Review Article

Gene Therapy for Hemophilia—Opportunities and Risks

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Summary

Background: AAV (adeno-associated virus)–based gene therapy is a new treatment for hemophilia and has recently received approval for the treatment of severe hemophilia A. It does not suffer from the limitations of the current standard treatment (regular prophylactic intravenous injections of the missing clotting factor; subcutaneous injection of a bispecific antibody in hemophilia A) and can, it is hoped, raise the concentration of the missing clotting factor over the long term. AAV-based gene therapy can only be performed once, however, because of the generation of antibodies to AAV.

Methods: This review is based on publications retrieved by a selective search in the MEDLINE/PubMed database employing the relevant key words, supplemented by expert opinions and the recommendations of the relevant medical societies.

Results: Data from non-randomized phase 1 to phase 3 trials reveal an adequate expression of factors VIII and IX in patients with mostly severe hemophilia A or B. Even though they were no longer receiving prophylactic treatment, most patients experienced a considerable reduction, by 53% to 96%, in the number of bleedings compared to previous therapy. Persistently elevated factor levels have been described for up to six years in hemophilia A and up to eight years in hemophilia B. The most common side effect of gene therapy is an inflammatory response with elevated alanine aminotransferase levels (17% to 89%, depending on the study), which may be associated with a reduced clotting factor level and requires treatment with transient immunosuppression.

Conclusion: Gene therapy for hemophilia holds out the prospect of freedom from hemorrhage without the need for regular treatment with drugs. The various steps that need to be carried out in gene therapy should be coordinated in a graded and partly overlapping integrated care model (a so-called hub-and-spoke model). Electronic platforms should be used for data acquisition and transmission.

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Hemophilia is an X-linked recessive genetic clotting disorder caused by a deficiency of clotting factor VIII (FVIII, hemophilia A) or clotting factor IX (FIX, hemophilia B). It occurs with a frequency of approximately 1 in 10,000 male newborns, with hemophilia A accounting for 80–85% of cases (1) and around half of these developing severe disease. Moderate and mild hemophilia account for the remaining 50%. In 2020, approximately 4600 patients were receiving treatment in Germany for hemophilia of differing levels of severity (2).

The severity of hemophilia and the extent of clinical symptoms are determined by the residual activity of FVIII and FIX detectable in blood. Depending on the reduction in clotting factor as determined in laboratory tests, a distinction is made between severe (factor level < 1 IU/dL), moderate (factor level 1–5 IU/dL), and mild hemophilia (factor level 5–40 IU/dL) (3). In the mild form, spontaneous bleeding is rare and treatment is performed on an on-demand basis for traumatic bleeding or surgery.

In the case of untreated severe hemophilia, there is a significantly increased risk for joint bleeding events (median, 27.3; Q1 14.9; Q3 41.1) (4).

In randomized controlled trials, multiple weekly intravenous injections to replace the missing clotting factor proved to be effective in the prophylaxis of bleeding in both children and adults (4, 5). Prophylactically pre-treated children experienced statistically significantly fewer joint bleeding events with a mean

BOX 1

The principle of the gene therapy approach in hemophilia

- Gene therapy for hemophilia is based on the transfer of a non-pathogenic and non-replicating recombinant adeno-associated virus (AAV), the viral DNA of which has been replaced by a bioengineered gene cassette, with a tissue-specific promoter and other regulatory elements (9).
- Following intravenous infusion and subsequent cell transduction, endocytosis and import into the nucleus occurs, where the genetic material is released as episomal DNA. The therapeutic gene can then be expressed, thereby resulting in the production of the therapeutic protein, such as FVIII or FIX.
- Disadvantages of AAV include pre-existing neutralizing antibodies to AAV, possible liver reactions, and a presumably non-permanent response; furthermore, due to the generation of neutralizing antibodies, the treatment can only be performed once.
- In contrast to other viral vectors, such as lentiviruses, AVV are largely not integrated in an individual's genetic information, explaining why hemophilia can still be passed on despite gene therapy. A future therapy that potentially has an overall lower side-effects profile is the CRISPR/CAS method (clustered regularly interspaced short palindromic repeats), which is able to permanently correct gene mutations in the cell in a targeted manner.

BOX 2

Suitability of hemophilia for gene therapy

- Hemophilia is a monogenic disease that is improved by the expression of functional clotting factor.
- Even a relatively small increase in clotting factor activity can significantly reduce the risk of bleeding.
- The genetic transcript for FVIII and FIX is small enough to fit in an adeno-associated virus (AAV).
- There are criteria that can be clinically well-monitored, such as factor activity measurement, bleeding events, and the amount of factor replacement.
- Hemophilia treatment is delivered in highly specialized multidisciplinary centers.

number of 0.63 (± 1.35) compared to 4.89 (± 3.57) without prophylaxis (5). Newly developed factor products with longer half-lives can reduce the injection interval to as little as once a week in hemophilia A and as little as once every 2 weeks in hemophilia B or increase trough levels (3).

A side effect of this treatment (with an incidence of up to 30%) that is burdensome and also costly for patients is the generation of an antibody (referred to as an inhibitor) against the therapeutically administered FVIII or FIX protein. The subcutaneous injection of a bispecific antibody that mimics the function of active factor VIII (FVIII) and, due to its long half-life, needs to be administered only once every 1–4 weeks is approved for both severe hemophilia A and hemophilia A with inhibitors (3).

Studies on long-term course indicate that a risk of bleeds remains despite the early initiation of regular prophylaxis and that, therefore, it is not possible to completely prevent the development of hemophilic arthropathy (6). Data from Germany covering a period of 26 years show that joint damage can still be seen after 10 years despite early initiation of prophylactic therapy, with the ankle joints being the first to be affected (7). Joint damage causes painfully restricted function and movement, and even stiffening.

Gene therapy represents a new therapeutic method that is being investigated in clinical trials for the treatment of hemophilia *(Box 1)*. Conditional marketing authorization for valoctocogene roxaparvovec has already been granted in the European Union for hemophilia A. This treatment method enables the longest possible rise in clotting factor, with the result that bleeds do not occur even after clotting factor replacement therapy has ended. For Germany, total annual per-patient costs of 320,000 Euros have been calculated (8).

Method

At present, 62 trials on gene therapy for hemophilia are underway (9).

This review article is based on a selective literature search of clinical trials from the PubMed database employing the relevant keywords (such as hemophilia, gene therapy), as well as recent relevant congress contributions. Particular focus was placed on fully published trials and phase-3 trials as well as on studies enabling a comparison of the effectiveness

TABLE 1

Results of gene therapy for hemophilia B

Study	Study phase/ follow-up period	Capsid	Gene	Dosage (vg/kg)	Number of patients (n)	Average factor activity (± SD, IU/dL)	Further follow-up period
UCL/St. Jude (11–13)	Phase 1 Median of 3.2 years	AAV 2/8	hFIX-LP1	2×10^{11} 6×10^{11} 2×10^{12}	2 2 6	1.8 ± 0.7 2.5 ± 0.9 5.1 ± 1.7	8 Years, stable factor activity
AMT-060 (14, 15)	Phase 1/2	AAV 5	hFIX-LP1	5×10^{12} 2×10^{13}	5	4.4 (95% CI: [1.5; 7.3]) 6.9 (95% CI: [2.6; 11.3])	5 Years, stable factor activity
AMT-061 (20)	Phase 2b 26 Weeks	AAV 5	Pd FIX-LP1	2×10^{13}	3	47 (33.2–57.0)	
HOPE-B (21)	Phase 3 18 Months	AAV 5	Pd FIX-LP1	2×10^{13}	54	36.9 ± 21.4	
SPK-9011 (18)	Phase 1/2 28–78 Weeks	AAV-Spark100	Pd FIX	5×10^{11}	10	33.7 ± 18.5	5 Years, stable factor activity, currently in phase 3 (19)
B-AMAZE (22)	Phase 1/2 26 Weeks	AAV S3	Pd FIX	3.84×10^{11} 6.4×10^{11} 8.32×10^{11} 1.28×10^{12}	2 2 4 2	44–46 7–64 53–190 71–280	Follow-up to maximum month 36

AAV, adeno-associated virus; hFIX-LP1, human clotting factor IX with liver promotor 1; Pd FIX, FIX-Padua variant; SD, standard deviation; vg, vector genome; 95% CI, 95% confidence interval

TABLE 2

Results of gene therapy for hemophilia A

Study	Study phase/ follow-up period	Capsid	Gene	Dosage (vg/kg)	Number of patients (n)	Average factor activity (± SD, IU/dL)	Further follow-up period
BMN-270 (23–26)	Phase 1/2 52 Weeks	AAV 5	hFVIII-SQ	6×10^{12} 2×10^{13} 6×10^{13}	1 1 7	< 1 < 3 93 ± 48	6 Years, declining factor activity
GENEr8–1 (28)	Phase 3 49–52 Weeks	AAV 5	hFVIII-SQ	6×10^{13}	134	41.9 *1 (95% CI: [34.1; 49.7])	
SPK-8011*2 (29)	Phase 1/2 Median of 36.6 months (5.5–50.3 months)	SPK 200		5×10^{11} 1×10^{12} 1.5×10^{12} 2×10^{12}	2 3 4 9	5.5 (5–6) 6.66 (3–12) 4.66 (3–8)*3 8.14 (3–14)*4	Currently phase 3

*1 132 Patients without HIV
*2 At 52 weeks
*3 Data for only three patients available
*4 Data for only seven patients available
AAV, adeno-associated virus; HIV, human immunodeficiency virus; hVIII-SQ, human clotting factor VIII; SD, standard deviation; vg, vector genome; 95% CI, 95% confidence interval

TABLE 3

Bleeding rate and factor replacement before and after gene therapy

Study	Number of patients	Annual bleeding rate before vs. after	Change in bleeding rate	Annual factor use (thousand IU/kg) before vs. after	Change in factor use	Annual factor infusion rate before vs. after	Change in factor infusion rate
Hemophilia A							
GENEr8–1*[1] (28)	134	Mean of 4.8 vs. 0.8 Median of 2.8*[1] vs. 0	−4.1 Bleeds (95% CI: [−5.3; −2.8]), reduction: 83.8% (p < 0.001)	Mean of 3961.2 vs. 56.9 Median of 3754.4 vs. 0	Reduction: 98.6% p < 0.001	Mean of 135.9 vs. 2.0 Median of 128.6 vs. 0	Reduction: 98.6%
SPK-8011*[2] (29)	18	Median: 8.5 (0–43) vs. 0.3 (0–6.5)	Reduction: 91.5% (95% CI: [88.8; 94.1])	Not specified	Not specified	Median of 57.5 (IQR 24–245) vs. 0.6 (IQR 0–28.6)	Reduction: 96.4% 95% CI: [95.7; 97.1]
Hemophilia B							
UCL/St.Jude (11)	6	Median of 15.5 (IQR 10.3–19.3) vs. 1.5 (IQR 1.0–4.0)	Reduction: 96% p = 0.009	Median of 2613 (IQR 1 671–4 513) vs. 206 (IQR 79–948)	Reduction: 92% p = 0.002		
SPK 9011 (18)	10	Mean of 11.1 (IQR 0–48) vs. 0.4 (IQR 0–4)	p = 0.02	Mean of 2908 (IQR 0–8090) vs. 49.3 (IQR 0–376)	p = 0.004		
AMT-060 (14)	10	Cohort 1: mean of 9.8 vs. 4.6 Cohort 2 (four patients): mean of 3.0 vs. 0.9	Cohort 1: Reduction: 53% Cohort 2: Reduction: 70%	Cohort 1: Mean of 1774 vs. 331 Cohort 2 (four patients): mean of 866 vs. 232	Cohort 1: reduction: 81% Cohort 2: reduction: 73%		
HOPE-B (21)	54	Mean: 4.19 vs. 1.51	Reduction: 64%, p = 0.0002	Mean of 257 vs. 8 (13–18 months)	p < 0.0001		

*[1] Investigation of treated bleeding episodes and factor use in 112 patients
*[2] In two patients, the data refer to levels before loss of factor expression.
IQR, interquartile range; 95% CI, 95% confidence interval

of the treatment with the comparator treatment. However, the rarity of the disorder and the low numbers of participants in trials limit the empirical relevance of some of the data.

Clinical trials on gene therapy for hemophilia are non-randomized, international, multicenter open-label trials with factor activity as the primary endpoint. Secondary endpoints included, among others, safety, bleed rate, and factor use compared to the time prior to gene therapy.

Gene therapy and hemophilia

As a monogenic disease, hemophilia is well suited to gene therapy for several reasons *(Box 2)*. Studies to date have included adult male patients with severe or, in some studies, moderate hemophilia (up to 2 IU/dL clotting factor activity). Exclusion criteria included advanced liver disease or coagulation factor inhibitors (which occur in up to 30% of patients with severe hemophilia) and mostly neutralizing antibodies to AAV. This sometimes significantly reduces the number of patients for whom gene therapy can be considered, depending on age (concomitance of hepatitis and other liver disorders) and region (prevalence of AAV antibodies) (10).

Trials results on gene therapy for hemophilia B

The first successful results from a trial on the intravenous administration of an AVV-based gene therapy for hemophilia was published in 2011 in six patients with hemophilia B. A dose-dependent expression of the factor IX transgene of 2–11 IU/dL was seen in all participants (11). Even after a period of 8 years, consistently increased FIX activity in the region of 2–5% was demonstrated in the dose cohorts (13).

These results were confirmed in a further phase-1/2 trial (AMT-060). In 10 hemophilia B patients, a mean increase in FIX activity of 4.4 IU/dL was achieved in the lower and of 6.9 IU/dL in the higher dose cohort (14). Stable FIX levels were also recorded in both cohorts at 5 years (15).

A further advance in gene therapy for hemophilia B was made with the introduction of the Padua variant of the FIX gene, which has five- to 10-fold higher activity and was initially found in familial thrombophilia (16). Here, the molecular regulation of activation, inactivation, and cofactor dependence is similar to FIX wild type, but the faster rate of factor X activation leads to hyperactivity and significantly higher factor levels (17).

For the first time, participants with pre-existing anti-AAV antibodies were investigated in a phase-2b trial (AMT-061), which showed mean FIX activity of 31 IU/dL (23.9 IU/dL–37.8 IU/dL), rising to 47 IU/dL (33.2 IU/dL–57.0 IU/dL) at 26 weeks (20). Initial data were recently reported from a phase-3 trial in which 54 patients with severe hemophilia B participated. Here again, patients with pre-existing anti-AVV antibodies were included, and the investigators found that up to a certain threshold value, independent of anti-AVV antibodies, mean FIX activity of 39.0 IU/dL could be achieved at 6 months and 36.9 IU/dL at 18 months (21).

Table 1 summarizes the results of six studies. For three studies, follow-up of 5–8 years is available.

Trial results on gene therapy for hemophilia A

The development of a study drug for the gene therapy of hemophilia A represented an additional challenge. Whereas hepatocytes are the physiological site of FIX synthesis, the sinusoidal endothelial cells are the main site of FVIII synthesis in the liver. Since the vector only works with gene constructs of a certain size, the B-domain of FVIII was dispensed with (10).

The first successful trial results on gene therapy for hemophilia were published in 2017 (BMN-270) (23). Six of seven patients in the high-dose group showed sustained normalization of factor VIII activity over a period of 1 year (mean, 93% ± 48), leading to a stabilization of hemostasis as well as to a comparatively sharp reduction in annual factor VIII use from 5286 IU/kg to 65 IU/kg. The primary adverse event was an increase in alanine aminotransferase (ALT) to 1.5 times the upper limit of the normal range or less. Other publications demonstrated the sustained, successively declining expression of FVIII over a period of up to 6 years (24–26). None of the patients permanently resumed FVIII prophylaxis, no severe adverse events occurred, and an improvement in quality of life was seen.

At present, quality of life has been investigated in only a small number of patients. It has been demonstrated that the questionnaire commonly used in hemophilia, Haemophilia-Specific Health-Related Quality of Life (Haemo-QoL-A), is also a reliable instrument for the evaluation of quality of life following gene therapy (27). This showed a persistent improvement in all domains in the Haemo-QoL-A for a period of up to 5 years in patients with hemophilia A in the highest dose cohort (25).

Meanwhile, data from a phase-3 trial (28) with 1-year follow-up of 134 patients have been published. In 132 HIV-negative participants, mean factor-VIII activity increased by 41.9 IU/dL by week 52 (95% confidence interval: [34.1; 49.7]; $p < 0.001$).

The results from three studies are summarized in *Table 2*.

Reduction in bleeding events following gene therapy

The studies varied in terms of the AAV isotypes and gene constructs used as well as in different dosages (2×10^{11} vector genome [vg]/kg to 6×10^{13} vg/kg). All studies have so far showed inter- and intraindividual variability for factor levels, making it impossible to accurately predict the achieved factor level. Whereas the phase-1 trials were often also conducted for the purposes of dose determination, phase-3 trials enabled the inclusion of higher patient numbers. In altogether six studies, the comparison of primary and secondary endpoints was possible for an observation phase prior to gene therapy, in which patients were mostly treated with conventional prophylactic factor replacement. All studies showed a significant and often statistically significant reduction in bleeds to 83.8% (decrease in median number of bleeds from 2.8 to 0 [28]) to 91.5% (decrease in median number of bleeds from 8.5 to 0.3 [29]) in hemophilia A gene therapy and to 64% (decrease in median number of bleeds from 4.19 to 1.51 [21]) to 96% (decrease in median number of bleeds from 15.5 to 1.5 [11]) in hemophilia B gene therapy, which was associated with a statistically significant reduction in the rate of factor infusions as well as the quantity of factor *(Table 3)*.

However, it should be critically noted that gene therapy of hemophilia A results in a subsequent decline in factor VIII activity, which can lead to an increased tendency to bleed. The most recent 6-year data on valoctocogene roxaparvovec yielded mean and median FVIII activity levels of 9.8 and 5.6%, respectively, following a dose of 6×10^{13} vg/kg (26). A decline in effectiveness has not been observed as yet for gene therapy of hemophilia B.

Side effects and limitations

Gene therapy is generally well tolerated. A number of studies have reported infusion-related side effects; for example, five of 18 patients developed symptoms such as vomiting, fever, and myalgia up to 12 h following gene therapy, with these symptoms persisting for up to 72 h following outpatient treatment (29).

In some cases of gene therapy for hemophilia A, transiently elevated FVIII activity levels have also been measured. For example, seven of altogether 134

patients had FVIII activity levels over 150 IU/dL (28). In an as yet unpublished phase-3 study (SB-525, AFFINE Trial), elevated factor VIII activity levels were measured in a number of treated patients (> 150 IU/dL). One patient developed deep vein thrombosis of the lower leg (30). Another thromboembolic even was reported while using the FIX-Padua variant in a study on gene therapy for hemophilia B (22).

The development of an inhibitor against FVIII or FIX has not been reported.

A common side effect of gene therapy is increased liver enzymes, in particular increased ALT, which can lead to a reduction in or loss of therapeutic effect. This occurs more frequently in phase-3 trials on gene therapy for hemophilia A (89%) (28) compared to gene therapy for hemophilia B (17%) (21). Elevated levels of other transaminases, such as aspartate aminotransferase (AST = glutamate oxaloacetate transaminase [GOT]), may also be measured, but not liver synthesis parameters or bilirubin.

In many cases, this is due to an unpredictable T cell-induced immune response to transduced liver cells that present capsid fragments of the viral vector on their surface, which can result in an asymptomatic and transient rise in transaminases (10). To date, all increases in liver values could be successfully treated with temporary immunosuppressive therapy, for example, glucocorticoids. In some cases, glucocorticoids have also been used prophylactically, such as in the B-AMAZE study, sometimes together with tacrolimus (22). However, in some patients, it was not possible to return to the originally achieved clotting factor level.

Therefore, close monitoring of liver enzymes is important in order to initiate immunosuppressive treatment as early as possible. It has been shown that prompt initiation of immunosuppression can contribute to the preservation of factor expression (10). In the open-label phase-3 trial on gene therapy of hemophilia A, the median duration of immunosuppression was 230 days (22–551 days) (28), which significantly contributed to the occurrence of corticosteroid-related side effects. The need for immunosuppression was comparatively lower in a phase-3 trial on gene therapy for hemophilia B with a median duration of 78 days and in no patients after week 26 (21). The reasons for these differences remain unclear and may be linked to the fact that hepatocytes require an adaptation period in order to carry out the production of FVIII.

The development of hepatocellular carcinoma, discovered during routine follow-up approximately 1 year after gene therapy for hemophilia B, was recently reported in a patient with a history of previously treated hepatitis C infection, raising the question of a causal relationship with gene therapy. Histopathological investigation revealed no link to gene therapy (31). At 2.6–4.1 years following gene therapy, five participants in a study on gene therapy for hemophilia A had liver biopsies showing no abnormal histopathological findings in the liver, with vector DNA present in episomal forms and not integrating into the genome (32).

Therefore, continued follow-up, particularly with regard to liver health and inclusion in national and international registries, such as The World Federation of Hemophilia (WFH) Gene Therapy Registry (33), is imperative, not least in view of the theoretical risk of malignancy.

Not only the prospect of freedom from hemorrhage with improved quality of life but also the risks of gene therapy should be discussed between patient and physician in order for a shared decision to be taken (34).

In view of the complexity of novel therapies and their interaction with coagulation factor products as well as of laboratory testing, treatment should be performed in an experienced hemophilia center and coordinated on the basis of a hub-and-spoke model. This model refers to a graded and partly overlapping integrated care model (35), whereby hub centers are hemophilia centers (36). Electronic platforms should be used for data acquisition and transmission since electronic data management using e-diaries plays an important role in the coordination of gene therapy (37).

Finally, the funding of hemophilia therapy that lasts as long possible will also be challenging, bearing in mind the potential uncertainties about the therapy, such as response to treatment, individual factor levels, and potential adverse events (38).

Due to the development of high-titer antibodies to AAV following gene therapy and cross-reactivity between various AAV serotypes, it is also not possible to repeat gene therapy.

In summary, it can be concluded that significant advances have been made over the last 10 years in gene therapy for hemophilia; compared to previous treatments, these raise the prospect of significantly lower bleeding rates and, to a great extent, freedom from hemorrhage.

It is likely that different concepts are needed for gene therapy in children, given that the liver is still growing in childhood—thus, one cannot assume a constant response to gene therapy. Further innovative gene therapy concepts are required in order to overcome these limitations (39, 40).

Conflict of interest statement
Prof. Miesbach received consultancy fees from Bayer, BioMarin, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Pfizer, Sanofi, Takeda/Shire, uniQure,
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He is a member of the Data Monitoring Committee or Advisory Board of Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire, uniQure and received research support from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Takeda/Shire.

He is head of the working group Gene Therapy Working Group of the German Society for Thrombosis and Hemostasis Research (*Gesellschaft für Thrombose- und Hämostaseforschung*, GTH) as well as Treasurer and Head of the Gene Therapy Working Group of the European Association for Haemophilia and Allied Disorders.

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He is Vice Chairman of the GTH and President of the European Association for Haemophilia and Allied Disorders.

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References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al.: Guidelines for the management of hemophilia. Haemophilia 2012; 19: e1–47.
2. World Federation of Hemophilia (WFH): Report on the Annual Global Survey 2020. Montreal, Canada, 2021.
3. Miesbach W, Schwäble J, Müller MM, Seifried E: Treatment options in hemophilia. Dtsch Arztebl Int 2019; 116: 791–8.
4. Manco-Johnson MJ, Lundin B, Funk S, et al.: Effect of late prophylaxis in hemophilia on joint status: a randomized trial. J Thromb Haemost 2017; 15: 2115–24.
5. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al.: Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; 357: 535–44.
6. Mazepa MA, Monahan PE, Baker JR, Riske BK, Soucie JM: Men with severe hemophilia in the United States: birth cohort analysis of a large national database. Blood 2016; 127: 3073–81.
7. Oldenburg J: Optimal treatment strategies for haemophilia: achievements and limitations of current prophylactic regiments. Blood 2015; 125: 2038–44.
8. O'Hara J, Hughes D, Camp C, Burke T, Carroll L, Diego DG: The cost of severe haemophilia in Europe: the CHESS study. Orphanet J Rare Dis 2017; 12: 106.
9. The National Library of Medicine: www.clinicaltrials.gov (last accessed on 20 April 2021).
10. Leebeek FWG, Miesbach W: Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. Blood 2021; 138: 923–31.
11. Nathwani AC, Tuddenham EG, Rangarajan S, et al.: Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. N Engl J Med 2011; 365: 2357–65.
12. Nathwani AC, Reiss UM, Tuddenham EG, et al.: Long-term safety and efficacy of factor IX gene therapy in hemophilia B. N Engl J Med 2014; 371: 1994–2004.
13. Nathwani AC, Reiss U, Tuddenham E, et al.: Adeno-associated mediated gene transfer for hemophilia B:8 year follow up and impact of removing "empty viral particles" on safety and efficacy of gene transfer. Blood 2018; 132 (Suppl. 1): 491.
14. Miesbach W, Meijer K, Coppens M, et al.: Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood 2018; 131: 1022–31.
15. Miesbach W, Meijer K, Coppens M, et al.: Five year data confirms stable FIX expression and sustained reductions in bleeding and factor IX use following AMT-060 gene therapy in adults with severe or moderate-severe hemophilia B. Abstract. Res Pract Thromb Haemost. 2021; 5 (Suppl. 2). https://abstracts.isth.org/abstract/five-year-data-confirms-stable-fix-expression-and-sustained-reductions-in-bleeding-and-factor-ix-use-following-amt-060-gene-therapy-in-adults-with-severe-or-moderate-severe-hemophilia-b/ (last accessed on 28 October 2022).
16. Simioni P, Tormene D, Tognin G, et al.: X-linked thrombophilia with a mutant factor IX (factor IX Padua). N Engl J Med 2009; 361: 1671–5.
17. Samelson-Jones BJ, Finn JD, George LA, Camire RM, Arruda VR: Hyperactivity of factor IX Padua (R338L) depends on factor VIIIa cofactor activity. JCI Insight 2019; 5: e128683.
18. George LA, Sullivan SK, Giermasz A, et al.: Hemophilia B gene therapy with a high-specific-activity factor IX variant. N Engl J Med 2017; 377: 2215–27.
19. Samelson-Jones B, Sullivan SK, Rasko JEJ, et al.: Follow-up of more than 5 years in a cohort of patients with hemophilia B treated with fidanacogene elaparvovec adeno-associated virus gene therapy. Blood (2021) 138 (Suppl. 1): 3975.
20. von Drygalski A, Giermasz A, Castaman G, et al.: Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B. Blood Adv 2019; 3: 3241–7.
21. Miesbach W, Leebeek FWG, Recht M, et al.: Final analysis from the pivotal phase 3 hope-B gene therapy trial: stable steady-sate efficacy and safety of etranacogene dezaparvovec in adults with severe or oderately severe haemophilia B. Haemophilia 2022; 28, S1, Special Issue: 15th Annual Congress of European Association for Haemophilia and Allied Disorders 2022, 2–4 February 2022, Virtual Meeting Presentation: 99–100.
22. Chowdary P, Shapiro S, Makris M, et al.: Phase 1–2 trial of AAVS3 gene therapy in patients with hemophilia B. N Engl J Med 2022; 387: 237–47.
23. Rangarajan S, Walsh L, Lester W, et al.: AAV5–factor VIII gene transfer in severe hemophilia A. N Engl J Med 2017; 377: 2519–30.
24. Pasi KJ, Rangarajan S, Mitchell N, et al.: Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for haemophilia A. N Engl J Med 2020; 382: 29–40.
25. Pasi KJ, Laffan M, Rangarajan S, et al.: Persistence of haemostatic response following gene therapy with valoctocogene roxaparvovec in severe haemophilia A. Haemophilia 2021; 27: 947–56.
26. Laffan M, Rangarajan S, Lester W, et al.: Hemostatic results for up to 6 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A [abstract]. www.abstracts.isth.org/abstract/hemostatic-results-for-up-to-6-years-following-treatment-with-valoctocogene-roxaparvovec-an-aav5-hfviii-sq-gene-therapy-for-severe-hemophilia-a/. (last accessed on 23 August 2022).
27. Quinn J, Delaney KA, Wong WY, Miesbach W, Bullinger M: Psychometric validation of the haemo-QOL-A in participants with hemophilia a treated with Gene therapy. Patient Relat Outcome Meas 2022; 13: 169–80.
28. Ozelo MC, Mahlangu J, Pasi KJ, et al.: Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med 2022; 386: 1013–25.
29. 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: 1961–73.
30. Johnson V: Hemophilia A gene therapy placed on clinical hold.CGTLive. www.cgtlive.com/view/hemophilia-a-gene-therapy-clinical-hold. (last accessed on 29 June 2022).
31. Schmidt M, Foster GR, Coppens M, et al.: Liver safety case report from the phase 3 HOPE-B gene therapy trial in adults with hemophilia B [abstract]. Res Pract Thromb Haemost. 2021; 5 (Suppl 2). https://abstracts.isth.org/abstract/liver-safety-case-report-from-the-phase-3-hope-b-gene-therapy-trial-in-adults-with-hemophilia-b/ (last accessed on 7 November 2022).
32. Fong S, Yates B, Sihn CR, et al.: Interindividual variability in transgene mRNA and protein production following adeno-associated virus gene therapy for hemophilia A. Nat Med 2022; 28: 789–97.
33. Konkle B, Pierce G, Coffin D, et al.: ISTH subcommittee on factor VIII, factor IX, rare bleeding disorders. Core data set on safety, efficacy, and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. J Thromb Haemost 2020; 18: 3074–7.

34. Miesbach W, O'Mahony B, Key NS, Makris M: How to discuss gene therapy for haemophilia? A patient and physician perspective. Haemophilia 2019; 25: 545–57.
35. Miesbach W, Chowdary P, Coppens M, et al.: Delivery of AAV-based gene therapy through haemophilia centres—a need for re-evaluation of infrastructure and comprehensive care: a joint publication of EAHAD and EHC. Haemophilia 2021; 27: 967–73.
36. Miesbach W, Baghaei F, Boban A, et al.: Gene therapy of hemophilia: hub centres should be haemophilia centres: a joint publication of EAHAD and EHC. Haemophilia 2022; 28: e86–e8.
37. Miesbach W, Eichler H, Holstein K, et al.: Electronic diaries in the management of haemophilia gene therapy: perspective of an expert group from the German, Austrian and Swiss Society on Thrombosis and Haemostasis (GTH). Haemophilia 2022; 28: 264–9.
38. Goodman C, Berntorp E, Wong O: International Haemophilia Access Strategy Council. Alternative payment models for durable and potentially curative therapies: the case of gene therapy for haemophilia A. Haemophilia 2022; 28 (Suppl. 2): 27–34.
39. Sanal MG, Srivastava A: Gene therapy for hemophilia. NEJM 2022; 386: 2247.
40. Pipe SW, Gonen-Yaacovi G, Segurado OG: Hemophilia A gene therapy: current and next-generation approaches. Expert Opin Biol Ther 2022; 22: 1099–115.

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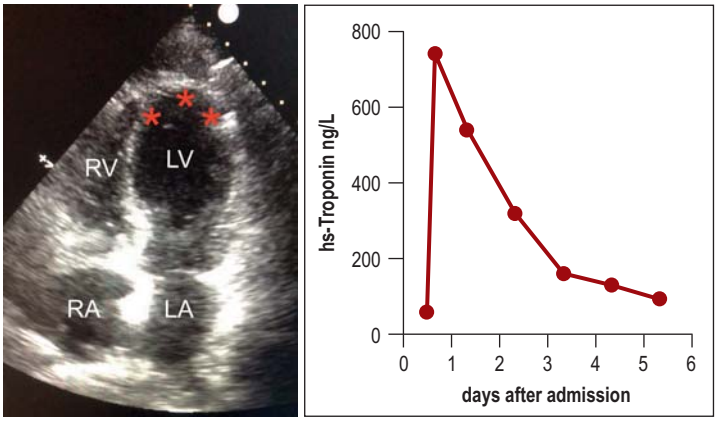
CLINICAL SNAPSHOT

Point-of-Care Ultrasound for the Diagnosis of Takotsubo Cardiomyopathy

A 71-year-old female patient presented to our emergency department with acute dyspnea in exacerbated COPD. Following transfer to a normal ward, laboratory tests revealed a pronounced increase in hs-troponin level *(Figure, right)* without an electrocardiographic correlate. Because an invasive exclusion of coronary macroangiopathy and an unremarkable echocardiography had been performed three months previously, an immediate cardiac catheterization was waived. Due to progressive dyspnea and newly diagnosed tachycardic atrial fibrillation, the patient was transferred to our intensive care unit (day 2 following admission). Point-of-care ultrasound (POCUS) on takeover showed takotsubo cardiomyopathy with ballooning in the apical region of the heart *(Figure, left)*. This was most likely triggered by severe dyspnea. The patient reported that this had caused her to fear for her life. The patient stabilized with standard therapy comprising beta blockers, ACE inhibitors, therapeutic anticoagulation, and anxiolysis with benzodiazepines and a morphine pump. The rise in troponin declined in the further course, and pump function normalized on standardized echocardiography (day 13 following admission). The case presented here illustrates the relevance of POCUS for the immediate differential diagnosis of acute symptom complexes.



Left: echocardiography, apical four-chamber view RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium; in systole, the LV shows ballooning (red asterisk) of the apical region of the heart with local akinesia. The basal wall segments exhibit good contraction. In terms of image morphology, the left ventricle resembles a Japanese octopus trap (*takotsubo*). Right: graphic representation of the trend in hs-troponin levels following the days after admission.

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Questions on the article in issue 51–52/2022:

Gene Therapy for Hemophilia—Opportunities and Risks

cme plus

The submission deadline is 26 December 2023. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

By which mode of inheritance is hemophilia passed on?

a) Autosomal dominant
b) X-linked dominant
c) Autosomal recessive
e) Autosomal intermediate
e) X-linked recessive

Question 2

Which clotting factor is deficient in 80–85% of hemophilia patients?

a) Clotting factor V
b) Clotting factor VII
c) Clotting factor VIII
d) Clotting factor IV
e) Clotting factor X

Question 3

Approximately how many patients with hemophilia were receiving treatment in Germany in 2020?

a) Approximately 1500
b) Approximately 2200
c) Approximately 3000
d) Approximately 4600
e) Approximately 6900

Question 4

How is mild hemophilia defined in terms of laboratory parameters?

a) Factor level 1–5 IU/dL
b) Factor level 5–40 IU/dL
c) Factor level 40–60 IU/dL
d) Factor level 50–400 IU/dL
e) Factor level 300–600 IU/dL

Question 5

At present, which is the vector mainly used in the gene therapy approach to the treatment of hemophilia?

a) Non-pathogenic adeno-associated viruses with increased replication capacity
b) Non-replicating and non-pathogenic lentiviruses
c) Non-pathogenic lentiviruses with increased replication capacity
d) Non-replicating pathogenic lentiviruses
e) Non-replicating and non-pathogenic adeno-associated viruses

Question 6

Which side effect is common in gene therapy for hemophilia?

a) Elevated bilirubin
b) Elevated blood pressure
c) Elevated liver enzymes
d) Elevated liver synthesis parameters
e) Elevated intraocular pressure

Question 7

What happens to the gene transferred into the cells in gene therapy for hemophilia?

a) It remains as episomal DNA in the cytosol.
b) It remains as RNA on the ribosomes.
c) It remains as RNA in the nucleus.
d) It remains as episomal DNA in the nucleus.
e) It is integrated in the chromosomal DNA of the cell.

Question 8

To date, what is the longest period of time—mentioned in the text—for which stable factor activity was demonstrated in a study on gene therapy for hemophilia B?

a) 2 Years
b) 3 Years
c) 5 Years
d) 8 Years
e) 11 Years

Question 9

It is possible that the CRISPR/CAS method will be used in the future for the treatment of hemophilia. Which potential advantage of this method is highlighted in the article?

a) The gene mutation is permanently corrected in the cell.
b) The treatment is low-risk.
c) There is more experience with CRISPR/CAS.
d) No viruses are needed as vectors.
e) There are no contraindications to this treatment.

Question 10

By what percentage were bleed rates reduced in the studies on hemophilia B following gene therapy compared to the previous treatment?

a) 2–11%
b) 6–26%
c) 18–30%
d) 33–40%
e) 53–96%