Treatment of Stage IA Cutaneous T-Cell Lymphoma With Topical Application of the Immune Response Modifier Imiquimod

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REPORT OF A CASE
A 52-year-old woman with cutaneous T-cell lymphoma (CTCL) presented to the dermatology clinic for treatment. She had a more than 10-year history of episodic dry, itchy patches over her trunk and extremities. Previous biopsy specimens obtained from the patches revealed histopathologic changes typical of CTCL. Treatment with a number of topical steroid preparations and topical nitrogen mustard and carmustine had been ineffective. On physical examination, she had 2 clinically similar, well-demarcated patches with mild erythema and scale involving less than 10% of her total body surface area (stage IA). She had no evidence of systemic involvement.

THERAPEUTIC CHALLENGE
Although patients with stage IA CTCL (less than 10% total skin surface involvement without lymph node or visceral metastases) experience long-term survival similar to that of a matched control population, approximately 10% progress to more advanced disease and 50% experience recurrence of disease despite appropriate therapy. The current standard therapies, such as topical steroids or chemotherapy, and γ irradiation are associated with adverse effects, including atrophy, telangiectases, allergic contact or irritant dermatitis, and radiation dermatitis. Also, in any stage of disease, patients can experience prominent pruritus and physical disfigurement. Therefore, alternative approaches to the treatment of CTCL are desired. Our purpose was to determine the efficacy of 5% imiquimod cream in comparison with placebo in the treatment of stage IA CTCL.

SOLUTION
The patient signed an informed consent agreement that had been approved by the Institutional Review Board at the University of Pennsylvania, Philadelphia. The results of a urine pregnancy test were negative before the initiation of therapy. The 2 patches were designated as site A on the left lower quadrant of the abdomen (Figure 1) and site B on the right breast (data not shown). The areas were measured and photographed, and 3-mm punch biopsy specimens were obtained from each site before the initiation of therapy. The patient received 2 different sets of sachets containing medication. One set contained 5% imiquimod cream and the other contained placebo vehicle. The 2 sites were designated for treatment with 1 of the 2 medications. The patient applied medication from the appropriate sachet to each lesion nightly for 4 months. Both the patient and the investigator (K.R.S.) were blinded to the therapy. The patient was seen and the treatment sites were examined and measured monthly (by K.R.S.) throughout the treatment period. Local or systemic effects reported by the patient were recorded at each monthly examination. At the end of 4 months of therapy, the 2 areas were photographed and measured, and 3-mm punch biopsy specimens were obtained from each site. The biopsy specimens were fixed in formalin, embedded in paraffin, and routinely stained with hematoxylin-eosin. The sections were reviewed by a dermatopathologist (J.M.J.-H.) who was blinded to therapy and treatment site.

During the first month of therapy, the patient developed prominent erythema, vesiculation, erosions, xerosis, and pruritus at site A. Also, a new area adjacent to site A became inflamed (Figure 2). Therapy was discontinued at site A for 2 days as a result. The treatment...
was restarted nightly and was tolerated throughout the rest of the study. Over the following months, the inflammatory response progressively resolved at site A despite the continued application of medication. The patient continued treatment and reported no symptoms at site B throughout the duration of the study. At the final examination, both sites A and B were asymptomatic. However, at site A, there was only macular hyperpigmentation without erythema or any remaining surface change or clinical evidence of inflammation (Figure 3). Site B was unchanged.

The biopsy specimens obtained from both sites before therapy was begun demonstrated similar findings, which included a moderate patchy interstitial to bandlike lymphocytic infiltrate in the upper dermis, with many lymphocytes aligned along the dermoepidermal junction on the epidermal side. There was prominent epidermotropism of lymphocytes, many of which had large hyperchromatic and hyperconvoluted nuclei. Foci of Pautrier microabscess formation were noted. There was associated papillary dermal fibroplasia (Figure 4). After 4 months of therapy, site A demonstrated only areas of subtle papillary dermal fibroplasia and very rare non-atypical lymphocytes (Figure 5). On histologic examination, site B remained unchanged, with a prominent lymphocytic infiltrate and epidermotropism of atypical lymphocytes into the epidermis.

After the completion of 4 months of therapy and evaluation of the pathologic findings, the treatments were unmasked. Site A received 5% imiquimod cream and site B received placebo. Ten months after the study was completed, there has been no recurrence at site A and the postinflammatory hyperpigmentation has progressively improved. In an attempt to minimize the inflammatory response, the patient is planning to apply 5% imiquimod cream to a new area of involvement every other night within the next few months.

**COMMENT**

In CTCL, the pathogenic cell type typically is a malignant CD4+ helper T cell that expresses a Th2 phenotype. Th2 cells produce interleukin (IL)-4, IL-5, and IL-10, which stimulate the production of IgE antibodies, enhance the differentiation and activation of eosinophils, and suppress Th1 cellular activity, respectively. Many therapies currently used in the treatment of more advanced CTCL, including extracorporeal photopheresis, recombinant interferon alfa, and IL-12 used alone or in combination, can reverse cytokine and immune abnormalities in patients with CTCL. Photopheresis is postulated to induce programmed cell death of the malignant cells, with a resultant enhanced cell-mediated immune response.
against the clonal apoptotic cells. Both interferon alfa and IL-12 have been shown to enhance cytolytic T- and NK-cell cytotoxic responses, to facilitate the development of T_{H1} cell differentiation, and to suppress T_{H2} cellular differentiation and cytokine production.

Imiquimod (Aldara) is a topical immunomodulatory agent that is approved for the treatment of external genital warts. It is a potent stimulator of T_{H1} cytokines, including interferon alfa, interferon gamma, and IL-12; it increases NK-cell activity; it up-regulates expression of tumor necrosis factor alpha; and it enhances antigen presentation by Langerhans cells. Also, imiquimod exhibits prominent antitumor activity. Topical application of 5% imiquimod cream has been shown to be effective in the treatment of both nodular and superficial basal cell carcinomas and may be therapeutically active against lentigo maligna and cutaneous melanoma metastases. Therefore, by inhibiting the clonal T_{H2} cells as well as stimulating a tumor-specific cytotoxic response, imiquimod may be an effective form of topical therapy for CTCL.

Our patient experienced complete clearance of CTCL in response to treatment with 5% imiquimod cream. Also, areas of subclinical disease were highlighted and eradicated at the application site. The adverse effects experienced during the treatment period did not prevent continuation of therapy and diminished with time. As a result of these encouraging findings, we have initiated a double-blind, placebo-controlled trial to better evaluate the efficacy of imiquimod in the treatment of CTCL. If imiquimod represents an effective form of therapy in CTCL, it may be used alone for possible cure of early-stage disease, or it may be used in combination with systemic immunomodulatory therapy to enhance therapeutic relief of skin symptoms in patients with extensive disease.

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REFERENCES


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