Biologic Therapy for Psoriasis: A Brief History, I

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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 immunotherapy for psoriasis.
2. Discuss research studies of peptide T, anti-CD4 antibody, and anti-Tac.
3. Review the efficacy and safety information for peptide T, anti-CD4 antibody, and anti-Tac.

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This article, the first in a 2-part series, reviews the treatment of psoriasis with biologic therapy. Although extensive research in this venue of treatment is currently being conducted, we review some of the pioneering clinical trials dealing with immunotherapy, including the use of peptide T, anti-CD4 antibody (OKTcdr4a and hIgG1-CD4), and anti-Tac. For each of these therapies, an extensive summation is given of the research, taking note of the investigators' procedural course, results, and side effects seen. Through the results of these studies, a

foundation was laid for the further exploration of the use of biologic therapy to combat psoriasis.

Psoriasis is one of the most common chronic skin disorders of modern time. In the United States alone, more than 3 million people have this disease, which affects approximately 1.5% to 2% of the population in the western world.[1] In 1991, Barker[2] described 3 traits of these plaques: epidermal hyperproliferation with a loss of proper stratified differentiation of the affected epidermis, expansion of the dermal vascular bed, and accumulation of T lymphocytes and other inflammatory cells in both the dermis and epidermis. These observations served as foundations for new research into possible avenues for treatment of this disease.

Currently a vast array of treatments, ranging from topically applied steroids and vitamin D_3 analogues to psoralen plus UVA (PUVA) phototherapy to powerful systemic drugs like methotrexate and cyclosporin A, are being used in an attempt to control psoriasis. We examine a new step in psoriasis therapy, biologic therapy, and review the extensive correlating research that has been done.

Peptide T

One of the first immunotherapies studied was peptide T. Peptide T is an octapeptide initially created as an antagonist ligand to the binding of the human immunodeficiency virus type 1 (HIV-1) to CD4 T cells. The hopes were that this treatment would stop the progression of the HIV-1 virus in infected patients. Structurally, peptide T is modeled after the V2 binding domain on the gp120 surface protein of HIV-1.[3-7] Peptide T is a threonine-rich polypeptide, which has been shown to have multiple effects on blood mononuclear sites. One such effect is the increased production of interleukin 10 (IL-10) from helper T (T_H) cells subtype 2 (T_H2). This phenomenon has been observed in several in vitro blood-sample studies. One such study showed there to be a direct correlation between the addition of peptide T and the amount of IL-10 that was produced from the study cultures. Furthermore, this increase in IL-10 production led to a measurable decrease in mononuclear cell interferon production.[8-11]

The original report of the effect of peptide T on psoriasis was an incidental finding in an HIV-positive patient initially treated with peptide T who had a comorbidity of severe psoriasis. When the patient was treated with peptide T intravenously 2 times a day for 28 days, the patient's psoriasis cleared.[6]

Marcusson and Wetterberg[12] reported a case of peptide T treatment of psoriasis and psoriatic arthritis. A 60-year-old man was given 1 mg of peptide T intravenously 2 times a day for 28 days. The patient started to respond to the medication 14 days after therapy initiation. Improvement continued, resulting in almost total clearance of the lesions on his upper body. He also experienced improvement in his arthritis, which was evident with decreased pain and tenderness upon physical examination of the affected joints. The patient's improvement lasted for 30 days after treatment cessation, and he did not report any ill effects from the medication at any time.

Marcusson et al[13] reported a 65-year-old man who had had psoriasis for 10 years. In this report, the patient received 1 mg of peptide T intravenously 2 times a day for 28 days. Improvement started to occur 4 days into treatment. This was apparent by an observable decrease in peeling of the lesions on the patient's upper body. By 2 weeks into the treatment, further improvement was apparent with total cessation of all desquamation on the patient's body. At the end of the treatment period, there was a continued reduction in all of the lesions' erythematous appearance and abnormal skin texture. The patient's nails, which had been affected by the disease, improved and normalized. Results of serial biopsies, which were taken from a lesional area on the patient prior to, during, and after the treatment period, showed temporary histologic improvement of the lesional area with respect to immune cell infiltrate and normalization of the epidermis. Results of the final biopsy taken 20 days after treatment cessation revealed evidence of the early hyperplastic change in the epidermis. Even though this abnormality was seen at the time of the final biopsy, the patient remained in clinical remission of the disease 5 months after treatment. The patient did not report any side effects from the medication at any time during the treatment or observation period.[13]

Faber et al[14] reported a study of 14 patients in which 2 lesions were selected on each patient to receive subcutaneous infusions of either peptide T or saline for 2 weeks. The treated areas were biopsied approximately one week after treatment concluded. The histologic results indicated that 9 of the 14 patients showed substantial improvement, while 3 other patients showed comparatively moderate improvement. Regardless of the level of improvement, the results were sustained for a prolonged period after the cessation of treatment.[14]

One side effect reported by the patients in this study was erythema that appeared at the infusion

sites in 2 patients. The reaction in both cases was short lived after the apparatus was removed. One of these patients was found to have simple cellulitis, which responded promptly to antibiotic treatment. In neither case were these reactions attributed to an allergic reaction. Further, one of these patients experienced erythema at the control site, while the other patient experienced erythema at the peptide T infusion site. No other side effects were noted in this study.[14]

Anti-CD4 Antibody

Another avenue of treatment for psoriasis was to combat the believed effector cells, the CD4 T lymphocytes. As early as 1991, the infiltration of skin with this class of T cells was described as the first stage of this disease. Studies also have shown CD4 cells to be numerous within the plaques.[2] When these cells are activated, they release high levels of cytokines, which are believed to contribute to the accelerated epidermal cycling seen in the disease, as well as to the maintenance of the immunologic cell infiltrate seen in the plaques.[15] Numerous studies have been performed to explore the use of antibodies to combat the CD4-cell populations that reside in these plaques.

Morel et al[16] reported the use of anti-CD4 monoclonal antibody therapy in severe psoriasis. Three patients who had all been on multiple therapies were treated for 8 days with the mouse antibody BB14mAb. The first patient received a dosage of 0.2 mg/kg per day throughout the entire treatment period, while the other 2 patients received dosages of 0.4 mg/kg per day for the initial 2 days and 0.8 mg/kg per day for the remaining 6 days. Upon completion of the treatment period, the patients were then monitored over a 3-month period until the study was complete. In the second patient, a decrease in Psoriasis Area and Severity Index (PASI) score was noted as early as the first week. Thereafter, the same patient achieved his minimum PASI score 20 days after the beginning of the study, having experienced a decrease from 16 to 4. Similarly, the first and third patients also experienced decreases in their PASI scores from 35 to 12 and 15 to 0, respectively. Unlike the second patient, maximum improvement for these patients occurred after one month. After their respective minimum PASI scores, the patients experienced a gradual rise throughout the rest of the study.[16]

Although the patients successfully tolerated the infusions of the antibody, they all experienced minor fever and chills after receiving the first dosage. Furthermore, prior to his eighth treatment, one of the patients also reported experiencing flu-like symptoms, which halted the administration of his final dosage of antibodies. Finally, all 3 patients were reported to have an immunoglobulin M (IgM) response to the mouse antibody, which was followed by an increase and then decline of an IgG titer by day 30.[16]

In another 6-month study with anti-CD4 antibody,[17] 6 patients who had a history of using systemic treatments and/or PUVA were chosen to receive infusions of a chimeric antibody known as OKTcdr4a. During the first week, the patients were given 1 mg/kg infusions of chimeric antibody on 3 alternating days. Until day 10, per the results of peripheral blood samples, the patients were noted as having OKTcdr4a coating their CD4 cells. However, the antibody was absent in all cases by day 15. At the 1-month mark of the study, as noted in 5 of the 6 patients, the mean PASI score decrease for the group was 46%, or a mean reduction from 17.7 to 9.5. Improvements, which led to this decrease, were noted as early as day 7. By the end of the 6-month period, the group's mean PASI score continued to fall and reached 7.9 for the 5 patients.[17]

Throughout the study, researchers noted and recorded several factors. By the second month of the study, the entire group had started on topical treatments to assist in the control of their psoriasis. During the third month, 2 of the original 6 patients began systemic therapy. One of the 2 was considered a nonresponder and was subsequently excluded from the study. Another patient responded so well that he required only topical calcipotriene to sustain his improvement.[17]

During the experiment, no acute side effects were noted at the time of the infusion of OKTcdr4a. However, 2 of the patients later experienced some pruritus that was controlled using antihistamines. Another patient complained of increased hair loss during the study. No illnesses or infections were noted by any of the patients. Blood samples taken from the patients showed that none of the group mounted an antibody response towards OKTcdr4a, and CD4 cell counts for the group remained stable throughout the entire study.[17]

A third study using anti-CD4 antibody reviewed the use of a chimeric antibody called hIgG1-CD4.[18] In this 3-month, 18-person study, the patient population contained 9 patients with psoriasis and 9 patients with rheumatoid arthritis. The patients with psoriasis had a history of being treated with topical or systemic medications. They were separated into 2 dosage groups for the study: the high-dose group received 100 mg of the

antibody intravenously for 5 days, and the low-dose group received 20 mg of the antibody intravenously for 10 days.[18]

Seven of the 9 patients with psoriasis could be assessed at the end of the study. Of these 7 patients, 5 were considered to have a favorable response to the therapy. One of the patients responded extremely well to their treatment, experiencing a drop in PASI score from 18.3 to 4.7 by the second week. By the end of the study, this patient's score stabilized at 7. The other 4 patients experienced initial declines in their PASI scores ranging from 18% to 42% and lasting for as long as one month after the final administration of the medication.[18]

There was a spectrum of adverse effects that the patient population experienced, mostly self-limited after infusions. During the study, one of the patients was diagnosed with bacterial cholangitis and was treated successfully with appropriate antibiotic therapy. Upon investigation of this incident, it was noted via liver function tests that this process started to develop prior to the study and may have even accounted for this patient's first-dose reaction. The etiology of this cholangitis was suggestive of being secondary to the passage of a gallstone.[18]

When peripheral blood lymphocytes were sampled 24 hours after the last treatment dose was administered, the 20-mg–dose group underwent an average CD4 cell count decrease of 25% from baseline, while the 100-mg–dose group experienced a 69% decrease from baseline counts. This was followed by a recovery to normal levels in all but 2 patients, who were both part of the 100-mg–dose group. These 2 patients showed a decreased CD4 count just below normal ranges at 70 days. By day 81, one patient's count had returned to normal, and the other remained just below normal. Finally, at no time during the study did any of the patients mount an antibody response against the chimeric antibody.[18]

Recently, Gottlieb et al[19] reported a large series of patients treated with OKTcdr4a. This study was performed to test the efficacy and safety of OKTcdr4a, given in sequential courses over a period of several weeks, in the treatment of moderate-to-severe psoriasis vulgaris. Twenty-eight patients were studied, with a mean pretreatment PASI score of 18.3. In the first double-blind phase of the study, patients were randomized to receive OKTcdr4a as a 225-mg course (low dose), 750-mg course (high dose), or placebo divided into 3 identical infusions over a 5-day period. After 42 days, patients who met the criteria for re-treatment

with OKTcdr4a were treated with the 750-mg course in an open phase of the study. At 15 days, after the double-blind course of treatment, the mean PASI score decreased by 11% in the placebo group, 4% in the low-dose group, and 17% in the high-dose group. Twenty patients met the criteria for re-treatment (ie, did not experience a decrease in PASI score of 50% at 42 days). They were re-treated with OKTcdr4a at 43 days with the 750-mg course in the open phase of the study. By day 99, the mean PASI score decreased from 19.9 at baseline to 17 in those patients who had received either placebo or low-dose OKTcdr4a followed by high-dose OKTcdr4a. In contrast, the mean PASI score decreased from 17.4 at baseline to only 7.7 in those patients who had received high-dose OKTcdr4a for both courses. Sustained CD4 saturation was not necessary for sustained clinical response. No patients had significant changes in circulating CD4 T-cell counts. The infusions were well tolerated. Gottlieb et al[19] concluded that targeting CD4 using sequential treatments with a humanized monoclonal antibody (OKTcdr4a) may offer another therapeutic option for the treatment of moderate-to-severe psoriasis.

Anti-Tac
An immunotherapeutic agent that has shown promise in the treatment of psoriasis is daclizumab or anti-Tac. This is a chimeric monoclonal antibody to CD25 (Tac subunit) on T cells. The significance of CD25 in connection with the development and maintenance of psoriasis was first shown by a study that used an IL-2 fusion toxin, $DAB_{389}IL-2$.[20] The results of this study showed that administration of the selective toxin led to the resolution of the disease.[20] Furthermore, in patients with psoriasis, it has been shown that activated T cells of both the CD4 and CD8 type that express Tac have been found in higher concentrations within psoriatic lesions more so than in unaffected skin or circulating blood samples.[21]

A 16-week study of 19 patients was conducted by Krueger et al[22] using anti-Tac. Of the patients, 17 had received at least 2 systemic therapies in the past, and the other 2 patients had received only one type of systemic therapy to control their disease. At the start of the study, the mean PASI score of the patient population was 27.4.[22]

At the beginning of the study, each patient was given an initial infusion of 2 mg/kg. This dose was later followed by infused doses of 1 mg/kg of anti-Tac at weeks 2, 4, 8, and 12. Eighteen of the patients were able to complete the study and were used in the final analysis of the data. One of the

points examined by the researchers was the level of CD25 expression on the T-cell population of each patient. It was found that the T-cell populations in all but one of the patients experienced a decrease in surface expression of CD25 by week 12. This decrease also was seen in the lesional skin biopsies taken from the 18 patients. The researchers also noted that although the mean peripheral T-cell population did not decrease during the study, the CD25 T-cell population experienced a 44.8% decrease by week 12. Evaluation demonstrated that CD25 was completely blocked until week 4. After week 4, at different times in the ensuing weeks of the study, all of the patients' CD25 cells became desaturated to some degree. The researchers attested this solely to the decreasing frequency of administration of anti-Tac.[22]

Clinically, the greatest mean reduction of the groups' PASI score (30%) was seen during the eighth week in patients who had a PASI score originally less than 36. After the eighth week, the average score started to increase at a comparatively slower rate than that which it had originally decreased. It was also during the eighth week that most patients had measurable desaturation levels of their CD25 T cells. At the end of the 16-week period, the remaining 18 patients had an overall 15% decrease in their PASI scores.[22]

After empirically plotting the PASI scores for each patient, the researchers showed that patients with an initial PASI score of less than 36 showed comparative improvement as a group with this therapy than those with a higher original score. Three of the 4 patients with PASI scores greater than 36 worsened on this therapy, and one improved. One of the patients responded so well to treatment that, by the eighth week, the patient experienced complete clearance of the disease and remained so for months after the study had been completed.[22]

Blood chemistry and peripheral blood-cell populations were monitored throughout this study, and only a slight increase in the T-cell population was noted during the 12th week of the study. This increase in T-cell population still kept the overall population within normal limits. No significant adverse events were produced by this therapy.[22]

The second part of the series will review interleukin 10 administration, mimic T-cell receptor–peptide, and CTLA4Ig. We also will review 4 of the most promising therapies currently being investigated: infliximab, etanercept, efalizumab, and alefacept.

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