Researchers refine gene therapy approach for hemophilia A

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SAN DIEGO — Patients with severe hemophilia A achieved factor VIII activity levels sufficient to reduce or prevent spontaneous hemorrhage after a single IV infusion of AAV8-HLP-hFVIII-V3, according to results of a phase 1/phase 2, open-label, nonrandomized dose-escalation trial presented at ASH Annual Meeting and Exposition.

Researchers observed the factor VIII levels in this trial using lower doses of adeno-associated viral (AAV) vector than in previous gene therapy studies for hemophilia A.

“A single infusion of AAV8-HLP-hFVIII-V3 was well tolerated by patients with [severe hemophilia A],” Pratima Chowdary, MD, co-center director for the hemophilia center at Health Service Laboratories, said during her presentation. “Transgenic factor VIII expression was achieved in all patients at both vector doses.”

Previous studies in hemophilia B have shown that a single peripheral vein administration of AAV vectors expressing the factor IX transgene leads to stable long-term expression of transgenic factor IX at therapeutic levels without long-term toxicity.

The use of adeno-associated vectors in hemophilia A gene therapy, however, have been limited because of inefficient expression of transgenic factor VIII and the large size of the factor VIII cDNA.

Chowdary and colleagues developed two AAV-factor VIII expression cassettes with a small synthetic liver specific promoter driving the expression of codon optimized factor VIII variants to overcome these challenges for the use of gene therapy for hemophilia A.

Previous results from the first of these cassettes — AAV-HLP-hFVIII-SQ encoding a B-domain deleted factor VIII variant — showed sustained normalization of factor VIII activity in six of seven participants following a single IV infusion of AAV.
serotype 5 pseudotyped vector. However, researchers had to use high vector
doses, which they hypothesized was due to its manufacture using the insect
cell/baculovirus system.

The second FVIII cassette — AAV-HLP-hFVIII-V3 — contains a 17 amino-acid
peptide comprising six N-linked glycosylation motifs from the human factor VIII B-
domain. Murine studies showed AAV-HLP-hFVIII-V3 mediated factor VIII
expression at threefold-higher levels than AAV-HLP-hFVIII-SQ.

The current analysis included three adult men with severe hemophilia A with factor
VIII activity levels of 1% or less of normal who received a single IV infusion of
AAV8-HLP-hFVIII-V3.

The first patient received a dose of $6 \times 10^{11}$ vg/kg, whereas the other two received
a dose of $2 \times 10^{12}$ vg/kg.

Researchers followed patients for 13 to 47 weeks.

Results showed detectable transgenic factor VIII within 2 weeks of the infusion.

Factor VIII activity levels reached more than 5 IU/dl by 6 weeks of gene transfer in
all three patients and remained steady at 7 IU/dl ($\pm 1$ IU/dl) in the first patient
through a period of 47 weeks.

The second patient, who was in his 20th week after infusion at the time of the
presentation, had steady-state factor VIII activity of 6 IU/dl ($\pm 2$ IU/dl).

The third patient had steady-state factor VIII activity almost 10 times higher than the
second patient, at 69 IU/dl ($\pm 7$ IU/dl).

Elevated serum alanine aminotransferase occurred in patients 1 and 3 between
weeks 4 and 6 after gene transfer and reached peak levels that were 1.5 times the
upper limit of the normal range. Both of those patients were treated with
corticosteroids within 48 hours of transaminitis and experienced no loss of
transgene expression.

None of the patients developed a factor VIII inhibitor. — by John DeRosier

Reference:

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