

The Treatment of Ankylosing Spondylitis and Psoriatic Arthritis with Etanercept: A Comprehensive Review

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Abstract: Etanercept is a dimeric recombinant soluble tumor necrosis factor (TNF) receptor protein utilized in the treatment of various inflammatory diseases, including ankylosing spondylitis and psoriatic arthritis. Etanercept binds the proinflammatory cytokine TNF and blocks its interaction with soluble TNF receptors, thus decreasing the inflammatory response. Several randomized controlled clinical trials have demonstrated the efficacy, safety and tolerability of etanercept in the treatment of both ankylosing spondylitis and psoriatic arthritis. These trials have also shown significant reductions in markers of systemic inflammation and improvements in patient-reported quality of life measures. Inhibition of radiographic progression has been established in etanercept-treated psoriatic arthritis patients, and ankylosing spondylitis patients have demonstrated decreases in bony inflammation; however, current data does not support a reduction in bone proliferation in ankylosing spondylitis patients. Concerns regarding long-term toxicity, efficacy, and cost-effectiveness considerations persist and guidelines have been published to assist the clinician with appropriate patient selection for this biologic therapy. Current data indicates etanercept therapy has been a very successful and well-tolerated therapy for numerous ankylosing spondylitis and psoriatic arthritis patients and will likely continue to be a cornerstone therapy for treatment of these challenging diseases in the foreseeable future.

Keywords: etanercept, ankylosing spondylitis, psoriatic arthritis, tumor necrosis factor antagonist

Introduction to Etanercept

It is rare for a single drug class to revolutionize the management of a disease; nevertheless this has been the impact of tumor necrosis factor (TNF) antagonist therapies on the treatment of the seronegative spondyloarthropathies. This assorted group of inflammatory arthritides that share clinical and radiological characteristics includes ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis (inflammatory bowel associated), reactive arthritis, juvenile spondyloarthropathy and the undifferentiated spondyloarthropathies. Of these, ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the most prevalent and most severe.¹

Historically, AS and PsA were difficult to manage, with limited treatment options. Following the successful treatment of rheumatoid arthritis with TNF antagonists, researchers and clinicians introduced these drugs to patients with AS and PsA. Several open-label and randomized controlled clinical trials demonstrated drug efficacy, and many physicians now consider this therapeutic class standard of care for patients unresponsive to conventional therapies. Currently there are three TNF antagonists available for use in AS and PsA patients in the US and EU, two monoclonal antibodies (infliximab and adalimumab) and one fusion protein (etanercept).

Etanercept (Enbrel[®], Immunex Corporation, Thousand Oaks, CA, USA), a dimeric recombinant soluble TNF receptor protein, which is self-administered by subcutaneous injection, was introduced in 1998. Etanercept is registered in the US and EU as a treatment for rheumatoid arthritis (RA), PsA, plaque psoriasis, AS and juvenile idiopathic arthritis (JIA). Etanercept gained EU and US approval for use in PsA in 2002 and licensing for AS followed in the US in 2003 and EU in 2004. The TNF antagonists have subsequently been widely utilized for these conditions. To date the exact mechanisms of action of TNF antagonists remain elusive, data regarding efficacy, safety and tolerability continues to be collected, and a debate regarding the therapeutic role of these medications persists. This review will focus on the role of etanercept in the treatment of AS and PsA.

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Review of Pharmacology, Mode of Action, and Pharmacokinetics of Etanercept

Pharmacology

The pharmacology and mechanism of action of tumor necrosis factor antagonists is complex. These biologic drugs have been extensively studied in murine models,² and were recently comprehensively reviewed³ in 2008. Etanercept is a dimeric soluble fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor linked to the Fc portion of human IgG1. Etanercept is manufactured utilizing recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. It consists of 934 amino acids and has a molecular weight of approximately 150 kilodaltons.⁴

Etanercept binds the proinflammatory cytokine TNF and blocks its interaction with soluble TNF receptors. This binding prevents TNF from interacting with TNF receptors on the surface of target cells and thus decreases the inflammatory response. Etanercept inhibits binding of both TNF and lymphotoxin alpha (previous nomenclature TNF α and TNF β) to cell surface TNF receptors, rendering the cytokines biologically inactive.³ Etanercept does not lyse cells in the presence or absence of complement.

Etanercept has been shown to bind soluble TNF with a high affinity. Scallon et al⁵ demonstrated with binding assays that etanercept binding is restricted to the trimer form of soluble TNF, while the monoclonal antibody infliximab binds to both the monomer and trimer forms. Etanercept binds TNF with less avidity than infliximab and releases bioactive TNF from binding more frequently. It is hypothesized that this difference in binding affinity is one of the explanations for the lack of efficacy of etanercept in the treatment of granulomatous diseases such as sarcoidosis and Crohn's disease.^{5,6} All three currently marketed TNF antagonists (etanercept, infliximab and adalimumab) have been shown to bind human cell transmembrane TNF with high affinity.⁷ In contrast to the other currently marketed TNF antagonists, etanercept has the additional binding ligand lymphotoxin alpha (LT α) and binds LT α similar to the binding action of native tumor necrosis factor receptor 2.³ No clinically significant effects of LT α binding have been described to date and the contribution of this binding to the effectiveness of etanercept remains unknown.

Pharmacokinetics

The majority of available pharmacokinetic data is taken from healthy persons and patients with RA or plaque psoriasis. Etanercept was first studied at a 25 mg twice weekly dosage and is now most commonly prescribed at a 50 mg weekly dosage due to a relatively short half-life and brisk clearance rate. The half-life of etanercept following a 25 mg dose is 102 ± 30 hours.⁴ The half-life of the 50 mg weekly dosage has not been strictly studied, however retrospective analysis of pharmacokinetic data has predicted that steady-state serum concentrations of the drug should be similar at both dosing regimens.^{8,9} Etanercept has a shorter plasma half-life (approximately 4 days) in comparison to infliximab (10 days) and adalimumab (14 days). It is hypothesized this shorter half-life indicates the Fc conformation or steric structure of etanercept may differ from the Fc regions of the other IgG1 antibodies,³ since binding of the Fc regions of antibodies to endothelial cell receptors dictates half-life binding time.¹⁰

Etanercept is absorbed slowly, attaining peak plasma concentrations at 48 to 60 hours following injection.⁹ Both weekly and twice weekly dosing regimens reach steady state plasma concentrations in 2–4 weeks and have similar peak and trough serum levels at that time.^{9,11} The absolute bioavailability is 76% with a volume of distribution at steady state of 10.4 L.⁴ Etanercept is metabolically processed similar to proteins and excreted in the urine and bile. There are no known effects of renal or hepatic impairment on etanercept clearance.^{4,12}

No significant change in the pharmacokinetics of etanercept has been demonstrated between men and women, RA and psoriatic patients, or among varying ethnicities or adult age groups.^{3,4} One study comparing AS patients with RA patients did not find any difference in etanercept pharmacokinetics between these two patient groups.¹³ Etanercept is a fixed-dose medication and studies examining dosage and clinical response at extremes of body weight in PsA and AS patients have not been carried out. However, initial studies examining the efficacy of etanercept in overweight and obese patients with psoriatic skin disease indicate a decreased response in these individuals.^{14,15}

Mechanism of action

TNF is expressed at high levels in humans and animals during periods of inflammatory disease.¹⁶

Normal serum values of TNF in humans are 75 ± 15 pg/ml; in comparison values ranged from 100 to 5000 pg/ml with a mean of 701 ± 339 pg/ml and a median of 250 pg/ml in a study of septic shock patients.¹⁷ This pro-inflammatory cytokine has diverse effects involving immune regulation and plays a role in cell recruitment, regulation, proliferation and apoptosis.^{18,3} TNF is known to induce other inflammatory cytokines including interleukins-1, 2 and 10, GM-CSF and interferon- γ and to facilitate bone destruction through the stimulation of osteoclasts and matrix metalloproteinases.³ Due to TNF's multifaceted role in the immune system and cytokine cascade, every function and mechanism of action of TNF antagonists has not yet been fully elucidated. TNF is a well-established contributor to synovial inflammation in RA and the mechanisms of action of TNF antagonists have been studied extensively in RA patients.^{19–21} There have been fewer studies characterizing these mechanisms in AS and PsA patients.

Murine models of AS have demonstrated increased expression of TNF in mice.²² In AS patients, elevated levels of TNF have been found in the SI joints,²³ synovium^{24,25} and serum.^{26,27} Kruithof et al²⁸ demonstrated that etanercept given to spondyloarthritis patients with peripheral joint synovitis resulted in a swift and persistent decrease in macrophages, T cells and the synovial expression of the cartilage turnover marker matrix metalloproteinase 3 (MMP-3). This study also illustrated a marked decrease in the inflammatory marker C-reactive protein (CRP) in spondyloarthritis patients treated with etanercept.²⁸

The significance of MMP-3 in AS patients was confirmed in a series of 97 AS patients in whom MMP-3 levels were shown to be independent predictors of radiographic progression over 2 years.²⁹ In 2007, Woo et al³⁰ reported significantly decreased serum levels of transforming growth factor- β (TGF- β), MMP-3, macrophage-colony stimulating factor (M-CSF), CRP and erythrocyte sedimentation rate (ESR) in AS patients following 12 weeks of etanercept treatment. Serum levels of bone-specific alkaline phosphatase and osteocalcin were significantly increased in these AS patients. In contrast to studies of the inflammatory arthritides that involve bone erosions (RA and PsA), serum levels of receptor activator of nuclear factor- κ B ligand (RANKL), and osteoprotegerin (OPG) were not changed. A decrease in MMP-3 was highly correlated with a decrease in the inflammatory

markers CRP and ESR.³⁰ The importance of MMP-3 in the pathogenesis of AS and the ability to significantly reduce MMP-3 levels with TNF antagonist therapy was recently reconfirmed by Wendling et al.³¹ Briot et al³² demonstrated a decrease in specific markers of type II collagen degradation and an increase in a marker of collagen synthesis in spondyloarthritis patients treated with etanercept for 24 months, suggesting the drug has beneficial effects on cartilage metabolism in these patients.

Patients with psoriatic skin disease are known to have increased TNF levels in the skin lesions¹⁸ as well as in areas of unaffected skin.³³ When treated with etanercept, there is a decrease in inflammatory chemokines as well as decreased cellular infiltration of neutrophils, dendritic cells and T cells in the psoriatic plaques.³⁴ TNF is also highly expressed in the synovial fluid of PsA patients³⁵ and etanercept treatment has been shown to significantly reduce CRP levels in PsA patients following 12 weeks of treatment.³⁶

The TNF antagonist monoclonal antibody infliximab was shown to decrease the cellularity of inflamed synovial tissue in PsA patients with a reduction in synovial lining macrophages and T cells, as well as epidermal T cells in psoriatic lesions.³⁷ Ritchlin et al³⁸ demonstrated that PsA patients have a marked increase in osteoclastic precursors (OCP) in their blood, osteoclasts at the pannus—bone junction, and that their peripheral blood mononuclear cells spontaneously secrete higher levels of TNF- α compared to healthy controls. The addition of an anti-TNF antibody inhibited osteoclast formation in these PsA patients. A subsequent study by Anandarajah et al recently demonstrated that etanercept decreased serum osteoclast precursors at three and six months, corroborating the pivotal role of TNF in osteoclastogenesis and erosive bone disease. It is important to note that while the OCP frequency was significantly reduced following etanercept therapy, it did not fall to the level seen in healthy controls.³⁹

Efficacy Studies

Ankylosing spondylitis efficacy studies

There have been several double-blinded placebo-controlled randomized clinical trials of etanercept in patients with AS. Trial patients met the modified

New York criteria for AS and had moderate to severe active disease. Measurements of disease activity are detailed in Table 1 and study results are compared in Table 2. Treatment efficacy has also been measured radiographically. Safety concerns in these trials were minimal and are discussed under *Safety and Tolerability*.

The first randomized clinical trial (RCT) investigating etanercept versus placebo in AS patients was a 4-month, phase II trial in which 40 patients were assigned to etanercept 25 mg twice weekly or placebo.⁴⁰ The primary end point was a composite of improvements in 3 of 5 outcome measures (morning stiffness, spinal pain, functioning, patient global assessment of disease activity, joint swelling). Patients were allowed to continue non-steroidal anti-inflammatory drugs (NSAIDs), low dose corticosteroids (≤ 10 mg per day) and disease-modifying anti-rheumatic drugs (DMARDs) at stable doses. At the study conclusion 75% of treated patients met the primary endpoint, in comparison to 30% of placebo patients.⁴¹ ESR and CRP were significantly decreased and patients reported improvement in multiple quality of life measures. Results were sustained during a six-month open-label extension of this trial.

In a small phase III RCT, 30 AS patients were treated with etanercept 25 mg twice weekly or placebo for 6 weeks and then followed during a 24-week observational period.⁴² In contrast to the 2002 RCT, all DMARDs and corticosteroids were discontinued 4 weeks prior to treatment. The primary outcome measure was a $\geq 50\%$ improvement in the BASDAI (BASDAI50); this was achieved in 57% of the etanercept-treated patients at 6 weeks, versus 6% of the placebo patients. Measures of pain, function, mobility and quality of life were all significantly improved and CRP levels were decreased at 6 weeks. Etanercept was stopped after a total of 12 weeks and patients were then observed for 12 weeks. Disease relapses were noted at a mean of 6.2 ± 3.0 weeks after drug discontinuation (75% relapsed by 6 weeks); indicating that TNF inhibition must be continuous to sustain efficacy. In a later published 54-week observational study, 26 of these patients were retreated with etanercept.⁴³ The primary outcome measure, the BASDAI50, was achieved by 46% at week 6 and 58% at week 54 in an intention to treat analysis. 83% of patients were able to discontinue NSAID use and 31% met partial remission criteria at the end of the study. These results were similar to those achieved in the

Table 1. Outcome measures utilized in ankylosing spondylitis clinical trials.

| Measure of disease activity | Definition |
|--------------------------------------|---|
| ASAS Response Criteria ⁵² | <p>An improvement of at least 20%, 50% and 70%, and improvement of 10 or more units on a 100 mm Visual Analog Scale (VAS), in at least 3 of these 4 domains, without a 20% worsening in any domain:</p> <ol style="list-style-type: none">1. Patient global assessment (by VAS)2. Pain assessment (by VAS)3. Physical Function (composite score of 10 items of BASFI)4. Inflammation (average of the VAS scores of the last 2 questions of the BASDAI regarding intensity and duration of morning stiffness) <p>ASAS40 requires at least 40% improvement and 20 units in 3 of 4 domains with no worsening in the remaining domain.</p> <p>Partial remission has been defined as achieving a value less than 20 in each of the four ASAS domains.</p> <p>ASAS 5/6 responders demonstrate $\geq 20\%$ improvement in 5 of 6 domains: the four ASAS20 domains, CRP levels and spinal mobility.</p> |
| BASDAI ⁵³ | A six item composite index including questions on fatigue, axial pain, peripheral pain, discomfort, duration and intensity of morning stiffness. |
| BASFI ⁵⁴ | A 10 item VAS based composite of functional and coping ability. |
| Spinal Mobility Scores ⁵⁵ | Forward flexion (Schober's test) Chest Expansion Occiput to wall distance. |

Anderson et al⁵² Brandt et al⁵³ Garrett et al⁵⁴ Calin et al⁵⁵

Table 2. Outcome measures in etanercept vs placebo in AS randomized controlled trials.

| Study | Duration (weeks) | # of Pts (etanercept/placebo) | ASAS20 % | ASAS50 % | ASAS70 % | BASDAI50 % | BASFI |
|------------------------------------|------------------|--|----------------|----------------|--------------|------------------|-------------------------------|
| Gorman et al ⁴⁰ | 16 | 20/20 | – | – | – | – | 2.2/3.1 ($p < 0.001$) |
| Brandt et al ⁴² | 6 12 | 14/16 | 78.6/25 | 43/12.5 | – | 57/6 71/56 | 4.3/5.1 ($p = 0.008$) |
| Davis et al ⁴⁴ | 12 24 | 138/139 | 59/28 57/22 | 45/13 42/10 | 29/7 28/5 | – | 36.0/54.7 ($p < 0.0001$) |
| Calin et al ⁴⁸ | 12 | 45/39 | 60/23 | 49/10 | 24/10* | 71/25.6 | 39.6/53.9 ($p < 0.001$) |
| van der Heijde et al ⁵⁰ | 12 | 150 (25 mg twice weekly) 155 (50 mg weekly) 51 (placebo) | 71 74 37 | – | – | 58 60 19.6 | – |

*Not statistically significant.

original study, demonstrating the safety and effectiveness of etanercept retreatment.

A large phase III multicenter RCT of etanercept 25 mg twice weekly in 277 AS patients was published in 2003.^{4,44} In this 24-week trial, the primary outcome was the ASAS20 at 12 and 24 weeks. Secondary outcomes included ASAS50 and 70 and the percentage of patients achieving partial remission. Patients were allowed to continue DMARDs at stable dosages. ASAS20 achievement was similar to that in the previous studies; ASAS50 and 70 were also statistically significant (Table 2). Seventeen percent of patients achieved partial remission versus 4% of the placebo group. This study also demonstrated statistically significant improvements in acute phase reactants and spinal mobility measures in the treatment group.

In a later published open label extension of the 2003 study, Davis et al⁴⁵ demonstrated sustained efficacy of etanercept at 96 weeks with 74% of 128 of the original etanercept treated patients achieving ASAS20 at 96 weeks. In the earlier placebo group, ASAS20 was met by 70% of the 129 patients at 24 weeks and 78% at 72 weeks. Both groups demonstrated decreased CRP values, improvements in the BASFI and improved spinal mobility. The adverse event and serious adverse event rates remained stable throughout the extension phase. Improvements in health-related quality of life were also sustained through 72 weeks.⁴⁶ The durability of response to etanercept was further demonstrated when this group published 192-week data of these patients.⁴⁷ Of patients who had received etanercept in the RCT, 126 completed the 168-week open-label extension. Eighty-one percent of these patients were ASAS20 responders at week 192% and 44% met partial remission criteria. All patients demonstrated significant improvements in BASDAI, BASFI, patient global assessment, back pain, morning stiffness, swollen and tender joint count and CRP. Overall, from the original group of study and placebo patients, 20 (7.8%) at 192 weeks withdrew due to lack of efficacy compared with 3 patients (2.2%) at 24 weeks, indicating a small but significant increase in treatment failures over time.

Calin et al⁴⁸ published a similar multicenter 12-week RCT of 84 AS patients randomized to etanercept 25 mg twice weekly or placebo. The primary endpoint was the ASAS20. Secondary outcome measures were the ASAS50 and 70, the BASDAI, ESR and CRP, and improvement in spinal mobility. ASAS20 response was seen as

early as week 2 and sustained throughout the trial. The treatment group had a significant ASAS50 response, improved BASDAI, decreased acute phase reactants and improved spinal mobility tests. An open-label extension of this RCT was recently presented in abstract form.⁴⁹ Of the original 84 patients, 59 were enrolled in the 252–264 week extension and 37 (56%) patients completed this 5-year extension phase. ASAS response criteria and clinical outcome measures were similar to the original study with 75% achieving ASAS 20, 31% meeting partial remission criteria and 66% demonstrating a BASDAI50 response. No new safety concerns occurred; the serious adverse event rate was 0.17 per patient-year and serious infection rate was 0.03 per patient year.

Etanercept dosed at 50 mg weekly was shown to be as effective as the 25 mg twice weekly dosing used in previous clinical trials in a 12-week RCT comparing etanercept 50 mg weekly with 25 mg twice weekly dosing and placebo (Table 2).⁵⁰ Disease activity measures including BASDAI50, back pain, morning stiffness and CRP levels were significantly improved in both etanercept groups as early as two weeks. Partial remission occurred in 32% of the once-weekly group and 21% of the twice-weekly group. No significant difference was found between the etanercept groups. Safety data was similar to previous trials.

There has been one comparative study of etanercept and infliximab in AS patients; data from this trial is currently available only in abstract form.⁵¹ In this study, patients received either etanercept 25 mg twice weekly or infliximab 5 mg/kg administered at weeks 0, 2 and 6 and then every six weeks. The primary study endpoint was the BASDAI50 at 102 weeks; this measure was met by 43% of etanercept-treated patients and 42% treated with infliximab, a non-significant difference. ASAS50 was attained by similar numbers of patients, 43% in the etanercept group and 45% in the infliximab group. There were no significant differences noted between patient groups in these outcome measures at either week 6 or at the 102-week endpoint. Measures of disease activity including back pain, morning stiffness, spinal mobility and CRP levels were significantly improved in both groups.

As a whole, these clinical trials demonstrate that etanercept produces a significant improvement in the signs and symptoms of moderate to severe AS, as well as in patient quality of life, and these results can be sustained over 5 years of treatment.

A minority of patients will achieve disease control to the point of partial remission. However, a significant percentage of AS patients did not significantly respond to etanercept therapy, and this should not be overlooked. To date there has been no statistically significant data indicating any increased efficacy of etanercept when combined with other DMARD therapies such as methotrexate in AS patients.

Several studies have examined the effectiveness of etanercept on the radiographic progression of disease in AS patients. In a subgroup analysis of 40 patients from the Davis et al⁴⁴ clinical trial,⁵⁶ patients underwent lower thoracic and lumbar spine MRI at 0, 12, 24 and 48 weeks. Nineteen AS patients received etanercept 25 mg twice weekly for 1 year and 21 patients in the placebo group received were switched to etanercept after 6 months. Bony inflammation regressed by 54% on T2-weight MRI images at 12 weeks in the etanercept treated patients and worsened by 13% in the placebo patients. Placebo patients demonstrated similar improvement following etanercept initiation and efficacy was maintained throughout 48 weeks. Both groups exhibited continued worsening of chronic spinal lesions such as syndesmophytes, leading the authors to speculate that the progression of already-present structural damage may be inevitable. Another examination of spine and SI joints of etanercept patients yielded similar results.⁵⁷

The relationship between inflammation and bone damage in AS has not been established. In a study utilizing patients originally enrolled in the Davis et al⁴⁴ RCT, radiographs of 257 of these patients receiving etanercept 25mg twice weekly for up to 96 weeks were compared with 175 patients from a large prevalence cohort.⁵⁸ The primary endpoint was change in the modified Stoke AS Spine Score (mSASSS) at 96 weeks. There was no significant difference in the mSASSS from baseline in either the treatment or comparison group. Thus there continues to be a lack of evidence to support the idea that TNF antagonists have an effect on bone proliferation. It remains to be seen if suppression of inflammation early in the disease course can decelerate or prevent bone formation and thus structural damage.

Psoriatic arthritis efficacy studies

There have been two randomized clinical trials (RCTs) examining etanercept as a treatment for

Table 3. Outcome measures utilized in psoriatic arthritis clinical trials.

| Measure of disease activity | Definition |
|--|---|
| American College of Rheumatology Response Criteria ⁶² | <p>To achieve ACR20, patients must exhibit a 20% improvement in:</p> <ol style="list-style-type: none"> 1. Tender Joint Count 2. Swollen Joint Count 3. 20% improvement in at least 3. of the following: <ul style="list-style-type: none"> • Patient global assessment of disease activity • Physician global assessment of disease activity • Patient's assessment of pain • Disability (measured with the Health Assessment Questionnaire) • Acute phase reactants: ESR or CRP <p>For an ACR50 or ACR70 response, 50% or 70% improvement must be met.</p> |
| Psoriatic Arthritis Response Criteria (PsARC) ⁶³ | <p>Improvement in 2 of the following 4 measures, 1 of which must be tender or swollen joint score, and no decline in any measure:</p> <ol style="list-style-type: none"> 1. Patient global assessment (1 unit on a 0–5 point scale) 2. Physician global assessment: (1 unit on a 0–5 point scale) 3. Tender joint score (30% improvement) 4. Swollen joint score (30% improvement) |
| Psoriasis Area and Severity Index (PASI) ⁶⁴ | <p>Psoriatic plaques are graded by erythema, thickness and amount of scale (0–6 scale). These scores are then weighted by severity (0–4 scale) and amount of body surface area involvement to give a composite score.</p> |

Felson et al⁶² Clegg et al⁶³ Fredriksson et al⁶⁴

PsA.^{59,60} The first RCT was a 12-week blinded study in which 60 patients with psoriasis and PsA were randomized to receive either etanercept 25 mg twice weekly or placebo.⁵⁹ Primary study endpoints were the PsARC and a 75% improvement in the PASI (see Table 3 for definitions of response criteria used in clinical trials). Secondary endpoints were the ACR20 and improvement in psoriatic skin target lesions. Patients on stable doses of methotrexate, low dose corticosteroids and NSAIDs were allowed to continue, but all other DMARDs and topical treatments for psoriasis were withdrawn.

Of the etanercept treated patients, 87% attained the PsARC, contrasted with 23% of placebo patients. 19 patients in the treated group had psoriasis of at least 3% body surface area; 5 of these patients (26%) had a 75% PASI improvement compared to none in the placebo group. Of the treated patients, 73% met ACR20 criteria versus 13% of placebo patients. ACR50 and 70 criteria were achieved by significantly more of the treated patients (Table 4). This data correlates to a statistically significant 75% median improvement in tender joint count and 72% improvement in swollen joint count in the treated patients. Median improvement in psoriatic skin target lesions was

50% in treated patients and 0% in placebo patients. ESR and CRP normalized in 82% and 75% of the etanercept-treated, significantly different than in the placebo group (48% and 32% respectively).

The second RCT was an analogous, but larger, multicenter RCT of 205 PsA patients studied over 24 weeks, with a subsequent 48-week open-label extension.⁶⁰ Patients received either placebo or etanercept 25 mg twice weekly. The primary endpoint was ACR20 response at 12 weeks and secondary endpoints included the PsARC, ACR50 and ACR70 responses, PASI 50 and PASI 75. The Health Assessment Questionnaire (HAQ) and Short Form 36 Health Survey (SF-36) were also evaluated. Hand and wrist radiographs were assessed at baseline 6, 12 and 24 months.

The primary and secondary endpoints were met by more of the treated than placebo patients, in a statistically significant manner (Table 4); these results were maintained at 24 and 48 weeks. The individual measures demonstrated a significant improvement patient quality of life and function. Psoriatic skin disease was also significantly improved with 47% achieving a PASI 50 and 23% a PASI 75 at 24 weeks. This was the first study to demonstrate a significant effect on radiographic

Table 4. Outcome measures in etanercept vs placebo in PsA randomized controlled trials.

| Study | Duration | # of Pts (etanercept/placebo) | ACR20% | ACR50% | ACR70% | PsARC% |
|----------------------------|----------|----------------------------------|--------|--------|--------|--------|
| Mease et al ⁵⁹ | 12 weeks | 30/30 | 73/13 | 50/3 | 13/0 | 87/23 |
| Mease et al ^{60*} | 12 weeks | 101/104 | 59/15 | 38/4 | 11/0 | 72/31 |
| | 24 weeks | 101/104 | 50/13 | 37/4 | 9/1 | 70/23 |

*Supplementary data published in Mease et al⁶⁵

progression in TNF antagonist-treated PsA patients, with an improvement in the mean annualized rate of change in the modified total Sharp score of -0.03 units compared to a $+1.00$ unit increase in the placebo group. Later published data of the same group at two years revealed these patients had sustained inhibition of radiographic progression.⁶¹ In the open-label extension, the percentage of etanercept treated patients achieving ACR20/50/70 responses at 48 weeks was 64%, 44% and 23% respectively and the PsARC was met by approximately 80%. Neither RCT demonstrated a significant difference in etanercept efficacy in patients concurrently treated with methotrexate.

Similar to the AS data, there have been few head-to-head comparison studies of the effectiveness of etanercept versus other therapeutic agents in PsA. In an observational study, Heiberg et al⁶⁶ investigated the effectiveness of anti-TNF therapy versus with methotrexate monotherapy in PsA patients over six months. Of 146 patients who received anti-TNF therapy, 33 received etanercept and 50 received etanercept and methotrexate. These patients were compared to 380 patients receiving methotrexate. At six months the anti-TNF group had significantly greater improvements in joint count, ESR, quality of life measures as well as patient's assessments of pain, fatigue and global disease activity, indicating the effectiveness of TNF antagonist therapy over methotrexate in a typical clinical practice population. In a subgroup analysis comparing anti-TNF monotherapy to anti-TNF and methotrexate combinations therapy, no significant differences were found.

Safety and Tolerability

Overall, etanercept therapy has been generally well tolerated in AS and PsA patients in studies and randomized clinical trials.^{43,67,68} However, significant safety concerns do exist and will be reviewed here. The majority of safety data has been gathered from the rheumatoid arthritis and inflammatory bowel disease populations.

In the US, etanercept carries a boxed warning regarding the risk of serious infections, including bacterial sepsis, tuberculosis and invasive fungal infections, similar to required labeling for the other TNF inhibitors. Other reported serious adverse events include injection site reactions, malignancy, induction of autoimmunity, demyelinating disease, and heart failure. Commonly reported side effects include non-serious infections, headaches, and skin rashes. It is generally accepted that all TNF antagonist medications should be avoided in patients with active infections, malignancies or a history of demyelinating disease.

The use of etanercept in AS and PsA patients greater than 65 years of age enrolled in clinical trials (only 16 patients in total), was not found to be associated with a greater rate of adverse events than that seen in those <65 years.⁶⁹

Infections

All TNF antagonists have been associated with an increased rate of infections, including serious bacterial, fungal and atypical infections. Patients with other medical conditions and those on multiple immunosuppressive medications appear to be at highest risk. In randomized controlled clinical trials of PsA and AS patients, no increased rate of serious infections versus placebo has been found. Infection rates in psoriasis patients taking etanercept in several clinical trials have also been similar to placebo.⁷⁰

TNF has a significant role in maintaining granuloma formation and reactivation of latent tuberculosis in patients on TNF antagonists has been reported. There have been numerous reports of disseminated tuberculosis involving extrapulmonary sites, although this is less common with etanercept in comparison to infliximab and adalimumab.^{6,71-73} It is advised that patients be screened for latent tuberculosis with tuberculin skin testing or interferon-gamma release assay prior to starting TNF antagonist agents and perhaps with chest radiographs for those at high risk or with previous

tuberculosis exposures.^{74–76} Those with latent tuberculosis should begin treatment prior to initiation of TNF antagonist therapy.⁷⁵ Repeated tuberculosis screening is recommended for patients at high risk for infection, who have been exposed to the disease, or traveled to an endemic area. However, there is no consensus regarding routine rescreening of anti-TNF treated patients and concerns have been raised regarding the ‘booster’ phenomenon, in which repeated tuberculin skin testing leads to a false-positive test due to recall of waned immunity to prior non-tuberculous mycobacterial exposure.⁷⁶ Overall, etanercept has been shown to be less likely to induce activation of latent tuberculosis, in comparison to the TNF antagonist antibody infliximab.^{71,77} Underreporting of reactivation of latent tuberculosis in patients taking TNF antagonists remains a concern.

A variety of uncommon opportunistic infections including histoplasmosis, coccidioidomycosis, cryptococcus, listeriosis, and aspergillosis, disseminated fungal infections and nontuberculous mycobacterial infections have been reported with all of the TNF antagonists,^{78,79} thus physicians must be vigilant regarding infection monitoring and have a clinical suspicion for atypical infections in their PsA and AS patients.^{80,81} Granulomatous infections and invasive fungal infections appear to occur at a lower rate during treatment with etanercept than with infliximab therapy.^{71,82,78}

Patients with chronic viral hepatitis C have been safely treated with etanercept.^{83–85} There have been reports of chronic hepatitis B reactivation with the use of etanercept and many physicians screen patients for hepatitis B infection, especially those at high risk for infection, prior to starting TNF antagonist therapy. Few patients with HIV have been treated with TNF antagonists and there is little data regarding their use in this patient population. A retrospective review of eight HIV patients including 3 with PsA and 1 with AS treated with etanercept showed no significant adverse effects of the treatment.⁸⁶

The use of live vaccines in patients taking TNF antagonists should be avoided due to the theoretical risk of developing a disseminated viral infection. Inactive attenuated vaccines, such as the influenza vaccine, are encouraged and studies have demonstrated protective effects, despite the fact some patients do not develop full immunity.^{87,88} A recent study demonstrated that anti-TNF treated patients, while developing lower post-vaccination antibody

titers to the influenza vaccine than control patients, still maintained equal protection rates.⁸⁹

Injection site reactions

The most commonly reported side effect of etanercept is an injection site reaction, which occurs in approximately 14% of psoriasis patients in clinical trials.⁷⁰ In general these reactions are not serious and tend to decrease in frequency and severity with prolonged use of the medication.

Malignancy

Long-term animal or human studies assessing the oncogenic potential associated with etanercept have not been carried out. An increased risk of lymphoma in rheumatoid arthritis patients treated with TNF antagonists has been suggested, however this association is controversial and studies have not consistently shown this risk.^{90,91} Patients with PsA and AS have not been strictly studied regarding lymphoma risk.

There is no consistent data supporting an increased risk of solid malignancies with etanercept therapy, excepting one study demonstrating an increased risk of malignancy in Wegener’s granulomatosis patients treated with cyclophosphamide and etanercept,⁹² leading to a drug label warning against the concomitant use of etanercept and cyclophosphamide.⁴ Patients with RA have been shown to have an increased risk of non-melanoma skin cancers (OR 1.5);⁹¹ data demonstrating this risk in AS and PsA patients has not been published.

There have been rare case reports of pancytopenia including aplastic anemia occurring in patients taking etanercept, however causality has not been proven.⁴

Induction of autoimmunity

There are reports of AS and PsA patients developing antinuclear antibodies and anti-double-stranded DNA antibodies with etanercept use, as well as signs and symptoms of systemic lupus erythematosus (SLE).^{93–95} SLE induced by etanercept is reversible with drug discontinuation and screening patients for antinuclear antibodies prior to treatment initiation has not been universally recommended.

Vasculitis, both cutaneous and systemic, has also been reported in patients treated with etanercept

and other TNF antagonists, including 3 patients with AS and 3 with PsA.⁹⁴ Greater than 90% of the vasculitis cases resolved following TNF inhibitor discontinuation. There have been infrequent reports of autoimmune hepatitis associated with the TNF antagonist antibodies and one recent report of a suspected exacerbation of autoimmune hepatitis in an RA patient two weeks after the start of etanercept.⁹⁶

TNF antagonists are paradoxically associated with the worsening or new-onset of psoriatic skin lesions in a minority of patients, with at least 180 case reports to date, including AS and PsA patients treated with etanercept. Patients may respond to conventional treatments for psoriasis or have resolution of the skin lesions with a switch to an alternative TNF antagonist.⁹⁷

Demyelinating disease

TNF antagonists should not be used in those with a history of demyelinating disease or patients who develop new-onset neurologic symptoms suggestive of these disorders. Etanercept has rarely been associated with multiple sclerosis, transverse myelitis, and optic neuritis in PsA and AS patients.^{98,47}

Heart failure

Two trials of etanercept for the treatment of congestive heart failure were terminated due to lack of efficacy and one of these trials suggested a higher mortality rate in patients treated with high dose infliximab. There have been sporadic reports of worsening or new onset of congestive heart failure in etanercept patients. New York Heart Association class III and IV heart failure is a contraindication to TNF antagonist treatment.⁹⁹

Pregnancy

There have been no large trials or studies of etanercept in pregnant women and the drug is rated "category B" for pregnancy (animal studies show no risk of fetal harm, human studies not available). There is no data available regarding lactation risk; approximately 0.0001% of the peak plasma concentration of etanercept has been found in breast milk.¹⁰⁰ In 2006 Carter et al¹⁰¹ reported a woman with PsA taking high-dose etanercept throughout her pregnancy who delivered a child with the VATER association of congenital birth defects (vertebral defects, anal atresia, tracheoesophageal

fistula/esophageal atresia, and renal defects). The authors subsequently presented a second case of VATER (VACTERL) associated birth defects in a child of a woman taking adalimumab, as well as adverse event data from the US Federal Drug Administration (FDA) demonstrating congenital anomalies in 41 children born to mothers taking a TNF antagonist during pregnancy; they hypothesized many of these anomalies were part of the VACTERL spectrum.¹⁰² Physicians have been urged to report pregnancy outcomes associated with TNF antagonists, and in North America to register their pregnant patients in The Organization of Teratology Information Specialists (OTIS) pregnancy register (1-877-311-8972).

Safety in ankylosing spondylitis patients

Davis JC et al⁶⁷ studied the efficacy and safety of etanercept in 257 AS patients over 192 weeks in an open-label extension of a previous 24-week randomized clinical trial.⁴⁴ The most common adverse reactions were injection site reactions (22.2%), headaches (20.2%) and diarrhea (17.5%). Twenty-one patients withdrew from the study due to adverse events. Serious adverse events occurred at an exposure-adjusted rate of 0.08 per patient-year (versus 0.07 in the RCT placebo group). The infection rate was 1.1 per patient-years (versus 1.0 in the RCT placebo patients). The most commonly reported infections were upper respiratory (45%), sinusitis (16%), flu-like (15%), and bronchitis (11%). One patient developed tuberculosis. Serious infections occurred at a rate of 0.02 per patient-year and no patients died in the course of the study. No incidents of lupus, demyelinating disorders, lymphomas or malignancies were reported. There were less uveitis flares than reported in the RCT placebo patients (0.11 versus 0.22).

AS patients in this study demonstrated a lower rate of reported serious adverse events than that reported in rheumatoid arthritis patients.⁶⁷ In a study of rheumatoid arthritis patients taking etanercept for 7 years the adverse event rate was 0.15 per patient years.¹⁰³ This difference is thought to be due to increased use of other immunosuppressive medications and comorbidities found in RA patients.

Safety in psoriatic arthritis patients

Saad et al⁶⁸ reported a meta-analysis of the safety risks found in randomized controlled trials of TNF

antagonists in PsA patients 2 RCT trials involving etanercept.^{59,60} They found that fewer patients withdrew from etanercept than placebo. Injection site reactions were significantly more likely in patients taking etanercept with a relative risk of 4.27. There were no significant differences in etanercept or placebo patients in regards to adverse events, serious adverse events or upper respiratory infections during the clinical trials (conducted over 12 weeks and 48 weeks respectively). No malignancies were reported.

The efficacy and tolerability of anti-TNF treatment of PsA patients in clinical practice was evaluated in 261 PsA patients followed through the South Swedish Arthritis Treatment Group (SSATG) register over 5 years.¹⁰⁴ Of these patients, 119 were prescribed etanercept 25 mg twice weekly. In this treatment group, drug continuation was significantly associated with a high CRP at baseline and simultaneous MTX use. An overall incidence of severe adverse events of 5%–6% was found (no data for etanercept-only incidence was reported) which included 2 malignancies and one patient who developed life-threatening bacteremia. Overall this is a lower rate of adverse events than that reported in rheumatoid arthritis patients, however this study relied on a voluntary adverse reporting system.

Patient Focused Perspectives

Several studies and investigations have indicated AS and PsA patients suffer from significant joint damage, poorly controlled pain, loss of function, and a decreased quality of life, all leading to work disability. Thus the long-term socioeconomic costs associated with poor disease control are high. Prior to the advent of TNF antagonists it was generally accepted that traditional therapies for AS (DMARDs, NSAIDs, corticosteroids) were inadequate to control disease activity, especially axial disease, in the majority of patients. This resulted in significant disability in most of these patients due to uncontrolled inflammatory back pain and stiffness, limited spinal mobility, and fatigue.¹⁰⁵ A study of 175 AS patients prior to the advent of TNF antagonist use demonstrated significantly reduced quality of life measures¹⁰⁶ and AS patients have pain and functional disability similar to RA patients.¹⁰⁷ The rate at which AS patients leave the labor force is increased 3 times over the general population.¹⁰⁸ TNF antagonist therapies have been

approved for use for moderate to severe AS in many countries, and the Assessment in Ankylosing Spondylitis (ASAS) working group has published recommendations for TNF antagonist use in these patients, recommending anti-TNF therapy after failure of at least two NSAIDs.¹⁰⁹

A survey undertaken in Britain during 2001 to 2003 demonstrated that nearly two-thirds of AS patients had poor functional status and quality of life with a BASDAI score ≥ 40 , thus meeting the British Society of Rheumatology criteria for anti-TNF use.¹¹⁰ Another 2005 study compared the health-related quality of life (HRQOL) of AS patients to the general US population, and other chronically ill populations, and evaluated the effect of etanercept therapy on HRQOL in AS patients.¹¹¹ They found lower scores in all quality of life scales in AS patients including physical and social functioning and mental health, which exceeded that seen in many other chronic diseases such as diabetes and hypertension. Etanercept treatment significantly improved these scores, especially in the physical domains, and this improvement in quality of life was observed in most patients after 12–16 weeks of therapy. Braun et al¹⁰⁵ similarly demonstrated that AS patients have QOL impairments and functional limitations equal or exceeding patients with cancer, congestive heart failure, diabetes or depression. In this subanalysis of the van der Heijde 2006 RCT, it was demonstrated that improvements in patient-reported outcomes including physical function, fatigue and pain were similar with either the 50 mg weekly or 25 mg twice-weekly dosing regimens.

Keat et al¹¹² studied 65 AS patients receiving anti-TNF therapy at 2 UK hospitals and found that prior to treatment one-third of working-age subjects were unable to work, and following TNF initiation one in four returned to work in 18 months. Average sick leave in the working patients was reduced from 15 days in the year prior to treatment, to 0.91 days in the year following treatment, and the patients reported that their perceptions of the impact of AS on their ability to work were dramatically improved.

In one cohort of 82 AS patients, it was demonstrated that those who were HLA-B27 positive were more likely to have more active disease including extra-articular manifestations and longer disease duration, with higher markers of disease activity, poorer functional status and quality of life, compared to their HLA-B27 negative counterparts.¹¹³

These patients were significantly more likely to meet ASAS criteria and receive biologic therapy. Acute anterior uveitis may occur less frequently in AS patients taking etanercept,¹¹⁴ however not to the degree that has been demonstrated with the TNF monoclonal antibodies.¹¹⁵ It has been hypothesized that etanercept may prevent uveitis flares, while infliximab is an effective treatment of active uveitis.^{114,115} Etanercept has proven to be effective in treating the axial and peripheral enthesopathy often associated with spondylarthropathy.^{116,117} Decreases in cachexia with increases in fat mass and bone mineral density have also been demonstrated in spondyloarthropathy patients following two years of anti-TNF treatment.¹¹⁸

The ASAS criteria are often utilized to measure disease activity in clinical trials, however their applicability to clinical practice has been questioned and the criteria has been revised over time.^{109,119} Criticisms of the criteria include that the measured parameters such as pain, stiffness, ESR and BASDAI cannot reflect disease activity for every patient, that it lacks sensitivity to changes over time, and does not encompass both doctor and patient perspectives.^{119,120} Recently the ASAS international society released four new indices for disease activity in AS (ASDAS) that resulted in a correct classification in disease activity in approximately 72% of cases and outperformed the BASDAI.¹²⁰ It remains to be seen if one of these indices will be accepted as the favored disease activity measure in clinical practice. At present, most clinicians continue to rely on single-variable outcome measures such as pain, ESR, and patient sense of well-being, in addition to easily administered disease activity measures such as the BASDAI, to measure disease activity in AS patients.

The clinical course of PsA is highly variable, ranging from minimal joint destruction to severe deforming arthritis. In one study, nearly half of PsA patients demonstrated joint damage on physical exam on their first visit to a rheumatology clinic,¹²¹ with the potential for significant morbidity. Similar to AS, some PsA patients may experience as much pain and functional disability as those with rheumatoid arthritis.¹²² Psoriatic arthritis has also been associated with an increased mortality rate.¹²³ Clinical depression rates in individuals with psoriatic skin disease have been estimated to be as high as 60%,¹²⁴ with 5% of patients in one series reporting active suicidal ideation.¹²⁵

Of the nonbiologic DMARD therapies, randomized clinical trials have indicated sulfasalazine, methotrexate and leflunomide are marginally to moderately effective in treating PsA.^{126–128} Due to the safety and effectiveness in treating joint disease, inhibition of structural damage, and improvement of quality of life demonstrated in the clinical trials, as well as lack of other effective therapies, TNF antagonists have been widely approved for use in this population. In 2005, the British Society for Rheumatology published guidelines for the use of anti-TNF therapy in PsA, recommending TNF antagonist use for patients with active disease who have not responded to 2 or more standard DMARDS.¹²⁹ The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recently published treatment guidelines for PsA recommended anti-TNF α therapy for patients who do not respond to at least 1 standard DMARD, or for those with poor prognosis, even if they have not failed a traditional DMARD.¹¹⁷

It is not uncommon for PsA patients to note improvement in their overall sense of well being, decreased morning stiffness, pain and joint swelling as early as two weeks after TNF initiation. It has been suggested that these effects are due to etanercept-induced improvement in the neurohormonal axis.¹³⁰ A 12-week RCT of etanercept in 618 moderate to severe plaque psoriasis patients (209 with PsA) demonstrated clinically reduced fatigue and depression in the treated patients.¹³¹ These improvements in fatigue and depressive symptomatology were sustained throughout an 84-week open-label extension of this trial.¹³²

The monetary costs of biologic therapy cannot be overlooked. Several cost analysis studies have implied cost-effectiveness of anti-TNF therapies in AS and PsA patients with moderate to severe disease.^{133–136} However, there have been no head-to-head pharmacoeconomic studies of etanercept in comparison with other biologic therapies or traditional DMARDS. Furthermore, it is very difficult to estimate cost-effectiveness of long-term therapies in chronic diseases, with short-term data often having to be mathematically modeled over a patient's lifetime. Cost-effectiveness estimates produced by drug manufacturers and those done by governmental health care organizations and independent groups have often resulted in widely disparate data. Currently available studies regarding

cost-effectiveness of these medications can only be taken as estimations.

A Markov model of the 5 year cost-utility of etanercept compared with usual care in active AS patients with a BASDAI ≥ 4 demonstrated that while the drug does have large clinical effects, the total cost (2002 data) was €52,137 compared to €21,261 for usual care with an approximate cost of €118,033 per quality-adjusted life year (QALY) gained, above the threshold considered an acceptable cost by most societies (implicit thresholds often cited are \$50,000 per QALY gained for the USA, £30,000 for the United Kingdom, and €18,000 for the Netherlands).¹³⁷ However this model could not take into account potential long-term cost savings such as decreases in health care utilization and work disability. In contrast, a mathematical model of long-term etanercept treatment of severe AS in the UK, compared to NSAID monotherapy, demonstrated cost-effectiveness with a cost of £22,700 per QALY gained.¹³⁴

A health economic model comparing methotrexate plus cyclosporin combination and leflunomide therapies to etanercept in PsA patients demonstrated an estimated cost-effectiveness of etanercept between £28 000 and £38 000 per QALY.¹³⁸ In a mathematical model investigating the cost-effectiveness of both etanercept and infliximab for the treatment of active PsA from a UK National Health Service perspective, only etanercept was found to be potentially cost-effective over a 10-year and lifetime horizon.¹³⁵ In a cost evaluation study of 107 PsA patients from Italian rheumatology clinics who were unresponsive to DMARD therapy and treated with TNF antagonists (87% etanercept) for 12 months, there was a 97% likelihood that anti-TNF therapy would be considered cost effective at the willingness to pay threshold of €60,000 per QALY gained.¹³⁶

Therefore, based on currently available pharmacoeconomic data, one can speculate that over time, that the indirect and direct cost savings including a reduced need for joint replacement surgeries, decreased health care utilization, diminished need for other medications and therapies, improved quality of life, decreased work disability, and increased life expectancy in AS and PsA patients could be substantial. However, the definitive long-term data to support this assumption is not yet available and the incremental cost-effectiveness ratio allocated to one QALY is

highly variable between societies and health care systems.

Conclusions, Place in Therapy

The goal of any rheumatic therapy is to maintain joint integrity and function and to improve quality of life with a minimal amount of toxicity. The advent of TNF antagonist therapy provided the first truly effective treatment for many AS and PsA. However this therapy is not without toxicity and the potential medication cost over a lifetime of treatment is enormous.

It remains up to the clinician to contemplate prescribing guidelines, efficacy, toxicity and cost concerns, and then to select appropriate patients for TNF antagonist therapy. At present there are few reliable tools to predict which spondyloarthropathy patients will do well over the long-term and which will do poorly. It has been suggested that poor prognostic factors in AS and PsA patients include elevated inflammatory markers, NSAID unresponsiveness, limitation of lumbar spine range of motion, dactylitis, oligoarthritis, hip arthritis, peripheral arthritis and the presence of extra-articular features.^{139,140} These patients are likely candidates for more aggressive, costly and potentially toxic therapies.

Patients found in clinical practice differ in severity of disease from those enrolled in clinical trials, and it has been suggested TNF antagonist response rates are higher in a typical clinical population than demonstrated in efficacy studies.¹³³ At present, it is unclear if or when TNF antagonist therapy can be decreased or discontinued in these strong responders. In contrast, there remains a subset of patients who do not respond to this novel therapy and investigations regarding the reasons for this lack of response and the loss of efficacy experienced by some patients are in progress. It has been demonstrated that AS and PsA patients who do not respond to infliximab often respond to etanercept and vice versa.^{141,142}

Several ongoing genotypic studies have identified TNF and TNF receptor polymorphisms that may predict independently whether any one patient will respond to a TNF antagonist.¹⁴³ Unfortunately, TNF genotyping is not available for routine use and there is a need for continued pharmacogenetic research and studies to predict which patients will respond to biological therapies.

Many questions regarding TNF antagonist therapy remain. It is unclear why some patients respond to these biologic therapies while others do not, if combination therapy with other DMARDS would be effective in these patients, whether structural damage can truly be inhibited in bone-forming diseases such as AS, and the utility of these agents in patients with long-standing disease, in comparison to those with early disease. Uncertainties regarding appropriate dosing, dose response, length of therapy and the effect of etanercept on work-related disability will only be answered with long-term studies and investigations. Large patient registries will likely be pivotal in providing additional important long-term efficacy and safety data. Despite these unknowns, etanercept therapy has been an exceptionally successful and well-tolerated for numerous ankylosing spondylitis and psoriatic arthritis patients, and will likely continue to be cornerstone therapy for these challenging diseases in the foreseeable future.

Disclaimers

The opinions or assertions contained herein are those of the authors and are not to be construed as official policy of the Department of the Army, Department of the Air Force, or the Department of Defense.

Disclosure

The authors report no conflicts of interest.

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