these results may be superior to outcomes of current gene therapies involving AAV-delivered factor VIII and replacement of factor VIII.

Are there downsides to the delivery of a lentiviral vector transgene? Unlike AAVs, which have an episomal location, lentiviruses integrate into the host genome.[8] A recent report in the *Journal* showed the development of hematologic cancers in 7 of 67 patients with cerebral adrenoleukodystrophy treated with lentiviral vector–delivered gene therapy. In the detailed integration-site analysis, all 7 patients had clonal lentiviral insertions in tumor cells near the *MECOM* and *PRDM16* genes.[9] All 7 had received busulfan and cyclophosphamide conditioning, a regimen known to be leukemogenic. In the study by Srivastava et al., treosulfan was used instead of busulfan in the conditioning regimen. The integration-site analysis performed 4 to 22 months after gene therapy revealed no safety concerns. Only time will tell whether this strategy of mitigating the risk of cancer and preserving fertility is successful. Because this study involved a limited number of participants and a short duration of follow-up, whether *F8* gene delivery through a lentiviral vector is a viable alternative to AAV-mediated *F8* gene therapy remains unclear. The good news is that if gene therapy fails, several acceptable options besides gene-therapy exist for persons with hemophilia A.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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A Milestone for Gene-Editing Therapies

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Are gene-editing therapies actually helping patients? Although there has been considerable excitement about the prospect of directly administering gene-editing therapy that is based on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9) into the bodies of patients to treat diseases,[1] we have only recently begun to see signs of success in clinical settings. In an early demonstration of the use of gene-editing therapy, reported in 2021, in vivo liver-directed CRISPR-Cas9 treatment substantially reduced serum transthyretin concentrations in a small number of patients with transthyretin amyloidosis.[2] A report from early 2024 described in vivo CRISPR-Cas9 treatment that targeted the gene *KLKB1* in the liver in a small cohort of patients with hereditary angioedema, with that therapy resulting in large reductions in plasma kallikrein protein levels.[3] A noteworthy aspect of the latter study was a marked decrease in the frequency of angioedema attacks after treatment. This observation was early evidence that in vivo gene editing resulted in improved quality of life. A third study, reported later in 2024, used in vivo CRISPR-Cas9 treatment to target a pathogenic *CEP290* variant in photorecep-

tor cells in a small number of patients with inherited retinal degeneration; the results were somewhat ambiguous, with only a subgroup of the patients having visual improvements as assessed by various metrics.[4] None of these studies had a control group, which raises the specter of placebo effects accounting for some of the changes.

Cohn et al. now provide in the *Journal* evidence from a randomized, controlled trial that a gene-editing therapy has resulted in clinical benefit.[5] They report the phase 2 portion of a phase 1–2 trial, the phase 1 portion of which was the aforementioned study of *KLKB1*-editing in patients with hereditary angioedema, with the therapy designated NTLA-2002.[3] Whereas the phase 1 study included 10 patients divided among three dose groups (25 mg, 50 mg, and 75 mg of NTLA-2002), the phase 2 trial randomly assigned 27 patients to one of two dose groups (25 mg or 50 mg) or a placebo group. The phase 2 cohort was still relatively small and the number of patients was not balanced among the groups (with 6 patients receiving placebo as compared with 10 receiving 25 mg of NTLA-2002 and 11 receiving 50 mg), factors that limit the ability to perform statistical comparisons, but the results were nonetheless revealing. During the 16-week primary observation period after treatment, the patients who received 25 mg of NTLA-2002 had a 75% reduction in the number of angioedema attacks per month (the monthly attack rate) as compared with the patients who received placebo, and the group that received 50 mg had a 77% reduction.

Besides confirming the clinical benefit of treatment with NTLA-2002, the phase 2 trial shows the importance of larger randomized, controlled trials for clarifying the magnitude of clinical benefit. The results of the phase 1 study showed an intraindividual reduction from baseline in the monthly attack rate of 91% in the 25-mg group and 97% in the 50-mg group during the 16-week primary observation period[3]; in the phase 2 trial, there was an intraindividual reduction of 16% in the placebo group,[5] a finding that suggests a modest placebo effect in the phase 1 study. Results from a future phase 3 randomized, controlled trial will better inform providers and patients as to the relative benefits of gene-editing therapy as compared with other methods of treatment for hereditary angioedema.

Although the phase 2 trial is the main focus of the article by Cohn et al., the authors have also provided an update on the status of the patients in the phase 1 study.[5] Relative to the initial findings published in early 2024, there is now an additional year of follow-up for the 10 patients in phase 1. During the newly reported follow-up period, there was just one angioedema attack in the entire cohort, even though none of the patients were on long-term prophylaxis during this period. (In the phase 2 trial, the number of angioedema attacks in patients who received NTLA-2002 was higher than that in the phase 1 study, and two patients who received NTLA-2002 have resumed long-term prophylaxis.) It is also notable that during that additional year, the reductions in total plasma kallikrein protein levels observed in all three dose groups of the phase 1 study remained stable, with 2 years of post-treatment data now available for patients in the low-dose (25-mg) group (the first to undergo treatment in the study). The durability of the therapeutic effect shows promise to last for the patients' lifetimes, making the CRISPR-based treatment a truly "one-and-done" proposition.

The answer to the opening question is now an unambiguous "yes." We can be confident that NTLA-2002 is helping patients with hereditary angioedema, and it is only a matter of time before we will see gene-editing treatments having a transformative effect on the care of patients with a broad spectrum of diseases.

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