Relationship between MAN2B1 gene variant subgroups, antidrug antibody detection, and long-term velmanase alfa treatment outcomes in patients with alpha-mannosidosis

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Velmanase alfa (VA):
A recombinant form of human lysosomal alpha-mannosidase developed as an intravenous enzyme replacement therapy (ERT) for the non-neurological symptoms of AM.3 ERTs are often associated with immune responses to the exogenous enzyme and development of antidrug antibodies (ADAs) that may result in a loss of efficacy and induce immune complex-related hypersensitivity reactions.4

Alpha-mannosidosis (AM):
An autosomal recessive disorder caused by pathogenic biallelic variants in the MAN2B1 protein-coding gene leading to a deficiency in lysosomal alpha-mannosidase and characterized by the accumulation of mannose-rich oligosaccharides with highly variable clinical symptom severity and progression.1,2

• A previous study in patients with AM identified 3 MAN2B1 variant subgroups and assessed their relationship to the localization of mutant alpha-mannosidase and severity of clinical symptoms.1

OBJECTIVE

• To evaluate a possible correlation between the 3 MAN2B1 variant subgroups, ADA-response dynamics, and infusion-related reactions (IRRs) in patients with AM treated with VA.
**METHODS**

**BASELINE DEMOGRAPHICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(N = 33)</th>
<th>Parameter</th>
<th>(N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean (SD) 17.1 (7.8)</td>
<td><strong>Sex</strong></td>
<td>Male 20 (60.6)</td>
</tr>
<tr>
<td></td>
<td>Median (min; max) 15.0 (6.0; 35.0)</td>
<td><strong>(n, %)</strong></td>
<td>Female 13 (39.4)</td>
</tr>
<tr>
<td>**Race (n, %)</td>
<td>White 33 (100.0)</td>
<td><strong>Weight (kg)</strong></td>
<td>Mean (SD) 58.8 (18.6)</td>
</tr>
<tr>
<td></td>
<td>Asian -</td>
<td><strong>(kg)</strong></td>
<td>Median (min; max) 65.0 (18.7; 95.2)</td>
</tr>
<tr>
<td></td>
<td>Black -</td>
<td><strong>Height (m)</strong></td>
<td>Mean (SD) 1.53 (0.18)</td>
</tr>
<tr>
<td></td>
<td>Other -</td>
<td><strong>(m)</strong></td>
<td>Median (min; max) 1.57 (1.12; 1.81)</td>
</tr>
</tbody>
</table>

- The patients were sorted into 3 MAN2B1 variant subgroups:

  **G1 subgroup**
  - 2 null variants not in lysosomes (n = 7)

  **G2 subgroup**
  - ≥ 1 non-null variant* in endoplasmic reticulum (n = 17)

  **G3 subgroup**
  - ≥ 1 non-null variant* in lysosome (n = 9)

*Non-null variant defined as missense variant or in-frame deletion/duplication of 1–5 amino acids.

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ADA, antidrug antibody; IRR, infusion-related reaction; IV, intravenous; SD, standard deviation; VA, velmanase alfa.
Detection of ADAs by MAN2B1 Variant Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ADA positive</th>
<th>ADA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAN2B1 subgroup 1 n = 7</td>
<td>ADAs n = 3</td>
<td>Positive at baseline n = 0</td>
</tr>
<tr>
<td>MAN2B1 subgroup 2 n = 17</td>
<td>ADAsa n = 7</td>
<td>Positive at baseline n = 5</td>
</tr>
<tr>
<td>MAN2B1 subgroup 3 n = 9</td>
<td>ADAs n = 0</td>
<td></td>
</tr>
</tbody>
</table>

*1 Patient had ADA-positive levels during placebo treatment, but not at baseline or during treatment with VA

- Of the 4 patients with treatment-emergent ADAsa, 2 had high ADA levels > 80 U/mL (440 U/mL [G2 subgroup]; 1012 U/mL [G1 subgroup]).

Impact of ADA Status on Serum Oligosaccharides (μmol/L) and IgG Levels (g/L)

<table>
<thead>
<tr>
<th>Serum oligosaccharidesa</th>
<th>Visit</th>
<th>Parameter</th>
<th>ADA positive</th>
<th>ADA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Actual value</td>
<td>% Change from baseline</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>10</td>
<td>6.34 (1.42)</td>
<td>–</td>
</tr>
<tr>
<td>Last observation</td>
<td>Mean (SD)</td>
<td>10</td>
<td>3.48 (3.62)</td>
<td>−45.8 (49.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum total IgGb</th>
<th>Visit</th>
<th>Parameter</th>
<th>ADA positive</th>
<th>ADA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Actual value</td>
<td>% Change from baseline</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>9</td>
<td>8.51 (4.00)</td>
<td>–</td>
</tr>
<tr>
<td>Last observation</td>
<td>Mean (SD)</td>
<td>9</td>
<td>11.24 (3.31)</td>
<td>42.36 (32.73)</td>
</tr>
</tbody>
</table>

*1 Patient had ADA-positive levels during placebo treatment, but not at baseline or during treatment with VA

- The difference in mean percent change for serum oligosaccharides between the two groups can be explained by 1 ADA-positive patient with a high ADA level of 1012 U/mL who experienced a 54.3% increase from baseline to last observation.

- Moreover, there was no significant difference in the mean (SD) change from baseline to last observation for the remaining 9 ADA-positive patients vs the 23 ADA-negative patients (−3.67 [2.56] μmol/L vs −5.34 [2.86] μmol/L; P = 0.136).
Impact of ADA on Velmanase Alfa Levels

A – Patient with high ADA level of 440 U/mL

• For the patient with a high ADA level of 440 U/mL (G2 subgroup), VA plasma concentration was not affected.

B – Patient with high ADA level of 1012 U/mL

• In contrast, for the patient with a high ADA level of 1012 U/mL (G1 subgroup), no quantifiable VA plasma concentration was detected at any timepoint during the high ADA sample evaluation.

Impact of High ADA Level on Serum Oligosaccharides

• For the patient with an ADA level of 440 U/mL, serum oligosaccharides normalized regardless of the presence of ADAs.
• In contrast, for the patient with an ADA level of 1012 U/mL, serum oligosaccharides decreased for 12 months, followed by an increase higher than baseline at month 36, which corresponded to the increase in ADA levels.

Safety

• 3 Patients experienced a total of 19 IRRs that were deemed related to VA administration.
• All IRRs were mild-moderate in severity and reported as resolved.
  o 2 ADA-positive patients with high ADA levels experienced a total of 18 IRRs:
    – 1 ADA-positive patient experienced 14 IRRs (G1 subgroup)
    – 1 ADA-positive patient experienced 4 IRRs (G2 subgroup)
  o 1 ADA-negative patient (G2 subgroup) experienced only 1 IRR

ADA, antidrug antibody; IRR, infusion-related reaction; VA, velmanase alfa.
• With up to 48 months of VA exposure, only a small number of patients with AM developed treatment-emergent ADAs (n = 4/33; 12.1%):
  – Of these 4 patients, only 2 developed high ADA levels that were associated with IRRs.
• Development of ADAs did not compromise the effectiveness of VA treatment, as measured by serum oligosaccharide and serum IgG levels, except for 1 patient with the highest ADA levels.
• Further classification by MAN2B1 variant subgroups suggest a possible correlation between MAN2B1 gene variants and ADA development, with patients in the G1 and G2 subgroup more likely to develop ADAs and subsequent IRRs.
• The outcomes assessed were similar between the MAN2B1 variant subgroups and efficacy of treatment was maintained for most patients regardless of ADA detection in each variant subgroup.
• Regardless of ADA development or MAN2B1 variant subgroups, IRRs were limited in occurrence, were only mild to moderate in severity, and all resolved.
• While further studies are necessary to assess the relationship between MAN2B1 variant subgroups and ADA development, this analysis suggests that ADAs have limited effect on the clinical benefit of VA in most patients with AM.

REFERENCES, ACKNOWLEDGMENTS, AND DISCLOSURES


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