

# Vorinostat for the Treatment of Bullous Pemphigoid in the Setting of Advanced, Refractory Cutaneous T-Cell Lymphoma

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*The Cutting Edge: Challenges in Medical and Surgical Therapeutics*

Histone deacetylase (HDAC) inhibitors represent a novel class of medication that is being targeted for use in the treatment of cancer. A member of this class, vorinostat, has recently been approved for the therapy of cutaneous T-cell lymphoma. Importantly, emerging data from animal studies have indicated that HDAC inhibitors may have the capacity to potentially suppress the development of autoimmune disease. In this report, we describe a patient with advanced cutaneous T-cell lymphoma who developed refractory bullous pemphigoid (BP) and then experienced the rapid resolution of the BP following initiation of treatment with vorinostat. This observation may be broadly applicable to the treatment of other autoimmune skin diseases.

## REPORT OF A CASE

Our patient, a 59-year-old woman, was diagnosed in 1996 as having mycosis fungoides/cutaneous T-cell lymphoma (MF/CTCL), stage IB, with a medical history of varicella zoster, gastritis, and osteopenia. She also had a history of sulfa allergy. Despite multiple treatments including psoralen-UV-A phototherapy, topical chemotherapy, topical corticosteroids, oral bexarotene, chemotherapy, autologous stem cell transplant, denileukin diftitox, and interferon gamma, she experienced disease progression to stage IVA with skin tumors, nodal involvement with large cell transformation, and peripheral blood involvement (6% CD4<sup>+</sup>CD7<sup>-</sup> cells and a discrete population of 38% CD4<sup>+</sup>CD26<sup>-</sup> cells). She subsequently underwent total skin electron beam radiation (TSEB) therapy and started treatment with extracorporeal photopheresis (ECP) in conjunction with interferon gamma.

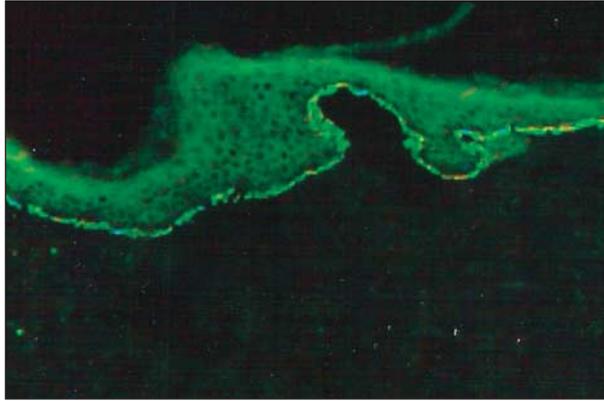
Three months later, she was admitted to the Hospital of the University of Pennsylvania, Philadelphia, with a 2-month history of progressive skin pain, itching, blisters on her buttocks and feet, oral and vaginal erosions,odynophagia, and lower extremity edema for which she was prescribed furosemide at an outside hospital. Initially, the concern was for radiation dermatitis vs disseminated herpetic infection. Despite aggressive skin care,

pain control, and negative results from tests for herpes simplex and varicella zoster virus, her skin condition progressed to erythroderma, erosions, and tense bullae over her arms, abdomen, chest, back, legs, and mouth (sparing the eyes), raising the possibility of Stevens-Johnson syndrome/toxic epidermal necrolysis (TEN) or bullous drug hypersensitivity reaction. However, findings from multiple skin biopsy specimens were inconclusive for TEN. Hematoxylin-eosin staining demonstrated a subepidermal blistering disorder; although findings were consistent with BP, other diagnoses could not be completely ruled out based on histologic results at that time, including radiation recall dermatitis, drug-induced blistering reaction, and erythema multiforme. The inflammatory infiltrate was especially sparse in biopsied bulla, suggesting that the CTCL was not playing a role in the bullous process. Direct immunofluorescence at that time was inconclusive, although repeated biopsies of specimens of both skin and buccal mucosa demonstrated focal linear IgG and complement factor 3 deposition at the mucosal-submucosal interface.

She was transferred to the medical intensive care unit, started on intravenous (IV) methylprednisolone and IV immunoglobulin, and had several suspected drugs discontinued. Her oral lesions and skin improved with decreased erythema and bullae formation. She was discharged while prescribed a tapered dose of prednisone, and treatment with low-dose interferon gamma was restarted.

Over the next month, as her corticosteroids were slowly tapered, she developed recurrent intense generalized pruritus, new bullae, and oral erosions. Indirect immunofluorescence examination of her serum performed on salt-split skin at Johns Hopkins was positive and diagnostic for BP (**Figure 1**) without evidence for paraneoplastic pemphigus. In addition, assays for circulating antibodies against the BP180 and BP230 antigens were positive. Treatment with a high dose of prednisone was restarted.

Over the next 3 months, she was treated with monthly IV immunoglobulins (2 g/kg for 3 days) as a corticosteroid and immunosuppressive drug-sparing agent owing to the fact that adding additional immunosuppressive



**Figure 1.** Indirect immunofluorescence on salt-split skin demonstrating linear deposition of interferon gamma in the basement membrane zone on the epidermal side consistent with bullous pemphigoid.



**Figure 2.** Tense bullae and erythematous macules and patches on the patient's neck 2 weeks before initiation of vorinostat therapy.

therapies would put her at risk for CTCL progression. Despite continuing low-dose interferon gamma, photopheresis, and topical corticosteroids, she developed multiple refractory CTCL plaques on her face, trunk, and extremities that required local radiation treatment. The IV immunoglobulin was discontinued because it was felt that it may have been contributing to the worsening of her CTCL. Once her prednisone taper approached 20 mg/d, her BP flared and she developed new, widespread skin blisters and oral erosions requiring increasing prednisone doses (**Figure 2**).

#### THERAPEUTIC CHALLENGE

Our patient with refractory aggressive MF/CTCL developed severe BP following TSEB therapy, which proved to be both a diagnostic and therapeutic challenge. Attempts at weaning her systemic corticosteroids or instituting treatments for CTCL, including interferon gamma, resulted in flares of her bullous disease. However, treatments aimed at control of the BP resulted in progression of her known MF/CTCL.



**Figure 3.** Patient's neck 6 weeks after initiating therapy with vorinostat, 300 mg/d, demonstrating no new blisters and continued healing.

#### SOLUTION

Vorinostat, an oral HDAC inhibitor, was recently approved for the treatment of refractory CTCL.<sup>1,2</sup> Vorinostat inhibits both class I and class II HDACs, and HDAC inhibitors target numerous proteins, including nonhistone targets, which regulate gene expression, cell proliferation, cell migration, and cell death.<sup>3,4</sup> Histone deacetylase inhibitors have been shown to alter inflammatory transcription factors and suppress proinflammatory cytokines and genes involved in the T<sub>H</sub>1 inflammatory response.<sup>5</sup> In addition, several animal models provide increasing evidence that HDAC inhibitors can inhibit graft-vs-host disease and allograft rejection, as well as upregulate T-regulatory (T-reg) cells.<sup>6,7</sup> Thus, we hypothesized that vorinostat would treat treatment-resistant, progressive CTCL in the setting of BP without causing a flare of the BP and perhaps act as a corticosteroid-sparing agent in the treatment of BP, thus obviating the need for other traditional immunosuppressive agents used in the treatment of primary blistering diseases.

Vorinostat, 400 mg/d, was added to her regimen of interferon gamma, ECP, prednisone, and topical corticosteroids. Within 2 weeks of starting treatment with vorinostat, she noted a significant decrease in pruritus and blister formation, and after 6 weeks on this regimen, most of her blisters had healed, and she was able to begin tapering her prednisone dose (**Figure 3**). Her existing MF/CTCL plaques responded to local radiation, and no new plaques appeared once treatment with vorinostat was initiated. Adverse effects have included fatigue and thrombocytopenia, which improved on decreasing the dosage of vorinostat to 300 mg/d, 5 days a week. Simultaneously, her prednisone dosage was tapered from 30 mg/d down to 15 mg/d, and she experienced no new blister formation and decreased pruritus (**Figure 4**). She remained blister free for 2 months. However, after 4 months, owing to fatigue and thrombocytopenia, her dose of vorinostat was decreased to 200 mg/d, and her CTCL progressed such that she required a change in therapeutic management. Multimodality therapy with vorinostat, interferon gamma, and ECP was discontinued, and she was

prescribed gemcitabine hydrochloride. It is worth noting that her BP flared within 2 weeks of discontinuation of the vorinostat such that her requirement for corticosteroids was increased to over 30 mg/d, and her symptoms of skin fragility and pruritus worsened.

#### COMMENT

To our knowledge, we present the first report of the use of an HDAC inhibitor for the treatment of BP, an autoimmune blistering disease characterized by tense, subepidermal bullae secondary to IgG autoantibodies against the hemidesmosomal antigens, BP230 (BPAg1) and BP180 (BPAg2), involved in dermoepidermal adhesion.<sup>8,9</sup> Pruritus is common, and oral involvement occurs in approximately 20% of cases.<sup>8</sup> Humoral immunity and autoreactive T cells, of both the T<sub>H</sub>2 and T<sub>H</sub>1 types, are thought to be important in pathogenesis.<sup>9</sup> Treatments include topical and systemic corticosteroids, tetracycline hydrochloride, dapsone, azathioprine sodium, mycophenolate mofetil hydrochloride, methotrexate, cyclophosphamide, chorambucil, IV immunoglobins, cyclosporine, and rituximab.<sup>10</sup> These therapeutic options are generally immunosuppressive or are associated with long-term complications, as is the case with systemic corticosteroids.

Mycosis fungoides and Sézary syndrome are CTCL variants characterized by clonal malignant CD4<sup>+</sup> T-lymphocytes.<sup>11</sup> It is believed that an intact immune system is important in controlling the disease and preventing its progression.<sup>11</sup> Commonly used multimodality treatment regimens for CTCL include interferon therapy in the form of either interferon alfa or interferon gamma. Interferons counteract several of the immune abnormalities of the skewed T<sub>H</sub>2 cytokine profile exhibited in CTCL.<sup>11</sup> A well-known adverse effect of interferon therapy is an increased risk of autoimmune disorders in predisposed individuals.<sup>12</sup>

Another accepted association is that between autoimmunity and lymphoid neoplasms: lymphocytic neoplasms are more common in the setting of autoimmune diseases, and autoimmunity occurs at increased frequencies in patients with lymphocytic malignant diseases.<sup>13,14</sup> Bullous pemphigoid has been rarely reported in the setting of CTCL, namely, in the context of phototherapy treatment.<sup>15,16</sup> It is worth noting that our patient had a history of phototherapy and preceding TSEBT, which may have increased her risk for developing the bullous disorder. In addition, furosemide may have contributed to the development of BP in our patient.

Although HDAC inhibitors, such as vorinostat, are thought to be targeted therapy for the treatment of neoplasia, they affect a number of histone and nonhistone proteins. They result in the accumulation of acetylated proteins, leading to changes in gene expression and in the acetylation of proteins important in cell proliferation, apoptosis, cell motility, and angiogenesis, which are all important in tumor suppression.<sup>4</sup> Anti-inflammatory effects of HDAC inhibitors have also been documented, including the reduction of proinflammatory cytokines (eg, TNF, interleukin 1 $\beta$  [IL-1 $\beta$ ], IL-8), the downregulation of immune stimulators (eg, IL-6), and the inhibition of



**Figure 4.** Patient's neck 10 weeks after initiating therapy with vorinostat, with no new blisters or erythematous macules noted despite decreased doses of systemic corticosteroids.

production of nitric oxide, a contributor of many inflammatory disorders.<sup>5,17</sup>

Impaired T-reg cells may contribute to autoimmune diseases.<sup>6,18</sup> Histone deacetylase inhibitors were shown to generate T-reg cells, leading to enhanced T-reg suppression with considerable T-reg–dependent effects on immune disease, including decreasing host injury in a murine model of autoimmune colitis in vivo.<sup>6</sup> It is possible that anti-inflammatory effects may be the result of a specific suppression of T<sub>H</sub>1 responses by HDAC inhibitors.<sup>19</sup> Another possibility is that these effects are mediated through the induction of T-reg cells.

In our patient with concomitant CTCL and BP, vorinostat proved to be corticosteroid-sparing within several weeks of beginning therapy. Likewise, on cessation of therapy with vorinostat, our patient's BP rapidly flared, and she again required increased doses of systemic corticosteroids in an attempt to control her blistering disorder. Taken together, we believe vorinostat may be effective for the treatment of BP, and it also may be a viable therapeutic option to treat autoimmune disease in the setting of malignant disease in an attempt to avoid other, more immunosuppressive, treatments. Although intriguing, this observation was made in a single case, and double-blind, controlled studies would be instrumental in further elucidating the efficacy and tolerability of vorinostat for the treatment of BP and perhaps other autoimmune blistering disorders.

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## Submissions

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors [<http://archderm.ama-assn.org/misc/ifora.dtl>] for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [[http://archderm.ama-assn.org/misc/auinst\\_crit.pdf](http://archderm.ama-assn.org/misc/auinst_crit.pdf)]). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD ([ghruza@aol.com](mailto:ghruza@aol.com)). Manuscripts should be submitted via our online manuscript submission and review system (<http://manuscripts.archdermatol.com>).