Effects of luspatercept on serum ferritin in patients with lower-risk myelodysplastic syndromes with ring sideroblasts in the phase 3 MEDALIST trial

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Background

Luspatercept (GPR173/ARVDF/GRS-141) is a recombinant protein that has been shown to induce erythroid maturation and differentiation in vitro and in vivo.1 Luspatercept specifically binds to the transcription factor nuDT (Deltex 1) in erythroid progenitors.2

The objective of this analysis was to describe the effects of luspatercept on serum ferritin (SF) levels in patients with lower-risk myelodysplastic syndromes (MDS) with ring sideroblasts (sideroblastic anemia) (RARS) or refractory anemia with ring sideroblasts and thrombocytosis (RASpT) in the phase 3, randomized, double-blind, placebo-controlled MEDALIST study (NCT02631070) of patients with RARS or RASpT.4

Methods

In the MEDALIST study, 221 patients with RARS (n = 153) or RASpT (n = 68) were randomized in a 2:1 ratio to luspatercept or placebo. The study was double-blind for all endpoints except the primary endpoint of response to luspatercept.5

All patients were followed for ≥ 24 weeks and ≤ 48 weeks. Patients had a median SF level of 1456 μg/L (range, 160–7280 μg/L) at baseline.6

Results

Baseline characteristics of luspatercept and placebo patients were similar (Table 1). 

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.0 (18.4)</td>
<td>62.9 (17.8)</td>
</tr>
<tr>
<td>Sex (M,F)</td>
<td>109/44</td>
<td>55/21</td>
</tr>
<tr>
<td>Race (C,W)</td>
<td>135/18</td>
<td>70/7</td>
</tr>
<tr>
<td>Baseline SF (μg/L)</td>
<td>1186 (333)</td>
<td>1429 (477)</td>
</tr>
<tr>
<td>LTBa, Overall HTBa</td>
<td>71 (46.4)</td>
<td>40 (52.6)</td>
</tr>
<tr>
<td>LTBb, Overall HTBa</td>
<td>122 (79.9)</td>
<td>75 (99.4)</td>
</tr>
<tr>
<td>LTBc, Overall HTBa</td>
<td>3 (2.0)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

Note: LTBa: low transfusion burden; LTBb: ≥ 2 U/8 weeks; LTBc: ≥ 6 RBC units/8 weeks; Overall HTBa and Overall HTBa: ≥ 6 RBC units/8 weeks.

The median time on treatment was 24 weeks (range, 1–48 weeks). In the luspatercept arm, 30.0% of patients continued treatment beyond 24 weeks and 19.5% continued beyond 48 weeks. In the placebo arm, 15.0% of patients continued treatment beyond 24 weeks and 9.5% continued beyond 48 weeks.

Table 2. Summary of mean daily dose of ICT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>883.6 (362.5)</td>
<td>54.2 (41.7)</td>
</tr>
</tbody>
</table>

Note: ICT: iron chelation therapy.

During the 12 weeks immediately prior to the first dose, the mean daily dose of ICT was 311.8 mg (range, 56–1531 mg).

The mean daily dose of ICT was 79.4 mg (range, 0–1386 mg) and 50.0 mg (range, 0–1050 mg) in the luspatercept and placebo arms, respectively.

Changes in SF over Weeks 9–24 and 33–48

An exploratory analysis was conducted to evaluate the effects of luspatercept versus placebo on SF levels in patients with RARS or RASpT. The SF levels were analyzed in a time-stratified analysis of covariance (ANCOVA) model with treatment (luspatercept vs placebo) as the main factor and baseline SF as a covariate. A significant treatment effect was observed in the weeks 9–24 and 33–48 analysis (Table 3).

Table 3. Multivariate analysis of Lk changes from baseline in SF levels over Weeks 9–24 (a) and Weeks 33–48 (b)

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF (μg/L)</td>
<td>1196 (333)</td>
<td>1429 (477)</td>
</tr>
<tr>
<td>LC (−73.4)</td>
<td>344.2 (229.2)</td>
<td>67.0 (284.5)</td>
</tr>
<tr>
<td>LC (−73.4)</td>
<td>255.2 (326.2)</td>
<td>72.0 (287.0)</td>
</tr>
</tbody>
</table>

Note: SF, serum ferritin; LC, luskptarcept change from baseline; ANCOVA, analysis of covariance; HI-E, hematologic improvement–erythroid; HTB, high transfusion burden; ICT, iron chelation therapy; HI-E, hematologic improvement–erythroid; HTB, high transfusion burden; ICT, iron chelation therapy; ICT, iron chelation therapy; LTB, low transfusion burden; RBC, red blood cell; SD, standard deviation; SF, serum ferritin.

Conclusions

Luspatercept has a positive effect on ferritin levels in patients with lower-risk MDS with ring sideroblasts, as evidenced by a significant treatment effect on SF levels in the weeks 9–24 and 33–48 analysis. These findings suggest that the effect of luspatercept on SF may be due not only to iron chelation, but also to a direct effect of the drug on iron erythropoiesis and/or iron metabolism.

Acknowledgments

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References


Disclosures

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