Biologic Therapy for Psoriasis: A Brief History, II

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GOAL

To understand new treatment modalities in psoriasis

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the mechanism of action of various immunotherapies for psoriasis.
2. Discuss research studies of interleukin 10, the T-cell receptor mimic peptide, and CTLA4Ig.
3. Review the efficacy and safety information for infliximab, etanercept, efalizumab, and alefacept.

CME Test on page 374.

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This article, the second in a 2-part series, will review interleukin 10 (IL-10) administration, the T-cell receptor mimic peptide, and CTLA4Ig. We also will review 4 of the most promising therapies currently being investigated for the treatment of psoriasis: infliximab, etanercept, efalizumab, and alefacept.

Interleukin 10

An interleukin (IL) that has been explored for application in the treatment of psoriasis is IL-10.[1]

IL-10 is one of the cytokines that is released by helper T (T_H) cells, subtype 2 (T_H2). Once secreted, IL-10 affects many cell types, including another major subtype of T_H cells known as the T_H1 class.

Inflammatory and somatic cells are among the other cell types that IL-10 affects. One such somatic cell type is the vascular endothelium. IL-10 causes the expression of E-selection molecules on the surface of these cells.[2] One of the immune system cell populations that IL-10 regulates is B cells. In this case, IL-10 acts as a signal for the upregulation of antibody production and B-cell clonal expansion.[3,4] IL-10 also has been shown to affect various antigen-presenting cells by downregulating their ability to present antigen to effector and T_H cells.[5,6] The final inflammatory cell class that IL-10 affects is the macrophages. IL-10 affects their ability not only to produce certain cytokines that cultivate the inflammatory response but also to hinder their ability to function as antigen-presenting cells.[7-13]

Many successful studies have been conducted using recombinant IL-10. In one 7-week study reported in 1999,[14] 10 patients were given subcutaneous administrations of recombinant IL-10 at either 8 or 20 μg/kg. The patients who received 8 μg/kg were given daily doses, and those who received 20 μg/kg were given doses 3 times a week. Upon conclusion of the study, 9 of the 10 patients responded favorably to the treatment. Their average Psoriasis Area and Severity Index (PASI) score improvement was 55%, with improvements as great as 90% in 3 patients. The patients who received treatment 3 times a week had a mean improvement of 65%, and the group who received daily doses had a mean improvement of 45%. These results include the patient who was a nonresponder.[14]

Upon cessation of treatment, 7 patients had slight recurrences of their psoriasis. Recurrences were more common and pronounced among the low-dose group[14] but were gradual and did not start immediately after cessation of treatment. One benefit noted by all patients was the complete relief of the pruritus associated with their condition.[14]

Various side effects resulted from this therapy, none of which were lasting or severe. The first was an overall dampening of delayed hypersensitivity in 6 patients, 4 of whom became completely anergic. The nonresponding patients had the same side effect, which reversed itself 2 weeks following cessation of treatment in all the affected patients. One patient reported mild flulike symptoms, and 2 other patients reported more severe symptoms, with elevated temperatures of 102°, headache, and fatigue.[14]

T-Cell Receptor Mimic Peptide

Another methodology in the treatment of psoriasis is to interrupt the signaling pathway of the T-cell receptor (TCR). The TCR is composed of 2 disulfide-linked transmembrane protein subunits. Proper alignment will initiate the transmembranous signaling pathway and stimulate the T cell.[15]

Within the transmembrane region of the TCR, there is a sequence of 8 amino acids, which is ultraconserved across species. It has been shown that this region is the noncovalent binding region between the TCR and a subunit of the CD3 complex.[16-18] An octapeptide was created to mimic this region. Addition of this mimic sequence, both in vitro and in lab rats, led to an interruption of the transmembranous signaling process.[19]

The cellular efficacy of the mimic TCR peptide was shown in murine and human cells in in vitro studies, as well as in in vivo testing using murine models. These tests showed that although proliferation of CD4 and CD8 cells was depressed in both murine and human cell cultures containing the mimic peptide, the addition of an anti-CD3 antibody led to the restoration of a normal population expansion rate of stimulated T cells. These cultures also showed that application of the mimic peptide has no cytotoxic effects in vitro.[20-21]

One mimic TCR peptide study conducted included 9 patients with an array of dermatoses, including lichen planus, atopic dermatitis, and psoriasis.[21] In this study, researchers compared the application efficacy of the mimic peptide with that of a control peptide. The patients were given a topical cream containing the mimic peptide, which was applied to a 1-cm^2 test area for 3 consecutive days. The control peptide also was applied to a separate 1-cm^2 test area for the same period. The test areas receiving the mimic peptide drastically improved or cleared completely in 8 of the 9 patients. One of the 2 patients with psoriasis showed marked improvement. The other did not respond to the course of the mimic peptide.[21]

The possible negative side effects of this treatment have been shown exclusively in murine models. Humans who received the topical mimic peptide reported no side effects from this treatment. However, results from an early murine experiment showed that systemic administration of the mimic peptide led to a prolonged immunosuppressed state in mouse models.[19]

CTLA4Ig

CTLA4Ig is a chimeric antibody that targets the cellular membrane protein B7, which is found on the cell surface of antigen-presenting cells. When

coupled with CD28 on T_H1 cells, this protein acts as a costimulatory pathway, which is required for proper activation and proliferation of T_H1 cells during a T-cell–mediated inflammatory reaction.[22-24] In the past, studies have shown that the antibody known as CTLA4Ig has successfully downregulated the T_H1/T-cell response in transplant patients and those suffering from certain autoimmune disorders by interrupting the B7 and CD28 coupling.[25-33]

A series of studies have been performed to test the effectiveness of a course of CTLA4Ig in controlling psoriasis. One such 26-week study divided 64 patients into various CTLA4Ig dosage groups (n=41) and a placebo group (n=23).[34] Treatment was administered intravenously on days 1, 3, 16, and 29. Within the CTLA4Ig group, 19 patients showed a greater than 50% improvement. It was further found that 9 of the 11 patients in the 2 highest dosage groups (25 mg/kg and 50 mg/kg, respectively) showed this level of improvement compared with only 1 of 9 patients in the 2 lowest dosage groups (0.5 mg/kg and 1 mg/kg, respectively). One of the patients in the higher dosage group experienced a 90% clearing, and improvement was sustained in some patients for as long as 147 days after completion of the treatment.[34]

Several histologic changes were noted after studying the plaque biopsies of patients in the CTLA4Ig group. Among them was the reversion of keratinocyte structure and maturation cycling towards normal. Biopsy results showed a decrease in the amount of angiogenic tissue present in the biopsied area and a decrease towards normal in the population of T cells at the dermal/epidermal junction during the study period.[34]

As the study progressed, researchers compiled a side-effect profile for the study group, which reported no detrimental effects or alterations to either the B7 antigen-presenting cell populations or the T-cell populations. In addition, none of the patients who received CTLA4Ig mounted an immune response to this antibody, and none of the patients experienced generalized suppression of the baseline antibody production of the immune system. The most commonly reported complaint, which occurred in 7 patients, was an upper respiratory tract infection. However, this side effect was not dose related, as 5 of the 7 patients who experienced this illness were in dosage groups of 2 mg/kg or less. No other side effects were reported within the study group throughout the duration of the study.[34]

Infliximab

Because tumor necrosis factor α (TNF-α) is thought to have a role in the pathogenesis of psoriasis, a double-blind randomized trial to assess the clinical benefit and safety of infliximab, a monoclonal antibody against TNF-α, was conducted.[35] Thirty-three patients with moderate-to-severe plaque psoriasis were randomly assigned intravenous placebo (n=11), infliximab 5 mg/kg (n=11), or infliximab 10 mg/kg (n=11) at weeks 0, 2, and 6. Patients were assessed at week 10 for the primary endpoint (score on the physicians' global assessment [PGA]).

Of the 33 patients enrolled, 3 dropped out. Nine of 11 (82%) patients in the infliximab 5-mg/kg group were responders (good, excellent, or clear rating on PGA), compared with 2 of 11 (18%) in the placebo group and 10 of 11 (91%) in the infliximab 10-mg/kg group. The median time to response was 4 weeks for patients in both infliximab groups. There were no serious adverse events, and infliximab was well tolerated. In this controlled trial, patients receiving the anti–TNF-α agent infliximab as monotherapy experienced a high degree of clinical benefit and rapid time to response in the treatment of moderate-to-severe plaque psoriasis compared with patients who received placebo. These findings suggest that TNF-α has a pivotal role in the pathogenesis of psoriasis.[35]

Etanercept

Etanercept, another TNF inhibitor, has shown efficacy in the treatment of rheumatoid arthritis. Psoriatic arthritis and psoriasis are diseases in which TNF, a proinflammatory cytokine, is present in increased concentrations in the joints and the skin. Therefore, it was postulated that psoriatic arthritis and psoriasis may be appropriate therapeutic targets for etanercept. In a randomized, double-blind, placebo-controlled, 12-week study, the efficacy and safety of etanercept (25 mg twice-weekly subcutaneous injections) or placebo in 60 patients with psoriatic arthritis and psoriasis was assessed.[36]

Psoriatic arthritis endpoints included the proportion of patients who met the Psoriatic Arthritis Response Criteria and the American College of Rheumatology preliminary criteria for improvement. Psoriasis endpoints included improvement in the PASI score and improvement in prospectively identified individual target lesions. In this study, 26 (87%) of patients treated with etanercept met the criteria compared with 7 (23%) of placebo-controlled patients. Of the 19 patients in each treatment group who could be assessed for psoriasis (≥3% body surface area), 5 (26%) patients in the etanercept group achieved a 75% improvement in the PASI compared with none in the placebo group

(*P*=.015). The median PASI improvement was 46% in the etanercept group versus 9% in the placebo group; similarly, median target lesion improvements were 50% and 0%, respectively. These results suggest that etanercept was well tolerated.[36]

Efalizumab

CD11a and CD18 comprise subunits of leukocyte function-associated antigen-1, a T-cell surface molecule important in T-cell activation, T-cell emigration into skin, and cytotoxic T-cell function. Gottlieb et al[37] explored the immunobiologic and clinical affects of treating moderate-to-severe psoriasis vulgaris with a single dose of humanized monoclonal antibody against CD11a (hu1124). This was an open-label study with a single 0.03- to 10-mg/kg dose of hu1124. Clinical (PASI) and immunohistologic parameters (epidermal thickness, epidermal and dermal T-cell numbers, and keratinocyte intercellular adhesion molecule-1 expression) were followed.

It was found that treatment with hu1124 at doses higher than 1.0 mg/kg (group 3), completely blocks CD11a staining for at least 14 days in both blood and psoriatic plaques. At 0.3 to 1.0 mg/kg, T-cell CD11a staining was completely blocked; however, blockade lasted less than 2 weeks (group 2). Only partial saturation of either blood or plaque cellular CD11a was observed at doses between 0.01 and 0.1 mg/kg (group 1). This pharmacodynamic response was accompanied by decreased numbers of epidermal and dermal $CD3^+$ T cells, decreased keratinocyte and blood vessel expression of intercellular adhesion molecule-1, and epidermal thinning. Statistically significant decreases in PASI scores compared with baseline were observed at weeks 3 and 4 in group 2 patients and at weeks 2 through 10 in group 3 patients. No significant decrease in PASI scores was observed in group 1 patients.[37]

Adverse events were mild at doses of 0.3 mg/kg or less and included mild chills, abdominal discomfort, headache, and fever. At a single dose of 0.6 mg/kg or higher, headache was the most common dose-limiting toxicity observed. The investigators concluded that targeting CD11a may improve psoriasis by inhibiting T-cell activation, T-cell emigration into the skin, and cytotoxic T-cell function.[37]

Alefacept

Psoriatic plaques are characterized by infiltration with $CD4^+$, $CD45RO^+$, $CD8^+$, and $CD45RO^+$ memory-effector T lymphocytes. The recombinant protein alefacept binds to CD2 on memory-effector T lymphocytes, inhibiting their activation. In a multicenter, randomized, placebo-controlled, double-blind study, Ellis et al[38] evaluated alefacept as a treatment for psoriasis. Two hundred twenty-nine patients with chronic psoriasis received intravenous alefacept (0.025, 0.075, or 0.150 mg/kg of body weight) or placebo weekly for 12 weeks, with follow-up for 12 additional weeks. Before treatment, the median PASI scores were between 14 and 20 in all groups (0 denotes no psoriasis and 72 the most severe disease possible).

In the study, alefacept was well tolerated and nonimmunogenic. The mean reduction in the PASI score 2 weeks after treatment was greater in the alefacept groups (38%, 53%, and 53% in the groups receiving 0.025, 0.075, and 0.150 mg/kg, respectively) than in the placebo group (21%)(*P*<.001). Twelve weeks after treatment, 28 patients who had received alefacept alone were clear or almost clear of psoriasis. Three patients in the placebo group were clear or almost clear; all 3 had received additional systemic therapy for psoriasis. Alefacept reduced peripheral blood memory-effector T lymphocyte ($CD45RO^+$) counts, which correlated with the improvement in psoriasis. The investigators concluded that treatment with alefacept for 12 weeks is associated with improvement in chronic plaque psoriasis. Alefacept selectively targets $CD45RO^+$ memory-effector T lymphocytes, suggesting that they have a role in the pathogenesis of psoriasis.

Conclusion

Biologic therapy is one of the most rapidly expanding experimental areas in the treatment of psoriasis. Perhaps in the future, through continued research, one of the aforementioned therapies will become the sole treatment for psoriasis or will be used in conjunction with one of the currently approved therapies. As our understanding of the pathways and interactions that lead to this disease become clearer, we will be able to move closer toward the overall goal of improved, and perhaps even total, control of psoriasis.

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