

Combination Therapy With Tumor Necrosis Factor Inhibitors in Psoriasis Treatment

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Practice Points

- The efficacy and safety of agents used as monotherapy has been established.
- Tumor necrosis factor inhibitors in combination with topical or systemic agents can be used in patients who are not responding to traditional monotherapy modalities.

Psoriasis is a systemic disease that affects approximately 2% of the US population. Traditional treatment modalities include phototherapy, topical therapy, methotrexate, cyclosporine, and retinoids. Three tumor necrosis factor (TNF) inhibitors have been approved by the US Food and Drug Administration for the treatment of plaque psoriasis: etanercept, infliximab, and adalimumab. The combination of TNF inhibitors with phototherapy and topical and systemic agents may be effective in treating patients who are recalcitrant to monotherapy. We examine clinical trials that evaluated the efficacy and safety of combination treatments with TNF inhibitors. This review elucidates that combination therapy is both effective and well tolerated among patients with refractory psoriasis. Furthermore, combination therapy may allow for reduction of required treatment doses, thereby

decreasing the potential for toxicity. It is important to note, however, that the studies reviewed here are limited in the long-term follow-up of patients. We conclude that dermatologists can safely and effectively incorporate combination therapy with TNF inhibitors in the treatment of patients with recalcitrant psoriasis.

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Psoriasis is a systemic disease that affects approximately 2% of the US population¹ and has the potential to negatively impact a patient's overall quality of life. Traditional treatment methods include phototherapy, topical therapy, methotrexate, cyclosporine, and acitretin. Ustekinumab, a biologic agent, also has been approved for psoriasis treatment. Currently, 3 tumor necrosis factor (TNF) inhibitors have been approved by the US Food and Drug Administration for treatment of plaque psoriasis: etanercept, infliximab, and adalimumab. Studies have demonstrated that these agents are efficacious in treating psoriasis.²⁻¹⁷ Clinical data continue to be obtained regarding the long-term safety and efficacy of these treatments. Recently, studies have explored the use of TNF inhibitors in combination with more traditional therapies for recalcitrant psoriasis. We conducted a PubMed search (January 5, 2012) of articles indexed for MEDLINE using the search terms *etanercept psoriasis combination therapy*,

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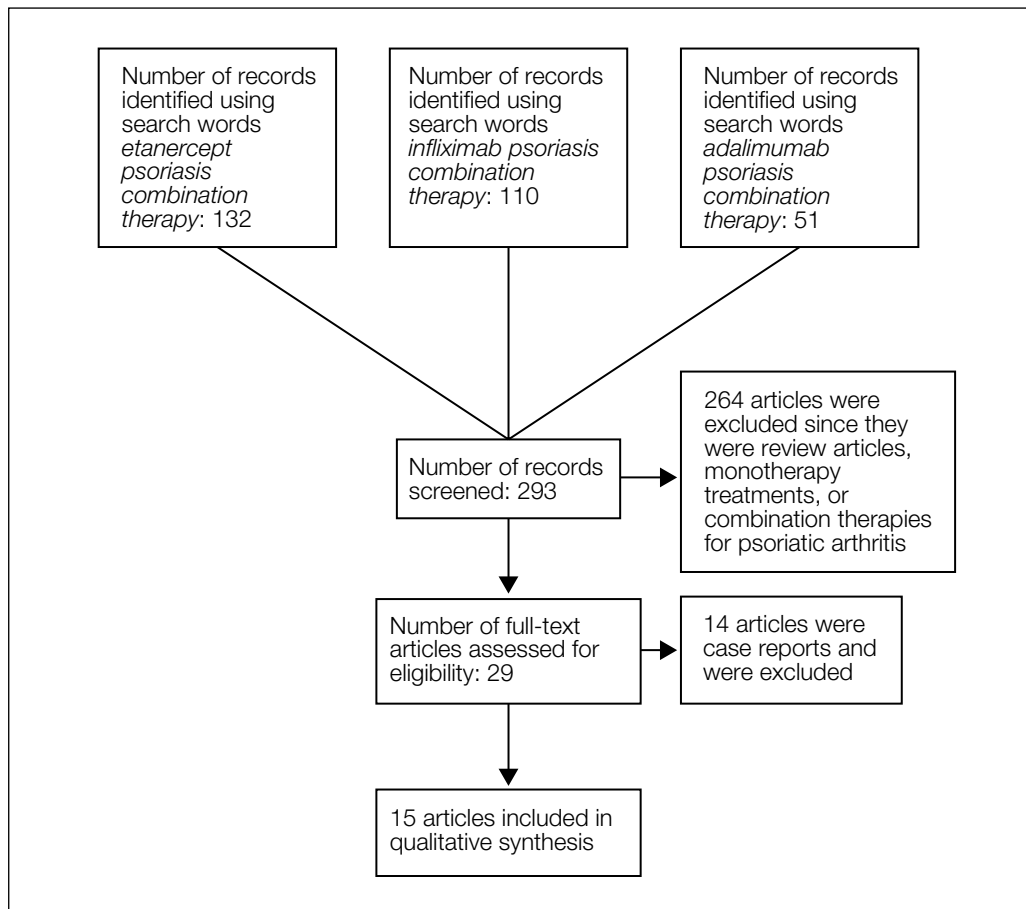
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infliximab psoriasis combination therapy, and *adalimumab psoriasis combination therapy*; articles on monotherapy treatments and combination therapies in psoriatic arthritis as well as case reports and other review articles were excluded from our analysis (Figure). Our review of the current literature revealed that TNF inhibitors used in combination with topical, oral, and systemic agents provide a new avenue for the treatment of psoriasis patients who are unresponsive to monotherapies. Combination therapies also may necessitate lower drug doses, thereby reducing the potential for toxicity.

Etanercept

Numerous clinical trials²⁻⁵ have demonstrated the efficacy and long-term safety of etanercept, a recombinant human tumor necrosis factor α (TNF- α) receptor that is fused with the Fc region of IgG1 to bind TNF- α . Studies conducted in patients with rheumatoid arthritis were the first to show the safety and efficacy of etanercept in combination with methotrexate.^{18,19}

Clinical trials examining combination treatment with etanercept and methotrexate have shown combination therapy to be effective in cases recalcitrant to monotherapy (Table 1). In all studies, no significant difference in occurrence of adverse events was observed between the treatment groups. Zachariae et al²⁰ performed a randomized, open-label, 24-week study to determine the results of adding etanercept for patients who experienced failed treatment with methotrexate or showed a suboptimal response. Fifty-nine patients with plaque psoriasis who did not respond to treatment with methotrexate (≥ 7.5 mg weekly for more than 3 months) randomly received etanercept with methotrexate tapered and discontinued or etanercept with continued methotrexate treatment. After 18 weeks, the mean percentage improvement in psoriasis area and severity index (PASI) score was significantly higher in the combination group versus the etanercept and methotrexate taper group (79.9% vs 62.8%; $P=.023$). At week 24, 66.7% of patients who had continued receiving methotrexate were assessed to be clear or



Data selection method for articles analyzed.

almost clear compared to 37.0% of those who had discontinued methotrexate ($P = .025$).²⁰

Driessen et al²¹ demonstrated the efficacy of combined therapy with etanercept and methotrexate

when treatment with etanercept alone was not successful or when psoriasis flared after discontinuation of methotrexate. Six patients were started on methotrexate therapy after unsuccessful treatment

Table 1.

Etanercept Combination Treatment

Reference	Combination Treatment	No. of Patients	Results
Zachariae et al ²⁰	Methotrexate	59	Combination therapy more effective than monotherapy
Driessen et al ²¹	Methotrexate	14	Combination therapy more effective than monotherapy
Gisoni et al ²²	Acitretin	60	Combination therapy showed the same efficacy as etanercept monotherapy with reduced etanercept dose; combination therapy more effective than acitretin monotherapy
Smith et al ²³	Acitretin, NB-UVB	4	Addition of etanercept to acitretin allowed for discontinuation of NB-UVB for disease control
Kircik and Del Rosso ²⁴	NB-UVB	86	Combination therapy effective and well tolerated
De Simone et al ²⁵	NB-UVB	33	Combination therapy with low-dose etanercept effective and well tolerated
Wolf et al ²⁶	NB-UVB	5	Combination therapy more effective than monotherapy
Lynde et al ²⁷	NB-UVB	75	Combination therapy more effective than monotherapy
Gambichler et al ²⁸	NB-UVB	13	Combination therapy more effective than monotherapy at a clinical and immunohistochemical level
Lee et al ²⁹	Cyclosporine	7	Combination therapy more effective in treating refractory psoriasis
Kircik ³⁰	Calcipotriene–betamethasone dipropionate	20	Combination therapy more effective than monotherapy

Abbreviation: NB-UVB, narrowband UVB.

with etanercept, which resulted in greater than 50% improvement in PASI scores relative to baseline PASI scores in 4 patients. Treatment with etanercept was initiated in 8 patients who had been treated with methotrexate. Discontinuation of methotrexate in 6 of these patients resulted in more than 20% reduction in PASI improvement for 5 patients, suggesting that combination therapy was more effective than replacing etanercept with methotrexate.²¹

In a randomized, multicenter, open-label trial, 2546 patients were administered uninterrupted etanercept (50 mg twice weekly) for 12 weeks followed by either continuous (n=1272) or interrupted (n=1274) administration of etanercept (50 mg once weekly) for another 12 weeks.³¹ Patients who were already taking methotrexate (<20 mg weekly) for at least 8 weeks were maintained on methotrexate therapy. Subgroup analysis of the study showed methotrexate to be a covariate affecting treatment response. The odds ratio of attaining a clear, almost clear, or mild rating on the physician global assessment scale was 2.3 with simultaneous methotrexate administration compared to treatment without etanercept.³¹

With combination treatments, improvement may be attained with reduced drug doses. In the Gottlieb et al³² study, administration of etanercept in patients with psoriasis and psoriatic arthritis allowed for either discontinuation or decreased doses of methotrexate in patients who were taking both. At week 24, the mean dose of methotrexate was reduced from 13.7 mg weekly to 9.2 mg weekly.³²

Combining etanercept with acitretin may allow for a reduction in the dose of etanercept administered. In a study by Gisondi et al,²² 60 patients were randomly selected to receive treatment with etanercept (25 mg twice weekly subcutaneously), oral acitretin (0.4 mg/kg daily), or a combination of both treatments (etanercept dose administered once weekly). At week 24, 45% (10/22) of patients in the etanercept group, 30% (6/20) in the acitretin group, and 44% (8/18) in the combination group had achieved 75% or greater improvement in PASI score ($P=.001$ for both etanercept groups compared to acitretin alone). The 3 treatment groups demonstrated similar safety parameters. Thus combination treatment with etanercept and acitretin was as effective as etanercept alone and more effective than acitretin alone.²²

Other studies also have supported the efficacy of combination therapy with etanercept and acitretin. When 4 patients who already had been unsuccessfully treated with other agents were administered acitretin in combination with etanercept, only 1 patient required continued phototherapy for

disease control.²³ It was noted that 1 patient developed squamous cell carcinoma of the left arm after 1 month of treatment, but the patient had a history of squamous cell carcinoma. Treatment was discontinued in 1 patient after 3 years of treatment, as he developed non-Hodgkin lymphoma.²³ Case series also have confirmed that combination therapy with etanercept and acitretin generally is efficacious and tolerable.^{33,34}

Etanercept also can be used in combination with narrowband UVB (NB-UVB) to treat psoriasis in patients who do not respond to etanercept alone. In an open-label, single-arm study, Kircik and Del Rosso²⁴ demonstrated that a 12-week course of etanercept plus NB-UVB phototherapy was both effective and well tolerated. De Simone et al²⁵ likewise evaluated the efficacy and safety of etanercept therapy in combination with NB-UVB with even a smaller dose of etanercept. Wolf et al²⁶ demonstrated that the addition of phototherapy can elicit a clinical response in patients who do not respond to etanercept monotherapy. Narrowband UVB treatment was administered to a randomly selected body half (left or right) for 6 weeks in 5 patients who did not experience 75% improvement in PASI score with a 6-week course of etanercept administered twice weekly. After 6 weeks of treatment, the mean PASI score was reduced from 10.7 to 1.6 in the NB-UVB-treated body halves and from 10.5 to 4.7 in the nonirradiated body halves. The overall mean PASI reduction was 89% and 68%, respectively ($P=.0009$).²⁶

In a study by Lynde et al,²⁷ 75 patients who had not achieved an improvement of 90% in their PASI score (PASI-90) after 12 weeks of treatment with etanercept (50 mg weekly) were randomized into 2 groups: continue etanercept monotherapy or receive combination therapy with NB-UVB (3 times weekly) for 4 weeks. At week 24, PASI-90 was achieved by 16.2% of patients in the combination group (n=37) versus 15.8% of patients in the monotherapy group (n=38). However, when strict adherence to the phototherapy treatments was taken into account, PASI-90 at week 16 was obtained by 42.9% of the patients in the combination group (n=7) versus 3.4% in the monotherapy group (n=29) ($P=.018$). Thus combination treatment with etanercept and NB-UVB improved clinical response in patients who did not respond to etanercept alone and were able to adhere to the phototherapy regimen.²⁷

The combination of etanercept and NB-UVB phototherapy also has been shown to improve psoriatic lesions at the immunohistochemical level. Thirteen patients were treated with etanercept (25 mg twice weekly) in addition to NB-UVB

administered 3 times weekly.²⁸ Six weeks posttreatment, the reduction in mean (standard deviation [SD]) PASI score was significantly greater in the combination group versus the etanercept monotherapy group (64% [27.8%] vs 53.7% [36.9%]; $P=.011$). The histology scores of the combination group also were more favorable (3.7 [2.4] vs 4.6 [2.7]; $P=.045$). Assays for epidermal immunoreactivity for CD1a, CD4, and CD8 exhibited greater reactivity in the etanercept monotherapy group.²⁸

Cyclosporine also has been used in psoriasis treatment; however, its long-term use is limited by its potential toxicities including hypertension, renal toxicity, and malignancy.³⁵ Guidelines suggest that cyclosporine should be used intermittently rather than on a continual basis. Lee et al²⁹ showed that etanercept and cyclosporine combination therapy can be used to improve clinical outcomes in patients with refractory psoriasis. Seven patients with refractory psoriasis were administered oral cyclosporine (200 mg daily) concomitant with subcutaneous etanercept 50 mg weekly until clinical improvement was observed, and then maintenance on a reduced dose was implemented. Within a mean of 6.85 weeks, 94.9% reduction in PASI was achieved in all patients with the initial dosing regimen and 93.2% reduction in PASI was determined on the maintenance regimen (mean, 56.5 weeks).²⁹ The combination of etanercept and cyclosporine also has been shown to be effective and safe in psoriatic arthritis.³⁶

Some patients experience a psoriasis flare when the etanercept dosage is reduced from twice weekly to once weekly. In these patients, combination therapy with topical agents may be applied to maintain disease control. In a single-center, open-label study, 20 patients underwent treatment with etanercept 50 mg twice weekly followed by etanercept 50 mg weekly.³⁰ After 4 weeks, patients who experienced an increase of more than 2% in body surface area affected were initiated treatment with calcipotriene 0.005%–betamethasone dipropionate 0.064% ointment for 4 weeks. With initiation of topical treatment, mean (SD) body surface area reduced from 9.24 (9.39) to 4.62 (8.19) by week 24 and was maintained at this level. Thus topical calcipotriene 0.005%–betamethasone dipropionate 0.064% is a tolerated therapeutic addition to 50 mg weekly etanercept treatment.³⁰

Infliximab

Infliximab is a monoclonal antibody that binds TNF- α . Its use in combination therapy has been shown to provide benefits for cases of recalcitrant psoriasis (Table 2). A retrospective analysis of 23 patients (17 had received infliximab 3 mg/kg in

combination with methotrexate; 1 had received infliximab 5 mg/kg in combination with methotrexate; and 5 had received infliximab 5 mg/kg in combination with azathioprine) demonstrated attainment of PASI-50 (>50% improvement in PASI) by 91.3% of patients and PASI-75 (>75% improvement in PASI) by 69.9% of patients at week 14.³⁷ Loss of response occurred in only 2 patients: 1 after 15 months and 1 after 3 years. Only 1 patient experienced lung embolism, and no other adverse events were reported.³⁷ There has been a reported case reviewing the development of alveolitis following therapy with infliximab and azathioprine for psoriasis, which resolved with withdrawal of both drugs and administration of prednisolone; thus close monitoring of pulmonary function of patients placed on infliximab and azathioprine is warranted.³⁹

The combination of infliximab and methotrexate also may allow for reduction in infliximab dose through inhibiting the production of antibodies to the murine component of infliximab.⁴⁰ Literature on rheumatoid arthritis has suggested that methotrexate induces reduced excretion of infliximab, thereby increasing the available levels of infliximab.⁴¹ The combination of infliximab and methotrexate also has been shown to improve psoriasis and psoriatic arthritis at the immunohistochemical level. In a prospective, single-center study performed by Goedkoop et al,³⁸ 11 patients with both psoriasis and psoriatic arthritis were administered infliximab infusions (3 mg/kg) at weeks 0, 2, 6, 14, and 22, in addition to methotrexate ranging from 5 to 20 mg weekly. At week 16, the mean (SD) PASI score had decreased from 12.3 (2.4) to 1.8 (0.4) ($P\leq.02$). The mean (SD) disease activity score had decreased from 6.0 (0.5) to 3.6 (0.6) ($P\leq.02$). Immunohistochemical assays conducted at week 4 on skin biopsies and synovium exhibited decreased expression of adhesion molecules and vascular endothelial growth factor, suggesting a role for infliximab and methotrexate therapy in decreasing angiogenesis and cellular infiltration, which may be responsible for the therapeutic benefits observed.³⁸

Adalimumab

Adalimumab is a human monoclonal antibody that binds to TNF- α . When used in combination with phototherapy, it has been shown to be both clinically effective and well tolerated in patients with moderate to severe psoriasis (Table 3). In a 24-week, open-label study, 20 patients were administered adalimumab (40 mg) every other week in addition to NB-UVB phototherapy 3 times weekly for 12 weeks.⁴² By week 12, 95% (19/20) of patients had attained a 75% reduction in PASI score. These

Table 2.

Infliximab Combination Treatment

Reference	Combination Treatment	No. of Patients	Results
Dalaker and Bonesrønning ³⁷	Methotrexate, azathioprine	23	Combination therapy effective and well tolerated
Goedkoop et al ³⁸	Methotrexate	11	Combination therapy effective and well tolerated

Table 3.

Adalimumab Combination Treatment

Reference	Combination Treatment	No. of Patients	Results
Bagel ⁴²	NB-UVB	20	Combination therapy effective and well tolerated
Thaçi et al ⁴³	Calcipotriol-betamethasone	730	No long-term difference from monotherapy

Abbreviation: NB-UVB, narrowband UVB.

clinical outcomes remained stable through week 24, and no adverse events complicated the study.⁴²

Adalimumab combination with topical treatments has been explored. In a phase 3, multicenter, double-blind study, 730 patients randomly received adalimumab 80 mg followed by 40 mg every other week for 15 weeks in conjunction with calcipotriol-betamethasone daily topical application or drug-free vehicle application for 4 weeks. At 4 weeks, the combination group showed a greater PASI-75 response; however, after 4 weeks, the monotherapy group showed enhanced PASI-75 response, and at 16 weeks, no statistical difference in therapeutic effect was found between the 2 groups.⁴³ Thus for patients who are intolerant or have contraindications to systemic therapy, adalimumab in combination with topical treatments may initially induce a more rapid and efficacious response; however, this combination therapy provides no long-term added benefits.

Conclusion

Although the safety and efficacy of agents used as monotherapy for the treatment of psoriasis is more established, recent studies have elucidated

the efficacy and tolerability of using combination therapies in patients who are recalcitrant to monotherapy. Tumor necrosis factor inhibitors used in combination with more conventional treatments can potentiate their therapeutic effects, which may allow for reduced drug doses and a subsequent decrease in the potential for toxicity. Thus TNF inhibitors used in combination with oral, topical, or systemic agents offer a new therapeutic option for patients not responding to traditional monotherapy modalities. In our opinion, TNF inhibitors used in combination with methotrexate or NB-UVB provide the most efficacious therapeutic regimens for those patients who are recalcitrant to monotherapies. More studies, however, are needed to evaluate the long-term efficacy and safety of these combination treatments.

REFERENCES

1. National Institutes of Health. Psoriasis factsheet. <http://report.nih.gov/nihfactsheets/Pdfs/Psoriasis%28NIAMS%29.pdf>. Updated October 2010. Accessed August 23, 2013.
2. Brimhall AK, King LN, Licciardone JC, et al. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab

- in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. *Br J Dermatol*. 2008;159:274-285.
3. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol*. 2003;139:1627-1632.
 4. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349:2014-2022.
 5. Papp S, Tying M, Lahfa J. A global phase 3 study of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152:1304-1312.
 6. Kamili QU, Miner A, Hapa A, et al. Infliximab treatment for psoriasis in 120 patients on therapy for a minimum of one year: a review. *J Drugs Dermatol*. 2011;10:539-544.
 7. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005;366:1367-1374.
 8. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis [published online ahead of print September 6, 2006]. *J Am Acad Dermatol*. 2007;56:31.e1-31.e15.
 9. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. a randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci*. 2010;59:40-49.
 10. Ardigò M, Giuliani A, de Felice C, et al. Efficacy of adalimumab in plaque psoriasis: experience on 28 patients. *J Drugs Dermatol*. 2008;7:935-939.
 11. Papp K, Ho V, Teixeira HD, et al. Efficacy and safety of adalimumab when added to inadequate therapy for the treatment of psoriasis: results of PRIDE, an open-label, multicentre, phase IIIb study [published online ahead of print October 25, 2011]. *J Eur Acad Dermatol Venereol*. 2012;26:1007-1113.
 12. Asahina A, Nakagawa H, Etoh T, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. *J Dermatol*. 2010;37:299-310.
 13. Gordon KB, Blum RR, Papp KA, et al. Efficacy and safety of adalimumab treatment in patients with moderate to severe psoriasis: a double-blind, randomized clinical trial. *Psoriasis Forum*. 2007;13:6-11.
 14. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study [published online ahead of print August 10, 2006]. *J Am Acad Dermatol*. 2006;55:598-606.
 15. Leonardi C, Langley RG, Papp K, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial [published online ahead of print December 20, 2010]. *Arch Dermatol*. 2011;147:429-436.
 16. Menter A, Tying SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106-115.
 17. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION) [published online ahead of print November 28, 2007]. *Br J Dermatol*. 2008;158:558-566.
 18. van der Heijde D, Klareskog L, Landewé R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum*. 2007;56:3928-3939.
 19. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomized, double-blind, parallel treatment trial [published online ahead of print July 16, 2008]. *Lancet*. 2008;372:375-382.
 20. Zachariae C, Mørk NJ, Reunala T, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Derm Venereol*. 2008;88:495-501.
 21. Driessen RJ, van de Kerkhof PC, de Jong EM. Etanercept combined with methotrexate for high-need psoriasis [published online ahead of print July 28, 2008]. *Br J Dermatol*. 2008;159:460-463.
 22. Gisondi P, Del Giglio M, Cotena C, et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial [published online ahead of print April 10, 2008]. *Br J Dermatol*. 2008;158:1345-1349.
 23. Smith ECA, Riddle C, Menter MA, et al. Combining systemic retinoids with biologic agents for moderate to severe psoriasis. *Int J Dermatol*. 2008;47:514-518.
 24. Kircik LH, Del Rosso JQ. Anti-TNF agents for the treatment of psoriasis. *J Drugs Dermatol*. 2009;8:546-559.
 25. De Simone C, D'Agostino M, Capizzi R, et al. Combined treatment with etanercept 50 mg once weekly and narrow-band ultraviolet B phototherapy in chronic plaque psoriasis. *Eur J Dermatol*. 2011;21:568-572.
 26. Wolf P, Hofer A, Legat FJ, et al. Treatment with 311-nm ultraviolet B accelerates and improves the clearance of psoriatic lesions in patients treated with etanercept [published online ahead of print November 25, 2008]. *Br J Dermatol*. 2009;160:186-189.
 27. Lynde CW, Gupta AK, Guenther L, et al. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis

- who do not exhibit an excellent response after 12 weeks of etanercept [published online ahead of print August 10, 2011]. *J Dermatolog Treat.* 2012;23:261-267.
28. Gambichler T, Tigges C, Scola N, et al. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. *Br J Dermatol.* 2011;164:1383-1386.
 29. Lee EJ, Shin MK, Kim NI. A clinical trial of combination therapy with etanercept and low dose cyclosporine for the treatment of refractory psoriasis [published online ahead of print May 17, 2010]. *Ann Dermatol.* 2010;22:138-142.
 30. Kircik LH. Topical calcipotriene 0.005% and betamethasone dipropionate 0.064% maintains efficacy of etanercept after step-down dose in patients with moderate-to-severe plaque psoriasis: results of an open label trial. *J Drugs Dermatol.* 2011;10:878-882.
 31. Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis [published online ahead of print November 17, 2006]. *J Am Acad Dermatol.* 2007;56:598-603.
 32. Gottlieb AB, Kircik L, Eisen D, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. *J Dermatol Treat.* 2006;17:343-352.
 33. Strober BE, Clarke S. Etanercept for the treatment of psoriasis: combination therapy with other modalities. *J Drugs Dermatol.* 2004;3:270-272.
 34. Conley J, Nanton J, Dhawan S, et al. Novel combination regimens: biologics and acitretin for the treatment of psoriasis—a case series. *J Dermatol Treat.* 2006;17:86-89.
 35. Klotz U, Teml A, Schwab M. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet.* 2007;46:645-660.
 36. D'Angelo S, Cutro M, Lubrano E, et al. Combination therapy with cyclosporine and etanercept in patients with psoriatic arthritis [published online ahead of print August 9, 2009]. *Ann Rheum Dis.* 2010;69:934-935.
 37. Dalaker M, Bonesrønning JH. Long-term maintenance treatment of moderate-to-severe plaque psoriasis with infliximab in combination with methotrexate or azathioprine in a retrospective cohort [published online ahead of print December 19, 2008]. *J Eur Acad Dermatol Venereol.* 2009;23:277-282.
 38. Goedkoop AY, Kraan MC, Picavet DI, et al. Deactivation of endothelium and reduction in angiogenesis in psoriatic skin and synovium by low dose infliximab therapy in combination with stable methotrexate therapy: a prospective single-centre study [published online ahead of print May 26, 2004]. *Arthritis Res Ther.* 2004;6:R326-R334.
 39. El-Hag K, Dercken HG, Prenzel R, et al. Drug-induced alveolitis associated with infliximab/azathioprine therapy. *Pneumologie.* 2008;62:204-208.
 40. Farrelly RJ, Alsahli M, Falchuk KR, et al. Human anti-chimeric antibody levels correlate with a lack of response and infusion reactions following infliximab therapy. *Gastroenterology.* 2001;120(suppl 1):A69.
 41. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998;41:1552-1563.
 42. Bagel J. Adalimumab plus narrowband ultraviolet B light phototherapy for the treatment of moderate to severe psoriasis. *J Drugs Dermatol.* 2011;10:366-371.
 43. Thaçi D, Ortonne JP, Chimenti S, et al. A phase IIIb, multicentre, randomized, double-blind, vehicle-controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: the BELIEVE study [published online ahead of print April 2, 2010]. *Br J Dermatol.* 2010;16:402-411.