STUDY

308-nm Excimer Laser for the Treatment of Psoriasis

A Dose-Response Study

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Objective: To determine the dose-response relationship of excimer laser–generated 308-nm UV-B radiation for treating psoriasis.

Design: Pilot study with a before-after design.

Setting: A university dermatology service.

Patients: Thirteen consecutive patients with at least 4 large, stable psoriasis plaques.

Interventions: Excimer laser–generated 308-nm UV-B radiation was given to each of 4 plaques, which received 1, 2, 4, and 20 treatments, respectively. Untreated areas within each plaque served as controls. Within each plaque, 8 doses based on multiples of a predetermined minimal erythema dose (MED) were tested in distinct sites. The multiples were 0.5 and 1 (low dose); 2, 3, 4, and 6 (medium dose); and 8 and 16 (high dose). At every treatment, the dose for each site remained fixed at the same MED multiple. A psoriasis severity index score was determined for each area before, every 2 weeks during, and 2 and 4 months after treatment.

Results: The mean±SD MED was 203.03±57.84 mJ/cm^2. Treatment with high fluences produced significantly better results than that with medium and low fluences at weeks 4, 6, 8, and 10 ($P<.05$). At 4 months' follow-up, all sites that received low or medium fluences had recurrences, whereas those that underwent a single treatment at 8 and 16 MED multiples remained in remission.

Conclusions: With 308-nm UV-B radiation generated by an excimer laser, it is possible to clear psoriasis with as little as 1 treatment with moderately long remission. In contrast to traditional phototherapy techniques, this handheld excimer laser UV-B therapy is selectively directed toward lesional skin, thus sparing the surrounding normal skin from unnecessary radiation exposure. Treatment of other inflammatory diseases and limited psoriasis seems reasonable to pursue with this modality.

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UV-B PHOTOTHERAPY is a well-established form of psoriasis treatment that generally requires 25 to 30 treatments to produce clearing. Supraerythemogenic fluences of UV-B and psoralen–UV-A are known to result in faster clearing of psoriasis[1,2]; however, the limiting factor for the use of such high fluences lies with the intolerance of the uninvolved surrounding skin since psoriatic lesions can often withstand much higher UV exposures. Furthermore, units capable of delivering such large fluences selectively to the psoriatic plaques within a reasonable time do not exist. Recently, narrowband UV-B phototherapy has been shown[3-5] to be effective in the treatment of psoriasis. Although long-term results are not firmly established, some evidence[6] suggests that this new modality might prove to be less carcinogenic. Presumably, this narrow wavelength is not very different biologically from the 308-nm radiation generated by the XeCl excimer laser. Indeed, preliminary work[7] has established some efficacy for excimer laser–generated 308-nm radiation in the treatment of psoriasis. This study was designed to determine the dose-response relationship of excimer laser–generated 308-nm UV-B radiation, which is selectively directed toward psoriatic plaques, with regard to efficacy of clearing and length of remission.

RESULTS

Thirteen patients were enrolled in and completed the study. There were no dropouts. Demographic data of patients are shown in **Table 1**. Minimal erythema doses ranged from 114.05 to 325.86 mJ/cm^2 (mean±SD, 203.03±57.84 mJ/cm^2).

PATIENTS AND METHODS

This study protocol was approved by the institutional review board of the Massachusetts General Hospital, Boston. Informed consent was obtained before the start of the study. Adults with stable plaque-type psoriasis were recruited. Stable psoriatic plaques were defined as those that had been present and unchanged for at least 8 weeks before inclusion in the study. Patients were also required to discontinue all topical therapy for at least 2 weeks; UV-B phototherapy for 4 weeks; and psoralen photochemotherapy and systemic therapies, such as methotrexate, etretinate, and acitretin, for at least 8 weeks before treatment. Patients who were pregnant or lactating or who had a history of photosensitivity or keloid formation were also excluded.

The laser was a 308-nm XeCl excimer (Laser Photonics Inc, San Diego, Calif). Its output consisted of a train of short pulses (20-40 nanoseconds) delivered through a fiberoptic handpiece. Maximal output was 8 mJ per pulse, and the laser could be operated at 20 to 200 pulses per second. For this study, laser radiation was delivered at 5 mJ per pulse and 50 to 100 Hz.

Before the start of treatment, the 308-nm UV-B minimal erythema dose (MED) was determined on unexposed, uninvolved gluteal skin. The MED was defined as the minimal fluence of laser capable of producing well-defined macular pink erythema with distinct borders. The MED was determined with a geometrically increasing series of laser-generated fluences, namely, 100, 140, 200, 280, 400, 560, 800, 1120, and 1600 mJ per 4.91-cm^2 circular area, thus actually representing fluences of 20.36, 28.51, 40.73, 57.03, 81.47, 114.05, 162.93, 228.10, and 325.86 mJ/cm^2, respectively. The MED readings were performed 24 hours later.

Immediately before laser administration, the area to be treated was marked with indelible ink, followed by liberal application of fragrance-free mineral oil to reduce scattering and enhance penetration, as is routinely done in many UV-B phototherapy centers. Because the laser pulses produced at most a sensation of only minimal warmth, anesthesia was not required during the laser exposures.

Four large plaques of similar-appearing psoriasis were selected in each patient. The first plaque received only 1 treatment, the second plaque received 2, the third plaque received 4, and the fourth plaque received 20. Untreated areas within each plaque served as controls. All multiple treatments were administered twice a week with 72 hours separating the 2 sessions in the same week. The total treatment period was 10 weeks.

To maximize our dose-determining efforts, the same range of 8 doses was given at adjacent but distinct areas within each of the 4 study plaques. Fluences were based on multiples of the predetermined MED, specifically, low (0.5 and 1 MED multiple), medium (2, 3, 4, and 6 MED multiples), and high (8 and 16 MED multiples) fluences. Each fluence treatment area was circular and measured 2.54 cm in diameter, the maximum field size of the laser delivery device. Thus, the first plaque received only a single treatment, and within that plaque for each patient were 8 separate test areas corresponding to the MED multiples described. The second plaque in each patient also had 8 areas corresponding to the MED multiples described, but each of these test areas received 2 treatments. The fluence at a given test site was never increased so that, eg, the site in the second plaque, which got 4 MED multiples, in fact received 4 MED multiples on 2 occasions. Similarly, the fourth plaque of psoriasis had 8 separate treatment areas corresponding to each of the MED multiples tested. Within that fourth plaque in each patient, the 0.5 MED area received 20 treatments at this fixed dose, the 1 MED area received 20 treatments at that fixed dose, etc. A schematic summary of the exposures is shown in **Figure 1**. **Figure 2** shows the various treatment areas outlined in indelible ink just before the first irradiation.

Clinical evaluation was done before and every 2 weeks during the 10-week treatment period and 2 and 4 months after completion of the treatments. At each evaluation visit, a psoriasis severity index (PSI) score, which excluded area and consisted of the sum of a 0 to 4 (absent to severe) score for each of erythema, induration, and desquamation, was assigned to each treated and untreated area. Standardized 35-mm photographs were also obtained at these visits.

Routine 4-mm punch biopsy samples were obtained under 2% lidocaine with epinephrine in selected patients at various points. Biopsy sites were closed with 4-0 nylon sutures. Wound care consisted of applying bacitracin zinc twice daily for 14 days until the sutures were removed.

Based on the study design, multiple measurements were obtained from each treatment site on every plaque from the same patient. Therefore, repeated-measures analysis of variance was used to examine the trends in fluence and number of treatments. Subset analyses stratified by time, fluence, and number of treatments were also used to compare the mean changes in PSI scores from baseline for different fluences and numbers of treatments.

Treatment of the first 3 patients with 8 and 16 MEDs resulted in blistering of the treated skin appearing at 24 hours and rupturing appearing around 48 to 72 hours (**Figure 3**). Although blistering was not totally unexpected, the degree of discomfort experienced by this initial cohort was sufficient to warrant restriction of subsequent fluences to multiples of 6 MEDs or less. As a result, 4 patients received test doses of up to 16 MED multiples from the laser and the remaining 9 received multiples up to a maximum of 6 MEDs. These fluences of 6 MED multiples or less were well tolerated by all patients. A slight increase in erythema accompanied by a moderate burning sensation was observed at sites receiving 4 and 6 MEDs once in each of 3 patients. In each case, only the next treatment was omitted before resumption of the protocol.

Table 2 illustrates the mean PSI scores for improvement (ie, score change compared with baseline) for each time and for each fluence. Note that PSI scores were not given to areas receiving 8 and 16 MEDs at 2 weeks because a hemorrhagic crust was still present then.

As soon as 2 weeks after single treatments with 2 and 4 MED multiples, some early but minimal clinical improvement was seen (**Figure 4**). In general, at this time, medium fluences produced more improvement than did low fluences ($P=.07$). In fact, after a single treatment, the dose of 0.5 to 1 MED multiple resulted in no visible change of the psoriatic lesions. For areas in which

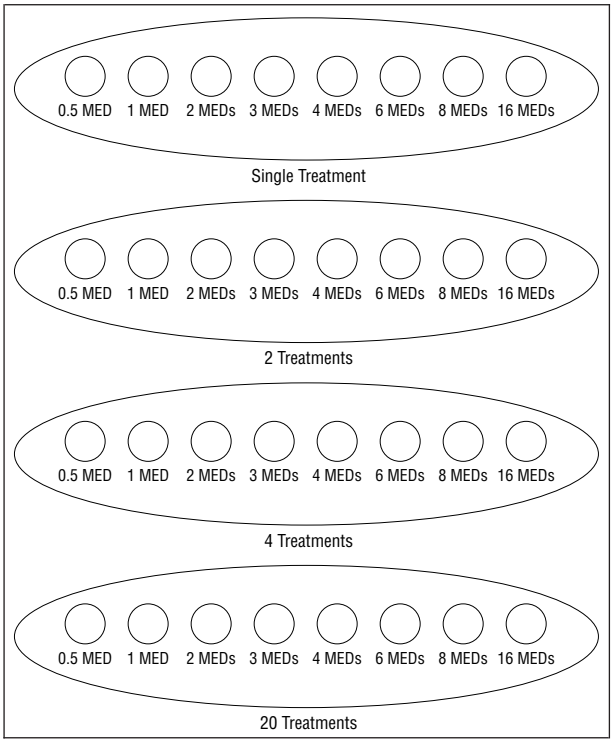

Figure 1. *Schematic summary of treatment. MED indicates minimal erythema dose.*

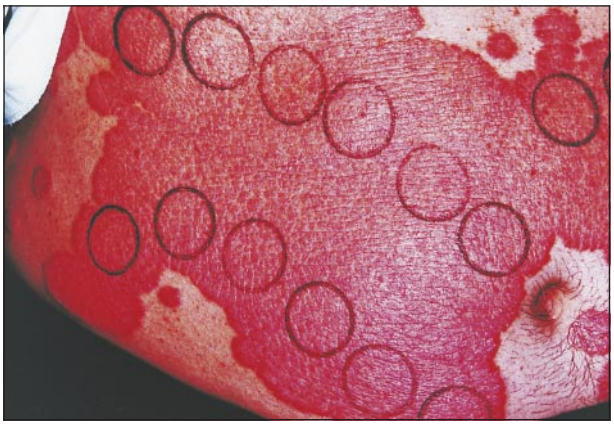

Figure 2. *Treatment allocations for a given plaque marked with indelible ink before laser administration.*

2 treatments were administered, a similar trend was seen in that 2 treatments at medium fluences tended to produce more improvement than did low fluences ($P=.08$). At this time, the areas that received high fluences were still crusted and hence no PSI scores were given. Contrarily, at this time, for areas receiving 4 or more treatments, there was no statistically different improvement among the different fluences.

When examined at 4, 6, 8, and 10 weeks of treatment, areas receiving high fluences produced better improvement than areas receiving medium or low fluences; however, none of the individual comparisons reached statistical significance because there were few data points available in the high-dose category. After blisters in the high-dose subset cleared, the psoriatic areas were perfectly clear in all tested patients. Despite the small number in the high fluence group, when data from all 4 plaques were combined, the improvement in this group was statistically better than in low or medium fluence groups at all follow-up points (all $P<.05$). This trend proved true not only for the test areas receiving a single treatment but also for areas receiving 2, 4, and 20 treatments. To demonstrate the possible combination of fluence and number of treatments necessary to achieve a PSI score of 1.5 or less, we plotted the results from the regression models in **Figure 5**.

When number of treatments was examined as an isolated predictor, there was no statistically significant difference among 1, 2, 4, and 20 treatments at 2 and 4 weeks of follow-up. The area with 4 or 20 treatments showed significantly better improvement than the area with 2 treatments at 6 weeks ($P=.02$ and .001, respectively), and the area with 20 treatments showed significantly better improvement than the area with 1, 2, or 4 treatments ($P=.008$, .008, and .03, respectively). The area with 20 treatments also showed significantly better improvement than the area with 4 treatments at medium fluences at 10 weeks ($P=.03$). **Figure 6** shows a typical example of the clinically apparent clearing of psoriasis at

Table 1. Summary of Patient Demographic Data*

Age, mean (range), y	36.9 (21-66)
Skin type, No. of patients	
I	1
II	1
III	8
IV	3
Duration (range), y	38.6 (4-31)
Previous treatments, No. of patients	
Topical corticosteroids	12
Calcipotriene	10
Topical retinoids	1
Systemic retinoids	3
Methotrexate	5
Psoralen–UV-A	7
Broadband UV-B phototherapy	8
Baseline PASI score, mean (range)	6 (3-8)
Baseline MED, mean (range), mJ/cm^2	203.03 (114.05-325.86)

**PASI indicates Psoriasis Area and Severity Index; MED, minimal erythema dose.*

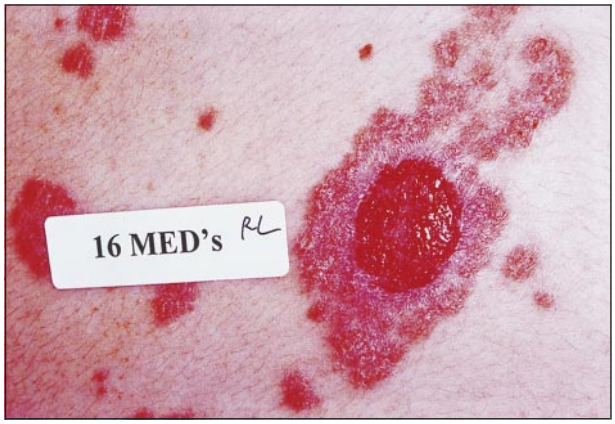

Figure 3. *The base of a ruptured blister 72 hours after laser treatment with high fluences.*

Table 2. Mean Psoriasis Severity Index Score Improvements*

Treatments, No.	Fluences		
	Low	Medium	High
Week 2			
1	1.0	1.6	. . .
2	0.2	1.5	. . .
4	0.5	1.0	. . .
20	0.7	0.9	. . .
Week 4			
1	1.9	2.8	6.5
2	1.4	3.1	4.0
4	2.3	3.7	6.5
20	2.3	3.2	4.0
Week 6			
1	2.2	3.3	6.5
4	2.2	3.9	6.7
20	3.2	4.2	7.0
Week 8			
1	1.8	2.7	6.5
2	2.0	2.9	4.3
4	1.5	3.5	5.8
20	3.1	4.3	6.8
Week 10			
1	1.7	2.4	6.5
2	2.5	3.2	4.3
4	1.8	2.7	5.9
20	3.1	4.0	4.5

*Ellipses indicate that scores were not given because a hemorrhagic crust was still present.

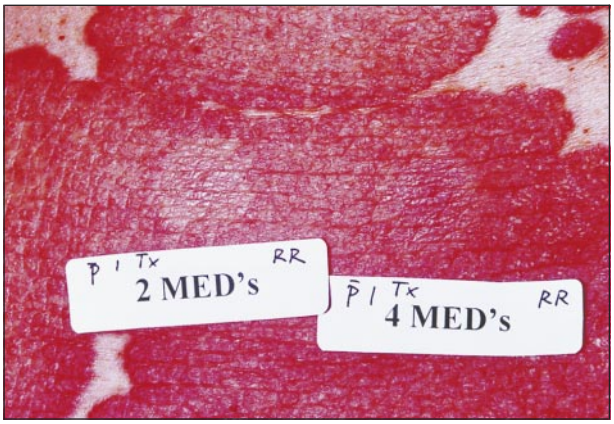

Figure 4. *Minimal clinical improvement noted after single treatments with 2 and 4 multiple erythema dose (MED) multiples.*

the end of treatment for a plaque that received 20 irradiations at 3 and 4 MED multiples.

At the first follow-up visit that took place 2 months after the last treatment, areas receiving 4 and 20 treatments with at least 3 MEDs remained free from lesions in 6 patients (**Figure 7** and **Figure 8**). Four months after the last treatment, sites receiving less than 8 MEDs all showed recurrence, whereas those receiving single irradiations with 8 and 16 MEDs were still in remission (**Figure 9**). Note, however, that these clear areas were ever-so-slightly smaller, perhaps indicating incipient progression of the surrounding psoriatic plaque because the

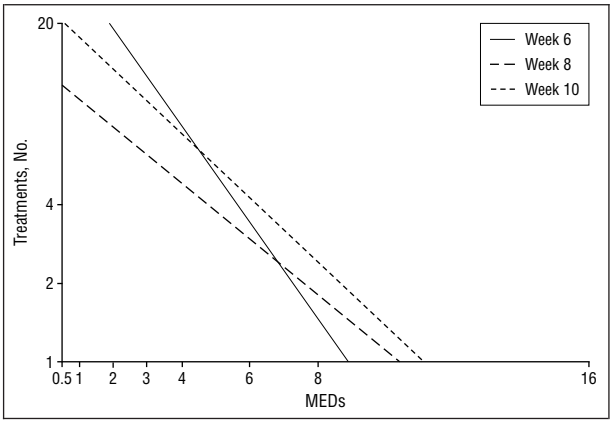

Figure 5. *Linear dose-response curves (number of treatments vs fluence) for achieving a psoriasis severity index score of 1.5 or less as observed at different times. Note that there is no information for times earlier than 6 weeks because no test site obtained a psoriasis severity index score as low as 1.5 so early on. MEDs indicates minimal erythema doses.*

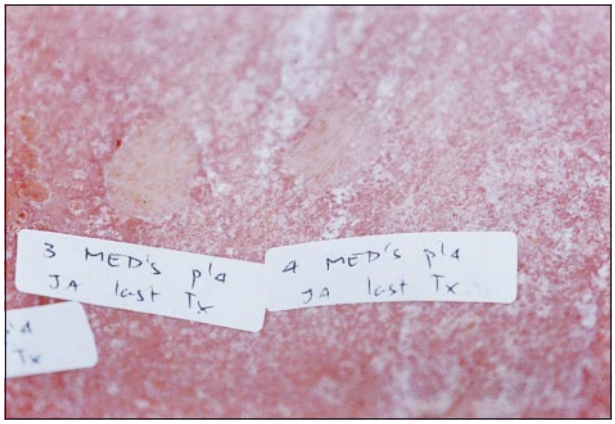

Figure 6. *Clinically apparent clearing of psoriasis as noted at the end of treatment on the plaque receiving 20 treatments with 3 and 4 multiple erythema dose (MED) multiples.*

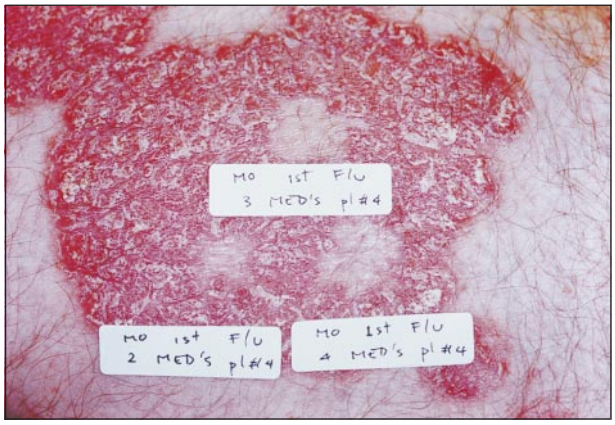

Figure 7. *At the 2-month follow-up visit, areas that received medium fluences are still reasonably clear clinically.*

treatments were given to small areas, not the entire plaques.

Adverse reactions included the previously mentioned blistering eruption at high fluences and transient erythema at moderate fluences. The treated skin, not unexpectedly, especially at sites receiving repeated expo-

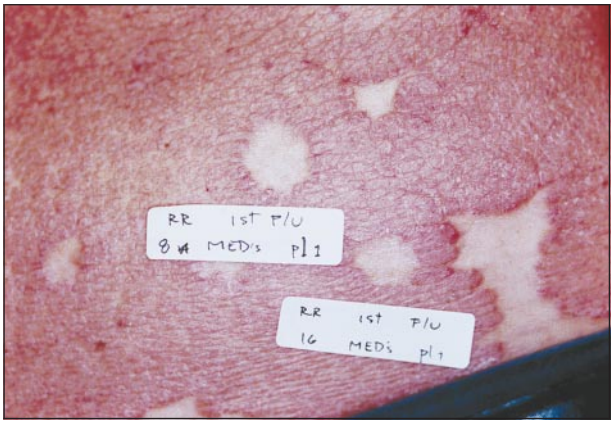

Figure 8. *Areas receiving single treatments with high fluences demonstrate clearing of psoriasis at 2-month follow-up.*

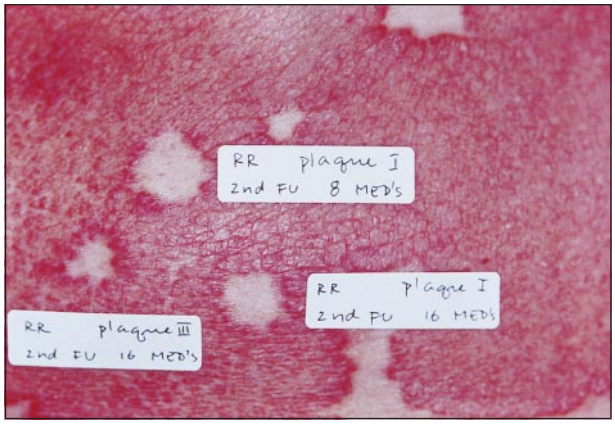

Figure 9. *Four months after the last treatment, areas receiving single irradiations with 8 and 16 minimal erythema doses were still in remission.*

sures, appeared slightly tanned. Biopsy samples taken from normal-appearing skin after 4 treatments with 2 MEDs from 2 patients revealed complete reversion of the pathological changes of psoriasis.

COMMENT

With conventional phototherapy and photochemotherapy, generally the whole body is unavoidably exposed to UV radiation. These undue exposures of uninvolved skin result in greater risks of short-term adverse effects such as burning and pruritus and long-term effects such as accelerated photoaging and photocarcinogenesis. Although UV-B irradiation is known to exert some systemic effects, its local effects are unequivocally important in the treatment of psoriasis.[8] In this study, local exposures were used, leading to rapid clearing of treated areas.

As demonstrated by Parrish and Jaenicke,[2] the action spectrum for psoriasis clearing is 300 to 313 nm, whereas wavelengths shorter than 290 nm do not have any therapeutic effects even when administered at supraerythemogenic doses. In this study, we demonstrated that exposures of lesional skin to only 308-nm laser could also clear psoriasis. This finding is not surprising given what is known about the psoriasis action spectrum and what is known about the overall efficacy of narrowband 311-nm phototherapy, which operates at a nearby wavelength.[3-5] The results of this study further exemplify the role of local UV exposures in psoriasis clearing.

In 1997, Bonis et al[7] also reported that the 308-nm XeCl excimer laser was useful in the treatment of psoriasis. The treatment protocol used in that study involved stepwise dose increments similar to conventional phototherapy. The conclusion was that psoriasis required 7 to 11 treatment sessions to clear. However, it was not stated whether an MED was determined, and the rationale for the choice of the fluences was not clear. In our study, fluences were based on the MED, and we examined the dose-response for a given multiple of the MED and the number of treatments.

In our effort to establish the role of various fluences on clearing of psoriatic plaques, we used 8 different fluences. The effects of fluences are more conveniently interpreted when these fluences were grouped as low (0.5 and 1 MED), medium (2, 3, 4, and 6 MEDs), and high (8 and 16 MEDs). In so doing, we could demonstrate that fluence was the single most important determinant in the clinical clearing of psoriasis. The number of treatments, on the other hand, was not so important.

It has been reported[1,2,9] that irradiation of psoriatic plaques with near or supraerythemogenic fluences of UV results in faster clearing compared with suberythemogenic fluences; however, total cumulative fluences may remain otherwise similar to the conventional treatment. The limitations for irradiation with supraerythemogenic fluences derive not only from the susceptibility of unaffected skin but also from the fact that units capable of delivering such fluences efficiently are lacking. The advent of lasers with the capacity to deliver such high fluences within a relatively short time represents a breakthrough in UV-B phototherapy.

A remaining question is how high one can go for supraerythemogenic fluences. It is known that normal-appearing skin can tolerate up to about 3 MEDs of solar-simulated radiation without blistering.[10] It is also known that psoriatic lesions can tolerate more UV irradiation than uninvolved skin.[1] This prompted us to use up to 16 times the MED. This high fluence, however, resulted in a blistering reaction on the psoriatic plaque itself. Nevertheless, we learned that use of such high fluences of UV-B resulted in a prolonged remission of psoriasis, even after a single treatment. The clinical significance of this finding lies in the fact that some patients with limited psoriasis might benefit substantially from a single large fluence of UV-B. The safety of this approach, however, must be questioned from an epidemiological point of view since blistering sunburns have been associated with an increased risk of cutaneous melanoma.[11-13] Clearly, mouse carcinogenesis studies will be needed once the optimal practical methodology is established.

In this study, we also demonstrated that repeated exposures to 0.5 and 1 MED did not result in significant clearing of psoriasis. This observation was not unexpected because phototherapy dose increments are usually given to compensate for acclimatization and tanning, which accompany phototherapy and limit UV-B's

ability to penetrate the skin. On the other hand, repeated exposures to moderate fluences of 308 nm (ie, 2-6 MEDs) resulted in significantly better improvement of psoriasis, which was clinically evident by 2 weeks. Such an approach would seem to lend credence to the concept of using high doses early on to effect clearing before acclimatization establishes a barrier.

The remission obtained with this treatment is also fluence dependent. Areas that received lower fluences showed recurrence of lesions shortly after the last treatment. It is possible, however, that the recurrence observed in this study might be hastened by the fact that the entire plaques were not treated, resulting in "invasion" from the adjacent plaques. When entire lesions are treated, it remains speculative at best to think that the remission may be longer.

For a given wavelength, each individual may respond differently in part because of different characteristics of the plaques.[2] As observed in this study, plaques with more scale tended to respond less favorably than those with minimal scale. It is known that thickened stratum corneum increases air-tissue interface and thus impedes light penetration. In fact, a 4-fold increase in the thickness of stratum corneum can decrease light penetration by 4 orders of magnitude.[2] It should be remembered that mineral oil was an integral part of our therapy.

The 308-nm excimer laser has several potential advantages for phototherapy of psoriasis. First, the capability of this novel laser/phototherapy system to deliver several multiples of the MED to the psoriatic lesions in only a few minutes without the need for anesthesia allows managing physicians to treat psoriatic patients efficiently and selectively on the affected areas. For the thousands of patients with recalcitrant elbow and knee plaque psoriasis, the treating physician, using the proper dose, can provide quick, painless therapy precisely to these involved areas, thus sparing the surrounding unaffected tissue from harmful unnecessary irradiation. The ability to use directed high-dose therapy allows for a reduction in the number of treatment sessions needed. Moreover, with the appropriate delivery systems, psoriasis on certain difficult anatomical locations, such as the scalp and nailfolds, could possibly be treated. Other UV radiation–responsive diseases, such as eczema and mycosis fungoides, seem logical therapeutic extensions. Furthermore, if the laser were to be equipped with a real-time scanner, it could potentially be used for selective total-body treatment. The scanner would have to be able to differentiate lesional skin from uninvolved skin based on color variations, hence allowing the scanner laser delivery system to impart the selectivity that treating physicians can now obtain visually.

In summary, we demonstrated that single exposures of lesional psoriatic plaques to high fluences or repeated exposures to moderate doses of excimer laser–generated 308-nm UV-B radiation resulted in clearing of psoriasis. The remission seen in the areas that received the high dose was approximately 6.5 months, namely, 2.5 months for the study period after the single treatment and 4 months for the follow-up period. Future investigations with this laser seem meritorious.

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