In reply

We appreciate the interest of Carlson et al in our article on vulvar VX1 as well as their comment about the possible etiologic role of lymphostasis and HPV. Our 10 vulvar VX cases were all associated with another vulvar condition, mainly LS but also lichen planus (2 cases), vulvar radiodermatitis (1 case), and Paget disease (1 case). Our findings sustain the hypothesis of Zegarelli et al that damage to the epithelium—particularly of the DEJ, in our opinion, could trigger the following cascade: (1) entrapment of epithelial cells in the papillary dermis; (2) subsequent degeneration of these cells and lipid formation; (3) engulfment of released lipids by macrophages; and (4) accumulation of foam cells between the rete ridges.

Carlson et al object that this hypothesis does not explain why macrophages accumulate in the papillary dermis. We think that the superficial location of the xanthomatous cells can be explained by the fact that the papillary dermis is the part of the dermis, which is the closest of the damaged epidermis. The poor lymphatic drainage reported by Carlson et al in 14 genital and 4 trunk LS cases could account for the accumulation of macrophages in the papillary dermis. However, to confirm this hypothesis one should demonstrate the following: (1) that all the other conditions associated with mucosal or cutaneous VX are associated with lymphostasis (eg, Paget disease, lichen planus, graft-vs-host disease, discoid lupus erythematosus, pemphigus vulgaris, recessive dystrophic epidermolysis bullosa, lichen planus, epidermal nevus); (2) that lymphostasis is not just an incidental finding related to inflammation, whatever its cause. In addition, if an increased number and dilation of lymphatic vessels is present in most LS cases, these abnormalities cannot alone explain the occurrence of VX with LS. Indeed, VX only exceptionally occurs concomitantly with LS.

The second hypothesis advanced by Carlson et al is that the verrucous epidermal hyperplasia that is a hallmark of VX could be related to an HPV infection. This HPV infection may have been facilitated by the lymphostasis, the source of the disrupted immune-cell trafficking and consequently of localized immunosuppression. This interesting assumption is not corroborated either by the pathologic features of VX or by the available virologic data. Indeed, we found that the verrucous hyperplasia of VX had specific, almost pathognomonic, histologic features that differ from those of HPV infections: wedge-shaped parakeratosis forming deep invaginations into the acanthotic epithelium and exhibiting a characteristic orange hue under hematoxylin-eosin stain; and neutrophilic infiltrate at the junction between the superficial parakeratotic layers and the underlying stratum spinulosum. In addition, neither keratoses nor atypia were observed.

In our retrospective study, no HPV search was performed. However, the data collected from the literature are mainly negative, even though very sensitive methods were used.1 A few cases with a positive HPV search have been reported, but these findings could have been incidental: HPV may be present on normal vulvar or oral mucosa in as many as 23.3% of the cases.2

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1. Fite C, Plantier F, Dupin N, Avril MF, Moyal-Barracco M. Vulvar verruciform xanthoma: ten cases associated with lichen sclerosus, lichen planus, or other conditions. Arch Dermatol. 2011;147(9):1087-1092.


Efficacy and Safety of Apremilast in Chronic Cutaneous Sarcoidosis

Pentoxifylline, a phosphodiesterase type 4 inhibitor, is reported to be effective for the treatment of sarcoidosis.3 However, the adverse events associated with this drug have limited its general use. Apremilast is a new phosphodiesterase type 4 inhibitor that blocks the synthesis of proinflammatory cytokines and chemokines, such as tumor necrosis factor, interferon γ, and the interleukins...
IL-2, IL-12, and IL-23. These cytokines are important in the initiation and perpetuation of sarcoidosis.

Methods. All the patients included in our trial were required to have active skin lesions consistent with chronic cutaneous sarcoidosis and to be receiving systemic therapy for sarcoidosis that was unchanged for the 3 months before the study entry.

An index lesion was determined at baseline for each patient. For patients with more than 1 skin lesion, the lesion with the highest combined score of induration, erythema, desquamation, and area of involvement was designated the index lesion.

Initially, all patients received oral apremilast, 20 mg, twice a day. If adverse events were reported, the dosage was reduced to 20 mg orally once a day. Patients received 12 weeks of treatment and were seen 1 month later.

Skin lesions were assessed in 2 ways: (1) by using the previously described Sarcoidosis Activity and Severity Index (SASI) and (2) by comparing photographs of the index lesion initially and at week 12, with the photographs presented in random order. The scores were subsequently normalized: 1 indicated much better after therapy and 5, much worse after therapy.

Results. Of 17 patients who provided written consent for participation in the trial, 2 were excluded because of predefined exclusion criteria (1 each for a history of hepatitis C virus and leukopenia). The remaining 15 patients received the drug for the entire study. Individual SASI scores were serially determined by the same investigator for each patient visit in 14 of 15 patients. Apremilast dosage reductions were necessary for 2 patients (1 each for jitteriness and nausea). Both patients completed the study while receiving 20 mg daily without reporting further adverse events.

Each patient’s condition was evaluated at weeks 2, 4, 8, 12, and 16 for adverse events, including changes in liver function test results.

Figure 1. Change in the Sarcoidosis Activity and Severity Index (SASI) induration scores. A, The change in the SASI induration scores for all 46 lesions after therapy. Significant improvement was seen in the score after 4 and 12 weeks of therapy (week 4, \( P < .002 \); week 12, \( P < .005 \)). B, The change in the SASI induration score from baseline for the index lesion in 14 patients. There was a significant decrease in the induration score at week 4 (median [range], −1 [−1 to 0]; \( P < .05 \)) and at week 12 (−1 [−3 to 1]; \( P < .02 \)). The dotted line indicates no change in the induration score from baseline.

Figure 2. A study patient with lupus pernio before and after therapy. A, Before therapy, lupus pernio is visible on the right cheek. B, The same patient after 12 weeks of therapy with apremilast, 20 mg, twice a day. All 3 readers scored this as 1, indicating that it was much better after therapy.
Of the 15 apremilast-treated patients, 14 were women and 10 were black. All patients were receiving stable systemic therapy, and no patient received topical therapy before or during the study.

**Figure 1** A shows the change in induration for all 46 lesions after 4 and 12 weeks of therapy. A significant reduction in the induration score was noted at both time points (week 4, P < .002; week 12, P < .005). Figure 1B demonstrates the change in induration from baseline for the index lesion for all 14 patients whose condition was evaluated. Again, we found a significant decrease in the induration at week 4 (P < .05) and week 12 (P < .02). Compared with baseline, there was no statistically significant difference in the erythema, desquamation, or area of involvement at week 4 or 12 for all the lesions or for the index lesion.

After 12 weeks of therapy, the normalized mean score was 2 ("somewhat better after therapy") for all 3 photographs. **Figure 2** shows a pair of photographs that were scored by all 3 readers as 1 ("much better after therapy”). There was good correlation between the different readers (Spearman rank correlation, 0.66-0.81; P < .02 for all 3 correlations).

Within 3 months after discontinuation of apremilast therapy, 3 patients developed significant worsening of their cutaneous lesions. In all 3 patients, increasing their prednisone dose only modestly improved these lesions.

**Comment.** To date, there is no consensus regarding the best method to assess response to therapy for cutaneous sarcoidosis. The current study used 2 independent instruments—the SASI score and paired photographs—to objectively report changes in cutaneous lesions. The SASI induration score decreased significantly with apremilast therapy (Figure 1). Analysis of paired photographs also demonstrated statistically significant improvement. Three patients experienced disease relapse within 3 months of treatment discontinuation.

We found apremilast effective for some patients who had persistent lesions despite multiple systemic treatments. This group of patients has been poorly responsive to most other drugs except for high doses of corticosteroids or the anti–tumor necrosis factor antibody infliximab. Further studies seem warranted to examine the safety and effectiveness of apremilast for the treatment of chronic cutaneous sarcoidosis.

**Author Contributions:** Drs Baughman, Judson, and Lower and Ms Ingledue had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Baughman, Judson, and Lower. Acquisition of data: Baughman, Judson, Ingledue, and Craft. Analysis and interpretation of data: Baughman, Judson, and Lower. Drafting of the manuscript: Baughman, Judson, Craft, and Lower. Critical revision of the manuscript for important intellectual content: Baughman, Judson, Ingledue, Craft, and Lower. Statistical analysis: Baughman. Obtained funding: Baughman. Administrative, technical, and material support: Baughman, Judson, Ingledue, Craft, and Lower. Study supervision: Baughman, Judson, and Lower.

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**VIGNETTES**

**Automobile Seat Heater-Induced Erythema Ab Igne**

E rythema ab igne (EAI), a netlike dermatosis, is caused by repeated exposure to moderate levels of heat (infrared radiation). Most seat heaters reach an upper limit of 43.0°C (109.4°F) with a deviation of about 1.8°C (3.8°F). Malfunctioning seat heaters have reached even higher temperatures, nearing 48.9°C (120.0°F), causing second-degree burns, especially in patients with mobility and sensory deficits. However, EAI can occur with chronic exposure to normally functioning heated car seats.

**Report of a Case.** A healthy 40-year-old white woman presented with a reticulated erythematous and hyperpigmented rash restricted to the posterior thighs (**Figure 1**).