Combining etanercept with traditional agents in the treatment of psoriasis: a review of the clinical evidence

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Abstract
Psoriasis is a chronic, systemic inflammatory disorder manifesting primarily in skin and potentially in joints, frequently necessitating treatment with conventional systemic therapies, phototherapy or biological agents. Patients with moderate to severe disease suffer a diminished quality of life, experience significant comorbidities and have a higher mortality. Although traditional treatments are effective in the short-term, their use is often limited by concerns over long-term toxicity, including end-organ damage and risk of malignancy. Combination therapy is a commonly used approach and is often more effective than any single agent. Lower doses of two treatments in combination can also minimize potential side effects from a single agent at higher doses. Etanercept is a recombinant human tumour necrosis factor (TNF)α receptor (p75) protein fused with the Fc portion of IgG1 that binds to TNFα. This article reviews the evidence on the efficacy and safety of etanercept in combination with methotrexate, acitretin, narrowband UVB and cyclosporin. The largest body of evidence assesses the combination with methotrexate, although evidence is available for the other combinations. Data suggest that although highly effective as monotherapy, etanercept in combination with a conventional systemic agent can enhance efficacy and allow drug sparing. Potentially, the combination may also result in faster treatment responses and permit safe transitioning from one systemic agent to another. Evidence to date suggests that these benefits can be achieved without significant additional toxicity, although long-term data on the efficacy and safety of the combination in psoriatic populations is limited and further evaluation is warranted.

Keywords
biological therapy, combination therapy, etanercept, methotrexate, psoriasis, psoriatic arthritis

Introduction
Psoriasis is a chronic, debilitating, inflammatory, multisystem disease manifesting primarily in the skin and potentially the joints.1,2 Patients with psoriasis suffer pruritic and disfiguring skin lesions and a significant percentage develop nail dystrophy and psoriatic arthritis.1,2 They have a higher risk of developing significant comorbidities and are at increased risk of death.3–9 Patients with moderate to severe disease generally require phototherapy or systemic agents to control their disease adequately. These treatments have proven to be highly effective but their suitability for long-term use is impacted by potential toxicity concerns including end-organ damage [methotrexate (MTX) and cyclosporin], teratogenicity (acitretin and MTX) and malignancy [cyclosporin and narrowband ultra-violet B (NB-UVB)].10–19
Combination therapy is frequently used in patients with moderate to severe plaque psoriasis. Combining two or more agents, biological and traditional therapies, may work synergistically. Furthermore, using lower doses of two treatments in combination can minimize side-effects from a single agent at a higher dose (Table 1).

Biological agents are ideal candidates to combine with traditional therapies because of their highly targeted modes of action, lack of end-organ toxicity and potential synergistic effect with traditional treatments. Because they are approved as second-line therapies in patients who have failed multiple conventional treatments, many patients receive biological and traditional therapies concurrently, either when transitioning between agents or to maintain optimal disease control.

There are currently two classes of approved biological drugs that reduce TNFα bioavailability: soluble TNF receptor-Fc fusion proteins (etanercept) and anti-TNF monoclonal antibodies (adalimumab and infliximab). Multiple clinical trials have shown that etanercept monotherapy is highly effective and has a favourable long-term safety profile in adults with moderate to severe plaque psoriasis. At a dose of 50 mg qw, up to 71% of patients achieve a PASI-75 response at 24 weeks. Clinical response is maintained with long-term treatment and etanercept can be used continuously or intermittently.

The combination of etanercept and agents such as MTX has been extensively studied in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriatic arthritis. In psoriasis, while a significant body of clinical evidence supports the use of etanercept or conventional treatments as monotherapy, data on combinations involving a biological agent are less complete. This article reviews studies relating to etanercept in combination with conventional psoriasis therapies.

### Search strategy

The PubMed, MEDLINE, and ClinicalTrials.gov databases were searched to March 2009 using the terms ‘psoriasis’, ‘psoriatic arthritis’, ‘etanercept’, ‘combination therapy’, ‘acitretin’, ‘methotrexate’, ‘cyclosporin(e)’, ‘phototherapy’, ‘UVB’, ‘UVA’, ‘corticosteroids’ and ‘topical treatment’. Searches were limited to studies involving adult humans that were published in English. Congress abstracts of American Academy of Dermatology, European Academy of Dermatology & Venereology and Gene to Clinic meetings from 2005 to 2008 were also searched. It was assumed that any abstract of sufficient quality published prior to 2005 would have been published in a formal full-length work. References were checked for additional sources. Unpublished clinical study reports of etanercept studies in psoriasis or psoriatic arthritis were obtained from Wyeth, the sponsor of etanercept.

### Combination therapy with methotrexate

Methotrexate is the most widely used systemic treatment for psoriasis. Despite being highly effective, a significant number of patients will fail to respond to MTX monotherapy and its long-term use is limited by the risk of toxicity. In practice, patients who respond inadequately are either rotated to alternative treatments or have concomitant agents added. Zachariae et al. conducted a randomized, open-label, 24-week study that evaluated the effect of adding etanercept in cases where MTX had failed or had insufficient effect. Outpatients with plaque psoriasis (PASI ≥ 8 and/or body surface area > 10%) despite MTX treatment (≥ 3 months; ≥ 7.5 mg/week) were randomized to either etanercept with MTX tapered and discontinued (n = 28) or etanercept with continued MTX (n = 31; Fig. 1). At baseline patients had a mean PASI score of 17 and were receiving a mean MTX dose of 13.7 mg/week.

The proportion of patients judged as ‘clear’ or ‘almost clear’ according to the PGA at week 24 was superior for etanercept with continued MTX treatment compared with etanercept/MTX taper (66.7% vs. 37.0%, respectively; P = 0.025; Fig. 1). The PGA results for the etanercept/MTX taper arm were consistent with those seen in etanercept monotherapy trials. PASI 75 responses at weeks 12 and 24 were also significantly better for combination treatment than etanercept/MTX taper. Safety profiles were similar between the two groups. Five serious adverse events (SAEs) were reported in four patients in the etanercept/MTX taper group and two events in one patient in the combination group. Three patients discontinued as a result of adverse events (AEs) in the etanercept/MTX taper group, but none in the combination treatment group. A total of 17.9% of patients in the etanercept/MTX taper arm recorded an abnormal elevation in hepatic enzymes compared to 12.9% of patients in the combination arm. All hepatic enzyme increases were mild to moderate in nature and did not result in treatment discontinuation (Wyeth Inc., personal communication). No cases of malignancy, opportunistic infection or tuberculosis were observed.

The EASE study was a multi-centre, randomized, open-label trial which evaluated continuous vs. intermittent etanercept in subjects with moderate to severe plaque psoriasis in a community dermatology setting (Amgen Inc., personal communication). All patients received continuous etanercept 50 mg BW during the first 12 weeks, followed by either continuous (n = 1272) or...
interrupted \( (n = 1274) \) etanercept 50 mg QW in the next 12 weeks. Subjects who had been on a stable dose of MTX \( \leq 20 \text{ mg/week} \) for a minimum of 8 weeks before baseline were permitted to continue MTX treatment. Subgroup analysis revealed that concomitant MTX \( (n = 73 \text{ patients}) \) was a significant covariate affecting response to etanercept at 24 weeks (Amgen Inc., personal communication). The odds ratio of achieving ‘clear’, ‘almost clear’, or ‘mild’, on the PGA scale if on concomitant MTX therapy was 2.246 (95% CI 1.25, 4.0; \( P = 0.0069 \)) compared with not being on MTX. The hazard ratio estimate for AEs was similar with or without concomitant MTX. A small case series has also demonstrated that etanercept in combination with MTX may be a useful approach to maximize efficacy in high-need psoriasis patients, without evidence of a significant difference in laboratory parameters or AEs compared with that expected with MTX alone.\(^{53}\)

Combination treatment can also allow dose reduction or discontinuation of potentially toxic agents while maintaining disease control. MTX sparing with etanercept has been demonstrated in two studies of psoriatic patients. In the EASE study 30% of patients on concomitant MTX were able to reduce their weekly dose of MTX and 16% were able to discontinue MTX altogether with the mean weekly dose of MTX decreasing from 23.9 mg/week at baseline to 15.9 mg/week at week 24 (Amgen Inc., personal communication). In the EDUCATE study of patients with concurrent psoriasis and psoriatic arthritis, among the 77 patients with MTX doses recorded at baseline, 29% were able to discontinue use and 7% were able to decrease their dose.\(^{54}\) Mean MTX dose fell from 13.7 mg/week at baseline to 9.2 mg/week at week 24.\(^{54}\) A number of small case series have also demonstrated the MTX sparing effect of etanercept in adult and juvenile psoriasis patients.\(^{28,55–57}\)

The pharmacological mechanisms underpinning the greater efficacy observed with anti-TNF agents and MTX in combination are unclear. A recent study by de Groot et al. evaluated the cellular effects of anti-TNF therapy in combination with MTX in lesional and non-lesional psoriatic skin.\(^{58}\) Monotherapy with either MTX or adalimumab resulted in down regulation of some but not all inflammatory markers assayed. By contrast, all inflammatory markers assessed (CD3, CD68, CD161, elastase, BDCA-2 & TNF\( \alpha \)) were down regulated in skin from patients treated with both adalimumab and MTX, suggesting that anti-TNF therapy and MTX in combination are more efficient in reducing inflammatory cell numbers in psoriatic skin than either drug alone.

To date, evidence on the safety of etanercept in combination with MTX in large-scale studies has come from rheumatology trials. In the TEMPO study, 682 patients with active RA were randomized to receive either etanercept 25 mg BIW, MTX up to 20 mg/week or both treatments combined.\(^{59}\) Over 3 years of follow-up, no significant differences were seen among the groups in the incidence of SAEs. Serious infections were reported for 6.7%, 8.3% and 7.4% of patients in the etanercept, MTX and combination groups, respectively. In the COMET study, 542 patients with moderate to severe early RA were randomized to receive etanercept 50 mg QW combined with MTX up to 20 mg/week, or MTX alone.\(^{40}\) Again, there was no difference in the rate of SAEs (combination 12%, MTX 12.7%) or serious infections (combination 2%, MTX 3%), between the groups. Similar safety outcomes have been seen in other etanercept/MTX combination studies in RA.\(^{60–62}\)

Partly because of the limited ability of randomized controlled trials to detect differences in the rate of rare AEs, post-marketing surveillance databases and observational registries have been utilized in several countries to monitor the use of biological agents in real-world settings.\(^{63–68}\) Granulomatous and opportunistic infections including tuberculosis, histoplasmosis, listeriosis, herpes

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**Figure 1** Etanercept plus concomitant methotrexate in psoriasis patients (Zachariae et al.\(^ {51} \)). (a) Study design schematic and (b) proportion of patients treated with either etanercept alone \( (\square) \); methotrexate tapered and discontinued \( (\square) \) or with etanercept plus continued methotrexate \( (\square) \) with a PGA rating of ‘clear’ or ‘almost clear’ at 12 or 24 weeks.

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\( n = 28 \)

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<th>n = 31</th>
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\( n = 60 \)
zoster and others have been observed with all therapies, although there is some evidence that rates of certain infections, such as tuberculosis, may be higher with the monoclonal antibody anti-TNF agents than the soluble TNF receptor, etanercept, because of the differences in their respective mechanisms of action.69–73

However, few of these observational analyses have assessed whether the use of an anti-TNF agent in combination with MTX compounds the rate of AEs. An exception is a study of 7791 rheumatoid arthritis patients from the CORRONA database in North America, which found that combination therapy with MTX and a TNF antagonist was not associated with a multiplicative risk of infection compared with either agent alone.74 A study of 261 psoriatic arthritis patients from a Swedish registry also found similar SAE rates in patients receiving an anti-TNF agent with (5.32 events/100 treatment years) or without (5.74) concomitant MTX.64 Nonetheless, the evidence base for the safety of anti-TNF agents in combination with MTX in psoriatic patients is limited. As such, patients should be monitored closely as serious infectious complications have been reported in this population.75

**Combination therapy with acitretin**

Acitretin is an ideal candidate for use in combination with biological agents because it is not immunosuppressive and may act synergistically without increased risk of toxicity.13,56,76,77 Gisondi et al. undertook a 24-week, randomized, controlled, investigator-blinded trial evaluating the combination of etanercept with acitretin.13 Patients with plaque psoriasis (n = 60) were randomized to receive either: etanercept 25 mg BIW; acitretin 0.4 mg/kg daily; or etanercept 25 mg QW plus acitretin 0.4 mg/kg daily. A PASI 75 response at week 24 was achieved by 45% of patients in the etanercept monotherapy group, 30% in the acitretin monotherapy group and 44% of patients treated with the combination (P = 0.001 for both etanercept groups compared with acitretin alone). Mean BSA improvement at week 24 was 78.2%, 45.8% and 80% respectively (P = 0.03; Fig. 2). The PASI-75 responses in this study were below those reported previously for etanercept at a dose of 50 mg/week, which may be because of patients having lower baseline PASI scores than in the previous etanercept studies (~10 vs. ~20), making comparison across studies difficult.34,78,79 The safety profiles of the three groups were similar. Four patients in the acitretin group withdrew from the study as a result of inefficacy of treatment, whereas no patients withdrew in the other two groups (P < 0.05). The results suggest the possibility that etanercept can be administered at a lower dose when used in combination without sacrificing efficacy, a potentially attractive option including in cases where the cost of full-dose biological therapy is prohibitive.

Several small clinical case series have also evaluated the use of etanercept in combination with acitretin.56,77,80 In these cases the combination of acitretin and etanercept was used from the outset, or one agent was added to the other in patients not adequately responding to monotherapy. In all cases, combination etanercept-acitretin therapy resulted in enhanced disease control with no adverse treatment outcomes.56,77,80 Some reports have suggested that acitretin may suppress the development of cutaneous malignancies such as squamous cell carcinoma, and as such, adding this agent to at-risk individuals currently receiving a biological therapy may provide an additional therapeutic benefit.81

**Combination therapy with narrowband UVB**

Etanercept in combination with NB-UVB for the treatment of psoriasis has been evaluated in three studies.82–84 A single arm open-label study (n = 86 patients) by Kiricik et al. evaluated the combination of etanercept (50 mg BIW) plus NB-UVB [3 times per week (TL-01 lamp)] for 12 weeks in patients naïve to phototherapy and biological agents (Table 2).82 Mean PASI score at baseline was 23 and most patients were either Fitzpatrick skin phototypes II (43%) or III (25.6%). At 12 weeks, 84.9% of patients achieved a PASI-75 with 58.1% and 26% reaching PASI-90 and PASI-100 respectively. The median time to achieve PASI-75 was 57 days. The most commonly reported AEs were UVB-induced skin injury and injection site reactions. Two AEs were noted, a case of angina pectoris in a patient with known coronary artery disease, and a photosensitivity reaction leading to patient withdrawal. Using a half-body study design, Wolf et al. studied the effect of adding NB-UVB therapy to patients who had not attained a PASI-75 response after 6 weeks of etanercept (50 mg BIW) monotherapy.85 Patients (n = 5) had previously received phototherapy but had not responded adequately or had rapid return of symptoms upon discontinuation. Mean PASI score at baseline was 16 (range 15.4 – 20.4). After 6 weeks of combination therapy, mean PASI scores for UVB vs. non-UVB treated body halves were 1.6 vs. 4.7 respectively (P = 0.0192). AEs comprised transient dizziness in a single patient with no other side-effects recorded.

De Simone et al. evaluated etanercept (25 mg BIW) in combination with NB-UVB (n = 20 patients) vs. etanercept monotherapy-
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<th>Author</th>
<th>Adjunctive treatment</th>
<th>Design/Population</th>
<th>Treatment(s)</th>
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<td>Zachariae et al.</td>
<td>MTX</td>
<td>24 weeks, open-label, randomized.</td>
<td>1. ETN (50 mg BIW/25 mg BIW) + MTX; 2. ETN (50 mg BIW/25 mg BIW) + MTX taper</td>
<td>PGA ‘clear’ or ‘almost clear’ at week 24</td>
<td>PASI 50%–75%/90%/DLQI</td>
<td>PAC ‘clear’ or ‘almost clear’ 66.7% (ETN + MTX) vs. 37%, ETN alone; P = 0.025</td>
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<td>Gisondi et al.</td>
<td>Acitretin</td>
<td>24 weeks RCT, investigator blinded.</td>
<td>1. ETN 25 mg BIW; 2. acitretin (0.4 mg/kg/day); 3. ETN 25 mg QW + acitretin (0.4 mg/kg/day)</td>
<td>PASI-75 response at week 24</td>
<td>Pts with LFTs ≥ 3 × ULN</td>
<td>No significant changes in mean AST, ALT, cholesterol and triglycerides in any arm. Four patients withdrew from acitretin arm (inefficacy). No withdrawals from other groups (P &lt; 0.05)</td>
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<td>Kircik et al.</td>
<td>NB-UVB</td>
<td>12 week, open-label, single arm.</td>
<td>ETN (50 mg BIW) + NB-UVB (3 sessions/week)</td>
<td>PASI-75 at week 12 PASI 90%/100 DLQI</td>
<td>At week 12, PASI-75 86% achieved PASI-90</td>
<td>No unexpected or untoward AEs noted</td>
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<td>De Simone et al.</td>
<td>NB-UVB</td>
<td>12 weeks, open-label, randomized.</td>
<td>ETN (25 mg BIW) + NB-UVB (3 sessions/week)</td>
<td>PASI-75 at week 12 DLQI</td>
<td>PASI-75 90% in combination arm vs. 40% ETN monotherapy</td>
<td>No significant AEs noted</td>
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<td>Wolf et al.</td>
<td>NB-UVB</td>
<td>12 weeks, open-label.</td>
<td>ETN (weeks 1–12) + half-body NB-UVB (3 sessions/week; weeks 6–12)</td>
<td>Mean PASI score</td>
<td>At week 12, mean PASI score (+UVB) 1.6 vs. 4.7 (−UVB; P = 0.0192)</td>
<td>Transient dizziness after ETN in 1 patient</td>
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AE, adverse event; MTX, methotrexate; PsO, psoriasis; QW, once weekly; BIW, twice weekly; RCT, randomized controlled trial; NB-UVB, narrowband UVB; ETN, etanercept; ULN, upper limit of normal; LFTs, liver function tests; DLQI, Dermatology Life Quality Index; Pts, patient.
py (25 mg BIW; n = 20). At 12 weeks, PASI-75 was achieved by 90% of the etanercept/NB-UVB combination group compared to 40% of the etanercept monotherapy group. The mean time to PASI-75 was 38.5 days in the etanercept/NB-UVB group compared to 73.4 days in the etanercept monotherapy arm. No significant AEs were reported.

**Combination therapy with cyclosporin**

Cyclosporin is a highly effective treatment for psoriasis yet long-term use is not recommended as a result of concerns about hypertension, renal toxicity and malignancy. Progressive multifocal leukoencephalopathy, a demyelinating condition caused by the JC virus, has also been reported in transplantation patients receiving cyclosporin as part of combination immunosuppressive treatment. Guidelines suggest that cyclosporin should be used intermittently in short courses rather than as continuous treatment. Appropriate strategies to ensure the safe discontinuation or withdrawal of cyclosporin – such as the use of a bridging agent – should be considered, as abrupt cessation carries a risk of rebound, defined as a 125% worsening of symptoms compared with baseline, or new generalized pustular, erythrodermic, or more inflammatory psoriasis occurring within 3 months.

In contrast to MTX, there are limited data on the use of cyclosporin in combination with anti-TNF therapy. In a recent pilot study, 11 psoriatic arthritis patients with insufficient skin response to etanercept (PASI ≥ 10) while in remission for arthritis, had cyclosporin 3.0 mg/kg/day added. Nine patients obtained a PASI-75 response at week 24. Cyclosporin was ceased in one patient for a raised serum creatinine at week 16, and the dose was lowered in another for deterioration of pre-existing hypertension. Most etanercept/cyclosporin combination studies have been confined to psoriasis patients currently on cyclosporin who require cyclosporin discontinuation. The results of these case series are encouraging and suggest that etanercept may be a useful tool in maintaining disease control previously established by cyclosporin; however, larger studies are needed.

A randomized study investigating the use of etanercept as replacement therapy in patients who have achieved an adequate response with cyclosporin is ongoing.

**Combination therapy in the setting of psoriasis and psoriatic arthritis**

A significant proportion of psoriasis patients who require systemic treatment are likely to have concurrent psoriatic arthritis. Despite limited trial data, MTX, sulphasalazine, cyclosporin and leflunomide are commonly used in systemic treatments to provide clinical improvement in psoriatic arthritis, although they have not been shown to reduce or arrest joint erosion. MTX and cyclosporin are highly effective agents for cutaneous psoriasis, but sulphasalazine and leflunomide have limited efficacy in skin. Phototherapy and acitretin, which are effective in treating the cutaneous manifestations of psoriatic disease, have limited or no effect in psoriatic joint disease. Hence anti-TNF therapy, with or without concomitant MTX, is considered to be the standard of care for patients with psoriasis and psoriatic arthritis. Etanercept is highly effective in psoriatic arthritis, with or without concomitant MTX, and has been shown to prevent progression of joint damage for up to 2 years. Unlike in psoriasis and RA, psoriatic arthritis studies indicate that the combination of an anti-TNF agent and MTX does not result in greater efficacy in either skin or joints. However, observational registry data indicate that concomitant use of MTX with anti-TNF agents may improve treatment persistence by reducing the number of patients discontinuing anti-TNF therapy because of AEs.

**Conclusions**

Combination therapy employing biological and systemic agents is becoming a more widely used approach in the treatment of psoriasis. Although highly effective as monotherapy, etanercept in combination with a conventional treatment offers the opportunity to optimize outcomes for high-need psoriasis patients. The combination of etanercept plus MTX, acitretin or NB-UVB can be instigated from the outset or alternatively, one of the agents can be added to existing treatment in patients inadequately responding to monotherapy. Limited data also suggest that etanercept may offer an efficacious and apparently safe method to avoid long-term use of cyclosporin. Reassuringly, the enhanced treatment responses seen with etanercept combination therapy do not appear to be associated with additional toxicities, although the combination has only been evaluated in relatively short-term analyses in psoriatic populations. The current evidence on the combination, along with data from further clinical studies and from psoriasis registries, such as those recently established in Europe and Australia, should be considered for inclusion in future guidelines on the systemic treatment of plaque psoriasis.

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Combination therapy with etanercept for psoriasis

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