To the editor:

Phase 1/2 trial of vorinostat in patients with sickle cell disease who have not benefitted from hydroxyurea

Worldwide, over 200 000 babies are born annually with sickle cell disease (SCD). In the United States, over 90 000 people have SCD.1 Induction of fetal hemoglobin (HbF) is a well-established strategy to inhibit sickle hemoglobin polymerization.2 To date, hydroxyurea, which induces HbF, is the only US Food and Drug Administration (FDA)-approved drug for SCD treatment. Hydroxyurea reduces morbidity,3 but patients continue to suffer complications such as renal failure and strokes.4 There is a significant need for novel therapies. Histone deacetylase (HDAC) inhibitors are powerful inducers of HbF in human erythroid progenitor cells in vitro.5,6 Moreover, agents with HDAC inhibitory activity, including valproic acid and butyrate, have previously been shown to induce HbF in patients with SCD.5,7 Vorinostat increased HbF in 3 patients undergoing therapy for Hodgkin lymphoma.5

We conducted a phase 1/2 study to evaluate the safety and efficacy of vorinostat (suberoylanilidine hydroxamic acid; Merck & Co) in adults with severe SCD who previously on hydroxyurea were intolerant or had no clinical improvement and no induction of HbF. A period of at least 90 days from hydroxyurea use was required for enrollment. Vorinostat is an oral hydroxamate-based pan-HDAC inhibitor, FDA approved in 2006 for the treatment of refractory cutaneous T-cell lymphoma. Given previous success with pulse-dose butyrate, patients received vorinostat in a pulsed fashion, once a day for 3 consecutive days every week to a maximum dose of 400 mg per dose (1200 mg/wk), for 12 to 16 weeks at the maximum dose.8-10 The primary objectives of the study were to characterize the safety and tolerability of vorinostat in SCD patients and to determine the efficacy of vorinostat in inducing a 4% absolute increase or a 100% relative increase in HbF percentage levels (HbF%). Secondary objectives were to assess the effect of vorinostat on F-cell levels and to determine the changes in β-globin, γ-globin, and ε-globin RNA levels during treatment with vorinostat. Investigational New Drug approval was obtained from the FDA, and the study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. Informed consent was obtained in accordance with the Declaration of Helsinki. This trial was registered at www.clinicaltrials.gov as NCT01000155.

Five adult patients were enrolled in this study: 3 women and 2 men (Table 1). Three of the 5 patients completed dosing requirements of the study. All patients completed 12 weeks of observation. The first 3 patients were enrolled in an intrapatient dose escalation schedule of 100 mg/d, then 200 mg/d, each for 3 consecutive days a week for 4 weeks, and then 400 mg/d, 3 consecutive days per week for 16 weeks. The last 2 patients were enrolled to receive 400 mg/d, 3 consecutive days per week for 12 weeks, without an initial dose escalation. Safety assessments by history, examination, and/or laboratory tests were performed weekly. Median baseline hemoglobin was 7.0 g/dL (range, 5.7-8 g/dL), and median baseline HbF% was 9.2% (range, 1.5%-17.1%). After a median duration of 3 months on vorinostat, 400 mg dosing, only 1 of 5 patients met the criteria for success, with an HbF% increase from 1.5% at baseline to a maximum value of 4.6. The median F-cell percentage increased from 9.8% at baseline to 12.1%, and the median relative change in the ratio of

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Table 1. Patients with sickle cell disease on vorinostat

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Gender</th>
<th>Baseline Hb, g/dL</th>
<th>End-of-study Hb, g/dL</th>
<th>Baseline HbF%</th>
<th>Highest HbF%</th>
<th>Grade 3/4 toxicity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>5.9</td>
<td>7.5</td>
<td>1.5</td>
<td>4.6</td>
<td>Pain, headache</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>F</td>
<td>5.7</td>
<td>5.3</td>
<td>13.8</td>
<td>12.8</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>F</td>
<td>8.9</td>
<td>8.9</td>
<td>5.6</td>
<td>6</td>
<td>Pain</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>F</td>
<td>7.5</td>
<td>7.5</td>
<td>9.2</td>
<td>10</td>
<td>Pain</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>M</td>
<td>8</td>
<td>16.55</td>
<td>20.5</td>
<td></td>
<td>Pain</td>
</tr>
</tbody>
</table>

All patients had HbSS genotype and all toxicities resolved completely. Hb, hemoglobin.

*Toxicity was graded based on Common Terminology Criteria for Adverse Events, version 4.0.
Peripheral blood γ-globin to β-globin messenger RNA was 0.89 (range, 0.34-1.4).

Vorinostat was well tolerated at the doses tested. Vorinostat toxicity (fatigue, abdominal pain) was mild to moderate, with the exception of pain, indistinguishable from sickle pain in 3 patients and headaches in 1 patient. With intermittent dosing, we were able to prevent thrombocytopenia, a common effect of vorinostat use in malignancy. However, it is unclear whether sufficient doses were used in this study because neither thrombocytopenia nor a convincing induction of HbF was produced.

We have demonstrated the safety and tolerability of an oral pan-HDAC inhibitor, vorinostat, in 5 patients with SCD, with minimal adverse events. Future studies with vorinostat should employ higher cumulative weekly doses, probably marked by induction of relative thrombocytopenia. Potentially more promising is the potential of using HDAC1 and HDAC2 selective agents that would mediate HbF induction (with tolerability that allows more robust dosing) and using combinations of HDAC inhibitors with hydroxyurea.

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References

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To the editor:

Serum hepcidin levels predict response to intravenous iron and darbepoetin in chemotherapy-associated anemia

Patients undergoing chemotherapy for cancer frequently experience anemia, which may require red blood cell (RBC) transfusions. The erythropoiesis-stimulating agents (ESAs) epoetin and darbepoetin reduce transfusion needs and increase hemoglobin levels in 40% to 70% of patients with chemotherapy-associated anemia (CAA) and are approved by the Food and Drug Administration for CAA.

In renal anemia, iron deficiency is the most common cause of suboptimal ESA response, and iron deficiency may also contribute to ESA nonresponse in other subsets of patients. Even patients with normal or elevated total-body iron stores may have diminished iron available to developing erythroid cells (“functional iron deficiency”) as a result of tumor-associated inflammation and macrophage sequestration of iron. IV iron may provide bioavailable iron and augment response to ESA therapy in both functional and total iron deficiency states.

At least 11 prospective trials have shown benefit from IV iron in combination with an ESA for patients with CAA, but one study did not show benefit. The sole trial that failed to reach its primary end point—the largest IV iron trial in CAA conducted to date—was a randomized multicenter study (MC04CC, clinicaltrials.gov #NCT00661999) of...
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