

Benefits of Vorinostat in Treating Advanced Cutaneous T-cell Lymphoma

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Abstract

Vorinostat (suberoylanilide hydroxamic acid) is the first US Food and Drug Administration (FDA)-approved histone deacetylase (HDAC) inhibitor for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphomas (CTCLs) who have progressive, persistent, or recurrent disease on or following two systemic therapies. In two phase II trials, vorinostat was safe and effective at an oral dose of 400mg/day, with an overall response rate of 24–30% in refractory advanced patients with CTCL including large cell transformation and Sézary syndrome. Most patients with CTCL also experience significant itching relief with vorinostat therapy. The most frequent side effects of vorinostat include gastrointestinal symptoms, fatigue, and thrombocytopenia. These side effects are dose-related and reversible upon cessation of therapy. Translational studies have shown that vorinostat has *in vitro* and *in vivo* antitumor activities against CTCL, including selective induction of tumor T-cells, inhibition of angiogenesis, suppression of STATs, and upregulation of proapoptotic proteins. Constitutive activation of STATs may predict vorinostat resistance in CTCL, and inhibitors of JAK/STAT combined with vorinostat may help to overcome resistance and improve the clinical response of vorinostat. Further identification of predictive biomarkers of vorinostat will help to select patients most likely to benefit from treatment and to develop better combination therapies for patients with CTCL.

Keywords

Cutaneous T-cell lymphoma, histone deacetylases, vorinostat, clinical trial, translational study

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Current Treatment Options for Cutaneous T-cell Lymphoma

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of extranodal non-Hodgkin's lymphomas characterized by their surface markers and biological behavior. Mycosis fungoides (MF) and its leukemic variant Sézary syndrome (SS) are the most frequently encountered CTCLs resulting from a progressive clonal expansion of CD4+CD45RO+CLA+CCR+ helper/memory T cells. The malignant clones may have loss of common T-cell markers (CD7 and/or CD26).¹ Progression of MF/SS is accompanied by clonal dominance,² secretion of Th2 cytokines,³ impaired immune responses, and cell growth advantage.^{1,4} The malignant T cells exhibit abnormal apoptotic mechanisms, such as loss of Fas or expression of Bcl-2, that result in loss of activation-induced cell death, prolonged life span, and accumulation. These cells typically become resistant to treatment over time.⁵

The choice of therapy should be based on the stage of disease. Patients with early MF have disease limited to the skin (T1–2N0–1M0; IA–IIA) and can be put into remission with topical agents (topical steroids, retinoids,

phototherapy or mustargen). More advanced or late stages (T1–4N0–3M0–1; IIB–IVB) of MF or SS require both systemic and skin-directed therapies. Patients who have extensive refractory skin involvement, blood involvement, tumors, or nodal disease require systemic therapy. Refractory or extensive skin involvement including SS responds to systemic biologic response modifiers (retinoids, bexarotene, interferon, and denileukin diftiox), skin radiation and photopheresis. Single- or multi-agent chemotherapies are used for patients with large numbers of transformed tumors or nodal/visceral disease. In general, a combination of either sequential or concomitant therapies gives a higher rate of response, but advanced patients often relapse and curative therapy is elusive for most.¹

The US Food and Drug Administration (FDA) approved the histone deacetylase inhibitor (HDAC-I) vorinostat (suberoylanilide hydroxamic acid [SAHA]) in 2006 for the treatment of cutaneous manifestations of CTCL based on data from two phase II clinical trials.^{6,7} Translational studies have shown that vorinostat has *in vitro* and *in vivo* antitumor activity against CTCL.^{6,8} As such, HDAC-Is represent an attractive new strategy for targeted therapy of advanced CTCL. This article provides a

Table 1: Human Histone Deacetylases

Class	Class I	Class IIa	Class IIb	Class III	Class IV
Members	HDAC1, 2, 3, and 8	HDAC4, 5, 7, and 9	HDAC6,10	SIRT1-7	HDAC11
Molecular weight	22–25kD	120–135kD	120-135 KD	40-50 KD	120-135 KD
Localization					
Nuclear	+	+	+	+	+
Cytoplasmic		+	+	+	+
Binding site	Zn ⁺⁺	Zn ⁺⁺	Zn ⁺⁺	NAD ⁺	Zn ⁺⁺
Homology with yeast	RPD3 deacetylase	HDA1 deacetylase	HDA1 deacetylase	SIRT2 family	HDA1 deacetylase

Table 2: Molecular Characteristics and Clinical Trial Status of Histone Deacetylase Inhibitors

Class and Compounds	HDAC Specificity	Clinical Trials
Short-chain Fatty Acid		
Butyrate	Class I, IIa	Phase I, II
VPA	Class I, IIa	Phase I, II
AN-9	N/A	Phase I, II
Hydroxamate		
Vorinostat	Class I, II	Phase I, II, III*
LAQ824	Class I, II	Phase I, II
PXD101	Class I, II	Phase I, II
LBH589	Class I, II	Phase I, II
Pyroxamide	Class I	Phase I
Cyclic Tetrapeptide		
Depsipeptide	Class I	Phase I, II
Benzamide		
MS-275	HDACs 1, 2, 3, 8	Phase I, II
CI-994	N/A	Phase I, II, III

*Approved by the US Food and Drug Administration.

brief overview of the biology of HDACs and HDAC-Is, as well as pre-clinical and clinical studies of vorinostat in CTCL.

Biology of Histone Deacetylases and Their Inhibitors

HDACs and histone acetylases (HATs) are key enzymes that remove or add acetyl groups to proteins including histones.^{9,10} Histones are acetylated by HATs on their lysine tails, which can then interact with the DNA sugar backbone. When HDACs remove acetyl groups on histones, the DNA becomes compacted, limiting access to transcription factor complexes. HDAC-Is interact with HDACs and block their function.¹¹ HDACs and HATs represent new targets for cancer therapeutics arising from the observation that the balance of acetylation and deacetylation controls transcription of tumor suppressors and other key proteins for cell growth.

To date, four classes of HDAC have been identified (see *Table 1*).^{9,10} Class I human HDACs (HDACs 1, 2, 3, and 8) are small, with an approximate molecular mass of 22–55kDa, and are homologous to the yeast HDAC Rpd3. Class II HDACs (HDACs 4, 5, 6, 7, 9, and 10) are larger enzymes with molecular masses between 120 and 135kDa and are related to yeast HDA1 deacetylases. HDAC-Is, including vorinostat, that block class I and II HDACs are known as pan-HDAC inhibitors. Class III human HDACs are homologues of yeast Sir2 and require nicotinamide–adenine dinucleotide NAD⁺ for activity. They also differ from class I and II HDACs in their catalytic site. HDAC11 is

more closely related to the class I and II HDACs; however, because it shares a similar level of homology with both classes, it has been assigned as the single class IV HDAC, found in all species evaluated except fungi. The key catalytic residues have been conserved in class I, II, and IV HDACs. Class I HDACs are primarily nuclear in localization and are ubiquitous. Class II HDAC expression is tissue-restricted; some shuttle between the nucleus and the cytoplasm, whereas others are primarily cytoplasmic. In cancer cells, class I and II HDACs have been shown to be over-expressed, aberrantly recruited to oncogenic transcription factors, and mutated. As such, they represent potential key targets for small-molecule inhibitors.^{9–11}

There are currently five classes of HDAC-I grouped according to their chemical structure and affinity for different HDACs (see *Table 2*).¹² Several pan-HDAC-Is have shown activity in CTCL, especially vorinostat (SAHA), probinostat (LBH589,) and belinostat (PXD101), as have the more selective inhibitors romidepsin (FK228 or depsipeptide) and SNDX-275 (formerly MS-275). Vorinostat (Merck, Whitehouse Station, US) was studied in two phase II trials and received FDA approval in October 2006 for treatment of cutaneous manifestations of CTCL in patients who have progressive, persistent, or recurrent disease on or following two prior systemic treatments.^{6,7} PXD101 and LBH589 are currently in clinical trials in both solid tumors and hematological malignancies, including CTCL.¹² FK228 (romidepsin, depsipeptide) is a natural product prodrug that is a selective inhibitor of class I HDACs. It has also exhibited considerable activity in CTCL and in peripheral T-cell non-Hodgkin’s lymphomas (PTCLs). SNDX-275 is a non-hydroxamic-based compound that exhibits selectivity for class I HDAC enzymes, and a combination regimen with azacitidine is in phase II development.¹²

Although the precise mechanisms of action of HDAC-Is are complex and under intense investigation, at the molecular level inhibition of HDAC activity by HDAC-Is leads to accumulation of acetylated histones in tumors and cell lines, as well as acetylation of non-histone proteins, including transcription factors, cytoskeletal proteins, molecular chaperones, and nuclear import factors.¹³ The increase in the acetylation state of these proteins alters their function, leading to alterations in transcription, mitosis, and protein stability. Collectively, these changes interfere with tumor cell proliferation, survival, and maintenance. HDAC-Is induce tumor cell apoptosis at concentrations to which normal cells are relatively resistant, making them well suited for cancer therapy.¹⁴ Although apoptosis is the most frequently observed effect,¹⁵ autophagic cell death has also been reported, and could prove beneficial for the treatment of cancers with defects in apoptotic pathways.¹⁶ In addition, HDAC-Is have shown anti-

angiogenic and immunomodulatory activity that may play an important role in mediating their antitumor effects.¹⁷⁻²⁰

Mechanisms of Action of Vorinostat in Cutaneous T-Cell Lymphomas **Selective Induction of Apoptosis**

Pre-clinical studies have shown that vorinostat affects proliferation of a variety of transformed cell lines in culture and of human cancer xenografts in mice.²¹ In particular, vorinostat induces cancer cell death at concentrations to which normal cells are relatively resistant.²² We previously showed that vorinostat at clinically relevant concentrations selectively induces apoptosis of CTCL cell lines and the peripheral blood lymphocytes of SS/MF patients compared with those of healthy donors.^{8,23} The findings from this study are similar to those for romidepsin, another HDAC-I that also induces apoptosis of Hut78 CTCL cells *in vitro*.²⁴ This difference in sensitivity to vorinostat-induced apoptosis appears not to be caused by a difference in the ability to inhibit HDAC activity owing to accumulation of acetylated histones in both transformed and normal cells.²² Vorinostat may cause an accumulation of reactive oxygen species and caspase activation in transformed, but not normal, cells, as well as an increase in the level of Trx, a major reducing protein for many targets in normal cells but not in transformed cells.²²

Inhibition of Angiogenesis

Angiogenesis is a key process during tumor development and metastasis.²⁵ Angiogenesis is tightly controlled by the balance between positive and negative environmental signals—inducers and inhibitors of angiogenesis in such a way that predominance of inducers results in angiogenesis and predominance of inhibitors—in vascular quiescence. Treatment with HDAC-Is has been shown to decrease the expression of several pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 α (HIF1 α).^{26,27} In addition, thrombospondin-1 (TSP-1), a potent inhibitor of angiogenesis, was increased eight-fold by vorinostat in the HH CTCL cell line using complementary DNA (cDNA) microarray analysis. Translational studies from paired skin lesions of patients at baseline compared with after vorinostat treatment (two hours, four weeks, and eight weeks) suggest that there were significant decreases in microvessel density and an increased tendency of dermal TSP-1 staining in the skin lesions of responding patients.⁶ Thus, inhibition of angiogenesis and upregulation of TSP-1 by vorinostat may contribute to the resolution of MF/SS lymphocyte infiltrates.

Increased Accumulation of Acetylated Histones

Histone acetylation is a defining event after treatment with HDAC-Is, and can thus be used as an indicator of HDAC-I activity in both normal and tumor cells. This has led to the widespread use of histone acetylation in peripheral blood mononuclear cells (PBMCs) as a surrogate marker in phase I clinical trials.²⁸ In CTCL, vorinostat treatment results in increased protein levels of acetylated histones (H2B, H3, and H4) regardless of resistant or sensitive CTCL cell lines.⁸ Furthermore, MF lesions had unexpectedly high histone H4 acetylation in keratinocyte and T-lymphocyte nuclei at baseline from either responders or non-responders, the significance of which is unknown. Thus, histone acetylation does not seem to be predictive of response in CTCL.⁶

Modulation of Signal Transducer and Activator of Transcription Signaling

CTCL cells have been shown to constitutively express signal transducer and activator of transcription (STAT) proteins that dimerize and become phosphorylated after growth factor stimulation, inducing gene transcription and promoting cellular proliferation.^{29,30} Vorinostat did not decrease protein expression of STAT-3 and p-STAT-3, but did decrease STAT-6 and p-STAT-6 in CTCL cell lines and SS patient PBMCs.⁸ Of interest, following vorinostat treatment p-STAT-3 protein changed from predominantly nuclear to cytoplasmic locations in skin lesions from responding patients.⁶ Nuclear accumulation of STAT-1 and high levels of nuclear p-STAT-3 were present in malignant T cells in CTCL skin lesions and correlated with a lack of clinical response to vorinostat.³¹ Thus, deregulation of STAT activity is likely to play a key role in vorinostat response and resistance in CTCL.

Upregulation of Pro-apoptotic Proteins

The cyclin-dependent kinase (CDK) inhibitor p21 (WAF1/CIP1) is one of the most commonly reported genes induced by HDAC-I.³² P21 regulates both the cell cycle and apoptosis.²⁹ In CTCL, although upregulation of p21 occurred in response to vorinostat, immunoblot analysis showed that this effect was independent of the tumor suppressor p53.⁸ In addition, the balance between expression of anti-apoptotic protein bcl-2 and pro-apoptotic protein bax is critical in controlling the activation of caspases by regulating release of cytochrome c from mitochondria.³³ Bcl-2 expressed in CTCL cells may increase survival and resistance of CTCL cells to radiotherapy and extracorporeal photochemotherapy.³⁴⁻³⁶ Of interest, vorinostat treatment did not change bcl-2 but increased bax, activated caspase-3, and cleaved PARP in three CTCL lines and patient PBMCs.⁸

Clinical Trials of Vorinostat in Cutaneous T-cell Lymphomas

Phase I Study of Oral Vorinostat in Patients with Cutaneous T-cell Lymphomas

A phase I study of patients with advanced cancer first identified the clinical effect of oral vorinostat in a CTCL patient who had failed to respond to five previous systemic therapies.³⁷ Oral vorinostat administered at a dose of 200mg twice daily for a total of four months resulted in stabilization of the disease. Although a second patient with peripheral T-cell lymphoma was enrolled, the report did not appear to describe the outcome of this patient.

Dose-ranging Phase II Trial of Oral Vorinostat in Patients with Cutaneous T-cell Lymphomas

A single-center phase II dose-ranging trial was initiated to determine response rate and the duration, safety, and tolerability of oral vorinostat in 33 heavily pre-treated patients with refractory or relapsed CTCL (stages IA–IVB).⁶ Eighty-five percent of the patients had advanced-stage CTCL and one-third had SS. Although patients were only required to be unresponsive to ≤ 1 conventional therapy, the patients had a median of five prior therapies (range: one to 15). Of the 33 patients, 29 had received prior chemotherapy (22 bexarotene and 14 denileukin diftitox). The patients who enrolled were treated with one of three oral dosing schedules, and their demographics such as age and gender were similar. The first cohort received 400mg/day, the

Table 3: Phase II Data on Oral Vorinostat in Patients with Cutaneous T-cell Lymphomas

	Treatment Group		
	Group 1	Group 2	Group 3
Dosing schedule	400mg qd*	300mg bid 3 days/week for 4 weeks, then 5 days/week	300mg bid for 14 days with 7 days rest; maintenance: 200mg bid
Dose modification			
First dose reduction	350mg qd	250mg 3 days/week	200mg bid
Second dose reduction	300mg qd	200mg bid 3 days/week	200mg bid 5 days/week
Clinical response			
Partial response (PR)	31% (4/13)	9% (1/11)	33% (3/9)
Median PR duration, weeks (range)	15 (8–24)	16 (8–24)	13 (3–21)
Mean time to PR, weeks	11	4	11
Lymph-node regression (at 4 weeks)	78% (7/9)	38% (3/8)	56% (5/9)
>50% reduction in pruritus	82% (9/11)	67% (8/12)	50% (4/8)
Adverse events (grade 3/4)			
Thrombocytopenia	8% (1/13)	8% (1/12)	42% (5/12)
Anemia	8% (1/13)	17% (2/12)	0% (0/0)
Deep vein thrombosis	0% (0/0)	25% (3/12)	0% (0/0)
Dehydration	8% (1/13)	0% (0/0)	17% (2/12)
Pyrexia	0% (0/0)	25% (3/12)	0% (0/0)
Hypotension	0% (0/0)	17% (2/12)	0% (0/0)
Pulmonary embolism	0% (0/0)	17% (2/12)	0% (0/0)
Sepsis	0% (0/0)	8% (1/12)	8% (1/12)

*Initial three patients treated with vorinostat 250mg/m²/day. Source: Duvic et al., 2007.⁶

second received 300mg twice daily (bid) for four days with rest for four days, and the third received 300mg bid for 14 days with rest for seven days followed by 200mg bid. The clinical response for each cohort and suggested dose modification schedule are shown in *Table 3*. The primary efficacy end-point of the study was complete response (CR) and partial response (PR) rate. Secondary end-points included time to progressive disease, response duration, pruritus relief, and safety. The response to therapy was categorized according to the Physician's Global Assessment for CR, PR, stable disease (SD) or progressive disease (PD).³⁸ Skin involvement was assessed as body surface area (BSA) involvement with patch, plaque, or tumor disease.

Considering unique patients for an intent-to-treat analysis, eight out of 33 patients (24%) achieved a documented PR, with no CRs.⁶ An additional 11 patients had pruritus relief, such that 19 of 33 study patients (58%) received clinical benefit from the drug. Responses to vorinostat were observed in a broad spectrum of the study population, including a patient with early-stage refractory MF, advanced tumors with histological large-cell transformation, and patients with nodal and/or blood involvement. The response rates in patients who had received prior bexarotene or not were similar, at 23 and 27%, respectively.

Secondary objectives were to determine the duration of response and to evaluate the safety and tolerability of vorinostat in these patients. The median duration of response overall was 15.1 weeks (106 days), and was in the range of 9.4–19.4 weeks (66–136 days). The median duration of response was numerically lowest in group 2, who received intermittent dosing (9.4 weeks [66 days]), and highest in group 1, who were treated with 400mg/day (16.1 weeks [113 days]). The most common major toxicities that were possibly or probably related to oral vorinostat therapy were fatigue and gastrointestinal symptoms, including diarrhea, altered taste, nausea, and dehydration from not

eating/drinking. Grade 3/4 thrombocytopenia was most common in cohort 3, who received 300mg bid for 14 days, than in the other cohorts (42 and 8%, respectively) (see *Table 3*). Overall, vorinostat 400mg/day orally (po) provided the most favorable risk–benefit profile, and the dose of 400mg/day was selected for evaluation in a phase IIb multicenter trial.

Phase IIb Multicenter Single-arm Trial of Oral Vorinostat in Patients with Cutaneous T-cell Lymphomas

Phase IIb was conducted as an open-label, multicenter trial of oral vorinostat 400mg/day administered in patients with stage IB–IVA MF/SS.⁷ Two dose modifications were allowed: 300mg/day or 300mg/day for five days/week. Safety assessments were performed with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0. Inclusion criteria were patients with MF/SS stage IB–IVB, progressive, persistent, or recurrent disease either receiving or following more than two prior systemic therapies, one of which must have contained bexarotene. Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and adequate hematological, hepatic, and renal function were included. Patients with prior use of HDAC-Is or anticancer treatment within three weeks of study entry were excluded.

Of the patients with treatment-refractory advanced MF/SS (≥stage IIB), ~30% had ≥1 PR, and one patient with facial tumors had a complete long-lasting response. The median time to response was less than two months. Clinically long-lasting responses were observed. Median response duration and time to progression in advanced-stage (at least IIB) responders were not reached, but were estimated to be ≥6.1 and 9.8 months, respectively. Median time to progression in all patients was 4.9 months. Vorinostat provided pruritus relief in 32% of evaluable patients with baseline pruritus, including 25% of those who did not

meet the criteria for objective cutaneous response. Vorinostat 400mg was well tolerated, with <15% of patients (n=11) requiring dose reductions. Only 11% of patients had any related serious adverse events: thrombosis, anemia, death, dehydration, thrombocytopenia, increased creatinine, gastrointestinal hemorrhage, ischemic stroke, syncope, and streptococcal bacteremia. The most common drug-related adverse events were gastrointestinal symptoms (diarrhea [49%], nausea [43%], anorexia [26%], dysgeusia [24%], dry mouth [11%], vomiting [12%], and constipation), fatigue (46%), thrombocytopenia (22%), weight decrease (20%), alopecia (18%), muscle spasms (16%), increase in creatinine (15%), anemia (1%), and chills (12%). Most were \leq grade 2. Drug-related \geq grade 3 events included fatigue (5%), pulmonary embolism (5%), thrombocytopenia (5%), and nausea (4%). There were three deaths in the study.⁷

Resistance and Potential Combination Therapies

Development of resistance to vorinostat is a major concern, as with any new antitumor therapy. Although vorinostat achieved about 24–30% response rate in two phase II trials on CTCL, a considerable proportion of patients with CTCL did not respond well enough to be considered as showing a partial response.^{6,7} Resistance has been observed in clinical trials with other HDAC-Is in different tumors.

The basis of resistance to vorinostat is not well understood. The antitumor activity of vorinostat may be affected by efflux mechanisms, drug deactivation, status of drug target, bypass/repair mechanisms for drug-induced damage, and alterations in the cell death pathway.³⁹ Recent studies have revealed that constitutive activation of STATs is involved in resistance to vorinostat across a variety of B-cell and T-cell lymphoma lines, including those of CTCL origin.³¹ Furthermore, high levels of p-STAT-3 and nuclear localization of STAT-1 in malignant T cells from skin biopsies of MF/SS patients correlate with a lack of clinical response to vorinostat.³¹ Thus, deregulation of STAT activity plays a role in vorinostat resistance in CTCL, and strategies that block this pathway may improve vorinostat response.

Translational studies show that CTCL cells can be sensitized to vorinostat by co-incubation with a JAK/STAT inhibitor. In addition, knock-down of individual STAT proteins improved sensitivity to vorinostat in HuT78 CTCL cells.³¹ These *in vitro* studies imply that inhibitors of JAK/STAT at clinically available concentrations may be combined with vorinostat to help overcome resistance to apoptotic death in patients whose tumors have constitutive STAT signaling.

Summary

Vorinostat is the first HDAC-I approved by the FDA to enter the clinical oncology market for treating cutaneous manifestations in patients with CTCLs who have progressive, persistent, or recurrent disease on or following two systemic therapies. Oral vorinostat has a rapid onset of action and exhibits significant clinical activity against transformed tumors, erythroderma, and nodes in heavily pre-treated refractory CTCL patients. Most patients with CTCL also experience significant itching relief with vorinostat therapy and, hence, a marked improvement in their quality of life. Overall, vorinostat appears to be generally well tolerated, with fatigue and gastrointestinal symptoms being the most common side effects at lower doses and thrombocytopenia at higher doses. These side effects were dose-related and reversible upon cessation of therapy. Although histone acetylation provides a useful pharmacodynamic end-point for monitoring HDAC inhibition, its use as a predictive marker for responsive disease is limited. The absence of biomarkers of responsive disease remains an important shortcoming in realizing the full clinical potential of vorinostat and other HDAC-Is. Undoubtedly, further identification of specific signaling pathways and biomarkers of response to vorinostat will help to select those patients most likely to benefit from treatment, to design novel isoform-specific HDAC-Is with better therapeutic index, and to develop hypothesis-driven combination therapies with agents that can be predicted to act synergistically or additively. ■



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