Etanercept, a TNF Antagonist for Treatment of Psoriatic Arthritis and Psoriasis

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ABSTRACT

Etanercept (Enbrel®, Amgen and Wyeth), a tumor necrosis factor (TNF) antagonist, was approved in January 2002, for the treatment of psoriatic arthritis (PsA). The anti-inflammatory effects of etanercept are due to its ability to bind to the pro-inflammatory cytokine TNF, preventing it from interacting with cell-surface receptors and rendering it biologically inactive. Etanercept was evaluated for the treatment of PsA and psoriasis in a preliminary study of 60 patients and in a confirmatory phase III study of 205 patients. In both studies, etanercept was shown to be significantly superior to placebo for the treatment of PsA, evaluated by Psoriatic Arthritis Response Criteria (PsARC) and American College of Rheumatology (ACR) criteria. It also was superior to placebo in improving psoriatic skin lesions, evaluated by the Psoriasis Area and Severity Index (PASI) and target lesion scores. Side-effects were minimal; mild injection site reactions, which resolved during continued therapy, were experienced by approximately one-quarter of the patients. Overall, etanercept is highly effective and well tolerated by patients with PsA, with a safety profile similar to that seen in rheumatoid arthritis. Key Words: psoriatic arthritis, etanercept, tumor necrosis factor

Psoriatic arthritis (PsA), an inflammatory arthropathy, affects 7% to 31% of patients with psoriasis.1,2 This broad range of potential prevalence varies based on the method of case finding and whether the study is population-based or arises from a referral center. PsA is characterized by flares and remissions, but the number of affected joints and the severity of joint damage tend to increase over time. Although oligoarticular presentation is often seen initially, over time up to 61% of PsA patients develop polyarticular disease, and deforming, erosive joint changes have been reported in 40% of patients.3 Nonsteroidal anti-inflammatory drugs and physical therapy may be useful for mild symptoms, but corticosteroids or disease-modifying antirheumatic drugs (DMARDs) are usually required for more severe disease.

Tumor necrosis factor (TNF) is a naturally occurring cytokine that is involved in normal immune responses and inflammatory conditions. Elevated levels of TNF are found in the synovium and psoriatic plaques of patients with PsA.4 TNF mediates a number of biologic processes that can result in joint damage. These include stimulation of bone resorption, inhibition of bone formation, inhibition of proteoglycan synthesis, and induction of collagen- and cartilage-degrading metalloproteinases and prostaglandin E2, as well as further production of TNF and other pro-inflammatory cytokines such as IL-1.5-8
Two TNF antagonists, etanercept (Enbrel®) and infliximab (Remicade®, Centocor), have shown considerable efficacy in the treatment of rheumatoid arthritis and have been approved by the US FDA for this indication. Etanercept has also been approved for the treatment of juvenile rheumatoid arthritis and, in January 2002, for the treatment of PsA. Infliximab has additionally been approved for the treatment of Crohn’s disease. The following is a brief review of phase II and III placebo-controlled trials of etanercept in PsA. The value of anti-TNF therapy is further underlined by preliminary results from a phase II placebo-controlled evaluation of infliximab in PsA. In this trial of 102 patients, infliximab was significantly more effective than placebo in improving both joint symptoms and skin lesions.

**Mechanism Of Action/Pharmacology**

Two distinct TNF receptors, a 55-kilodalton and a 75-kilodalton protein, exist naturally as monomeric molecules on cell surfaces. The biological activity of TNF is dependent on binding to either cell-surface receptor. Etanercept is a dimeric, soluble form of the 75-kilodalton TNF receptor. The anti-inflammatory effects of etanercept are due to its ability to bind to TNF, preventing it from interacting with cell-surface receptors and rendering it biologically inactive. Etanercept can also modulate biological responses that are induced or regulated by TNF, including both expression of adhesion molecules responsible for leukocyte migration and serum levels of cytokines and matrix metalloproteinase-3. Etanercept is self-administered at a dose of 25mg subcutaneously twice weekly. Etanercept may be given as monotherapy or in combination with other DMARDs.

**Clinical Trials**

The efficacy of etanercept in rheumatoid arthritis raised the possibility that this agent might also be efficacious in patients with PsA, thus leading to an initial placebo-controlled, randomized clinical study in which 60 patients with PsA received either etanercept (25mg subcutaneously, twice weekly) or placebo. Patients previously achieving partial benefit from methotrexate were allowed to continue its use. This subgroup of 47% of patients was evenly randomized to placebo or etanercept. Background use of nonsteroidal anti-inflammatory drugs or prednisone ≤10mg/day was allowed. All other DMARDs and topical medicines for psoriasis were discontinued.

The primary arthritis efficacy response measure was the Psoriatic Arthritis Response Criteria (PsARC). Four clinical improvement criteria make up this scale: an improvement of at least 1 unit (0-5 Likert scale) on the physician global assessment, an improvement of at least 1 unit (0-5 Likert scale) on the patient global assessment, and at least 30% improvement in tender and swollen joint counts. To achieve a clinical response, the patient had to improve in two of the four PsARC criteria, one of which was required to be tender- or swollen-joint score, and none of the four scores could worsen. At 12 weeks, 87% of etanercept-treated patients were responders by PsARC criteria compared with 23% of placebo-treated patients (p<0.0001). The effect was rapid. By 4 weeks, 77% of patients receiving etanercept qualified as responders. Also evaluated were the percentages of patients who met the American College of Rheumatology (ACR) criteria for 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvement in rheumatoid arthritis. At 12 weeks, an ACR20 response was achieved by 73% of the etanercept group vs. 13% of the placebo group (p<0.0001); an ACR50 response by 50% vs. 3% (p=0.0001), respectively; and an ACR70 response by 13% vs. 0% (p>0.05), respectively.

Of the 60 patients with active PsA, 38 (19 etanercept, 19 placebo) had ≥3% body surface area involved with psoriasis, the minimum requirement for the evaluation of skin response. Evaluating dermatologists used the Psoriasis Area and Severity Index (PASI) and target lesion score to evaluate skin lesions. The PASI is a composite measure based on scale, erythema, and induration that is weighted by severity and body surface area. The target lesion is a prospectively identified psoriatic lesion assessed for plaque elevation, scale, erythema, and induration. At 12 weeks, the median improvement in PASI score in etanercept-treated patients was 46% compared with 9% for the placebo group (p=0.0032). Twenty-six percent of the etanercept group achieved at least a 75% improvement in PASI score. A median 50% improvement in target lesion score was observed for the etanercept group.

Patients who completed this trial (n=58) were given etanercept during a 6-month, open-label extension. The patients originally assigned to placebo had prompt and dramatic PsARC responses. The median improvement in PASI score in patients receiving etanercept during the blinded phase of the study improved from 46% at 12 weeks to 62% at 9 months. Patients who had originally received placebo during the double-blind phase and then were switched to etanercept also achieved a 62% median improvement in PASI score during the 6 months of etanercept treatment. Twenty-five percent of patients previously taking methotrexate and 44% of those...
previously taking low-dose prednisone were able to discontinue those drugs.

A Phase III clinical trial of etanercept in patients with PsA confirmed and extended these observations. In this double-blind, placebo-controlled study, 205 patients with PsA and psoriasis were randomized to receive 25mg etanercept (n=101) or placebo (n=104) twice weekly for 24 weeks. An ACR20 response at 12 weeks, the primary endpoint of the study, was achieved by 59% of the etanercept group and 15% of the placebo group (p<0.001). By PsARC criteria, 72% of the etanercept group achieved a clinical response at 12 weeks vs. 31% of the placebo group (p<0.001). Clinical improvement was maintained through 24 weeks of etanercept treatment, demonstrated by an ACR20 response of 50% and a PsARC response of 70%, compared with 13% and 24%, respectively, for placebo (p<0.001 for each evaluation).

Improvement in psoriasis was also observed. Of the 205 patients in this study, 66 in the etanercept group and 62 in the placebo group met the criteria for evaluation by the PASI. At 24 weeks, the etanercept group showed a median PASI improvement of 47% and a median target lesion improvement of 33% compared with no improvement in the placebo group for either evaluation (p<0.001).

**Adverse Effects**

TNF antagonists, including etanercept, affect host defenses and have been rarely associated with development of new infections and exacerbation of existing infections. The only reaction that occurs with any frequency is injection site reaction, occurring in less than one-third of patients. This is usually mild, well tolerated, and resolves within a few weeks to months after initiation of drug without need to interrupt therapy. Overall, the safety profile of etanercept in PsA is similar to that in rheumatoid arthritis.

During the initial 12-week, placebo-controlled trial in PsA, etanercept was well tolerated. No serious adverse events were reported in the 30 patients receiving etanercept, and no patients developed infections that required hospitalization or intravenous antibiotics. Injection site reactions occurred in 20% of the etanercept patients. Of note, no patient developed Koebner phenomenon at the sites of injection. During the 6-month open-label extension of this initial trial, etanercept continued to be well tolerated. Etanercept was also generally safe and well tolerated during the phase III study in PsA. During the course of the trial, eight adverse events that were considered serious were reported for four placebo-treated patients (one each with angina, gastroenteritis, and gastritis, and the fourth patient with atrial fibrillation, gastrointestinal bleed, congestive heart failure, bowel perforation, and intraperitoneal hemorrhage). In the etanercept group, four serious adverse events were reported for four patients (one each with transient symptoms consistent with demyelinating disease, chest pain, syncope, and renal calculus).

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<th>DMARD</th>
<th>Regimen/Control</th>
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<th>Statistically Significant Results</th>
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<tr>
<td>Methotrexate15</td>
<td>Pulse 7.5-15mg once weekly vs. placebo</td>
<td>37</td>
<td>Small improvement in physician assessment of disease activity and skin involvement</td>
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<tr>
<td>Gold16</td>
<td>50mg IM once weekly vs. auranofin 3mg b.i.d. vs. placebo</td>
<td>82</td>
<td>Improvement in joint pain and erythrocyte sedimentation rate at 23 and 24 weeks with IM gold (no significant changes with oral gold)</td>
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<tr>
<td>Sulfasalazine17</td>
<td>2gm per day vs. placebo</td>
<td>30</td>
<td>Improvement in arthritis at 1 and 6 months; no effect on psoriasis</td>
</tr>
<tr>
<td>Sulfasalazine18</td>
<td>2gm per day vs. placebo</td>
<td>221</td>
<td>Slightly better overall response in arthritis</td>
</tr>
<tr>
<td>Infliximab9</td>
<td>5mg/kg IV at 0, 2, 6, and 14 weeks vs. placebo</td>
<td>102</td>
<td>Significant improvement in arthritis and psoriasis at 16 weeks</td>
</tr>
<tr>
<td>Etanercept11</td>
<td>25mg SC twice weekly vs. placebo</td>
<td>60</td>
<td>Significant improvement in arthritis and psoriasis at 4, 8, and 12 weeks</td>
</tr>
<tr>
<td>Etanercept14</td>
<td>25mg SC twice weekly vs. placebo</td>
<td>205</td>
<td>Significant improvement in arthritis and psoriasis through 24 weeks</td>
</tr>
</tbody>
</table>

*Table 1: Controlled, Double-Blind Studies of DM ARDs in Psoriatic Arthritis*
Conclusions
PsA is an inflammatory arthropathy that commonly affects patients with psoriasis, with a significant and often severe impact on their health and well-being. Levels of the pro-inflammatory cytokine TNF are elevated in the synovium and psoriatic plaques of patients with PsA. The anti-inflammatory effects of etanercept arise from its ability to bind to TNF and block its interaction with cell-surface receptors. Etanercept has been shown to be effective and generally well tolerated in the treatment of PsA. Based on the results of two randomized, placebo-controlled studies, etanercept is the first biologic to be approved for the treatment of PsA. With respect to psoriasis, preliminary data suggest that both etanercept and infliximab have promise in treating plaque-type psoriasis in patients without PsA. Given the favorable clinical results achieved with etanercept, it is likely that other targeted biologics currently in development will also prove to be useful in PsA and psoriasis. The availability of targeted therapies will increase the opportunity for more effective management of these difficult diseases.

References
What’s New In Hair Transplants?

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ABSTRACT

As hair transplant surgery has evolved, combinations of micrografting and minigrafting have enabled physicians to produce ever more natural combinations of both. A wide range of men and women can now receive significant aesthetic benefits from hair transplants. In recent years, practitioners have further refined hair-transplant techniques to ensure that the hairs available for transplantation are used most efficiently. Specifically, methods of harvesting hair, preparing grafts, creating recipient sites, and placing grafts are designed to permit the maximum percentage of hairs to survive and thrive after transplantation. Careful planning, close cooperation with the patient, and a staged surgical approach can also result in hair conservation and optimal cosmesis.

Key Words: hair transplant, micrografting, minigrafting

This paper is not intended to describe surgical techniques in general; we refer readers to other publications for that.1,2 Rather, it will address new concepts and techniques in hair transplantation, which have evolved over the last approximately 10 years.

Planning

Rather fortunately, the definition of an “acceptable candidate” for hair transplantation has broadened substantially in the last 10 years. New donor area removal techniques, as well as micrografting and minigrafting, have revolutionized the procedure. Moreover, patients who have poor donor areas, secondary to genetics or previous “old” transplanting techniques, may still achieve an acceptable aesthetic improvement because of these advances.

We now think of the recipient area in men as being composed of three segments: the frontal, midscalp, and “crown” areas.3 Generally, only one of these is treated in any single session, although later sessions may include thickening of portions of the two previously transplanted areas. Most patients can ultimately treat at least the anterior two areas because of the innovations that will be described here. If this is done, a patient will look like he has hair from the frontal view, as well as the side view. Because micrografting and minigrafting can produce natural-looking results with the use of less donor tissue than was necessary with larger grafts, one can now choose to treat larger portions of the area of male pattern baldness (MPB) with lighter coverage, or alternatively to concentrate the available donor tissue in regions where high density is preferred. Some individuals can even treat their entire eventual area of MPB, especially if they are willing to have portions of the alopecic areas excised.4 Also many more female patients are acceptable candidates for the procedure now that hair-transplanting techniques do not involve the removal of any hair in the recipient area hair. Especially in females, however, a careful history to rule other medical and/or dermatologic conditions is necessary.5

Whether the patient is male or female, the physician should also try to determine the future donor/recipient area ratio. It is always preferable to err on the side of conservative estimates if there is any doubt. In addition, the physician and patient need to come to an agreement as to how much of the area can be treated and with what kind of grafts and hair density objectives. The better the donor/recipient area ratio, the more options are available. A wide, dense donor rim allows the patient the choice to aim for high density in the recipient area. Higher density is achieved with the use of minigrafts, slot grafts and small round grafts.6 These are always situated behind a hairline zone that is approximately 2.5cm in width and is composed entirely of follicular units (FUs). The treatment plan should include areas of future loss, so that the donor area can be apportioned appropriately. For example, if a patient is destined to be a Norwood Class VI or VII, and wants to cover his whole head with hair, then Follicular Unit Transplanting (FUT) is the best option. If, on the other hand, the patient has good hair characteristics, and the physician predicts that he will be a Norwood Class IV, many other treatment plans can be considered.

Donor Area

The physician excises an ellipse or uses a multi-bladed handle to excise contiguous narrow strips from the donor area. A tumescent solution and/or normal saline is injected into the donor area to help reduce transection of follicles during this stage. In our office, we do not aim for a specific number of grafts, rather our goal is to take a donor strip as long and as wide as we believe is prudent. Its size is limited by scalp laxity, by scar tissue, which may or may not be present, and (of
course) by the blood supply. Overzealous donor harvesting can leave patients with wide scars, poor wound healing and other problems. The authors use two donor areas in many patients, one inferiorly in the occipital region and one superiorly on the contralateral, occipital, parietal, and temporal areas. This allows us to obtain hair of different textures and colors for use in the recipient area. During the second session, contralateral donor sites that end at the scars from the first session are employed. After the first two sessions, there will be two fine linear scars and these are excised as part of any subsequent sessions. A single donor area from ear to ear is used if hair density or scalp laxity is lower than average, if very large numbers of grafts are required, or if we believe that the patient is destined to develop types VI or VII MPB with a correspondingly narrow permanent rim of hair.

**Graft Preparation**

The excised donor strip is placed into a petri dish with cold saline. Graft preparation generally begins with division of the strip into “slivers” that are one FU wide, much as one would slice a loaf of bread. FUs consist of two to five closely bound follicles. These slices are then sectioned into smaller pieces of tissue, containing the desired number of FUs. The dissection is usually carried out with the aid of an 8x-10x microscope and a backlighting box, to minimize follicle injury. Larger grafts are created by producing slices, which are wider; slots, for example, are two FUs wide and three FUs long while 2mm grafts are usually three FUs x three FUs.

Every effort is made to minimize physical injury to the follicles and to keep them moist and cool. Given the central role of technicians in the preparation, storing, and handling of grafts, it becomes much more important, than in the past, to ensure that they are highly trained and that quality control is rigorously checked.

**Recipient Area**

In most offices, all of the recipient sites are created prior to graft insertion. Sites for FUs are made with 16 to 21-g needles, those for “slit” grafts with various types of small blades, and for slot grafts or round grafts with special “slot punches” or round trephines, respectively. As implied, the recipient area can be treated in several different ways:

1) exclusively with FU (FUT) (Fig. 1).
2) with a combination of FUs and “slit grafts” that are one FU wide and two to three FUs long (Fig. 2).
3) with a combination of FUs, “slit grafts” and larger grafts (“slot” or “round” grafts) (Fig. 3).
FUT is ideal in several situations, including patients who begin treatment when they are already completely alopecic, those who have very limited available donor hair, and those who are seeking only light-to-moderate hair density. FUT can produce very natural looking results after only one session in any given area. Some physicians attempt to produce denser coverage in a single session by employing “megasessions” of 3000 or more FU/sessions and “dense packing” FUs at 35 to 40 FU/cm². We believe that the level of follicle death with this approach is unacceptable in a large majority of offices; survival is far more reliable with smaller sessions and when the density is 20-25 FU/cm². A combination of FUs and larger grafts is often the “best of all worlds” for most patients, because one can ultimately produce more density with such combinations. As patients age, hair density in both donor and recipient areas can be expected to decrease. Thus, starting with denser transplanted hair may prove to be advantageous.

A wide hairline zone (usually at least 2.5cm) is always created with FUs: single hair FUs are utilized most anteriorly, and larger FUs are usually placed more posteriorly and/or in a central “egg-shaped” region in the midline of the anterior frontal area (Fig. 4). Posterior to this zone, one may continue using only FUs or various combinations of multi-FU, “slit”, “slot”, or “round” grafts.

The treatment of hair loss in women is somewhat different. The hairline zone is treated in a similar manner, but the rest of the surgical plan is carefully tailored to the needs of the patient. Some women are most concerned about filling the temporal triangles, others want greater hair density in their part-line, and still other patients want general thickening in the center of the frontal region. Depending on donor area hair density, some (or all) of these strategic areas can be treated. Each session is usually done with a combination of FUs and small slit grafts and will nearly always create a significant aesthetic improvement (Fig. 2).

Graft Placement

The final step in the procedure is graft placement. This is performed by technicians in most offices, but some physicians take an active role in this stage. Communication and training are of vital importance. Specifically, grafts must always be kept well hydrated, handled minimally, carefully placed, and the physician’s instructions should be clear with regard to the appropriate hair caliber and number of hairs in given locations. There are many possible errors that can occur during the filling of recipient sites and for these reasons all staff should have extensive training and regular quality checks. It is important that all sites are filled with the appropriate graft, that none are “buried” beneath the level of the skin, and that each site is filled only once (no “piggybacking”).

Conclusion

Hair transplant surgery is continually evolving and many of the new techniques have improved patient results. They also introduce some new problems. For example, FUT and micro-minigrafting rely heavily on a group of very well trained technicians. Physicians who are unable to create or maintain such a team are unlikely to consistently produce good results. Another potential problem is that although the density achieved with smaller grafts may be acceptable to many patients in the short term, they will likely require future periodic hair transplant procedures. If too large an area is covered initially and donor area is limited, there may not be enough hair “left in the bank” to finish the regions that were started. It is our opinion, therefore, that conservative estimates must guide treatment plans, the “transplant team” needs to be highly trained and supervised, and that patients should be offered a variety of reasonable treatment options.

References

### Update on Drugs

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<td>Immuno-modulatory Agents</td>
<td>Alefacect &lt;br&gt; AMEVIVE&lt;sup&gt;®&lt;/sup&gt; Biogen</td>
<td>The US FDA approved this selective immunomodulator in January 2003, for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.</td>
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<td>Photoaging</td>
<td>Tazarotene Cream 0.1% &lt;br&gt; AVAGE&lt;sup&gt;™&lt;/sup&gt; Allergan</td>
<td>The US FDA approved this cream in September 2002, as an adjunctive agent in the topical treatment of facial fine wrinkling, mottled hypopigmentation, and benign facial lentigines in patients using a comprehensive skin care and sunlight avoidance program.</td>
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<td>Hormonal Preparations</td>
<td>Testosterone Replacement Therapy Gel &lt;br&gt; Testim&lt;sup&gt;™&lt;/sup&gt; Auxilium Pharmaceuticals</td>
<td>The US FDA approved this novel topical gel in October 2002, for use in treating men with low testosterone levels.</td>
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<td>Vaccines</td>
<td>Vaccine for Diphtheria, Tetanus, Pertussis, Hepatitis B and Polio &lt;br&gt; Pediart&lt;sup&gt;™&lt;/sup&gt; GlaxoSmithKline</td>
<td>The US FDA approved this vaccine in December 2002, to be given to infants at 2, 4 and 6 months of age for the prevention of diphtheria, tetanus, pertussis, hepatitis B, and polio. This is the first 5-in-1 vaccine to be approved, which will result in 6 fewer injections for infants.</td>
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### Drug News

**Sunscreens**

Skinvisible, Inc. announced in January 2003, that it has signed an agreement to manufacture a range of sunscreen products including its patent-pending SPF 15 and SPF 30 sunscreen formulations for SunSpots International who will market the products internationally through major retail outlets. The sunscreen products incorporate Skinvisible’s patent pending Invisicare<sup>®</sup> polymer-based delivery system. Independent clinical studies demonstrate that this system bonds with the skin, holding active sunscreen ingredients in place for extended periods and is very water resistant.

Source: Press release from Skinvisible, Inc.

**Anti-acne Agent**

The Society of Obstetricians and Gynaecologists of Canada recently expressed concern about a recent news story that “chose to sensationalize an incomplete scientific report submitted as a letter to the *Lancet* in October 2001, which claimed that Diane 35®/Dianette® (cyproterone acetate/ethinylestradiol, Schering-Plough) caused more blood clots than other oral contraceptives.” The SOGC is concerned that many users of Diane 35® will stop the medication without consulting their doctors. According to Dr. Donna Fedorkow, President of the SOGC, “All oral contraceptives raise the risk of blood clots very slightly. A more comprehensive study reported in 2002, examined the risks of blood clots in all oral contraceptive users in Denmark between 1994 and 1998. This report indicated the risk of blood clot associated with Diane 35® was not greater than with other oral contraceptives.” Because of its unique ability to block the male-like hormones that contribute to acne, Diane 35® has become a popular recommendation of physicians for treating acne in women who also desire an oral contraception.

Source: Press release from the Society of Obstetricians and Gynaecologists of Canada

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