Immune response to pneumococcal polysaccharide vaccine in adults with chronic plaque psoriasis treated with alefacept

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Background: Alefacept is a T cell—modulating biologic therapy for psoriasis that could affect patients' ability to mount immune responses.

Objective: This open-label, phase IV, multicenter study assessed the ability of adults with chronic plaque psoriasis receiving alefacept to generate antibodies to a pneumococcal polysaccharide vaccine (PPV).

Methods: Patients were treated with a standard 12-week course of alefacept and administered the 23-valent PPV at week 6. Antipneumococcal antibodies were measured at baseline and weeks 6, 9, 12, and 33. The primary end point was the percentage of patients with a 2-fold or greater increase from prevaccination (week 6) to 6 weeks postvaccination (week 12) in antibody titers to 2 or more of 5 designated PPV antigens.

Results: Of 43 patients enrolled, 42 were included in the full analysis set, with 86% of patients exhibiting a 2-fold or greater increase and 57% of patients exhibiting a 4-fold or greater increase in antibody titers to 2 or more of 5 designated antigens from prevaccination to 6 weeks postvaccination. At 6 months postvaccination, 78% of patients had a 2-fold or greater increase and 47% of patients had a 4-fold or greater increase in antibody titers to 2 or more of the 5 designated antigens. There were statistically significant increases in mean antibody titers to all 23 antigens in PPV from prevaccination to 6 weeks postvaccination.

Limitations: This was an open-label study with no comparator.

Conclusions: Most patients mounted immune responses to PPV; increases in antibody titers in these patients were consistent with those seen in healthy individuals. (J Am Acad Dermatol 2011;65:799-806.)

Key words: alefacept; biologics; pneumococcal polysaccharide vaccine; psoriasis; T cells; vaccines.

Psoriasis is a chronic, inflammatory, T cell—mediated skin disease. The pathogenesis of psoriasis involving type 1 T cells has been well documented.[1] Recently, T-helper 17 cells, which are activated by interleukin (IL)-23 and produce IL-17 and IL-22, have been implicated in the development of

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psoriasis.[2] Biologic agents that modulate either T cells or effector cytokines, namely tumor necrosis factor (TNF)-α, IL-12, and IL-23, are treatment options for patients with psoriasis.[2,3]

Alefacept (Amevive, Astellas Pharma Global Development Inc, Deerfield, IL) was the first biologic therapy approved for treatment in adults with moderate to severe chronic plaque psoriasis (PSO) who are candidates for systemic therapy or phototherapy. Alefacept is a fusion protein comprising the first extracellular domain of lymphocyte function antigen-3 fused to the Fc domains of IgG_1.[4] Because of its mechanism of action, alefacept causes apoptosis primarily of memory effector T cells and has minimal effect on circulating naïve T cells.[5,6] In clinical studies, alefacept has been shown to be effective in the treatment of PSO and to have a favorable safety profile.[7-9]

CAPSULE SUMMARY

- Patients are able to mount immune responses to a pneumococcal polysaccharide vaccine during treatment with alefacept.
- The increase in antibody titers to pneumococcal antigens in patients treated with alefacept is consistent with increases in antibody titers in healthy individuals after vaccination with the 23-valent pneumococcal polysaccharide vaccine.
- The safety and efficacy profile of alefacept in this study is similar to published data.

Although alefacept affects primarily a subpopulation of T cells,[5,6] it has the potential to alter immune system function in treated patients. Patients undergoing therapies that affect the immune system may be at greater risk than they otherwise might be for contracting infections, some of which could be prevented by vaccines.[10,11] It is important for physicians to understand which vaccines may be administered to patients with psoriasis undergoing treatment with immunosuppressive drugs. Therefore, the ability of patients to generate immune responses to vaccines they may receive and the safety associated with vaccination during exposure to these drugs needs to be assessed.[12] A prior study analyzed T cell–dependent primary and secondary immune responses in patients with PSO treated with alefacept by vaccinating them with the protein-based antigens derived from bacteriophage φX174 (an experimental neoantigen) and tetanus toxoid (a recall antigen).[10] Patients treated with alefacept generated immune responses comparable with control patients for both of these vaccines.

This study was undertaken to assess the ability of patients treated with alefacept to mount an immune response to the 23-valent pneumococcal polysaccharide vaccine (PPV), which is the only pneumococcal vaccine approved in the United States for adults.[13] This vaccine contains polysaccharides from the 23 most prevalent and/or invasive types of *Streptococcus pneumoniae*, including 6 serotypes (6B, 9V, 14, 19A, 19F, and 23F) that frequently cause invasive and drug-resistant pneumococcal infections.[14] Although T cells are not required for initial antibody generation in response to PPV vaccination,[15] they may regulate the magnitude and quality of the immune response.[16] The ability to mount an immune response to PPV while undergoing various immunosuppressive therapies has previously been evaluated in patients with psoriasis[11] and psoriatic or rheumatoid arthritis.[17-20] In nonimmunosuppressed populations, there are variable changes in antibody titers to the antigens in PPV,[21] but an approximately 2-fold increase in antibody titers to most serotypes typically occurs.[21,22] In some prior studies assessing the immune response to PPV in patients treated with immunosuppressive drugs, the threshold for an immune response was defined as a 2-fold increase in antibody titers to a subset of pneumococcal antigens.[17-19]

METHODS

Study design and patients

This was an open-label, phase IV, multicenter study (NCT00493324) conducted at 7 sites in the United States and Canada. The study design is shown in Fig 1. The study was initially designed to last 14 weeks but was extended to 33 weeks at the request of the US Food and Drug Administration. Some patients had already completed the study before this protocol change. Patients included in the study were age 18 years or older, had PSO affecting 5% or more of body surface area, were otherwise healthy, and agreed to comply with study requirements. Exclusion criteria included known hypersensitivity to alefacept or PPV, previous injection with any pneumococcal vaccine, and/or screening $CD4^+$ T-lymphocyte count less than 400 cells/mm^3. This study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol was reviewed and approved by the institutional review board or independent ethics committee at each site.

Treatments

Alefacept was administered as a 15-mg intramuscular injection once weekly for 12 weeks followed by

Abbreviations used:

AE: adverse event
CI: confidence interval
IL: interleukin
PPV: pneumococcal polysaccharide vaccine
PSO: chronic plaque psoriasis
TNF: tumor necrosis factor

an observation period. Patients' $CD4^+$ T-lymphocyte counts were evaluated every other week, and if a patient's $CD4^+$ T-lymphocyte count was less than 250 cells/mm^3 the dose was withheld and weekly $CD4^+$ T-lymphocyte monitoring instituted. Dosing resumed when the patient's $CD4^+$ T-lymphocyte count was greater than or equal to 250 cells/mm^3. Alefacept was permanently discontinued if the patient's $CD4^+$ T-lymphocyte count remained less than 250 cells/mm^3 for 4 consecutive weeks. The 23-valent vaccine (Pneumovax 23, Merck & Co Inc, Whitehouse Station, NJ)[23] was administered as a subcutaneous injection at the week-6 visit. The PPV was not administered to febrile patients or to patients with a $CD4^+$ T-lymphocyte count less than 250 cells/mm^3.

Assessments

Blood samples were collected to quantify antibody titers at baseline (week 0) or week 1, prevaccination (week 6), 3 weeks postvaccination (week 9), 6 weeks postvaccination (week 12), and 6 months postvaccination (week 33) and were processed by a central laboratory using opsonophagocytic activity methodology, which detects IgG antibodies to the 23 serotypes in PPV. Immune response was measured by fold increase in antibody titers and change in geometric mean of antibody titers over time. Psoriasis was assessed at screening and/or baseline/week 1 and week 14 using the 7-point Physician Global Assessment with 1 = severe; 2 = moderate-severe; 3 = moderate; 4 = mild-moderate; 5 = mild; 6 = almost clear; and 7 = clear. A patient with a score of 6 or 7 at week 14 was considered a treatment success.

Safety

Vital signs were recorded at screening and/or baseline, week 6, and week 12/end of treatment. Physical examinations were performed, and blood chemistry and hematology were assessed at screening and/or baseline and week 12. $CD4^+$ T-lymphocyte counts were assessed at screening and/or baseline and at weeks 3, 5, 7, 9, 11, and 12. Adverse events (AEs) were recorded from the initial alefacept administration through week 33 of the study period.

Study end points

The primary end point was the percentage of patients with a 2-fold or greater increase in antibody titers to 2 or more of 5 designated pneumococcal antigens (9V, 14, 18C, 19F, and 23F) from prevaccination to 6 weeks postvaccination. The secondary end points included the percentage of patients with a 2-fold or greater increase in antibody titers to 2 or more of 5 designated antigens from prevaccination to 6 months postvaccination; the percentage of patients with a 4-fold or greater increase in antibody titers to 2 or more of 5 designated antigens from prevaccination to 6 weeks postvaccination; changes in mean antibody titers over time; the percentage of patients with a 2-fold or greater increase in antibody titers to each of the remaining 18 antigens in the pneumococcal vaccine from prevaccination to 6 weeks postvaccination and to 6 months postvaccination; and clinical efficacy as measured by the Physician Global Assessment at week 14.

Statistical methods

Based on a prior study,[18] a response rate of 34.5% to PPV was assumed in patients with psoriasis without administration of alefacept. The full analysis set was defined as all enrolled patients who were administered at least 6 doses of alefacept, were vaccinated, and had at least one postvaccination evaluation. The safety analysis set was defined as all enrolled patients who received at least one dose of alefacept. Data for 2- or 4-fold increases in antibody titers were summarized by providing the number and percentage of patients and the 95% confidence interval (CI) for the percentage of responders. Paired *t* tests were used to compare the geometric means of antibody titers prevaccination and 6 weeks postvaccination.

RESULTS

Of the 43 patients enrolled, one patient was withdrawn for taking a prohibited concomitant medication after receiving one dose of alefacept and was not administered PPV. Of the 42 remaining patients, one patient withdrew consent after receiving 8 doses of alefacept and one patient was discontinued from the study because of a migraine after receiving 9 doses of alefacept, which was considered an alefacept treatment–related AE. Thus, 43 and 42 patients were included in the safety and full analysis sets, respectively; 40 patients completed the study through the week-14 visit, and 32 patients completed the study through the week-33 visit. Patient demographics and baseline characteristics are shown in Table I.

In all, 86% of patients (95% CI: 72%-95%) had a 2-fold or greater increase and 57% of patients (95% CI:

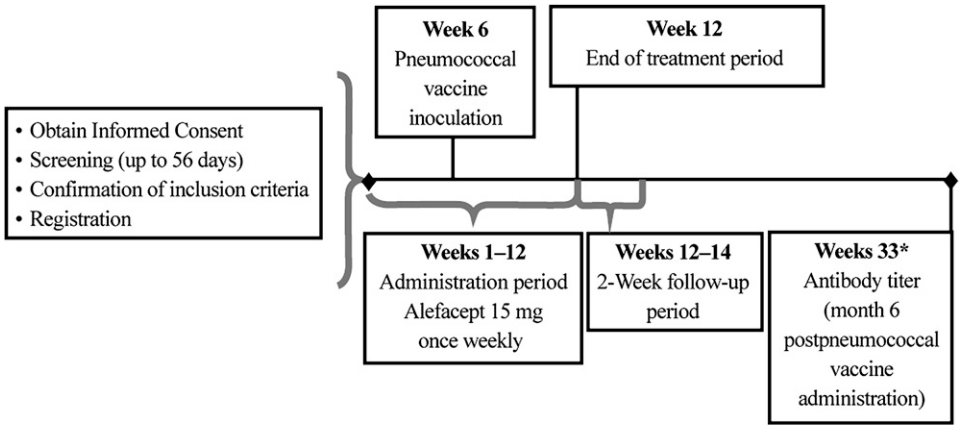

Fig 1. Study design. *FDA*, US Food and Drug Administration.

41%-72%) had a 4-fold or greater increase in antibody titers to 2 or more of the 5 designated antigens from prevaccination to 6 weeks postvaccination (Fig 2, *A*). The designated antigen with the highest percentage of patients having a 2-fold or greater increase in antibody titers was 18C, followed by 9V, 19F, 14, and 23F. At 6 months postvaccination, 78% of patients (95% CI: 60%-91%) had a 2-fold or greater increase and 47% of patients (95% CI: 29%-65%) had a 4-fold or greater increase in antibody titers to 2 or more of the 5 designated antigens (Fig 2, *B*).

In addition to the 5 designated antigens, immune responses to the 18 remaining antigens in PPV were assessed. There were statistically significant increases in mean antibody titers to the 5 designated antigens (Fig 3) and the 18 remaining PPV antigens (data not shown) from prevaccination to 6 weeks postvaccination. More than half of the patients had a 2-fold or greater increase in antibody titers to 13 of the 18 other antigens from prevaccination to 6 weeks postvaccination (Fig 4, *A*). At 6 months postvaccination, 50% or more of patients had a 2-fold or greater increase in antibody titers to 14 of the 18 other antigens compared with prevaccination (Fig 4, *B*).

At baseline, 38 of 42 patients had moderate or moderate-severe PSO according to the Physician Global Assessment. At week 14, 21 patients (50%) had mild or mild-moderate PSO, with 20 demonstrating improvements in PSO score. Three patients (7%; 95% CI: 2%-20%) were considered psoriasis treatment successes (clear or almost clear).

There were no clinically meaningful changes in vital signs or clinical laboratory evaluations during the course of this study. The mean (± SD) change in $CD4^+$ and $CD8^+$ T-cell counts from baseline to end of treatment were −279.7 (± 205.90) and −180.3 (± 200.86), respectively. Of the 43 patients, 37% experienced an AE attributed to alefacept, which included a decrease in $CD4^+$ lymphocyte counts to less than 250 cells/mm^3 (9%), headache (7%), injection site erythema (5%) or pain (5%), nausea (5%), and pyrexia (2%). A total of 26% of patients experienced an AE attributed to PPV, which

Table I. Patient demographics and baseline characteristics (N = 42)

Characteristic	
Sex, n (%)	
Male	25 (60)
Female	17 (40)
Race, n (%)	
White	37 (88)
African American	4 (10)
Native Hawaiian/other Pacific Islander	1 (2)
Ethnicity, n (%)	
Non-Hispanic or non-Latino	33 (79)
Hispanic or Latino	9 (21)
Age group, y, n (%)	
18-64	37 (88)
≥ 65	5 (12)
Age, y	
Mean ± SD	44.60 ± 14.468
Median	43.00
Minimum-maximum	18.0-75.0
Total BSA affected, %	
Mean ± SD	12.71 ± 10.372
Median	9.00
Minimum-maximum	5.3-52.0
PGA rating, n (%)	
Mild	1 (2.4)
Mild-moderate	3 (7.1)
Moderate	21 (50.0)
Moderate-severe	17 (40.5)

BSA, Body surface area; *PGA*, Physician Global Assessment.

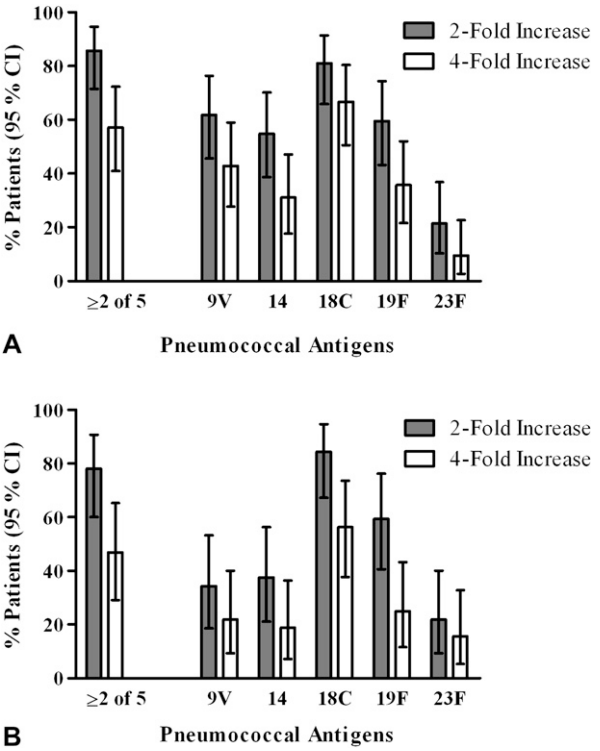

Fig 2. Percentage of patients with increase in antibody titers to 5 designated antigens. Prevaccination to 6 weeks (**A**) and to 6 months (**B**) postvaccination. *CI*, Confidence interval.

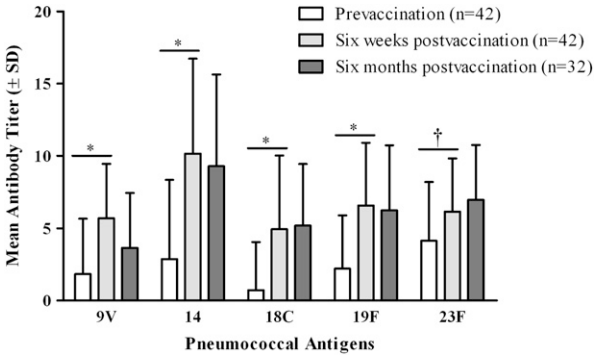

Fig 3. Mean antibody titers for designated antigens prevaccination, 6 weeks postvaccination, and 6 months postvaccination. $^{*}P < .0001$; $^{\dagger}P < .002$.

included a decrease in $CD4^+$ lymphocyte counts to less than 250 cells/mm^3 (5%), injection site erythema (5%) or pain (5%), pyrexia (5%), and headache (2%). In all, 21% of patients experienced AEs that were attributed to administration of both alefacept and PPV, which included a decrease in $CD4^+$ lymphocyte counts to less than 250 cells/mm^3 (5%), injection site erythema (5%) or pain (5%), headache (2%), and pyrexia (2%). Treatment-related AEs were generally mild to moderate in intensity. There was a single AE of chest pain rated severe in intensity, which was considered possibly related to alefacept. The chest pain lasted 31 days and resolved with treatment with acetaminophen/hydrocodone combination therapy. There were no serious AEs reported during the course of this study.

DISCUSSION

Patients with PSO treated with immunomodulatory drugs, including alefacept, may benefit from vaccinations. However, the ability of patients with psoriasis to generate immune responses to vaccines while undergoing biologic therapy is not established for all therapies and vaccines. In this open-label, multicenter study, most patients with PSO treated with alefacept generated an adequate immune response to PPV, defined as a 2-fold or greater increase in antibody titers to 2 or more of 5 designated antigens. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends vaccination with PPV for all individuals aged 65 years or older and patients with chronic illnesses that raise the risk of pneumococcal infection.[13] Because it is likely that some patients treated with alefacept will receive the 23-valent PPV, the information from this study is useful.

Correlating an increase in antibody titers with a protective response to *S pneumoniae* remains a challenge of PPV. The immune responses to antigens in PPV vary among healthy individuals[21,22]; a meta-analysis of antibody titer increases to 12 PPV antigens found that postvaccination to prevaccination antibody titer ratios ranged from 1.1 to 43.6.[21] Two-fold increases in antibody titers to PPV antigens are the most common immune responses in healthy individuals[21,22] a population that would be predicted to achieve protective immunity through vaccination. Accordingly, other studies investigating the immune response in patients taking immunosuppressive drugs used a 2-fold increase in antibody titers to a subset of pneumococcal antigens as the criterion for determining an immune response.[17-19] Because of the differences in the methodologies used,[24] direct comparisons of the immune responses to PPV between healthy individuals and patients with psoriasis treated with alefacept cannot be made at this time. Patients with rheumatoid arthritis and psoriatic arthritis undergoing treatment with TNF-α inhibitors and/or methotrexate, which are therapies also used for the treatment of PSO,[1] have also been evaluated for their ability to generate immune responses to PPV.[17-20,25] Different criteria were used to assess the immune response, eg, the number of PPV antigens evaluated, the timing of vaccination relative to treatment with

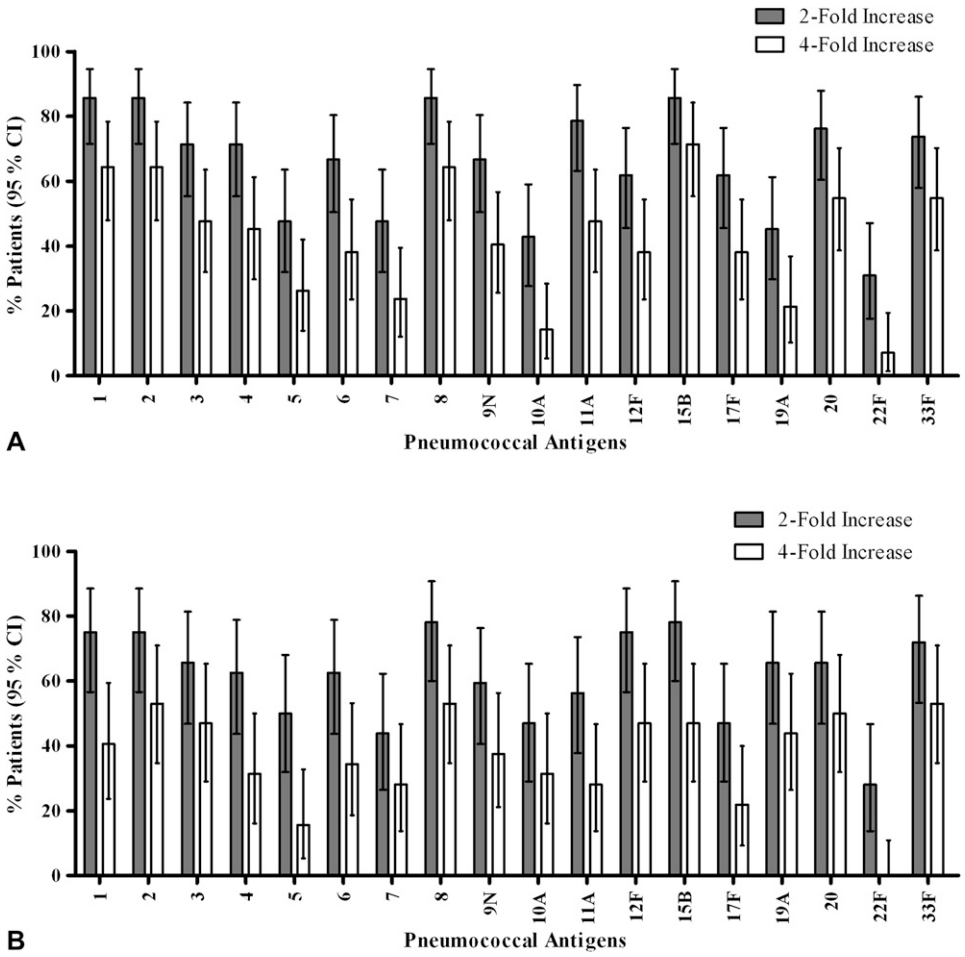

Fig 4. Percentage of patients with increase in antibody titers to other antigens in pneumococcal polysaccharide vaccine. Prevaccination to 6 weeks (**A**) and to 6 months (**B**) postvaccination. *CI*, Confidence interval.

immunosuppressive drugs, and the timing of antibody titer relative to vaccination; nevertheless, treatment with the TNF-α inhibitors etanercept, infliximab, or adalimumab did not affect the ability of patients to generate an immune response to PPV when compared with patients treated with a placebo[17,19] or healthy individuals.[18] A reduced immune response to PPV was associated with the use of methotrexate when used alone or as cotreatment with TNF-α inhibitors.[17-20]

Polysaccharide-based vaccines such as PPV differ from protein-based or conjugated vaccines in that they do not elicit memory T and B cells during the initial immune response. However, data from studies in mouse models and human cells suggest that T cells may regulate the magnitude of an immune response to PPV[26-29] and, thus, may have a regulatory role. This role for T cells could, in turn, be affected by exposure to alefacept. Importantly, T cell–dependent immune responses to protein-based vaccinations in patients undergoing treatment with alefacept have been evaluated in a prior study, and alefacept has not been shown to have an effect on these responses.[10] Together, these data suggest that patients treated with alefacept can mount immune responses to the vaccines tested, and that these responses are consistent with those previously observed in nontreated individuals.[21,22] Further studies with other vaccines may provide a more thorough understanding of the immune responses in patients treated with alefacept.

Limitations

The design of the current study as open label with no comparator and a 6-month follow-up period after PPV vaccination presented limitations. A comparison of increases in antibody titers to PPV antigens between alefacept-treated patients and placebo-treated or untreated patients with PSO would have provided a more rigorous comparison. In healthy individuals, levels of antibody to PPV remain elevated for at least 5 years postvaccination.[14] In the current study, at least half of the patients had a 2-fold

or greater increase in antibody titers to 16 of the 23 antigens (2 of the 5 designated antigens and 14 of the 18 remaining antigens) in the PPV vaccine at 6 months postvaccination.

CONCLUSIONS

In adult patients with PSO treated with alefacept, the majority (86%) mounted an immune response to PPV as defined by a 2-fold or greater increase in antibody titers to 2 or more of 5 designated PPV antigens. The increases in antibody titers to PPV antigens in patients treated with alefacept observed in this study are consistent with those seen in healthy individuals.[21,22] The safety and efficacy of alefacept in this study were similar to those seen in published results.

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APPENDIX

Participating Investigators and Sites

The following investigators and investigational sites participated in this study: Neil Korman, MD, PhD, (University Hospitals of Cleveland, Cleveland, OH), James Krell, MD (Total Skin and Beauty Dermatology Center, Birmingham, AL), Ian Landells, MD (Nexus Clinical Research, St. John's, NL, Canada), Charles Lynde, MD, FRCPC (Lynderm Research Inc, Markham, ON, Canada), Ellen Marmur, MD (Mount Sinai School of Medicine, New York, NY), Stacy Smith, MD (Therapeutics Clinical Research, San Diego, CA), Bruce Strober, MD, PhD (NYU School of Medicine. New York, NY).