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Gene Therapy for Hemophilia A: How Long Will It Last?

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It was 10 years ago that the first successful adeno-associated vector (AAV)-based gene therapy trial in hemophilia B was published.[1] It took another 5 years to modify this approach to be suitable for the larger factor VIII (FVIII) gene. Recent clinical trials provided us with a longer follow-up in hemophilia A (Table 1).[2–5]

In general, one can say that AAV-based gene therapy for hemophilia A is successful. Patients demonstrate ongoing FVIII expression in the majority of cases, which is associated with a dramatic positive effect on bleeding rates.

However, there are still several concerns that might mitigate our ongoing enthusiasm over time. First, the search for the optimal dosing is still ongoing. Where previous low dose cohorts were not successful in rendering FVIII expression,[4] high dosages were associated with loss of expression due to liver aminotransferase elevation.[3] On the other hand, the phase 3 Study to Evaluate the Efficacy and Safety of PF-07055480 / Giroctocogene Fitelparvovec Gene Therapy in Moderately Severe to Severe Hemophilia A Adults trial with giroctocogene fitelparvovec is temporarily on hold due to FVIII levels >150% in some patients; the exact dosing is not available in the public domain but could well be the highest dose cohort from the phase 1/2 trial. Second, transient elevation of liver aminotransferase is a common adverse event. As this might be associated with FVIII expression loss, this requires glucocorticoid treatment in the majority of patients, sometimes up to several months. Finally, the most important issue is loss of response in both the BioMarin and the Pfizer trials over time. It is as yet unknown whether this decline will continue over the next years, but it certainly differs from the long-term results in hemophilia B. A recent cost-effective analysis calculated a break-even time of 8 years for valoctocogene roxaparvovec, assuming an annual FVIII decrease of 5.7%.[6] This decrease was based on the earlier BioMarin trial in 15 patients.[4] With the phase 3 data now available, it is clear that this decline seems too optimistic. The FVIII expression after the first year was 43 IU/dL, but 24 IU/dL after 2 years,[2] indicating a decline of 44%.

Data from the Spark trial suggest a different pattern, with more stable FVIII expression after 2 years.[3] However, these data need to be interpreted with great caution. First, when comparing FVIII levels between trials, it is important that similar assay methods are used. It is known that the results of a 1-stage FVIII assay are 1.5 times as high as that determined with the use of a chromogenic FVIII assay.[3] Where the other gene therapy trials report their results from the chromogenic assays, the Spark trial meanly reports on the 1-stage. In fact, the initial mean FVIII expression in the Spark trial was only 6.9%. Second, although the figure given from this trial shows a somewhat horizontal stable expression, a closer look at the figure shows that the y-axis has been adapted to form a more horizontal pattern. In fact, the majority of patients do show a decline over time after 2 or 3 years as can be seen in the supplementary data provided.

Meanwhile, the alternative treatment for hemophilia A with emicizumab has shifted the treatment landscape tremendously. This success story of emicizumab will have a huge impact on patient preferences. Long-term efficacy data on durability are needed before gene therapy in hemophilia A will take a major role in our current treatment arsenal.

DISCLOSURES

The author has no conflicts of interest to disclose.

REFERENCES

1. Nathwani AC, Tuddenham EG, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011;365:2357–2365.

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Table 1.

Overview of Recent Gene Therapy Trial in Hemophilia A

Study Characteristics	Visweshwar et al[5]	Ozelo et al[2]	Pasi et al[4]		George et al[3]
Sponsor	Pfizer/Sangamo	BioMarin	BioMarin		Spark
N	11	134	15		18
Product	Giroctocogene fitelparvovec	Valoctocogene roxaparvovec	Valoctocogene roxaparvovec		SPK-8011
Gene cassette	AAV6-hFVIII-SQ	AAV5-hFVIII-SQ	AAV5-hFVIII-SQ		Spk200 (AAV3 based)-hFVIII-SQ
Dose	Cohort 1 (n = 2): 9×10^{11} vg/kg Cohort 2 (n = 2): 2×10^{12} vg/kg Cohort 3 (n = 2): 1×10^{13} vg/kg Cohort 4 (n = 5): 3×10^{13} vg/kg	6×10^{13} vg/kg	Cohort 1 (n = 1): 6×10^{12} vg/kg Cohort 2 (n = 1): 2×10^{13} vg/kg Cohort 3 (n = 7): 6×10^{13} vg/kg Cohort 4 (n = 6): 4×10^{13} vg/kg		Cohort 1 (n = 2): 5×10^{11} vg/kg Cohort 2 (n = 3): 1×10^{12} vg/kg Cohort 3 (n = 9): 2×10^{12} vg/kg Cohort 4 (n = 4): 1.5×10^{12} vg/kg
Phase	1–2	3	1–2		1–2
Follow-up	2–4 y	1–2 y	2–3 y		Median, 36.6 mo (range, 5–50 mo)
Factor levels after gene transfer (IU/dL)	Cohort 4 1 y Mean 42.6[a] 2 y Mean 25.4[a]	1 y Mean 42.9 (±45.5)[a] 2 y Mean 24.4 (±29.9)[a]	Cohort 3 1 y Mean 64[a] 2 y Mean 36[a] 3 y Mean 33[a]	Cohort 4 1 y Mean 21[a] 2 y Mean 15[a]	26–52 wk Mean 12.9 (±6.9)[b] >1 y Mean 11.0 (±6.8)[b]; 6.9 (±3.8)[a] >2 y Mean 12.0 (±7.1)[b] >3 y Mean 12.0 (±7.1)[b]
Increased liver aminotransferase	5 (45%)	115 (86%)	14 (93%)		7 (39%)
Glucocorticoids	4/5 in cohort 4 (80%)	106 (79%), median duration 230 d	11 (73%)		7 due to liver abnormalities, 5 preemptive
Comments			No FVIII expression in cohorts 1 and 2		2 patients in cohort 3 lost expression

[a]Chromogenic assay.

[b]1-stage assay.

AAV = adeno-associated vector; FVIII = factor VIII; hFVIII-SQ = B-domain-deleted human coagulation factor VIII; vg = vector genomes.

2. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. *N Engl J Med*. 2022;386:1013–1025.
3. George LA, Monahan PE, Eyster ME, et al. Multiyear factor VIII expression after AAV gene transfer for hemophilia A. *N Engl J Med*. 2021;385:1961–1973.
4. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med*. 2020;382:29–40.
5. Visweshwar N, Harrington TJ, Leavitt AD, et al. Updated results of the Alta study, a phase 1/2 study of giroctocogene fitelparvovec (PF-07055480/SB-525) gene therapy in adults with severe hemophilia A. Paper presented: 63rd Annual Meeting and Exposition of the American Society of Hematology; December 11–14, 2021; Atlanta, GA.
6. Ten Ham RMT, Walker SM, Soares MO, et al. Modeling benefits, costs, and affordability of a novel gene therapy in hemophilia A. *HemaSphere*. 2022;6:e679.