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FORUM

Corticosteroid use to mitigate transaminitis-associated decline in FVIII levels following valoctocogene roxaparvovec gene therapy: clinical practice guidance

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Abstract

Valoctocogene roxaparvovec is the only factor VIII (FVIII) gene therapy currently approved for adults with severe hemophilia A in Europe and the USA. Elevated alanine transaminase (transaminitis) has been the most common adverse event observed during valoctocogene roxaparvovec clinical trials. Typically mild and transient, this marker of hepatocyte injury coincides, in some patients, with reduced FVIII levels and is generally managed with a reactive course of corticosteroids. An essential step in optimizing outcomes for patients who receive valoctocogene roxaparvovec is reviewing the extensive evidence currently available on this topic to determine practices for

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managing transaminitis, if it occurs. This forum article provides practical guidance based on the available clinical data and expert opinion for evaluating and managing transaminitis with corticosteroids to mitigate potential declines in FVIII activity levels in adults with severe hemophilia A who have received valoctocogene roxaparvovec.

KEYWORDS
factor VIII, gene therapy, hemophilia A, transaminitis, valoctocogene roxaparvovec

1 | INTRODUCTION

The development of gene therapy has heralded a new era of treating severe hemophilia A, allowing endogenous production of factor VIII (FVIII) following the transfer of a functional copy of the FVIII coding sequence. Valoctocogene roxaparvovec is currently the only FVIII gene therapy approved by the European Medicines Agency and the United States Food and Drug Administration for the treatment of adults with severe hemophilia A [1]. Valoctocogene roxaparvovec consists of a B-domain–deleted human FVIII coding sequence with a hybrid liver-selective promoter packaged in an adeno-associated virus (AAV) serotype 5 vector [2].

Clinical trial data indicate that valoctocogene roxaparvovec offers the potential for multiyear production of FVIII [3], durable bleed control, and reduced treatment burden in adults with severe hemophilia A [2,4–7]. However, using an AAV vector to deliver DNA to hepatocytes to allow transgene expression—a technique commonly employed with gene therapies across a wide range of monogenic diseases—may also lead to immunologic and cellular responses and potential hepatoxicity [8]. In clinical trials with valoctocogene roxaparvovec, as well as with other AAV-mediated liver-directed gene therapies for hemophilia [9,10], the most common adverse event (AE) was transaminitis (elevation of alanine transaminase [ALT]), a marker of hepatocyte injury, that appeared to coincide with reduced FVIII levels in some patients [2,4,6,7].

As with other AAV gene therapies, corticosteroids have been used with valoctocogene roxaparvovec to manage transaminitis and mitigate the potential decline in transgene expression [11]. Extensive data on this topic have been collected during the valoctocogene roxaparvovec clinical development program in adults with severe hemophilia A [2,4–7,12,13] over 7 years from recipients in the phase 1/2 BMN 270-201 study (NCT02576795) and over 4 years in the phase 3 GENEr8-1 trial (NCT03370913) [3,13,14]. Ongoing clinical trials and a real-world registry continue to collect further information on the relationship between ALT levels, corticosteroid use, and FVIII activity levels.

The production of FVIII and maintenance of its activity level are key measures of success with valoctocogene roxaparvovec. An essential step is, therefore, to navigate the available evidence to determine the best approach for managing transaminitis with corticosteroids to mitigate the potential decline in FVIII activity levels, which is sometimes associated with ALT elevations. Accordingly, a panel of experienced hematologists and hepatologists convened in October 2023 to consider the evidence with valoctocogene roxaparvovec in its totality, as well as their collective clinical experience, to develop practical guidance for clinicians. The recommendations made by the panel have been further developed into this clinical guidance article. The guidance provided is specific to valoctocogene roxaparvovec and may not apply to other gene therapies for hemophilia.

2 | MONITORING LIVER FUNCTION IN PATIENTS RECEIVING VALOCTOCOGENE ROXAPARVOVEC

Per study protocols, liver enzymes and function were monitored closely in all clinical trials with valoctocogene roxaparvovec in adults with severe hemophilia A, both before and after treatment. Patients with significant baseline liver disease (substantial liver fibrosis [3 or 4 on the Batts–Ludwig or METAVIR scoring systems] or cirrhosis [by ultrasound]) or active damage/dysfunction (conservatively defined as ALT, aspartate transaminase [AST], gamma-glutamyl transferase, total bilirubin, alkaline phosphatase >1.25× the upper limit of normal [ULN], or international normalized ratio ≥1.4) were excluded [2,6]. Following administration of valoctocogene roxaparvovec, markers of hepatocellular damage (AST, ALT), cholestasis (alkaline phosphatase, gamma-glutamyl transferase), and liver function (eg, albumin, total proteins, and cholinesterase) were measured at least weekly for weeks 1 to 36, at least every 2 weeks from weeks 37 to 52, and at least every 3 months thereafter at a central laboratory; any abnormalities were acted upon (described in detail below) [2,6]. The frequency and duration of liver testing could be changed at the discretion of the investigator.

GENEr8-1 is an ongoing, open-label, single-group phase 3 trial assessing the efficacy and safety of valoctocogene roxaparvovec in 134 adults with severe hemophilia A [6]. After 2 years of follow-up, AEs of elevated ALT (≥1.5× baseline or above ULN, herein referred to as "transaminitis") had been observed in most (88.8%) patients following treatment with valoctocogene roxaparvovec [7]. Transaminitis was mild in most cases (84.9% grade 1 [>ULN to 3× ULN]), usually of short duration (median: 21 days), with no life-threatening or fatal cases observed [7]. Transaminitis remained the most common AE during year 3 (23.7%), with most events being mild (90.3%) or

moderate (9.7%) [13]. The duration of the elevations ranged from 8 to 138 days [13]. The rates of ALT elevations observed at year 3 were consistent with the background rate in the general population [15]. During all follow-up of GENEr8-1, the median duration of ALT elevation above the ULN was 10.0 (range: 0.6-144.6) weeks [13]. Grade 3 (>5× ULN to 20× ULN) AEs of transaminitis occurred in 8.2% of patients and were mostly observed in first 26 weeks, with 1 event at week 70 postinfusion. Overall, the safety profile of valoctocogene roxaparvovec was favorable, with no events meeting Hy's law criteria (a measure designed to assess hepatocellular/cholestatic drug-induced liver injury). Furthermore, following valoctocogene roxaparvovec administration, no events of acute liver failure have been observed to date [13].

Rates of transaminitis observed in GENEr8-1 were generally consistent with those observed in the open-label phase 1/2 BMN 270-201 study with valoctocogene roxaparvovec; that is, in the 6×10^{13} vg/kg cohort, 85.7% of patients experienced AEs of transaminitis, all of which were mild (grade 1) [2].

Across all clinical studies with valoctocogene roxaparvovec, ALT elevations generally showed a characteristic biphasic pattern, with an initial increase in ALT levels within 14 weeks of infusion and a second, lower peak at ~28 weeks. The cause of the ALT increases remains unclear. This may involve contributions from innate and adaptive immunity but also cellular stress related to FVIII expression [16–24]. Indeed, a cytotoxic T cell response has been postulated as the cause of the ALT elevations observed following the systemic administration of AAV gene therapies (reviewed in ref 25). However, it remains unclear whether sampling the peripheral blood mononuclear cell population accurately reflects effector cells that may be present in the liver. Elucidation of the mechanisms underlying transaminitis will inform appropriate targeted treatment. As we gain further insights into the etiology of transaminitis, long-term monitoring of all treated patients with ongoing transaminitis is especially important, and appropriate hepatological support should be provided on a case-by-case basis in consultation with a hepatologist.

2.1 | Clinical practice guidance for liver assessment before valoctocogene roxaparvovec administration

Before considering valoctocogene roxaparvovec as a treatment option, baseline liver health should be established, including assessment of liver enzymes and function tests within 3 months, ultrasound exploration to rule out morphological signs suggestive of advanced chronic liver disease (eg, irregular liver surface, caudate liver lobe hypertrophy, focal liver lesions, and indirect signs of portal hypertension), and recent fibrosis assessment within 6 months. Measurement of liver stiffness based on ultrasound elastography (eg, FibroScan) is the preferred method; laboratory assessments (eg, AST to Platelet Ratio Index or Fibrosis-4 Index) may be a suitable alternative to rule out advanced fibrosis/cirrhosis when ultrasound elastography is unavailable [26–28]. However, in candidates treated with successful antiviral therapy, the final exclusion of advanced fibrosis/cirrhosis should be taken by a hepatologist to overcome the limitations of noninvasive fibrosis tests [29–31].

ALT levels are subject to significant intraindividual variation, so at least 2 measurements should be taken to establish a baseline, with ALT levels consistently within the normal range before commencing valoctocogene roxaparvovec therapy [26,27]. A reliable measurement of baseline ALT is vital in the context of the conservative cutoffs used to define abnormalities in ALT (outlined below), particularly for patients with low baseline ALT levels, to ensure a reliable foundation from which potential elevations can be assessed [32]. Some additional considerations when measuring ALT levels are summarized in Figure 1. As ALT diurnal variations of up to 45% have been observed (and many of these are highest in the afternoon), the time of day when samples are collected should be considered [33]. Other factors that can influence ALT levels include changes in medication, use of herbal products, diet, alcohol intake, strenuous exercise, and infection.

Currently, administration of valoctocogene roxaparvovec therapy is contraindicated in patients with acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic hepatic infections (such as chronic active hepatitis B), significant hepatic fibrosis (currently conservatively defined as >8 KPa on FibroScan), cirrhosis, a history of hepatic malignancy, or hepatic laboratory abnormalities (ALT, AST, gamma-glutamyl transferase, or total bilirubin >1.25× ULN) [26,27].

2.2 | Clinical practice guidance for monitoring ALT levels after valoctocogene roxaparvovec administration

Based on the clinical trial data and Prescribing Information, it is recommended that ALT levels be monitored at least weekly for the first 26 weeks after valoctocogene roxaparvovec therapy, at least every 2 to 4 weeks through year 1, at least every 3 months through year 2, and every 6 months thereafter (Figure 1), or as clinically indicated. Accumulating evidence and patient-specific factors may alter this recommendation in the future. All patients with ALT increases should undergo a hepatological workup to rule out causes other than gene therapy. Additional biochemical investigations, including measurement of AST and creatine phosphokinase, can help rule out alternative causes for ALT elevations; autoimmune hepatitis and acute hepatitis infection should also be excluded. As described below, a decrease in FVIII activity may accompany ALT elevation; FVIII activity levels should be monitored on the same schedule and as clinically indicated [26,27]. Patients with ALT levels ≥1.5 × baseline or above ULN could, therefore, be candidates for corticosteroid therapy (see below). Consideration should be given to absolute ALT levels; for example, individuals with very low ALT levels at baseline could surpass 1.5× baseline but still be within normal levels. Physicians should use their clinical judgment to guide intervention in such cases, in accordance with the advice in section 3.1, although the benefit/risk ratio of immunosuppression is unclear in cases where ALT levels remain in the physiologic range and FVIII does not decline [32].

Monitoring ALT levels before valoctocogene roxaparvovec administration
☐ At least two ALT measurements to determine baseline
When interpreting ALT measurements, consider the following:
☐ Consistent time of day for blood draw?
☐ Same laboratory/hospital?
☐ Same equipment used?
Check for changes in:
☐ Medication
☐ Herbal products
☐ Dietary habits
☐ Alcohol intake
☐ Exercise
☐ Environmental factors
☐ Ensure ALT consistently within the normal range
☐ Rule out acute or uncontrolled chronic hepatic infections, significant hepatic fibrosis (3 or 4 on the Batts-Ludwig or METAVIR scoring systems), cirrhosis (by ultrasound, a history of hepatic malignancy, or hepatic laboratory abnormalities)
☐ Consult hepatologist
Monitoring ALT levels after valoctocogene roxaparvovec administration
Monitor ALT levels:
☐ Weekly for the first 26 weeks
☐ Every 2 to 4 weeks through year 1
☐ Every 3 months through year 2
☐ Every 6 months thereafter or as clinically indicated
☐ Patients with ALT levels ≥1.5 × baseline or >ULN: consider immediate corticosteroid treatment
☐ Rule out other causes of ALT elevation
☐ Measure FVIII activity levels at the same time as blood draw to monitor any accompanying changes

FIGURE 1 Liver health checklist before and after patients receive valoctocogene roxaparvovec. ALT, alanine transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; FVIII, factor VIII; ULN, upper limit of normal.

Hepatologists with expertise in gene therapy are a recommended component of the multidisciplinary team [34]. Detailed guidance for hepatologists regarding liver-related complications with AAVs for gene therapy has recently been published [25,32]. Liver biopsies are currently not required in patients receiving valoctocogene roxaparvovec, although liver biopsy substudies in the clinical trial setting have helped to begin elucidating the mechanisms underlying transaminitis [35,36] and further biopsies in selected patients may add further information in the future.

TABLE Corticosteroid strategy across clinical trials with valoctocogene roxaparvovec [2,3,5,6,12].

Study name	Corticosteroid strategy
BMN 270-201 (6×10^{13} vg/kg cohort, *N* = 7)	• Early (2-4 wk) prophylactic corticosteroid use in all patients • Reactive corticosteroids if ALT ≥ 1.5× baseline, or ALT > ULN; tapered after ALT improved
GENEr8-1 (directly enrolled population, *N* = 22)	• Reactive corticosteroid use only • Used if ALT ≥ 1.5× ULN, or ALT > ULN and >2× baseline
GENEr8-1 (rollover population, *N* = 112)	• Reactive corticosteroid use only • Used if ALT > ULN, or ALT ≥1.5× baseline; tapered once ALT reached baseline
GENEr8-3 (*N* = 22)	• Prophylactic corticosteroid use starting on day 1 • Starting dose: 40 mg; taper ended at 19 wk • Additional reactive use if ALT > ULN, or ALT ≥ 1.5× baseline; tapered after ALT improved

ALT, alanine aminotransferase; ITT, intent-to-treat; ULN, upper limit of normal; wk, weeks.

3 | MANAGEMENT OF TRANSAMINITIS WITH CORTICOSTEROIDS IN PATIENTS RECEIVING VALOCTOCOGENE ROXAPARVOVEC

In clinical trials with valoctocogene roxaparvovec, corticosteroid therapy was used to treat transaminitis to mitigate actual and potential declines in FVIII activity levels [2,6]. Indeed, most (79.1%) patients received corticosteroids to treat transaminitis after infusion in GENEr8-1 [2,7]. The median total duration of corticosteroid use to treat ALT elevation per patient in GENEr8-1 was 33 (range, 3-120) weeks, and the median total dose was 6420 (range, 960-31 760) mg [13].

The corticosteroid strategy employed in the clinical trials with valoctocogene roxaparvovec evolved over time (Table) [6,7]. In GENEr8-1, after dosing the initial directly enrolled cohort of patients with valoctocogene roxaparvovec, ALT elevations 1.5× ULN were observed with some reductions in FVIII levels in some patients; consequently, the threshold for ALT elevation was lowered for patients in the directly enrolled and rollover cohort population (>ULN or 1.5× baseline). Furthermore, after analysis of the directly enrolled subjects, corticosteroid tapering was not initiated until ALT levels returned to <1.5× baseline [6,7]. Despite prolonged use in the rollover population, minimal differences were observed in FVIII activity during longitudinal follow-up for up to 4 years. The US Prescribing Information is generally aligned with the GENEr8-1 study protocol; at the same time, the European Medicines Agency Summary of Product Characteristics recommends a less intensive reactive corticosteroid regimen administered for a shorter duration than used in the GENEr8-1 study (described in detail below) [26,27].

Regarding the impact of prophylactic steroids, the phase 3 GENEr8-3 trial (NCT04323098) evaluated the safety and efficacy of valoctocogene roxaparvovec in combination with prophylactic corticosteroids (initiated on day 1) in 22 patients with severe hemophilia A. One-year data from this trial did not indicate a clear benefit of prophylactic corticosteroids in mitigating ALT elevations [12]. In year 1, 90.9% of patients experienced transaminitis. Mean peak ALT elevation above the ULN was higher in GENEr8-3 (192.0 U/L) than in GENEr8-1 (114.5 U/L), although the proportion of patients with ALT > ULN or ≥1.5× baseline was lower in GENEr8-3 (77.3% vs 93.3%) [12].

3.1 | Clinical practice guidance on the use of corticosteroids to manage transaminitis in patients receiving valoctocogene roxaparvovec

As per the Prescribing Information, early (eg, up to 26 weeks) elevations in ALT that reach thresholds (≥1.5× baseline or >ULN) following administration of valoctocogene roxaparvovec should be treated with corticosteroids started as early as possible on a reactive basis to prevent potential worsening of the ALT elevation and possible FVIII decline (Figure 1) [7,26,27]. Oral prednisolone at a dose of 1 mg/kg/d up to a maximum dose of 60 mg/d or the equivalent dose of another corticosteroid is recommended, in line with the current Prescribing Information (Figure 1) [26,27]. Patients receiving valoctocogene roxaparvovec should have undergone screening before treatment; therefore, ALT elevations that are delayed or nonresponsive to corticosteroids should be investigated. Severe (grade 3) ALT elevations without any obvious alternate etiology should be managed with corticosteroids to potentially mitigate transaminitis-associated decline in FVIII levels pending workup. While some patients may experience elevated transaminases beyond year 1 following valoctocogene roxaparvovec treatment [7], there is minimal benefit of starting a corticosteroid course in these circumstances, and it is not recommended to treat transaminitis to mitigate potential decline in FVIII activity levels after 6 months. Clinical trial data also do not support a safety benefit with a prophylactic corticosteroid regimen starting on day 1 in preventing ALT elevations and, unlike during the first year of therapy, later ALT elevations are not associated with unexpected declines in FVIII activity levels [12].

ALT levels should be assessed at least weekly during corticosteroid therapy. A corticosteroid "exit strategy" based on a prompt taper of therapy upon response is recommended, with the course finished as quickly as appropriate once ALT levels return to <1.5× baseline or <ULN according to the schedule outlined in Figure 2. Following successful treatment with corticosteroids, continued monitoring of ALT levels is recommended.

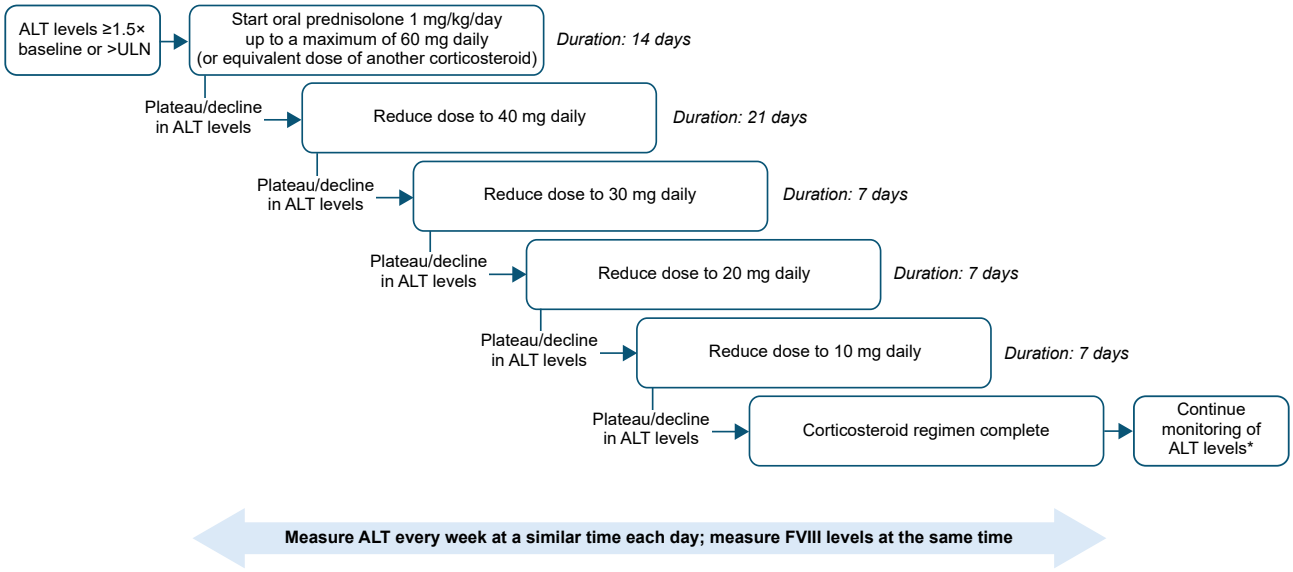


FIGURE 2 Monitoring ALT levels during corticosteroid treatment and a recommended corticosteroid tapering strategy [24][#]. *If ALT levels are ≥1.5× baseline or >ULN, resume corticosteroid treatment. [#]When response is inadequate, clinical judgment is needed to decide on an appropriate schedule of taper and discontinuation of corticosteroid treatment, and on the use of alternative immunosuppressants as warranted. ALT, alanine transaminase; FVIII, factor VIII; ULN, upper limit of normal.

There is no known benefit to long-term corticosteroid therapy, and long-term immunosuppression with corticosteroids should be avoided for safety reasons. The safety profiles of corticosteroids are well characterized; as per good clinical practice, any treatment-related AEs should be monitored and managed according to the relevant Prescribing Information. Common steroid-related AEs include hypertension, weight gain, diabetes, mood disorder, and opportunistic infections. Patients with a history of previous hepatitis B virus (HBV) infection, particularly those who are hepatitis B core antibody (HBcAb)–positive, could have, under prolonged immunosuppressive therapy, activation of occult HBV infection and should be monitored for this potential risk.

For patients who do not respond adequately to corticosteroids, clinicians should use their clinical judgment on when it is appropriate to taper and discontinue corticosteroid treatment. Alternative immunosuppressive treatment options (eg, tacrolimus, mycophenolate, and budesonide) have been used in a small number of participants in valoctocogene roxaparvovec clinical trials and can be considered if corticosteroids are contraindicated, not tolerated, or ineffective [26,27]; however, experience with these agents in patients who received valoctocogene roxaparvovec is limited (n = 24 patients received tacrolimus in GENEr8-1, n = 13 received mycophenolate, and n = 6 received budesonide) [7] and no firm recommendation can be made for their use in the management of transaminitis in individuals receiving valoctocogene roxaparvovec.

4 | DOES TREATING TRANSAMINITIS WITH CORTICOSTEROIDS MITIGATE THE DECLINE IN FVIII EXPRESSION?

Analyses of clinical trial data on the influence of transaminitis and its subsequent treatment with corticosteroids on FVIII levels have been conducted. In GENEr8-1, meeting the ALT threshold for initiating corticosteroids was not consistently accompanied by a decrease in FVIII levels in all patients [6,7,26,27]. However, patients with early ALT elevations (1.5× baseline or >ULN) tended to have lower FVIII levels, and use of corticosteroids to treat transaminitis reactively mitigated the decline in FVIII levels in most cases [6,7,26,27]. Heterogeneity in the relationship between transaminitis, corticosteroid regimen, and FVIII production suggests that the underlying pathogenic mechanism is complex and multifactorial, and may be pleiotropic. The time the ALT elevation occurs in relation to treatment with valoctocogene roxaparvovec is an important factor.

Clinical trial data do not support a prophylactic corticosteroid regimen starting on day 1 to manage transaminitis and mitigate the decline in FVIII levels; moreover, such a regimen may, in fact, adversely impact the overall FVIII expression outcome [12]. Compared with year 1 mean FVIII activity in GENEr8-1 (42.9 IU/dL), year 1 mean FVIII activity in GENEr8-3 was lower with concomitant prophylactic corticosteroids (16.1 IU/dL) [12]. The underlying reasons for this observation have not yet been fully elucidated.

4.1 | Clinical practice guidance on treating transaminitis with corticosteroids to mitigate the potential decline in FVIII production

In response to the detection of transaminitis, corticosteroid therapy should be promptly initiated as per the guidance outlined. The course should be tapered once ALT levels plateau/start to decline and finished as quickly as appropriate upon return of ALT levels to baseline, with the critical prerogative that the course be decisively

withdrawn if deemed ineffective. FVIII levels should, of course, be monitored in parallel following valoctocogene roxaparvovec dosing.

This recommendation is based on the fact that patients may benefit from reactive corticosteroid therapy to manage transaminitis and mitigate potential decline in FVIII levels. However, based on available evidence, the magnitude and frequency of benefit to transgene expression remains uncertain. Physicians should remain cognizant of the known safety profile of corticosteroids. Importantly, there are insufficient data to support "no corticosteroid intervention."

5 | CONCLUSIONS

The availability of gene therapy for hemophilia A represents an important therapeutic milestone that offers the potential to improve the lives of adults with this severe disease. As more patients across the world are treated with valoctocogene roxaparvovec, in both clinical trials and a real-world setting, timely sharing of valuable clinical experience and cross-specialty collaboration are essential to ensure optimal outcomes for patients. This summary of our current knowledge builds upon the recommendations within the valoctocogene roxaparvovec Prescribing Information [26,27] and also upon general hemophilia gene therapy guidance documents recently published by several scientific societies and working groups [34,37–39] to provide practical advice for evaluating and managing transaminitis with corticosteroids to mitigate the potential decline in FVIII levels.

If needed to manage transaminitis and mitigate potential decrease in FVIII levels, prompt corticosteroid use on a reactive basis is recommended for early ALT elevations, with the course finished as quickly as appropriate upon the return of ALT levels to <1.5× baseline or <ULN, and withdrawn if deemed ineffective at preventing FVIII decline. The ongoing collection of data through long-term follow-up of clinical trial participants and in the real world via registries, including the World Federation of Hemophilia Gene Therapy Registry [40–43], will continue to be vital to furthering our understanding of the relationship between gene therapy dosing, ALT levels, corticosteroid use, and continued FVIII production. The recommendations described here reflect current understanding and experience with valoctocogene roxaparvovec as described in the published literature. New data will inevitably become available in the future. With this in mind, it will be important that this guidance is reviewed and updated regularly by a panel of appropriately qualified experts.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the manuscript, were actively involved in drafting the manuscript and reviewing it critically for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work.

DECLARATION OF COMPETING INTERESTS

G.R.F. has received consulting fees from BioMarin, CSL Behring, GSK, Gilead, and Pfizer and has received speaker bureau fees from BioMarin, CSL Behring, Gilead, and Pfizer. C.H. has received research funding from Bayer, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda, and Sobi and honoraria and speaker bureau fees from Bayer, BioMarin, CAF-DCF, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Shire/Takeda, Sobi, and uniQure. B.A.K. has received institutional research grants from CSL Behring, Pfizer, Sanofi, Spark Therapeutics, and Takeda; royalties from UpToDate; consultancy fees from Be Biotherapeutics, BioMarin, hC Bioscience, Metagenomi, and Regeneron; speaker bureau fees from Pfizer; has participated in advisory boards/data monitoring committees for BioMarin, Novo Nordisk, Pfizer, Sanofi, Spark Therapeutics, and Veralox; and has leadership positions with the Foundation for Women and Girls with Blood Disorders and the World Federation of Hemophilia. D.L. has received research support from BioMarin, CSL Behring, and Sanofi and consulting fees from BioMarin, CSL Behring, Novo Nordisk, Pfizer, Roche, and Sanofi. J.M. has received research support from BioMarin, Novartis, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, Spark Therapeutics, and Vega Therapeutics; consultancy fees from BioMarin, Novo Nordisk, Roche, Sanofi, Spark Therapeutics, and Takeda; and speaker bureau fees from Novo Nordisk, Pfizer, Roche, Sanofi, Takeda, WFH, and the International Society on Thrombosis and Haemostasis (ISTH). W.M. has received institutional grants from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, and Takeda/Shire; consulting fees from Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Sobi, Takeda/Shire, and uniQure; speaker bureau fees from Bayer, BioMarin, Biotest, CSL Behring, Chugai, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda/Shire; and support for attending meetings from Bayer, BioMarin, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda/Shire, and uniQure. V.L.M. has received consulting fees from Alfasigma, BioMarin, CSL Behring, Gore, and Pfizer; speaker bureau fees from Alfasigma, BioMarin, CSL Behring, and Gore; travel support from BioMarin, Sanofi, and Takeda; and has leadership roles with the Italian Association for the Study of the Liver (scientific group), Digestive and Liver Disease (editorial board), *Journal of Hepatology* (editorial board), and Baveno Cooperation Group (scientific group). A.D.L. has participated in a sponsored clinical trial and received consulting fees from BioMarin. M.C.O. has received institutional research grants from BioMarin, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; consultancy fees from Pfizer; speaker bureau fees from Bayer, BioMarin, Novo Nordisk, Roche, Sanofi, and Takeda; has participated in advisory boards for Bayer, BioMarin, Novo Nordisk, Roche, Sanofi, and Takeda; has a leadership role in the Novo Nordisk Haemophilia Foundation; and has been paid to review grants by CSL Behring and Novo Nordisk. F.P. has received speaker bureau fees from Spark Therapeutics and Takeda and has participated in advisory boards for BioMarin, CSL Behring, Regeneron, Roche, Sanofi, and Sobi. S.P. has received consultancy fees from ApcinteX/Centessa, ASC Therapeutics, Bayer, BioMarin, CSL Behring, HEMA Biologics, LFB, Metagenomi, Novo

Nordisk, Pfizer, Poseida Therapeutics, Precision Bioscience, Regeneron, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics, and uniQure; and has participated in advisory boards for GeneVentiv and Equilibra Bioscience. M.R. has received institutional research support from Bayer, BioMarin, CSL Behring, Genentech, Grifols, HEMA Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, and uniQure; consultancy fees from CSL Behring, Genentech, HEMA Biologics, Novo Nordisk, Pfizer, Sanofi, Takeda, and uniQure; is on the board of directors of Partners in Bleeding Disorders; and is employed by Yale School of Medicine, National Bleeding Disorders Foundation. A.S. has received speaker bureau fees from BioMarin, Novo Nordisk, Octapharma, Roche, Sanofi, and Takeda; has participated in advisory boards for BioMarin, Novo Nordisk, Pfizer, Roche, Sanofi, Spark Therapeutics, and Takeda; and has received research grants from Novo Nordisk, Pfizer, Roche, and Sanofi. G.Y. has received an investigator-initiated grant from Sanofi; royalties/licenses from Viatris; consultancy fees from BioMarin, CSL Behring, Genentech, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark Therapeutics, and Takeda; speaker bureau fees from Genentech, Octapharma, Sanofi, Spark Therapeutics, and Takeda; travel support from BioMarin, CSL Behring, Genentech, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark Therapeutics, and Takeda; and has participated in advisory boards for ASC Therapeutics.

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