Biologic Therapies for Psoriasis

CATIA de FELICE, MARCO ARDIGO, and ENZO BERARDESCA

ABSTRACT. Psoriasis is a common chronic inflammatory skin disease that may lead to disability and significant effects on patients' quality of life. A challenge in psoriasis management is to use an effective therapy early in the disease course in order to achieve a safe and well tolerated maintenance of remission with an improvement of both skin and joint manifestations. Recent advances in knowledge of the pathogenesis of psoriasis helped develop targeted treatment options that may be effective and well tolerated over long periods of administration, thus improving the patient's quality of life. These novel "biologic" agents specifically target tumor necrosis factor–α (infliximab, etanercept, and adalimumab) or T cells (efalizumab). J Rheumatol 2009;36 Suppl 83:62-64; doi:10.3899/jrheum.090228)

Key Indexing Terms:
TUMOR NECROSIS FACTOR INHIBITORS PSORIASIS BIOLOGIC THERAPIES

Psoriasis is a common, chronic, relapsing, and disabling inflammatory disease that has enormous physical, functional, and psychosocial effects on patients' quality of life. Standard systemic therapies available for the treatment of moderate to severe plaque psoriasis include photochemotherapy, retinoids, cyclosporine, methotrexate, and fumarates. The aim of a chronic treatment is to minimize disease-associated morbidity and disability, and to reduce side effects and organ toxicity consequent to prolonged use of a single agent. A challenge in psoriasis management is to use an adequate therapy early in the disease course and to achieve effective and safe maintenance of remission by improving both skin and joint manifestations, as well as to prevent joint destruction and disability[1-7].

Recent advances in knowledge of the pathogenesis of psoriasis have been fundamental to development of novel targeted treatment options that may be effective, safer, and well tolerated for longterm administration, thus improving patient's quality of life. In particular the identification of key cytokines and immune cells, e.g., tumor necrosis factor (TNF–α) and T cells, revolutionized the management of this chronic disease.

Biologics are agents designed to block specific molecular steps in the pathogenesis of psoriasis, and include 2 main groups: (1) agents targeting the cytokine TNF–α (e.g., etanercept, infliximab, adalimumab) and (2) agents targeting T cells or antigen presenting cells (efalizumab)[1,7,8].

Infliximab, a chimeric monoclonal antibody that binds membrane bound and soluble TNF–α, is the first TNF–α blocker studied for the treatment of psoriasis. It is administered as endovenous infusions generally at a dosage of 5 mg/kg initially at week 0, week 2, week 6 (induction phase) and then every 8 weeks (maintenance phase)[7,8]. Efficacy of infliximab has been demonstrated in patients with psoriasis in randomized, placebo controlled Phase II trials. Results of an international multicenter, randomized, placebo controlled Phase III trial of adult patients with plaque psoriasis treated with infliximab 5 mg/kg were recently reported. The percentage of patients who achieved a response rate of 75% improvement in the Psoriasis Area and Severity Index 75 (PASI75) was 80.4% in the infliximab treated group at week 10 and was sustained through week 24. The safety profile for infliximab during this extended treatment Phase III trial appears to be comparable to those observed during earlier studies. The incidence of adverse events and serious adverse events in infliximab-treated patients was slightly elevated through the first 24 weeks of treatment (e.g., sepsis, elevations in aminotransferases, infections)[9,10].

In a randomized comparison, continuous (every 8 weeks) versus intermittent (as needed) infliximab maintenance regimens for treatment of moderate to severe psoriasis demonstrated that, through week 50, response was best in the continuous infliximab therapy group[10].

It was also demonstrated that therapy with infliximab at the dose of 5 mg/kg significantly improved the signs and symptoms of arthritis, dactylitis, and enthesitis in patients with active PsA that had been resistant to disease modifying antirheumatic drugs. Results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) showed that a continuous infliximab treatment led to sustained benefit through 50 weeks with a favorable benefit-to-risk ratio[11].

Infliximab has been associated with several adverse events. Infusion reactions, reported in 19% of patients in clinical trials, usually consists of fever or chills, chest pain, hypotension, hypertension, and dyspnea. Neutralizing antibodies are formed, and patients can develop a serum sickness reaction days after drug administration. Multiple reports have indicated mild and seri-

From the San Gallicano Dermatological Institute, Rome, Italy.

C. de Felice, MD; M. Ardigo, MD; E. Berardesca, MD, San Gallicano Dermatological Institute.

Address correspondence to Dr. E. Berardesca, San Gallicano Dermatological Institute, Via Chianesi 53, 00144, Rome, Italy.
E-mail: berardesca@berardesca.it

ous infections during treatment with infliximab, in particular reactivation of latent tuberculosis (TB).

Etanercept is a TNF–α receptor recombinant fusion protein, comprising domains of the 75-kDa human TNF receptor and human IgG1; it competitively inhibits the interaction of this cytokine with cell surface receptors and binds soluble TNF, preventing its mediated cellular responses and modulating the activity of other proinflammatory cytokines regulated by TNF. Etanercept is self-administered as subcutaneous (SC) injections once or twice weekly[7,8]. The efficacy and safety benefits of etanercept after 12 and 24 weeks of therapy in patients with moderate to severe chronic plaque psoriasis have been demonstrated in Phase III clinical trials.

The recommended dosage is 25 mg administered SC twice weekly for up to 24 weeks, although dosing at 50 mg twice weekly is also possible for the first 12 weeks, followed by a dose reduction to 25 mg twice weekly or 50 mg once weekly. Moreover, on the basis of published clinical data, European guidelines indicate that non-responders should discontinue etanercept after 12 weeks and that retreatment is possible after discontinuation.

A double-blind, randomized, placebo controlled Phase III clinical study demonstrated the safety and efficacy of 12 and 24 weeks of etanercept treatment. Results showed that etanercept was well tolerated, and the adverse events observed during the first 12 week placebo controlled period were mild to moderate and the etanercept and placebo groups showed no significant differences[12,13].

Etanercept has been used safely over the past few years. Injection-site reactions are the main adverse events noted. There have been observations of demyelinating disorders such as multiple sclerosis, allergic reactions, and aplastic anemia. Etanercept possesses a good safety profile in regard to risk of malignancy and infection. There was no apparent temporal association between the onset of clinical TB and introduction of etanercept therapy. TNF antagonists might induce new onset heart failure or exacerbate existing disease[7,8].

A recent randomized, open-label study evaluated the effectiveness and safety of continuous versus interrupted etanercept therapy. All patients received uninterrupted etanercept 50 mg twice weekly during the first 12 weeks, followed by either continuous or interrupted 50 mg once weekly in the next 12 weeks. At week 12, comparable high proportions of responders were in the continuous (71.3%) and interrupted (72%) groups. At week 24, the proportion of responders was greater in the continuous group (71% vs 59.5% of the interrupted group; $p < 0.0001$). Both treatment groups were generally well tolerated[14].

Adalimumab is a fully human anti-TNF–α monoclonal antibody administered as 40 mg SC once every other week. It has been approved by the US Food and Drug Administration for treatment of rheumatoid arthritis and is currently being evaluated in Phase II and III clinical studies for treatment of moderate to severe plaque psoriasis and PsA. These trials showed impressive PASI responses, with 53% of patients on 40 mg every other week and 80% of patients on 40 mg weekly achieving a 75% reduction in the PASI. Adverse events reported were similar to placebo (e.g., headache, injection site pain, nausea, elevated tryglicerides). Adalimumab was found to be effective for psoriasis refractory to other treatments including infliximab and etanercept[7,8,15-17].

Results of a double-blind, randomized, placebo controlled study showed that patients with moderate to severe active PsA and chronic plaque psoriasis treated with adalimumab had significantly improved joint and skin manifestations, inhibited structural changes on radiographs, lessened disability due to joint damage, and improved quality of life[17].

The available *in vitro* and epidemiologic evidence for the TNF inhibitors infliximab and etanercept shows that the risk of development of active TB is higher with infliximab. Further, a decrease of TNF–α activity is demonstrated to be correlated with an increase of susceptibility to TB. The reason that only some patients succumb to rapidly disseminated infection is unknown, but may be related to the extent of TNF blockade in different individuals.

Efalizumab is a humanized monoclonal antibody against the CD11a molecule. CD11a and CD18 are subunits of leukocyte function associated antigen 1 (LFA-1), a T cell surface molecule important in T cell activation, T cell migration into skin, and cytotoxic T cell function. This drug binds to CD11a on T cells blocking the interaction between LFA-1 and intercellular adhesion molecule 1 (ICAM-1), its partner molecule for adhesion. The blockade is reversible and does not deplete T cells. The agent is part of the group of biologics considered T cell inhibitors. The currently available formulation of efalizumab is delivered as a once-weekly SC injection[18]. Multiple Phase III clinical trials have demonstrated the efficacy, safety, and health-related quality of life benefits of 12 weeks of efalizumab therapy (1 mg/kg/week) in patients with moderate to severe chronic plaque psoriasis. Efalizumab has shown a good safety profile, no opportunistic infections, and no clinical signs of immunosuppression, hepatotoxicity or nephrotoxicity associated with its use. The Phase III trials showed no evidence of T cell depletion or increased risk of end organ toxicity, malignancy, or infection. Most common adverse events associated with efalizumab therapy are acute flu-like symptoms observed primarily after the first 2 doses. Worsening of psoriasis and psoriasis variants has been observed in 3% of efalizumab patients during therapy and in 14% of patients following abrupt discontinuation of efalizumab,

respectively a generalized inflammatory reaction and a rebound. Further, new onset or worsening arthritis has been infrequently reported during clinical trials[19,20].

While the 12-week, double-blind, placebo-controlled, first-treatment CLEAR trial period demonstrated the efficacy/safety of efalizumab in moderate-to-severe plaque psoriasis including patients refractory or contraindicated for other systemic treatments, a further study of Sterry, *et al* assessed the efficacy/safety during open-label extended 24-week continuous treatment. In all, 26.6% of patients treated with efalizumab who had < 75% PASI improvement at week-12 achieved PASI75 after extended treatment; 47.5% of patients who had > 50 and < 75 PASI improvement at week-12 achieved PASI75 in extended treatment; among patients achieving PASI75 at week-12, median time of relapse was 58 days; and retreatment after relapse led to an improvement of mean PASI of 62.3% from baseline. Safety results were consistent with other previous studies, and efficacy results demonstrated additional benefit of continuing efalizumab[21,22]. Early in 2009, efalizumab was withdrawn from the market in Europe due to safety issues, following reports of progressive multifocal leukoencephalopathy.

Biologic agents appear to offer an effective and safe alternative to conventional systemic therapies for the treatment of moderate-to-severe psoriasis. However, these agents have potential limitations, which include the expected high costs of treatment, lack of longterm followup, and the selective nature of the patient populations treated.

REFERENCES

1. Smith CH, Anstey AV, Barker AD, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis. B J Dermatol 2005;153:486-97.
2. Sampogna F, Sera F, Abeni D, et al. Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis. J Invest Dermatol 2004;122:602-7.
3. Stern RS, Nijsten T, Feldman SR, et al. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Invest Dermatol Symp Proc 2004;9:136-9.
4. Griffiths CEM, Clark CM, Chalmers RJG, et al. A systematic review of treatments for severe psoriasis. Health Technol Assess 2000;4:1-125.
5. Saraceno R, Griffiths CEM. A European perspective on the challenges of managing psoriasis. J Am Acad Dermatol 2006;54:S81-S83.
6. de Rie MA, Goedkoop AY, Bos JD. Overview of psoriasis. Dermatol Ther 2004;17:341-9.
7. Rapp SR, Feldman SR. The promise and challenge of new biological treatments for psoriasis: how do they impact quality of life? Dermatol Ther 2004;17:376-82.
8. Papp KM. The long-term efficacy and safety of new biological therapies for psoriasis. Arch Dermatol Res 2005;298:7-15.
9. Reich K, Nestle FO, Papp K, et al. EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double blind trial. Lancet 2005;366:1367-74.
10. 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 psoriasis. J Am Acad Dermatol 2007;56:31.
11. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). Arthritis Rheum 2005;52:1227-36.
12. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;49:2014 -22.
13. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152:1304-12.
14. Moore A, Gordon KB, Gottlieb A, et al. A randomized, open label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. J Am Acad Dermatol 2007;56:598-603.
15. Backer DE. Adalimumab: human recombinant immunoglobulin Gastroenterol Disord 2004;4:196-210.
16. Menter M, Gordon K, Leonardi C, et al. Adalimumab efficacy and safety results in patients with moderate to severe chronic plaque psoriasis with and without psoriatic arthritis [abstract]. American Academy of Dermatology Annual Meeting, New Orleans; February 18B22, 2005; Poster 2713.
17. Chen DM, Gordon K, Leonardi MD, et al. Adalimumab efficacy and safety in patients with moderate to severe chronic plaque psoriasis: Preliminary findings from a 12-week dose-ranging trial. J Am Acad Dermatol 2004;50 Pt II and PS 491; Ps.
18. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001;345:248-55.
19. Leonardi CL, Papp KA, Gordon KB, et al. Extended efazilumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. J Am Acad Dermatol 2005;52:425-33.
20. Menter A, Gordon K, Carey W, et al. Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. Arch Dermatol 2005;141:31-8.
21. Sterry W, Dubertret L, Papp K, et al. Efalizumab for patients with moderate to severe chronic plaque psoriasis: results of the international, randomized, controlled phase III clinical experience Raptiva (CLEAR) trial. J Invest Dermatol 2004;123:A64.
22. Sterry W, Stingl G, Langley RG, et al. Clinical Experience Acquired with Raptiva (CLEAR) trial in patients with moderate to severe plaque psoriasis: results from extended treatment in an international, Phase III, placebo-controlled trial. J Dtsch Dermatol Ges 2006;4:947-56.