.) No cases or erythrodermic or pustular psoriasis were reported, suggesting that etanercept can be safely stopped.

In the same study etanercept was reintroduced when the disease relapsed, and the PASI-75 response was assessed following retreatment. The percentage of patients achieving a PASI-75 response was the same after retreatment as that seen in patients who received etanercept for the first time.[3] These studies suggest that etanercept can be stopped and reinitiated without the induction of rebound or loss of clinical response.

Etanercept has also been shown to reduce the signs and symptoms of psoriatic arthritis and has been approved in the US since June 2002 and in Canada since Jan 2004 for this indication.[4] Etanercept should be considered as a treatment option in patients with both plaque psoriasis and active psoriatic arthritis.

Mechanism of Action

Etanercept binds soluble TNF-α, thus preventing its interaction with TNF-α cell surface receptors. This inhibits the effects of TNF-α in the skin, such as the release of proinflammatory cytokines by keratinocytes and lymphocytes, as well as the increase in expression of adhesion molecules on endothelial cells. This mechanism seems to differ from some of the other TNF-α antagonists that have an affinity for soluble as well as membrane bound TNF therefore enabling cell lysis following interaction with TNF-α.[5,6]

Adverse Events

The current information on etanercept safety comes from clinical studies conducted in patients with various diseases such as psoriasis, psoriatic arthritis, RA, ankylosing spondylitis, and juvenile arthritis as well as from post-marketing experience. To date it is estimated that more than 337,000 patients worldwide, including over 74,000 patients with psoriasis, have received etanercept. Clinical studies are ideal to study the incidence and severity of frequent side-effects but are usually not powerful enough to assess less frequent adverse events. For example, clinical studies conducted with etanercept have given precise information on injection site reactions but cannot adequately assess the incidence of less frequent events such as serious infections.

The most commonly reported adverse event is injection site reactions, which occurred in 14%-20% of patients in psoriasis studies.[1] These are characterized by erythema and edema at injection sites and are usually mild.

Serious infections, sometimes resulting in death, have been reported in patients treated with all anti-TNFα agents including etanercept. In patients with psoriasis who participated in placebo-controlled studies, the number of serious infections per patient per year was similar in patients treated with placebo and patients treated with etanercept.[1,2] In an ongoing long-term, open-label study of patients treated with etanercept for RA, there was no increase in serious infections.[7] There were 1272 patients with either early RA or long-standing RA enrolled in this trial, with some having received continuous etanercept for more than 8 years. The rate of serious infections did not increase over time, and there was no significant difference between what had been observed in the etanercept group vs. the placebo-treated patients, as well as cohorts of patients with RA. The exact role of etanercept in these serious infections is currently unknown.

Cases of demyelinating disorders have been reported in patients treated with anti-TNFα, including etanercept. A study conducted in the past with another anti-TNFα agent (lenercept), used to treat patients with multiple sclerosis, was stopped because of worsening of the disease under study.[8] Cases of new onset multiple sclerosis, exacerbation of established multiple sclerosis, as well as optic neuritis and myelitis have been reported in patients treated with anti-TNFα agents, including etanercept.[9] Some of these cases were reversible upon

cessation of etanercept whereas others were not. In an ongoing long-term, open-label study in patients with RA, two cases of MS were reported.[7] The causality of etanercept in these events as well as the exact risk of demyelinating disease with etanercept is unknown.

Patients with active tuberculosis should not be initiated on anti-TNFα agents. Cases of reactivation of latent TB have been reported with anti-TNFα agents, including etanercept, infliximab and adalimumab.[10] Most cases were reported from patients treated with anti-TNFα antibodies as opposed to the etanercept fusion protein. The current US and Canadian monographs do not require TB screening before initiating etanercept,[9,11] but many physicians currently prefer to perform a purified protein derivative of Mycobacterium tuberculosis (PPD) skin test and/or a chest X-ray. This should at least be considered for patients at higher risk of TB including patients coming from countries where TB is more frequent.

Clinical trials with etanercept, including a long-term, open-label RA trial, have not shown that patients are at higher risk of solid tumors.[7] Cases of lymphoma were reported in patients treated with etanercept.[7] In a long-term, open-label RA study, four cases of lymphoma were reported in patients with early RA and 7 cases in patients with long-standing RA when the expected number, based on the SEER database, were 0.8 and 1.1, respectively.[7] These data should be interpreted with caution as patients with RA are at higher risk of developing lymphoma, and the risk increases with severity of the disease.[12,13] It is currently unknown if the lymphoma cases seen in etanercept treated patients represent the fact that severe patients with RA are more at risk of lymphoma than the general population, or

Adverse Events	Comments
Injection site reactions[1]	• Most common adverse event • Characterized by erythema and edema • Usually mild
Serious infections[1,2]	• Reported with all anti-TNFα agents, including etancercept • Number of events per patient per year for psoriasis patients similar in placebo and etanercept groups
Demyelinating disorders[7]	• Reported in postmarketing experience with etanercept • Cases include - new onset multiple sclerosis (MS) - exacerbation of established MS - optic neuritis - myelitis • Causality and risks are unknown
Tuberculosis	• Anti-TNFα agents should not be given to patients with active TB • Most cases were reported from patients treated with anti-TNFα antibodies as opposed to the etanercept fusion protein • PPD or chest X-ray should be considered at least for patients at risk for TB
Solid tumors/ lymphomas[7,9-11]	• Cases of lymphoma have been reported in RA patients taking anti-TNFα treatments including etanercept; however, patients with RA are at higher risk of developing lymphoma • Whether etanercept has a role in the genesis of lymphomas is currently unknown • Psoriasis patients (not treated with biologics) are also at higher risk of developing lymphomas.
Congestive heart failure (CHF)	• Cases of an increase in pre-existing and new onset CHF have been reported. • The role of etanercept in these cases is unknown.
Hepatitis B Virus (HBV) relapse[16]	• Very rare (<1 adverse event/10,000 treated patients) • Reported for all anti-TNFα agents including etancecept • Patients at risk for HBV should be evaluated for prior evidence of HBV infection before beginning treatment with any biologic agent.

Table 1: Reported adverse events for anti-TNFα agents

if etanercept has a role in the genesis of lymphomas. Interestingly patients with psoriasis (not treated with biologics) have also been reported to have an increased risk of lymphoma.[14]

Cases of an increase in pre-existing as well as new onset congestive heart failure (CHF) have been reported.[9] The role of etanercept in these cases is unknown. Two clinical trials that were designed to assess the safety and efficacy of etanercept in the treatment of CHF were stopped because of lack of efficacy.[9]

Cases of an increase in liver enzymes, as well as cases of liver failure, have been reported in post-marketing experience in patients taking etanercept.[15] It is difficult to assess the relationship of these adverse events to etanercept, as many of these cases occurred in patients taking concomitant hepatotoxic medications or in patients who were previously exposed to hepatotoxic drugs like methotrexate. Health Canada recently sent out a Dear Healthcare Professional letter reporting very rare cases of hepatitis B virus (HBV) in patients receiving biologic agents, including etanercept.[16]

Other side-effects reported with etanercept include an increase in antinuclear antibody (ANA) and anti-dsDNA (double-stranded) antibody sometimes associated with lupus-like symptoms, as well as rare cases of neutropenia, leucopenia, thrombopenia, anemia, or pancytopenia.[9]

Conclusion

Etanercept is a biological agent that has shown excellent efficacy for the treatment of psoriasis. As opposed to other biologics previously approved for psoriasis, etanercept has been extensively used in rheumatology both in adults and in children. The current information on safety is based on more than 337,000 patients treated with the product and includes a long-term, open-label study in patients with rheumatoid arthritis where patients have been on continuous therapy for as long as 8 years.

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Reduction of Face and Neck Laxity With Anchored, Barbed Polypropylene Sutures (Contour Threads™)

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ABSTRACT

The use of nonabsorbable sutures for lifting lax, aging skin is an increasingly popular option for cosmetic surgeons. Contour Threads™ (Surgical Specialties Corp.) are novel modified polypropylene sutures recently approved for this purpose by the US FDA. Design and technical modifications incorporated into this implant may reduce complications and limitations seen with previous, similar products. Early experience has been positive, although the durability of cosmetic effect and the potential for long-term complications remain to be seen.

Key Words: *Contour Threads™, aging skin, suture*

Aging of the face and neck results in ptosis of soft tissues and the appearance of more prominent facial lines.[1] For correction of these changes, surgeons are increasingly reporting procedures with fewer incisions and shorter postoperative recovery periods. Many of these procedures utilize nonabsorbable sutures in the dermis and subcutis to lift lax skin.[2-10] Limitations of these implants have included the protrusion of sutures through the skin,[2-3] asymmetry of cosmetic effect requiring correction with additional sutures,[3-5] and limited durability of effects.[4] A new modified polypropylene suture marketed as Contour Threads™ was approved in 2005 by the US FDA for lifting ptotic skin of the face and neck. This implant is supplied as a 25cm polypropylene suture with a barbed middle portion. It is attached to a 7-inch straight needle distally and a 26mm 1/2 circle taper needle proximally.

There are several potential advantages of this new implant. It is designed to tie with a paired suture and be anchored to underlying fascia or periosteum, theoretically reducing the likelihood of migration and loss of cosmetic effect. Similar to the Isse Endo Progressive Face Lift Suture,[6] and in contrast to the Aptos thread, the barbs along this suture are oriented in only one direction. These unidirectional barbs when combined with more secure anchoring ideally limit and lock motion into one well-controlled vector. This also allows for postoperative correction of asymmetry of tightening. Finally, the suture material is clear, making it difficult to visualize under thin or transparent skin.

Procedure and Technique

Placement of Contour Threads™ to reduce ptosis of the brow, neck, middle and lower face may be performed in an outpatient setting under local anesthesia. The surgeon first establishes the degree and direction of the desired tightening. This determines the course and number of sutures that will be placed. Infiltration of local anesthesia is limited to these lines and the insertion points of the straight needle.

For lifting of the brow, middle, and lower face, 3-4mm incisions for insertion of the straight needle are made posterior to the frontal and temporal hairline. For lifting of the neck, incisions are made posterior to the sternocleidomastoid muscle of the lateral neck. To place an individual thread, the surgeon guides the straight needle through the incision and into the subcutaneous plane. For some anatomic locations, it is advantageous to bend the needle to more easily allow it to follow the curves of the face. The needle is advanced in this plane in a zig-zag movement along the marked trajectory. Once anchored, this zig-zag placement of the suture limits retrograde motion along the suture and results in an implanted suture that is longer than the drawn trajectory. This maximizes the number of barbs in the subcutis and theoretically provides more stability of the translocated skin.

Movement of the needle and suture through the subcutis is generally well tolerated by patients. If the straight needle moves superficially to this plane it is immediately apparent as linear dimpling of the

overlying skin. If the needle enters the deep subcutis or approaches the muscle fascia or periosteum, the patient will report the sensation of pain or pressure. At any point, the straight needle may be partially or completely removed and repositioned.

The straight needle exits the skin inferior to the eyebrow or near the medial face or neck. It is cut from the thread after pulling the attached suture through the skin. This leaves the barbed portion of the thread buried in the subcutis with the free ends extending from the proximal insertion point and the distal medial face exit point. The curved needle on the proximal end of the suture may then be used to anchor the suture near its insertion to the underlying fascia or periosteum. A 3-4mm incision, 1-2cm posterior to the insertion points serves as an exit point for the curved needle after deep suturing to the fascia or periosteum. Greater security of this anchor point is achieved by tying this suture at its proximal end with a paired suture running a similar parallel course in the skin. The resulting knot can be seated in this posterior incision by gentle traction on the distal ends of the paired sutures.

When all planned sutures have been placed and anchored, the patient returns to the seated position. Holding the distal end of the suture protruding from the medial face, brow, or neck with one hand, the surgeon uses the other hand to push the lax skin overlying the suture towards the anchoring point. The unidirectional barbs catch on the fibrous septae of the subcutis preventing retrograde movement. Together, the surgeon and patient decide the degree of tightening along any given suture. The distal end of the suture extending from the medial face, brow, or neck is cut at its exit point and retracts under the skin. Incisions used for insertion of the straight needle and anchoring heal rapidly by secondary intention.

Translocation of the skin along the suture causes the lax skin of the face and neck to accumulate at the hairline and lateral neck. The resulting folds of skin are quickly and almost completely remodeled or redistributed to the scalp and neck in several days to weeks, even in older patients with relatively inelastic skin. Mild complications such as swelling, bruising and subjective feelings of "tightness" usually resolve within 1-3 weeks. Transient neuropathy of the greater auricular nerve has occurred in several patients when using the sternocleidomastoid muscle fascia as an anchoring point on the lateral neck. Leaving the knotted proximal ends of the paired sutures unanchored in the subcutis is a cosmetically acceptable alternative in this location. It is not clear if this will reduce the incidence of mononeuropathy or be as stable as an anchoring point, although preliminary results suggest that the incidence of neuropathy drops significantly with this technique modification.

After the resolution of initial postoperative swelling, any subjective discomfort from tightening or perceived asymmetry of tightening may be addressed without inserting more sutures or creating new incisions. Carefully applied firm retrograde pressure along a suture will result in the focal release of several underlying barbs from their attachment to fibrous septae. This release can be appreciated as a subtle clicking sensation under the surgeon's finger. Threads have been successfully released up to 9 weeks postoperatively.

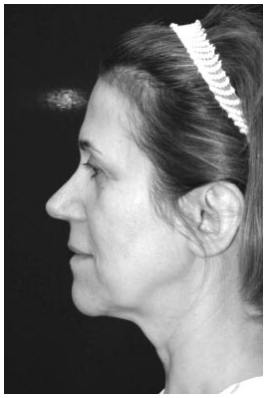

Figure 1: 55-year-old female prior to Contour Thread lift of the neck, middle, and lower face.

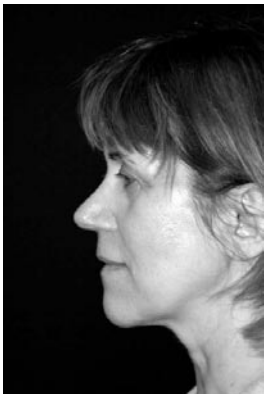

Figure 2: 55-year-old female 8 weeks after Contour Thread lift of the neck, middle, and lower face.

Discussion

Because the Contour Thread™ barbs may be released with intense pressure, patients must initially avoid strenuous exercise or movements that could dislodge the tightened skin from the hundreds of barbs along the sutures. Non-peer reviewed data from the manufacturer demonstrate that in laboratory rats these sutures develop a fibrous capsule that becomes well integrated into the dermis and subcutaneous tissue over several months.[11] Theoretically, a similar process in human skin could lead to a secure and long-lasting cosmetic effect. The actual long-term durability of the tightening effects of these sutures is unknown. Early adopters of this procedure have demonstrated maintenance of cosmetic effects at 6 months.[12]

Outcomes with more than 25 patients at our center for up to 12 weeks have been excellent. All but one of these patients have maintained greater than 90% of their initial correction, and all have been satisfied with their results. One of our earliest patients reported a subjective appreciation of a 50% loss of tightening at 11 weeks. This loss of tightening effect may be a result of the fact that early in our experience we used fewer threads on the middle and lower face than we do now.

Conclusion

The use of barbed sutures appears to be a viable strategy for lifting and repositioning of facial tissue. The recently US FDA approved Contour Threads™ provides advantages to the surgeon and patient that other thread systems do not. However, the early success seen with Contour Thread™ lifts must stand the test of time. Longer follow-up studies are essential, and final judgments as to the utility of these threads cannot be made in the absence of longer term (i.e., greater than 6 months) data.

The optimal techniques for placement and removal of sutures, the consequences of long-term subdermal polypropylene placement, and the potential for revision and retightening of extant sutures should be the subjects of future investigation.

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Class	Name/Company	Approval Dates and Comments
Rosacea	**Doxycycline** *Oracea*® CollaGenex	The US FDA accepted a NDA in October 2005 for this orally administered, systemically delivered drug for the treatment of rosacea.
Atopic Dermatitis Agent	**Hydrogel Dressing** *MimyX*™ *Cream* Stiefel Laboratories	The US FDA approved this topical nonsteroidal treatment in October 2005 for the treatment of atopic dermatitis in patients of all ages. This product provides a new approach for treating AD by restoring the natural structure and components of the stratum corneum, helping to repair and restore skin barrier function.
Anti-aging Treatment	*Aluma*™ *Skin Renewal System with FACES*™ Lumenis	The US FDA approved this new technology in October 2005 for the noninvasive treatment of fine lines and wrinkles. The FACES™ technology combines radiofrequency energy with a vacuum to allow superficial as well as deep dermal heating for effective treatment with a very low risk of adverse events.
Antipsoriatic Agent	**Clobetasol Propionate** *CLOBEX*® *Spray 0.05%* Galderma Laboratories	The US FDA approved this super-high potency corticosteroid in October 2005 for the treatment of moderate-to-severe plaque psoriasis. This product comes in a non-aerosol spray formulation.
Antipsoriatic Agent	**Infliximab** *REMICADE*® Centocor	The US FDA accepted a supplemental Biological License Application (sBLA) in November 2005 for the treatment of moderate-to-severe plaque psoriasis.

Drug News

Oncologic Agent	In October 2005, the independent Data and Safety Monitoring Board (DSMB) recommended that Cancervax and Serono discontinue their Phase 3 clinical trial of Canvaxin™ in patients with Stage III melanoma. The DSMB found that the data are unlikely to provide significant evidence of an overall survival benefit for patients with Stage III melanoma who were treated with Canvaxin™ vs. those who received placebo. These clinical trials were not discontinued because of any potential safety concerns.
Drug Warning	A black box warning was added to the package labeling in the US for the small pox vaccine Dryvax®. The new warning alerts prescribers to the incidence of acute myopericarditis in healthy volunteers. Ischemic cardiac events and fatalities have occurred, but the relationship between these events and the vaccine isn't known. Because of the potential risk, nonemergency use of Dryvax® isn't recommended for patients with risk factors for cardiac disease.
Melanoma Research	Researchers at Northwestern University recently discovered a key signaling mechanism that may promote the ability of highly aggressive malignant melanoma cells to metastasize from a primary tumor to distant sites within the body.* They found elevated activity of an enzyme known as focal adhesion kinase (FAK) in aggressive melanoma cells that correlated with the cells' increased invasion, migration and vasculogenic mimicry behaviors. When FAK signaling was blocked in these cells, they found a reduction in these activities suggesting a new mechanism for promoting melanoma spread. This could provide new insights into possible therapeutic intervention strategies. FAK is important for many cellular processes including cell survival, invasion and migration. **Cancer Res* 65(21):9851-60 (2005 Nov 1).

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