Alefacept with methotrexate for treatment of psoriatic arthritis: Open-label extension of a randomized, double-blind, placebo-controlled study

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Background: A single course of alefacept intramuscularly in combination with methotrexate (MTX) was effective in treating both psoriasis and psoriatic arthritis (PsA).

Objective: We sought to determine the efficacy and safety of an additional course of alefacept intramuscularly in combination with MTX in patients with PsA.

Methods: In this open-label extension study, patients with PsA on stable doses of MTX were treated with an additional 12 weekly intramuscular injections of alefacept followed by 12 weeks of observation. Efficacy of PsA treatment was measured as 20% reduction in American College of Rheumatology criteria (ACR20).

Results: At the end of the open-label extension phase, 86 of 160 (54%) patients achieved ACR20, of which 28 of 55 had received placebo plus MTX and 58 of 105 received alefacept plus MTX in the prior double-blind phase. Although there was no increase in the proportion of patients achieving ACR20 after a second course of alefacept plus MTX, those achieving ACR50 and ACR70 increased from 17% and 7%, respectively, in the double-blind phase to 32% and 12%, respectively, in the open-label extension phase.

Limitations: In this open-label extension phase of the study there was no control group and the effect on psoriasis in these patients was not measured.

Conclusions: Patients with psoriasis and PsA on stable doses of MTX derive benefit for both conditions from one or more courses of alefacept, with further benefit in PsA apparent after a second course of treatment. No additional toxicity was observed. (J Am Acad Dermatol 2009;60:402-11.)

Psoriasis has a worldwide prevalence of about 1% to 3%.[1-4] Approximately 10% to 30% of patients with psoriasis also present with psoriatic arthritis (PsA).[4-7] Although PsA can occur in the absence of psoriatic skin lesions,[7] psoriasis usually manifests before onset of joint disease in approximately 80% of patients with PsA.[8] Thus, while treating patients with psoriasis, dermatologists may often be the first to encounter PsA, requiring them to be the first to treat this disease.[9,10]

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*Please see Appendix for a list of participating investigators and sites.

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Abbreviations used:

ACR:	American College of Rheumatology
ACR20:	20% Reduction in American College of Rheumatology criteria
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
MTX:	methotrexate
PASI:	Psoriasis Area and Severity Index
PsA:	psoriatic arthritis
ULN:	upper limit of normal

Both psoriasis and PsA are immune-mediated chronic inflammatory diseases that appear to be facets of a multisystem disease complex affecting skin, joints, enthesium (the sites of tendon, ligament, and joint capsule fiber attachment to bone), and spine.[8,11] Mild PsA has traditionally been treated with nonsteroidal anti-inflammatory drugs. Moderate to severe disease has required systemic therapy, for example, with oral disease-modifying antirheumatic drugs such as methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide, which often have treatment-limiting toxicities and limited efficacy,[12,13] or with biologic agents such as etanercept, infliximab, and adalimumab.[14] Although only 3 randomized clinical trials have evaluated the efficacy of MTX (two against placebo,[15,16] and one against cyclosporine[17]) for treating PsA, this drug has been standard systemic therapy for PsA, and is reasonably effective.[13] However, this treatment is associated with hepatic, pulmonary, and bone-marrow toxicity, as well as teratogenicity.[13,18] Biologic therapies, including alefacept, efalizumab, and the 3 available antitumor necrosis factor-α agents, have significantly benefited patients with psoriasis.[19] In patients with PsA, the 3 antitumor necrosis factor-α agents improve signs and symptoms of arthritis and reduce progressive joint damage.[8,14]

Alefacept, a targeted biologic agent, is a fully human fusion protein that inhibits T-lymphocyte activation by binding CD2 on T cells and thus inhibiting leukocyte function antigen-3/CD2 interaction with antigen-presenting cells. Alefacept also bridges between CD2 on target lymphocytes and immunoglobulin F_c receptors on natural killer cells. By binding CD2 on memory T cells and interacting with CD16 receptors on natural killer cells and monocytes, alefacept induces apoptosis of memory T cells while largely sparing naïve T cells,[20] thereby selectively decreasing circulating $CD4^+$ and $CD8^+$ T-lymphocyte counts. Alefacept is approved in the United States for the treatment of moderate to severe chronic plaque psoriasis in patients who are candidates for systemic therapy or phototherapy.

A small (n = 11) exploratory study suggested that alefacept was safe and effective in the treatment of patients with PsA.[21] In that study, serial synovial biopsy specimens in patients treated with alefacept demonstrated reductions in $CD4^+$ and $CD8^+$ T cells and $CD68^+$ macrophages, all of which are cells implicated in the pathogenesis of PsA. Many patients with active PsA are on stable doses of MTX over time. A larger, randomized, double-blind, placebo-controlled study undertaken to assess the safety and efficacy of adding alefacept to these patients' therapeutic regimen showed that 54% of patients treated with alefacept plus MTX versus 23% of those treated with placebo plus MTX achieved a 20% reduction according to the American College of Rheumatology (ACR) criteria (ACR20).[22] The current report compares the time courses of the rheumatologic and dermatologic responses to treatment during the double-blind phase of the study, and the rheumatologic response to alefacept plus MTX in the open-label extension phase of the study.

METHODS

Patients

The eligibility, inclusion, and exclusion criteria have been previously reported.[22] Briefly, patients aged 18 to 70 years who had persistently active PsA despite treatment with MTX were eligible.[22] Active PsA was defined as 3 or more swollen joints and 3 or more tender joints. Patients must have been treated with MTX (10-25 mg/wk, inclusive) during the 3 months immediately before enrollment in the double-blind phase of the study and were to continue stable doses throughout.

Patients were required to have $CD4^+$ T-cell counts of at least 404/mm^3, the lower limit of normal, unless they were on stable doses of prednisone, in which case they were required to have had $CD4^+$ T-cell counts of at least 300 cells/mm^3. Only patients with 3% or more of their body surface area affected with psoriasis were evaluated for dermatologic response.

To be included in the open-label extension phase, patients must have received a minimum of 8 alefacept or placebo injections during the double-blind phase and completed the final study visit of that phase, received MTX during the double-blind phase and were to continue their stable MTX doses during the extension phase, and had $CD4^+$ T-cell counts at or above lower limit of normal as in the double-blind phase of study. Patients with liver function test values more than 3 times the upper limit of normal (ULN) were not automatically excluded if the treating physician considered it appropriate for the patient to enter the study. Patients who received treatment with rescue medication or other investigational drug