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Gene therapy increases factor VIII activity, reduces bleeding in severe hemophilia A

Lawrence R.

Valoctocogene roxaparvovec induced endogenous factor VIII production and significantly reduced bleeding and factor VIII concentrate use relative to factor VIII prophylaxis in patients with severe hemophilia A, according to study results.

Researchers reported findings of the open-label, single-group, multicenter phase 3 study in *The New England Journal of Medicine*.

"I believe there is an unmet need in men with severe hemophilia A," **Margareth C. Ozelo, MD, PhD,** professor of hematology and transfusion medicine in the department of internal medicine at the school of medical science at University of Campinas (UNICAMP) in Campinas, Sao Paulo, told Healio. "Although the current treatments have improved outcomes for people with severe hemophilia A, many still experience breakthrough bleeds."

Background and methodology

Hemophilia A is caused by pathologic variants in the gene encoding coagulation factor VIII, researchers wrote, and adeno-associated virus (AAV) vector gene therapy may both improve patient outcomes and reduce treatment burden.

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ, BioMarin), an AAV5-based gene therapy vector that expresses a B-domain-deleted human VIII factor coding sequence from a liver-selective promoter, provided sustained endogenous factor VIII production along with reductions in bleeding and factor VIII use for up to 5 years, according to results of a phase 1/phase 2 study.

In the current study, researchers sought to evaluate the efficacy and safety of the gene therapy in men with severe hemophilia A (factor VIII level of 1 IU/dL or lower).

The analysis included 134 men (median age at enrollment, 30 years; range, 18-70; 71.6% white) enrolled at 48 sites in 13 countries who did not have preexisting

anti-AAV5 antibodies or prior development of factor VIII inhibitors and had been receiving prophylaxis with factor VIII concentrate.

Treatment with valoctocogene roxaparvovec consisted of a single infusion of $6x10^{13}$ vector genomes/kg.

Change from baseline in factor VIII activity during weeks 49 through 52 after infusion served as the primary endpoint; secondary endpoints included treated bleeding rate and change in annualized factor VIII concentrate use.

Median follow-up was 60.2 weeks (range, 51.1-150.4).

Key findings

Results showed mean factor VIII activity level at weeks 49 through 52 increased by 41.9 IU/dL (95% CI, 34.1-49.7), for a median change of 22.9 IU/dL (interquartile range, 10.9-61.3).

Researchers also reported that among the 112 participants enrolled from a prospective noninterventional study, a decrease in both mean annualized rates of factor VIII concentrate use (by 98.6%) and treated bleeding after week 4 (by 83.8%) occurred after infusion.

"I was pleased to see consistency between the earlier study with smaller sample size and this study, which is the largest gene therapy study conducted to date for severe hemophilia A," Ozelo said. "I was still surprised by the magnitude of the decrease in treated bleeding from standard-of-care factor VIII prophylaxis."

Ozelo and colleagues reported all men experienced one or more adverse events, the most common of which included headache (38.1%), nausea (37.3%) and elevations in aspartate aminotransferase levels (35.1%). Twenty-two men (16.4%) experienced serious adverse events, including increased alanine aminotransferase and diarrhea.

None of the men developed factor VIII inhibitors or thrombosis.

"I am encouraged that during the first year of treatment, 90% of study participants had either zero treated bleeds or fewer treated bleeds after infusion than with factor VIII prophylaxis. In addition, there was a 99% decrease in the use of factor VIII concentrate and an 84% decrease in the treated bleeding rate," Ozelo said. "As a

treating physician, these data are exciting to me and could someday become a real treatment choice for people to consider."

Implications

Ozelo told Healio further studies will aid researchers in understanding the duration of clinical benefit of the treatment, in addition to uncovering the best ways to manage liver enzyme elevations and long-term safety.

"I am proud to be part of this pioneering effort to understand this gene therapy and pursue investigational treatments that could someday make a tremendous impact on the lives of people with severe hemophilia A," Ozelo said. "This treatment could enable people with hemophilia A to make their own factor VIII, effectively moving them into the moderate, mild or nonhemophilic factor VIII activity range."

In an accompanying editorial, **Courtney D. Thornburg, MD, MS,** medical director of the Hemophilia and Thrombosis Treatment Center at Rady Children's Hospital-San Diego and director of its hemostasis and thrombosis research program, referred to the first-generation valoctocogene roxaparvovec treatment as one that "could be truly transformative and liberating for eligible men with hemophilia" if approved.

"More investigation is needed for children and women with hemophilia and for persons currently excluded because of preexisting AAV immunity, factor VIII inhibitors, liver disease, or HIV infection," she wrote.

"Ultimately, highly anticipated gene therapies such as valoctocogene roxaparvovec and others in the therapeutic pipeline will improve the health and well-being of many persons with hemophilia," Thornburg continued. "Health care systems, policymakers, insurers, clinicians and community partners must prepare the way!"

References:

Ozelo MC, et al. *N Engl J Med*. 2022;doi:10.1056/NEJMoa2113708.

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