Concomitant Hydroxyurea and Voxelotor Results From the HOPE Study

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BACKGROUND

Voxelotor is a first-in-class sickle hemoglobin (HbS) polymerization inhibitor being developed for the treatment of sickle cell disease (SCD). In phase 3 HOPE trial, treatment with voxelotor 1500 mg and 900 mg daily demonstrated rapid and sustained improvements in hemoglobin (Hb) levels and markers of hemolysis compared with placebo (Wagner et al. 2019; Ware et al. 2019).

Hydroxyurea induces fetal hemoglobin (HbF) and is approved by both the US Food and Drug Administration and the European Medicines Agency as a treatment for SCD. Because both voxelotor and hydroxyurea can affect anemia and hemolysis, and potentially have additive mechanisms of action against HbS polymerization,1,3,4,5 the effects of concomitant hydroxyurea in the setting of voxelotor treatment were investigated.

OBJECTIVES

To examine the safety of concomitant voxelotor and hydroxyurea use and the effect on laboratory parameters associated with hydroxyurea in participants from the phase 3 HOPE study.

METHODS

Study Design

The HOPE study was a phase 3, randomized, placebo-controlled, double-blind, multicenter study comparing the efficacy and safety of voxelotor (1500 mg and 900 mg daily) versus placebo in participants with SCD aged 12 to 65 years (Figure 1).

A post hoc analysis of concomitant hydroxyurea use was performed using all available data. Hydroxyurea use was available in 3 treatment arms and evaluated for specific laboratory parameters including average percentage of HbF, MCV, ANC, and ARC.

RESULTS

Baseline Characteristics

A total of 179 of 274 (65%) participants were receiving hydroxyurea at baseline (voxelotor 1500 mg, 45.2%; voxelotor 900 mg, 44.8%; placebo, 52.9%). Percentages of participants reporting any serious TEAE were also similar among participants treated with hydroxyurea (voxelotor 1500 mg, 95.3%; voxelotor 900 mg, 96.6%; placebo, 97.1%).

The HOPE study, participants treated with voxelotor had increased Hb levels compared with placebo, irrespective of hydroxyurea use. Significant voxelotor-associated Hb increases were observed for participants on concomitant hydroxyurea use and were equivalent to those observed in participants not taking hydroxyurea.

The lack of observed changes in percentage of HbF, MCV, and ANC was consistent with stable hydroxyurea exposure throughout the study and suggests that voxelotor treatment was not associated with changes in hydroxyurea adherence.

Comparable TEAE rates were observed across study arms and between participants with or without hydroxyurea use.

The additive treatment effects on anemia and hemolysis by voxelotor as well as the comparable TEAE rates observed across study arms suggest that combination therapy with hydroxyurea may be safe and effective for older child and adult SCD patients.

Voxelotor-associated Hb improvements were similar among participants treated with hydroxyurea, consistent with previous studies demonstrating stable hydroxyurea exposure during voxelotor treatment.

Figure 1. HOPE Study Design

Table 1. Baseline Characteristics and Demographics Across Treatment Arm

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No Hydroxyurea Use</th>
<th>≤15 Years</th>
<th>&gt;15 Years</th>
<th>≤15 Years</th>
<th>&gt;15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>14 (11-17)</td>
<td>14 (12-17)</td>
<td>14 (11-17)</td>
<td>14 (12-17)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea, mean (SD), mg/kg/day</td>
<td>8.9 (5.4)</td>
<td>8.9 (5.4)</td>
<td>8.9 (5.4)</td>
<td>8.9 (5.4)</td>
<td></td>
</tr>
<tr>
<td>HbF, %</td>
<td>2.3 (1.3)</td>
<td>2.3 (1.3)</td>
<td>2.3 (1.3)</td>
<td>2.3 (1.3)</td>
<td></td>
</tr>
<tr>
<td>MCV, mean (SD), fl</td>
<td>78.2 (11.5)</td>
<td>78.2 (11.5)</td>
<td>78.2 (11.5)</td>
<td>78.2 (11.5)</td>
<td></td>
</tr>
<tr>
<td>ANC, mean (SD), x10⁶/L</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Mean Change in Hb From Baseline to Week 24 by Hydroxyurea Use (n=274)

Voxelotor Treatment Was Not Associated With Changes in Hydroxyurea Adherence Parameters

Table 2. Mean Change From Baseline to Week 24 (95% CI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Hydroxyurea Use</th>
<th>≤15 Years</th>
<th>&gt;15 Years</th>
<th>≤15 Years</th>
<th>&gt;15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dL</td>
<td>10.0 (9.5)</td>
<td>10.0 (9.5)</td>
<td>10.0 (9.5)</td>
<td>10.0 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Hb, %</td>
<td>81.1 (8.1)</td>
<td>81.1 (8.1)</td>
<td>81.1 (8.1)</td>
<td>81.1 (8.1)</td>
<td></td>
</tr>
<tr>
<td>MCV, fl</td>
<td>78.2 (11.5)</td>
<td>78.2 (11.5)</td>
<td>78.2 (11.5)</td>
<td>78.2 (11.5)</td>
<td></td>
</tr>
<tr>
<td>ANC, x10⁶/L</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS

In the HOPE study, participants treated with voxelotor had increased Hb levels compared with placebo, irrespective of hydroxyurea use. Significant voxelotor-associated Hb increases were observed for participants on concomitant hydroxyurea use and were equivalent to those observed in participants not taking hydroxyurea.

The lack of observed changes in percentage of HbF, MCV, and ANC was consistent with stable hydroxyurea exposure throughout the study and suggests that voxelotor treatment was not associated with changes in hydroxyurea adherence.

Comparable TEAE rates were observed across study arms and between participants with or without hydroxyurea use.

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Acknowledgments

We thank all the patients, families, caregivers, researchers, research staff, coordinators, and support staff who contributed to this study.

Disclosures

P. Ware serves on the following boards of directors: Amgen, Novartis, and Global Blood Therapeutics. M. Abboud is an inventor on a patent issued to Global Blood Therapeutics and has ownership interest (5%) in Global Blood Therapeutics. B. Tong serves on the board of directors of Global Blood Therapeutics. J. Lehrer-Graiwer has ownership interest (5%) in Global Blood Therapeutics. C. Hoppie serves on the board of directors of Global Blood Therapeutics. S. Chiu has ownership interest (5%) in Global Blood Therapeutics. B. Tong and K. Nguyen serve as consultants to Global Blood Therapeutics. C. Hoppie serves as a consultant to Global Blood Therapeutics.

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