STUDY

Narrowband UV-B Phototherapy, Alefacept, and Clearance of Psoriasis

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Objective: To determine whether the addition of 311-nm narrowband UV-B (NB UV-B) phototherapy accelerates and improves the therapeutic efficacy of alefacept, a biological antipsoriatic drug approved for the treatment of moderate to severe psoriasis.

Design: Randomized half-body comparison study.

Setting: Ambulatory section of a university hospital photodermatology unit.

Patients: Fourteen patients with moderate to severe psoriasis.

Interventions: All patients were treated with 7.5 mg of intravenous alefacept once weekly for 12 weeks. Three times each week, a randomly selected body half (left or right) was treated with NB UV-B light until complete remission, defined as a reduction in the Psoriasis Area Severity Index (PASI) to 3 or lower, was achieved on the irradiated body half.

Main Outcome Measures: Modified PASI, self-assessed visual analogue scale rating of skin lesions, and self-assessed therapeutic efficacy.

Results: After 12 weeks of treatment, the mean PASIs on UV-irradiated and nonirradiated body halves were significantly reduced by 81% and 62%, respectively (P < .001). From week 3 to week 12, the mean PASI was significantly lower on UV-irradiated body halves than on nonirradiated body halves (P < .001). At week 12, PASI reductions of greater than 75% had been achieved significantly more often on UV-irradiated body halves (86%, 12 of 14) than on nonirradiated body halves (43%, 6 of 14), and complete remission had been achieved significantly more often on UV-irradiated body halves (43%, 6 of 14) than on nonirradiated body halves (0 of 14) (McNemar test P = .03).

Conclusions: In this randomized half-side comparison of alefacept with and without phototherapy for psoriasis, alefacept with NB UV-B phototherapy accelerated and improved the clearance of psoriasis. This suggests a promising future for this combination as antipsoriatic therapy.

Trial Registration: clinicaltrials.gov Identifier: NCT00407342

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Psoriasis is an inflammatory skin disease that affects an estimated 2% to 3% of the world’s population.1 The lesions typical of this disease—erythematous psoriatic plaques covered with silvery white scales—are clinical signs of chronic skin inflammation accompanied by hyperproliferation of keratinocytes and dermal infiltration by lymphocytes consisting mainly of memory type 1 helper T cells (CD4+), and type 1 cytotoxic T cells (CD8+).2,3 These memory T cells are abundant in psoriatic skin lesions and the blood of patients with psoriasis and are considered to be of major importance for the expression of psoriatic skin lesions.4

A wide range of local and systemic clinical treatments and agents are available for clearing, or at least reducing the expression of, psoriatic skin lesions.5,6 Among these is a new generation of antipsoriatic drugs that specifically target T-cell-mediated inflammatory pathways and that are approved for the treatment of moderate to severe psoriasis in the United States.7 One of these new drugs is alefacept, an immunomodulatory recombinant, fully human fusion protein and biological agent that combines the lymphocyte function-associated antigen 3 (LFA-3) with the Fc portion of IgG1.8 Alefacept targets memory-effector T cells by binding the CD2 receptors on their surface, thereby blocking interaction between LFA-3 and...
CD2. In addition, through its IgG1 moiety, alefacept binds the Fc receptors located on the surface of natural killer cells and macrophages, thereby inducing them to cause the apoptosis of T lymphocytes and in particular the memory-effector T cells implicated in sustaining psoriatic skin lesions.8 Alefacept appears to be therapeutically efficacious: several studies have demonstrated a correlation between reductions in the number of memory-effector T cells in the peripheral circulation10-11 and in skin lesions of patients with psoriasis and reduced Psoriasis Area Severity Index (PASI).12

Alefacept appears to have several advantages over other systemic antipsoriatic agents such as methotrexate and cyclosporine and also over other agents in its own class such as infliximab, etanercept, and efalizumab. Alefacept is very well tolerated by patients, producing relatively weak adverse effects that in most cases are comparable to those seen in placebo controls. Concerns about an increased risk of infections and malignancies as well as systemic immunosuppression due to reductions in lymphocyte count (particularly CD4+ T lymphocytes) have been allayed by the clinical experience in patients with psoriasis.13 Unlike the case for tumor necrosis factor α blockers infliximab and etanercept, there have been no reports of alefacept-induced reactivation of tuberculosis.14,15 Unlike efalizumab, alefacept does not appear to cause sudden flare-ups of psoriasis during or after abrupt termination of therapy.12 Conversely, as 1 recent study has shown,16 alefacept clears moderate to severe psoriatic skin lesions in patients with psoriasis at approximately the same rate as do etanercept and efalizumab. In that study, weekly administration of alefacept for 12 weeks reduced the PASI by greater than 75% in 30% of patients.17

The maximum antipsoriatic effect, however, apparently occurs after the 12-week course has ended.11,18 Recently, Sugiyama et al19 have suggested that alefacept’s antipsoriatic effect may be augmented when it is administered in combination with UV-B phototherapy. In their in vitro study, Sugiyama et al observed that apoptosis increased and interferon gamma production decreased in activated T cells after they had been irradiated with UV-B light in the presence of alefacept. This observation is supported by several case reports of increased clinical antipsoriatic efficacy of alefacept when combined with UV-B phototherapy.20,21 Together, these findings prompted us to conduct a prospective, randomized, half-body comparison study in which we investigated whether the clinical response of psoriatic lesions to alefacept could be improved by combining alefacept with standard narrowband (311-nm) UV-B (NB UV-B) phototherapy.

STUDY DESIGN AND PARTICIPANTS

This was a single-center, prospective, randomized, half-body (left vs right) comparison study. It was approved by the local ethics committee of the Medical University of Graz and was conducted according to principles of the Declaration of Helsinki and the good clinical practice guidelines of the European Community. All patients gave their informed consent before enrollment in the study. The study end points were modified PASI, self-assessed visual analog scale (VAS) rating of skin lesions, and self-assessed therapeutic efficacy. The outcome after the first 12 weeks of antipsoriatic treatment was considered to be the overall result. The active phase of the study was performed between February and June 2004 in patients at our institution.

Inclusion criteria for enrollment into the study were as follows: moderate to severe plaque-type psoriasis for more than 6 months and PASI above 10. Exclusion criteria were as follows: age younger than 18 years; pregnancy or lactation; presence of a dysplastic nevus syndrome, photosensitive skin disease, autoimmune disease, or severe renal or hepatic disease; presence or history of malignant skin tumors; presence of antinuclear antibodies; a history of previous treatments with arsenic, methotrexate, or x-rays; recent history (within the last 4 weeks before enrollment into the study) of UV-B or psoralen–UV-A (PUVA) treatment, immunosuppressive and/or immunomodulating drugs including corticosteroids, cyclosporine, and biological agents such as infliximab, etanercept, or efalizumab. During the study, besides alefacept and UV-B, no concomitant antipsoriatic treatment (including retinoids) was allowed. However, patients were allowed to use topical emollients ad libitum; on treatment days, emollient use was not allowed until after the NB UV-B treatment had been delivered.

ALEFACEPT THERAPY

All patients received weekly intravenous bolus injections of alefacept (7.5 mg) for a total of 12 weeks. Every week during alefacept treatment, CD4+ T-cell counts were determined. Weekly injections were not given when CD4+ T-cell counts fell below 250 cells/µL and were resumed when CD4+ T-cell counts rose above this threshold. If CD4+ T-cell counts remained below 250 cells/µL for more than 4 consecutive weeks, alefacept treatment was discontinued.

NB UV-B THERAPY

All patients were treated with NB UV-B phototherapy on a randomly selected body half (left or right side) 3 times per week until complete remission of psoriasis on the irradiated body half was observed. For this study, complete remission was defined as a reduction in PASI to 3 or lower on the irradiated body half. Narrowband UV-B light was delivered by a Waldmann UV 7001 cabin equipped with TL-01/100 W fluorescent lamps and an integrated UV radiometer (Waldmann Medizinische Technik, Gevelsberg, Germany). For each patient, NB UV-B was delivered at a starting dose of 50% of the patient’s individual minimal erythema dose, determined as previously described by Hofer et al,22 and increased depending on erythema reaction to previous treatments.

DISEASE SCORING

Before and during the weekly alefacept treatment regimen, psoriatic skin lesions of all patients were scored in a nonblinded fashion by 1 of 2 physicians (F.J.L. or A.H.). Each patient’s PASI was determined separately for both the irradiated and nonirradiated body halves; psoriatic lesions on the head were not included in these evaluations. Thus, the PASI values recorded in this study ranged from 0 to 64.8, instead of the possible maximum of 72 originally described by Fredriksson and Pettersson.23 After the 12-week alefacept treatment regimen was completed, the PASI was evaluated every 4 weeks for 12 weeks. In addition, at each scoring session, patients were asked to assess (1) the severity of their skin lesions and (2) the overall therapeutic effect of combined treatment for each body half by using a continuous VAS ranging from 0 (no skin lesions and no therapeutic effect, respectively) to 10 (most severe skin lesions ever and best therapeutic effect imaginable, respectively).
End

Thirteen of 14 patients received all 12 intravenous alefacept treatments. For 3 of 14 patients, alefacept treatment was restarted when CD4 lymphocyte counts climbed again above 250 cells/µL; for 1 patient, weekly alefacept treatments had to be prematurely terminated according to the protocol because CD4 lymphocyte counts remained below 250 cells/µL for more than 4 weeks. In all of these patients, NB UV-B treatment was continued until the PASI was 3 or lower on the UV-B-treated side irrespective of alefacept treatment interruptions. Four other patients interrupted their alefacept as well as their UV-B treatment regimens for 1 week each during the study owing to personal reasons (holidays). After 12 weeks, each of these 4 patients received another week of alefacept treatment (prolonging the active study phase for 1 week) to administer 12 alefacept injections according to the protocol.

**STATISTICAL ANALYSES**

**Power Analysis**

Sample size was estimated using 1-sample \( t \) test with a power of 0.9 and a 2-sided type 1 error of 0.05. An increase in PASI reduction by 10 percentage points through the addition of UV-B treatment (eg, increase in PASI reduction from 50% to 60%) within 12 weeks was considered to be a clinically significant treatment effect. Using data from a half-body comparison study of PUVA treatment,24 and assuming a dropout rate of 20%, we estimated the sample size needed to be 14 patients.

**Data Analysis**

For patients who did not receive all 12 alefacept treatments, the scores at termination of alefacept treatment were carried forward to the 12-week time point. For patients who missed follow-up assessments at 4, 8, or 12 weeks after termination of alefacept treatment, the last observation was carried forward. For patients who did not receive all 12 alefacept treatments, the scores at termination of alefacept treatment were carried forward to the 12-week time point. For patients who missed follow-up assessments at 4, 8, or 12 weeks after termination of alefacept treatment, the last observation was carried forward. For patients who did not receive all 12 alefacept treatments, the scores at termination of alefacept treatment were carried forward to the 12-week time point. For patients who missed follow-up assessments at 4, 8, or 12 weeks after termination of alefacept treatment, the last observation was carried forward.

**RESULTS**

Fourteen individuals (4 women and 10 men) with moderate to severe psoriasis (PASI > 10) were enrolled in this study. The mean patient age was 48 years (range, 25-59 years). The mean disease duration was 22 years (range, 4-50 years). The median total NB UV-B dose was 28.8 J/cm² (range, 13.7-58.9 J/cm²). The median number of NB UV-B treatments delivered was 21 (range, 16-34).

**COMPLIANCE WITH THE TREATMENT PROTOCOL**

Thirteen of 14 patients received all 12 intravenous alefacept administrations. For 3 of 14 patients, alefacept treatment had to be stopped owing to reduced CD4⁺ lymphocyte counts during weekly alefacept treatments; for 2 patients, alefacept treatment was restarted when CD4⁺ lymphocyte counts climbed again above 250 cells/µL; for 1 patient, weekly alefacept treatments had to be prematurely terminated according to the protocol because CD4⁺ lymphocyte counts remained below 250 cells/µL for more than 4 weeks. In all of these patients, NB UV-B treatment was continued until the PASI was 3 or lower on the UV-B-treated side irrespective of alefacept treatment interruptions. Four other patients interrupted their alefacept as well as their UV-B treatment regimens for 1 week each during the study owing to personal reasons (holidays). After 12 weeks, each of these 4 patients received another week of alefacept treatment (prolonging the active study phase for 1 week) to administer 12 alefacept injections according to the protocol.

**CLINICAL RESPONSE**

Within the first 12 weeks of antipsoriatic half-body treatment, the mean PASIs on irradiated and nonirradiated body halves were reduced by 81% and 62%, respectively (Figure 1). From week 3 to week 12, the mean PASIs for irradiated body halves were significantly lower than those for nonirradiated body halves (Figure 1). The lowest PASIs reached during the first 12 weeks of treatment were significantly lower on the UV-irradiated body halves than on the nonirradiated body halves at the same time points (Figure 2A). By week 12, PASI reductions of greater than 75% had been achieved significantly more often on UV-irradiated body halves (86%, 12 of 14) than on nonirradiated body halves (43%, 6 of 14) (Figure 2B) (McNemar test \( P = .03 \)). More remarkably, complete remission (PASI ≤ 3) was achieved significantly more frequently on UV-irradiated body halves than on nonirradiated body halves (43%, 6 of 14 vs 0) (McNemar test \( P = .03 \)). A good clinical response to treatment (PASI reduction of ≥ 50%) was achieved at a similar rate on irradiated and nonirradiated body halves (Figure 2B).

Overall, most patients achieved a good antipsoriatic response to alefacept (PASI reduction of ≥ 50%) within the first 12 weeks of treatment with or without NB UV-B treatment (Figure 2B). The response to treatment in a representative patient is shown in Figure 3A-C. Only 1 patient responded moderately (PASI reduction of < 50%), and only 1 patient responded poorly (PASI reduction of < 25%) to alefacept without NB UV-B. While the poor responder had a moderate response to combination therapy on the other body half, the moderate responder had a very good response (PASI reduction of > 75%) to combination therapy (Figure 3D-F).

**PATIENT SELF-ASSESSMENT**

The patients’ self-assessed VAS scores for skin lesion severity (data not shown) and therapeutic efficacy paralleled the physician-based PASI evaluations. According to the self-assessments, combination treatment with alefacept and NB UV-B was therapeutically more effective than treatment with alefacept alone from the second week of treatment on.
FOLLOW-UP

One week after the last administration of alefacept, a good clinical response to antipsoriatic treatment (PASI reduction of ≥ 50%) was achieved on the irradiated body half in 14 patients (100%) and on the nonirradiated body half in 12 of 14 patients (86%). During the 12-week follow-up period, the 2 patients who had PASI reductions of < 50% on the nonirradiated body half required further NB UV-B irradiation to control their psoriasis. Another 2 patients whose psoriatic lesions on the nonirradiated body half did not completely clear during alefacept treatment also requested further NB UV-B phototherapy. Each of these 4 patients received whole-body NB UV-B phototherapy for at least 4 weeks during follow-up, which further reduced PASIs on the previously nonirradiated body half (Figure 5). The remaining 10 patients (71%) required no further phototherapy during follow-up and remained clear, or almost clear, of psoriatic lesions on both body halves (Figure 5).

ADVERSE EVENTS

Alefacept-related adverse events occurred. During the 12-week alefacept treatment phase, 9 of 14 patients reported at least 1 adverse event. The most frequent adverse event was fatigue (7 of 9 patients). Other, much less frequent adverse events were painful muscles, joints, or head (2 of 9 patients each) and numbness, dizziness, nausea, fever, and diarrhea (1 of 9 patients each). Most adverse events occurred only during the first weeks of alefacept treatment and lasted very briefly (usually less than 1 day) after intravenous alefacept administration. Two of 14 patients had to have their weekly alefacept treatments interrupted (3 and 7 times, respectively) because their CD4+ T-cell counts fell below 250 cells/µL. These 2 patients also had upper respiratory tract infections (ie, common colds) for 1 week during 1 of these pauses. In 1 patient’s case, the CD4+ T-cell count fell below 250 cells/µL after the third weekly alefacept administration and remained below that level for more than 4 consecutive weeks. As a result, alefacept treatment was discontinued in this patient, per protocol.

No erythematous reactions or other adverse events related to NB UV-B half-body treatments were observed in this study.

COMMENT

In this study, the addition of NB UV-B phototherapy to alefacept treatment accelerated and improved the overall antipsoriatic treatment effect in our patients. In previous studies, the therapeutic effects of weekly intramuscular or intravenous alefacept administration in patients with psoriasis was first detected 4 to 8 weeks after the start of therapy. In our study, they were first noted within 2 to 3 weeks. Alefacept had a significantly better therapeutic effect when given in combination with NB UV-B phototherapy than when given alone, and this superior therapeutic effect was maintained throughout the active phase of alefacept treatment. Within the 12-week window of antipsoriatic treatment with alefacept, PASI reductions of more than 75% were achieved significantly more often on irradiated body halves than on contralateral nonirradiated body halves (McNemar test P = .03). Moreover, the rate of complete remission (PASI ≤ 3) during the 12 weeks of alefacept treatment was significantly higher on irradiated body halves (86%, 12 of 14 patients) than on nonirradiated body halves (0) (McNemar test P < .001). Although stopping NB UV-B treatment of an irradiated body half after clearance led to a slight increase in PASI until the end of the 12-week alefacept treatment regimen, 6 of 14 patients (43%) still remained completely clear of psoriasis on the irradiated body halves (P = .03).

According to a recent survey by the Psoriasis Foundation, patient satisfaction with an antipsoriatic treatment regimen depends on whether the treatment regimen can significantly reduce or cause complete remission.
of psoriatic skin lesions. Patient satisfaction, however, also depends on the number of adverse events the treatment will cause and how fast the treatment will restore the patient to an acceptable and/or satisfying skin condition and quality of life. There is an urgent need for new innovative treatment regimens that can rapidly clear psoriatic lesions and produce long disease-free intervals while producing relatively few adverse effects. The combination of alefacept and NB UV-B therapy partly meets this need and thus may have a promising future as antipsoriatic therapy.

Alefacept produces a durable therapeutic effect that reaches its maximum efficacy several weeks after the active phase of treatment has ended. Narrowband UV-B phototherapy is well tolerated by patients, is easy to use, and becomes effective more quickly than alefacept does, improving psoriasis lesions within only a few weeks of treatment. Theoretically, combining a new antipsoriatic biological treatment (alefacept) with an established antipsoriatic phototherapy (NB UV-B) would make perfect sense. The results of our present study, to our knowledge the first randomized trial of such a combination, support this theory. The addition of NB UV-B phototherapy not only significantly sped up the clearance of psoriatic skin lesions, but PASIs in most patients also remained stable or tended to de-
crease even further in the 12 weeks following the last alefacept administration. The combination was well tolerated by our patients, confirming previous reports.19

Adverse events related to intravenous alefacept treatment were generally mild, brief, and similar to those reported elsewhere in the literature.8,11,13,17,18 Meanwhile, no adverse events related to NB UV-B phototherapy and no increased susceptibility to NB UV-B on irradiated body halves were detected during alefacept treatment. However, little is known about possible long-term effects of using biological treatments such as alefacept in combination with other systemic antipsoriatic treatments including UV-B. While an increased photocarcinogenic effect due to the combined treatment of alefacept with NB UV-B cannot be totally excluded, the likelihood appears to be rather small since alefacept apparently lacks general immune suppression13 and does not increase short-term photosensitivity, consistent with the observations of our study.

The findings of this half-body comparison study lead us to conclude that NB UV-B accelerates and improves the clearance of psoriatic skin lesions in alefacept-treated patients. Combining alefacept with phototherapy thus appears to be a viable approach to the treatment of psoriasis that warrants further study, particularly comparing the combination of the 2 treatments against phototherapy alone. Possible future trials would also combine NB UV-B phototherapy or PUVA phototherapy24 with other biological agents such as the tumor necrosis factor α inhibitors (eg, etanercept or infliximab) or other biological agents that interfere with T-cell activation.

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Author Contributions: Dr Wolf had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Figure 4. Patients’ self-assessment on a visual analog scale (VAS) of the therapeutic effect of antipsoriatic half-side treatment with alefacept alone and in combination with narrowband UV-B (NB UV-B) phototherapy. Data are illustrated as mean±SEM. *P<.02 for the difference between VAS values for contralateral body halves at the end of a particular treatment week or after the end of alefacept treatment (ie, 1 week after the final alefacept treatment).

Figure 5. Changes over time in the Psoriasis Area Severity Index (PASI) during the 12-week period that followed the end of antipsoriatic half-side treatment with alefacept alone and in combination with narrowband UV-B (NB UV-B). Data are shown as mean±SEM. The dashed line indicates the level at which complete remission (PASI=0) was achieved. A, Patients who did not require further NB UV-B phototherapy during follow-up (n=10; in 3 of these 10 patients, the last observation was carried forward owing to missing data). *P<.05 for the difference between the PASIs for contralateral body halves at the respective time points. B, Patients who had NB UV-B phototherapy for at least 4 weeks during follow-up (n=4).

Drs Legat and Hofer contributed equally to the study.

Study concept and design: Wolf. Acquisition of data: Legat, Hofer, Wackernagel, and SalmoHofer. Analysis and interpretation of data: Legat, Hofer, Quehenberger, Kerl, and Wolf. Drafting of the manuscript: Legat, Hofer, and Wolf. Critical revision of the manuscript for important intellectual content: Wackernagel, SalmoHofer, Quehenberger, and Kerl. Statistical analysis: Quehenberger. Administrative, technical, or material support: Legat, Hofer, Wackernagel, SalmoHofer, and Wolf. Study supervision: Kerl and Wolf.

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REFERENCES


