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ORIGINAL ARTICLE

Gene therapy for people with hemophilia B: a proposed care delivery model in Italy

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Abstract

Background: Gene therapy is designed to provide people with hemophilia B with a steady and elevated factor (F)IX activity, thereby strengthening protection and relieving the burden of frequent replacement therapy infusions. The European Medicines Agency has approved gene therapy for the severe and moderately severe forms of hemophilia B that uses the FIX-Padua variant (etranacogene dezaparvovec).

Objectives: The aim was to provide a document dedicated to hemophilia B gene therapy and give a comprehensive overview of the topic.

Methods: An Italian group of experts in hemophilia carried out a narrative review of the literature and discussed during a virtual meeting several key aspects of the delivery of this treatment in Italy. The discussion covered the organizational model, the role of the multidisciplinary team, the laboratory surveillance, and the patient's journey, from the follow-up to the identification of safety issues and outcome measures.

Results: This article highlights the need to follow the Hub and Spoke organizational model and sheds light on the role of each professional figure within the multidisciplinary teams to favor patient engagement, management, and retention. Moreover, this article stresses the need to perform laboratory tests for patient screening and follow-up and proposes a checklist to help patient identification. Finally, the needs of Italian hemophilia centers have been considered to ensure an efficient implementation of the care delivery model.

Conclusion: It is crucial to ensure that centers are appropriately organized, equipped, and trained to adequately select patients, deliver the gene therapy, and perform follow-up.

KEYWORDS
factor IX-Padua, gene therapy, hemophilia B, organizational model, patient care team, patient outcome assessment

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1 | INTRODUCTION

Hemophilia B (HB) is an X-linked recessive bleeding disorder caused by mutations in the *F9* gene, resulting in a variable deficiency of factor (F)IX in blood [1,2]. There are different phenotypes of the disease, usually associated with the severity of FIX activity reduction. The severe, moderate, and mild forms of HB are characterized respectively by FIX activity <1%, 1% to 5%, and >5% to 40% [3–5]. Bleeding tendency is usually associated with this classification, and joint bleeding (hemarthrosis), the hallmark of the disease, is particularly frequent in the severe form and has a major negative impact on quality of life (QoL) [6,7]. The current standard of care for HB consists of the infusion of plasma-derived or recombinant FIX (rFIX) in case of bleeding or for bleeding prevention (prophylaxis). In people with HB (PWHB) who display severe/moderate forms associated with severe clinical phenotypes, the therapy consists of lifelong prophylactic infusions of rFIX to prevent bleeding and hemarthrosis. Ideally, it should start within the first 3 years of life or soon after the first episode of joint bleeding or after a major bleeding [8,9]. To reduce the burden derived from frequent infusions and to improve bleeding prevention, extended half-life rFIX concentrates have been developed and maintain efficacy when infused every 3 weeks at the lowest frequency [10–15]. Although prophylaxis with extended half-life rFIX minimizes the occurrence of spontaneous bleeding [15], lifelong regular infusions are required, and the fluctuating FIX activity levels can still result in some breakthrough bleeds [16,17]. In addition, 15% to 25% of PWHB are not adherent to prophylaxis [18], resulting in breakthrough bleeding with a possible impact on the progression of arthropathy [19,20]. In this scenario, gene therapy (GT) could provide PWHB with a constant and sustained expression of FIX, thus reducing or abolishing the need for prophylaxis, improving protection, and freeing PWHB from the burden of frequent FIX infusions [21,22]. While some GTs for HB are currently under investigation [23], etranacogene dezaparvovec has already received approval in 2023 from the European Medicines Agency. This GT is indicated for the treatment of adult patients with severe and moderately severe forms of HB without a history of FIX inhibitors. It consists of an adeno-associated viral serotype 5 (AAV5) vector that codifies for the FIX-Padua variant (R338L, FIX-Padua) [24] under the control of a liver-specific promoter [25]. Such therapy has been demonstrated to decrease the need for prophylaxis and diminish annual bleeding, showing superiority vs standard of care. Mean FIX activity was stable and durable for up to 3 years (up to 4 years in 3 patients from the phase 2b study) with values close to the normal range [26–31]. Furthermore, the homologous AMT-060 expressing wild-type FIX confirmed the safety, durability, and stability of FIX expression after 6 years [32]. Data concerning the safety profile of etranacogene dezaparvovec obtained so far showed that about 20% of patients had an asymptomatic elevation of transaminases, and 9 (16.7%) participants received reactive corticosteroids for a mean duration of 79.8 ± 26.6 days (range, 51-130 days) [26].

Given the change of treatment paradigm introduced by GT for HB, this article aims to provide a dedicated document that poses the basis to define the best organizational model able to ensure the efficient delivery of this therapy to the patients. Therefore, the need for a structured organization that follows the Hub and Spoke model, comprising a multidisciplinary team able to guarantee appropriate patient screening, engagement, management, retention, and follow-up, will be highlighted [33].

2 | METHODOLOGY

An Italian multidisciplinary working group composed of hemophilia care professionals, hepatologists, and representatives from patient associations identified the key points that need to be discussed to lay the foundations for a care delivery model of HB GT in Italy. During a virtual meeting, the authors discussed the statements of the Delphi consensus paper published for hemophilia A (HA) [34] with regard to i) the organizational model; ii) patient engagement, management, and retention—role of the multidisciplinary team; and iii) the laboratory surveillance, patient follow-up, and outcomes.

The authors were asked to give their opinions, consider the Italian scenario of HB GT, and reflect on the implementation of this therapy in Italy. The aspects that have reached a consensus (at least 70% of the panelists) throughout the discussion of the working group are presented in this paper. A narrative review of the literature has also been carried out to provide a comprehensive overview of the topics listed above. See Supplementary Methods for details.

3 | RESULTS

3.1 | The organizational model

Hemophilia GT is a treatment for which the Hub and Spoke organizational model has been proposed in a joint publication by the European Association for Haemophilia and Allied Disorders and the

TABLE 1 Possible checklist to identify potential candidates for gene therapy.

Patient's past medical history			
Hemophilia history			
Patient with severe/moderately severe hemophilia B			▫
No (history of) FIX inhibitors			▫
No previous GT treatment			▫
Screening for comorbidities			
List of all current comorbidities (eg, cardiovascular diseases and metabolic disease)			▫
No active infections, uncontrolled, either acute or chronic			▫
Concomitant treatments			
List of all concomitant treatments 1._____ 2._____ 3._____			
Laboratory test results			
FIX inhibitors (BU/mL)	Date	Results	
First determination		Pos. Neg.	▫ ▫
Second determination (if first was positive)		Pos. Neg.	▫ ▫
Liver biomarkers	Date	Results	
ALT (U/mL)[a]		N E	▫ ▫
AST (U/mL)[a]		N E	▫ ▫
ALP (U/mL)		N E	▫ ▫
Total bilirubin		N E	▫ ▫
Other biomarkers' assessment (eg, CPK and AFP)		N E	▫ ▫
Liver health (no later than within 6 mo before GT administration)	Date	Results	
Liver ultrasound[b]		N P	▫ ▫
Liver elastography[b]		N P	▫ ▫
NABs	Date	Results	
AAV5 NAB test		Pos. Neg.	▫ ▫

(Continues)

TABLE 1 (Continued)

Patient's past medical history	
Factors to consider	
Mean alcohol consumption units per week (1 unit = 12 g alcohol = 1 glass of wine/1 mug of beer/1 shot of spirits)	0-6 ▫ 7-14 ▫ >14 ▫
Use of medication or substances	▫
Use of medicinal herbs (eg, green tea, red rice, please specify)	▫
Realistic expectations toward GT outcomes, possible benefits, and uncertainties	▫
Commitment to short-term and long-term follow-up	▫
Exploration of potential issues (such as transportation, distance, etc.)	▫
Acceptance of steroid use if needed	▫
Interference with personal/social/professional life	▫
Support from family/partner/working environment	▫
Family plans for the next 12 mo after treatment	▫
Vaccinations are up to date prior to GT administration	▫
Proposal to be accompanied by a psychosocial worker	▫
GT education	
Hemophilia and GT basics	▫
GT specific information	▫
Process/patient journey	▫
Acceptance of steroid use if needed	▫
Patient has received information according to the patient guide	▫

AAV5, adeno-associated viral serotype 5; AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BU, Bethesda units; CPK, creatine phosphokinase; E, elevated; FIX, factor IX; GT, gene therapy; N, normal; NAB, neutralizing antibody; Neg., negative; P, pathologic; Pos., positive.

[a] Within 3 months prior to treatment.

[b] No later than within 6 months before GT administration. Check the GT summary of product characteristics for details about the timing of laboratory assessments.

European Haemophilia Consortium [33,35]. This model relies on the delivery of services by a network of establishments in which, at the center, there is a highly specialized structure (Hub), which acts as a

coordinator, and to which a series of secondary establishments (Spokes) are connected [36]. In the case of hemophilia GT, this model relies on the collaboration of the comprehensive care/infusion center (Hub) and the connected hemophilia treatment/referral center (Spoke), where the patient is routinely managed [33]. Together with the Spoke center, the Hub center will prepare a list of items that would allow the identification of patients by the Spoke center. The authors propose a possible checklist in Table 1. The Spoke center will check the patient's suitability for GT by filling out the checklist, and the Hub center will verify the accordance of the data to the eligibility criteria; furthermore, the Spoke center is responsible for patients' long-term follow-up and management [33,37]. The Hub center is responsible for educating patients about HB GT by discussing the benefits and possible adverse events (AEs), obtaining the informed consent form, prescribing and administering the GT, and collecting data on patients to be submitted to the national authorities [34]. The Hub center should have the necessary facilities, equipment, and a clinical infusion site for the GT, while the Spoke center should implement suitable follow-up policies and must be in close collaboration with the Hub center. Manufacturers must develop appropriate training tools for the preparations and dissemination of the information at the Hub and Spoke centers. For the best implementation of HB GT, the Hub and the Spoke centers should constantly communicate, share information and experiences, and be able to consistently educate patients about all the phases of the treatment and follow-up [33,37,38]. The Spoke center should inform about the patient selection process, and the Hub center should facilitate the shift of responsibilities to the Spoke center during follow-up [39]. Teleconsultations and regular meetings on shared clinical cases might facilitate the exchange of information between Hub and Spoke. To optimize GT, it is also fundamental that comprehensive communication is established within networks of Hub centers [40].

3.2 | Patient engagement, management, and retention: role of the multidisciplinary team

According to the World Federation of Hemophilia 2020 guidelines, one of the pivotal aspects of the success of GT relies on the presence of multidisciplinary teams in both the Hub, which acts as coordinators, and the Spoke centers [9]. The multidisciplinary team should be composed of specialized hemophilia treaters, hepatologists, immunologists, psychologists, physiotherapists, orthopedists, clinical pharmacists, and dedicated nurses/case managers, and collaboration between these healthcare providers (HCPs) is essential. It is vital that updated information about HB GT is given to all the members of the multidisciplinary team, who must also be trained on every clinical aspect and potential safety issues, guaranteeing an adequate education of patients [40]. Specialized hemophilia treaters who have experience in the diagnosis and treatment of bleeding disorders act as team leaders both at the Hub and Spoke centers. In both centers, the specialized hemophilia treater has the role of discussing GT with eligible patients. Patients should be given appropriate information about GT to fully understand the therapy and its role in providing the *F9* gene that expresses a fully functional FIX protein. Information about the GT infusion, the inclusion and exclusion criteria, and all the clinical visits and tests that need to be performed during screening and short and long-term monitoring should be provided [38]. In this scenario, the need for adherence to the scheduled follow-up visits should be stressed. The discussion with the patients should also cover the possible benefits that have been observed in treated patients, such as reduction in bleeding and stopping of prophylaxis, as well as the durability of FIX expression. A comprehensive explanation of the possible AEs with a special focus on the frequency of elevation of transaminases, its management with corticosteroid therapy [38,41,42], and the possibility of the insurgence of unknown complications should be provided. Also, the possibility of not expressing or losing the expression of the transgene, the need for contraception for 1 year after GT infusion, the logistics, and costs should be considered. Patients receiving potentially hepatotoxic medications or substances should also be informed of possible reduction of efficacy and potential increased risk for more serious hepatic reactions after GT administration [25]. It is crucial to implement the shared decision-making approach in which information is given over multiple visits to allow patients to make a truly informed decision and commit patients and clinicians to medical decisions [43,44]. It is essential to understand the goals, preferences, doubts, and worries of each patient through unbiased discussions that use correct language to avoid miscommunications. Adequate communication would also appropriately manage expectations to ensure all potential implications, including those related to family planning or career. Patient associations could have an essential role in assisting people with hemophilia (PWH) in their decision by providing support, easily understandable information, and informative material about GT. Moreover, patient associations could promote the sharing of information about the experiences of patients already treated with GT with eligible patients. This peer-mentoring approach would be useful to patients to understand what to expect from GT and the modalities of treatment and follow-up [45,46].

Once patients have understood GT and available approaches, the specialized hemophilia treater of the Hub center should 1) verify whether patients who are candidates for adeno-associated virus–based GT meet the requirements (Tables 1 and 2); 2) be responsible for having the patient eventually sign the informed consent form; 3) perform the infusion; and 4) manage the monitoring of the FIX and short-term AEs [34,46]. According to the Health Outcome with Padua Gene: Evaluation in Hemophilia B (HOPE-B) study protocol, subjects are allowed to continue their prophylaxis with rFIX in the first weeks after GT infusion until reaching a sufficient transgene expression. During the posttreatment follow-up visits, endogenous FIX activity will be assessed. If the endogenous FIX activity is ≥5%, rFIX prophylaxis will be discontinued, and further management will be based on specialized hemophilia treaters' judgment and subject preference. Continuation or reinitiation of the prophylaxis may be considered if the endogenous FIX activity is between 2% and 5% at least in 2 consecutive laboratory measurements, based on specialized

TABLE 2 Criteria for selection of patients who will receive hemophilia B gene therapy.

Inclusion criteria	Exclusion criteria
Age ≥18 y	✔ Patients with severe hepatic impairment, including cirrhosis and severe liver fibrosis (e.g., suggestive of or equal to Meta-analysis of Histological Data in Viral Hepatitis stage 3 disease or liver elastography [FibroScan; Echosens, Paris, France] score of ≥9 kPa) ✔ Active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as active chronic hepatitis B) ✔ (If there are signs or symptoms of acute or uncontrolled chronic active infections, the treatment must be postponed until the infection has resolved or is controlled)
Diagnosis of a severe or moderately severe form of hemophilia B (FIX activity ≤2% of normal)	Hypersensitivity to the active ingredient or any excipient
Current treatment with exogenous FIX concentrates	
Signed consent form	History or presence of FIX inhibitors

Check etranacogene dezaparvovec summary of product characteristics for details. FIX, factor IX.

hemophilia treaters' judgment and subject preference. If endogenous FIX activity is <2%, prophylaxis must be continued or reinitiated [47].

The role of the hepatologist is fundamental for the assessment of liver health before GT and in the management of liver monitoring in the follow-up [23,48]. The hepatologist should also assess lifestyle and diet, emphasizing the importance of liver health and suggesting possible interventions (e.g., reducing alcohol consumption) that aim to minimize side effects related to the HB GT. In collaboration with specialized hemophilia treaters, close monitoring of alanine aminotransferase (ALT) and FIX levels together with other liver parameters is important for the early initiation of immunosuppression to preserve transgene expression, monitor the effect of treatment, and allow for timely tapering of corticosteroids and ensure the long-term success of GT [25,48]. Particular attention must be paid to the identification of possible residual burden of liver disease after hepatitis C virus eradication that could represent a risk factor and, thus, an exclusion criterion for HB GT. In the case of hepatitis C virus infection history, the liver morphology of patients should be assessed, and residual liver disease progression should be ruled out (Table 3) together with liver stiffness measurement by transient elastography [49]. To date, no post-GT transaminase elevation has been apparently attributed to occult hepatitis B virus (HBV) infection reactivation, nor has such reactivation been described in subjects exposed to immunosuppressive therapy after GT. Nevertheless, hepatitis B surface antigen-negative and hepatitis B core antibody-positive subjects receiving immunosuppressive therapy following ALT elevation may need periodic serum HBV DNA monitoring to search for possible occult HBV infection reactivation and thus initiate the most appropriate treatment [50].

TABLE 3 Risk factors for liver disease progression.

Risk factors	Liver assessment
Type 2 diabetes	Liver morphology and liver stiffness assessment
Arterial hypertension	
Dyslipidemia (triglycerides >150 mg/dL, HDL <40 mg/dL, or need of lipid-lowering drugs)	
Overweight (BMI 25-30 kg/m^2)	
Obesity (BMI>30 kg/m^2)	

BMI, body mass index; HDL, high-density lipoprotein.

Another important professional figure is the immunologist, who should manage inflammatory and allergic reactions [51], while possible anaphylactic reactions should be managed by the anesthesiologist present during the GT infusion. Due to the type of treatment (1-shot therapy), patients should be given psychological support throughout the GT phases. During screening, it is of paramount importance to perform a familial and psychosocial evaluation as well as a mental status screening. Together with the psychologist, the specialized hemophilia treaters should aid the patient in breaking down barriers toward GT and in deciding whether the outcomes, as well as possible AEs of the HB GT, are acceptable. The psychologist will help manage expectations, accept uncertainties, and help patients in their choice to opt for GT [40,41]. Patients routinely managed at a Spoke center who choose to be treated with GT could need the support of a psychologist to feel confident to discuss the therapy, doubts, and worries with the new physician at the Hub center (Figures 1 and 2). HB patients should also be aware of the positive psychological impact that GT could bring to their lives due to amelioration of QoL, decreased or absent need for FIX infusions, and lower psychosocial burden [38,46]. The role of the orthopedist is to educate patients on how to prevent hemarthrosis, perform musculoskeletal assessments, and choose the best pharmacological approach to alleviate joint issues and pain. The role of the physical therapist is to define the best physical therapy and make PWHB aware of the physical activities that should be avoided [9]. Both

FIGURE 1 The role of the multidisciplinary team in the Hub center. AE, adverse event; ALT, alanine aminotransferase; GT, gene therapy; QoL, quality of life.

the orthopedist and the physical therapist should inform the patients about the impossibility of GT in reversing joint damage and its potential to prevent the progression of hemophilic arthropathy [20,40]. During the monitoring period, the orthopedist should evaluate over the years the efficacy of GT in avoiding hemarthrosis and joint issues [52]. In this regard, ultrasound evaluation before and during the follow-up after GT would also be useful, possibly applying the Hemophilia Early Arthropathy Detection with Ultrasound score [53].

Another important healthcare professional is the dedicated nurse/case manager who coordinates all the procedures, schedules visits,

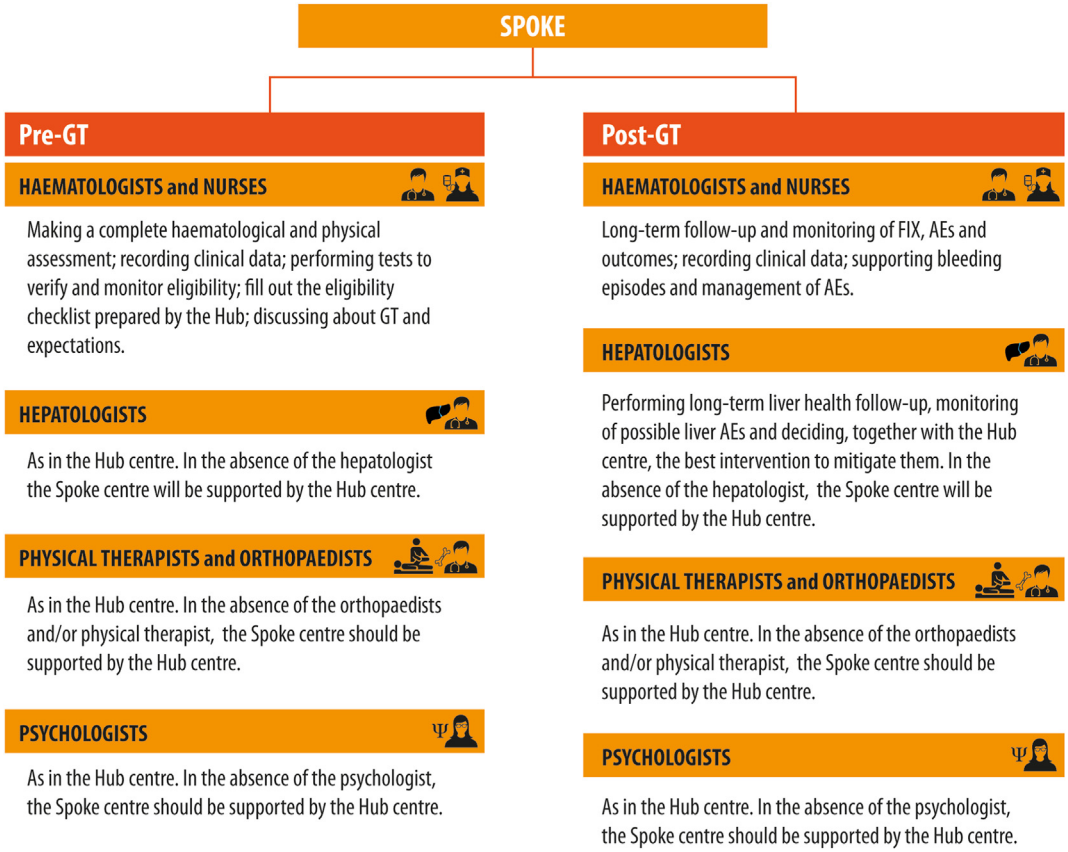

FIGURE 2 The role of the multidisciplinary team in the Spoke center. AE, adverse event; FIX, factor IX; GT, gene therapy.

guarantees adherence to timelines, coordinates patient logistics, identifies problems, and creates mitigation actions. Moreover, she/he is essential in coordinating the cooperation and communication between the Hub and Spoke centers and patients [40]. In addition, the clinical pharmacist plays an essential role by ensuring that the biosafety requirements are met and that proper equipment for product handling is available. The clinical pharmacist is also responsible for the receipt, storage, transport, reconstitution, and preparation of the GT and, in collaboration with the specialized hemophilia treater, for the calculation of the dose [33]. Altogether, such a team should inform the patient about every aspect of HB GT and the possible outcome in a way in which obtaining patient consent is a process made by several steps rather than only a single discussion meeting where the prescription is finalized [54]. The role of the multidisciplinary team at the Hub and Spoke centers is summarized in Figures 1 and 2.

3.3 | Laboratory surveillance, patient follow-up, and outcomes

To be eligible for treatment with etranacogene dezaparvovec, PWHB should fulfill a series of criteria (Table 2). Several laboratory tests must be performed to evaluate efficacy, as well as to monitor liver health status and AEs. Therefore, the reliability of laboratory tests is of utmost importance, and laboratory surveillance is needed to guarantee the quality of the results. The analyses that should be performed at the baseline and follow-up levels are described in Tables 4 and 5, respectively.

3.3.1 | Analysis of preexisting neutralizing anti-AAV5 antibodies and FIX inhibitors

High preexisting neutralizing anti-AAV5 antibodies may reduce the efficacy of etranacogene dezaparvovec. Thus, the titer of preexisting anti-AAV5 neutralizing antibodies should be tested even if their presence does not represent an exclusion criterion for the eligibility to GT, at least for etranacogene dezaparvovec [25]. After collecting samples for detection of anti–adeno-associated virus antibodies, samples will be sent to a central laboratory before deciding the eligibility for GT [55]. The research for neutralizing antibodies against FIX (inhibitors) is also essential since their presence constitutes an exclusion criterion. This analysis should be performed by using the Bethesda–Nijmegen protocol, which allows the identification of inhibitors even at low titer [56].

TABLE 4 Laboratory tests to assess baseline characteristics of patients.

Laboratory tests		Note
Liver biomarkers	ALT	Within the 3 mo that precede the GT infusion and repeated at least once prior to administration
	AST	Within the 3 mo that precede the GT infusion
	Total bilirubin	Within the 3 mo that precede the GT infusion
	ALP	Within the 3 mo that precede the GT infusion
	Hepatic ultrasound and elastography assessment	Within the 6 mo that precede the GT infusion
Anti-AAV5 antibodies titer		Before GT infusion
FIX inhibitors		In case of a positive test result for FIX inhibitors, a retest within approximately 2 wk should be performed. If both the initial test and retest results are positive, the patient should not receive the GT

AAV5, adeno-associated viral serotype 5; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIX, factor IX; GT, gene therapy.

3.3.2 | FIX assays

The summary of product characteristics recommends monitoring the FIX activity after dose administration to follow the patient's response to etranacogene dezaparvovec according to the parameters mentioned in Table 5 (eg, weekly for the first 3 months). Moreover, the summary of product characteristics recommends using the same assay and reagents to monitor FIX activity over time [25].

Looking at the HOPE-B clinical trial, both chromogenic substrate assay (CSA) and 1-stage clotting assay (OSA) were used to measure endogenous FIX activity, and the results were lower if measured with CSA compared with OSA [31]. According to the characteristics of etranacogene dezaparvovec, which uses the FIX-Padua variant, OSA appears more suitable for measuring FIX after GT [23,24,57–59].

Moreover, the OSA test is the most used in the clinical monitoring of HB, both for diagnostic purposes and for follow-up prophylaxis with exogenous FIX [60] and, since in Italy the CSA is available in only 44% of the hemophilia centers' laboratories (unpublished data from Associazione Italiana Centri Emofilia [AICE]) [61], the use of OSA in HB GT is desirable.

TABLE 5 Laboratory tests and timeline for liver biomarkers and factor IX level monitoring.

Period after infusion	ALT[a] and FIX
First 3 mo	Weekly
Month 4-12	Every 3 mo
Year 2	Every 6 mo
After y 2	Every year

ALT, alanine aminotransferase; FIX, factor IX.

[a] Monitoring of ALT should be accompanied by monitoring of aspartate aminotransferase and creatine phosphokinase to rule out alternative causes for ALT elevations (including potentially hepatotoxic medications or agents, alcohol consumption, or strenuous exercise).

3.3.3 | Hepatic enzymes and liver ultrasound monitoring

Even though the frequency of hepatic AEs with etranacogene dezaparvovec is lower compared with HA GT, occurring respectively in 20% and 88.8% of patients [26,48,62,63], particular attention must be paid to liver enzymes and hepatic function monitoring. For this reason, baseline levels of the liver biomarkers, ALT, aspartate aminotransferase, alkaline phosphatase, and bilirubin, should be assessed before GT administration (Table 4) [25]. Elevation of ALT is the most important AE observed and needs a rigorous follow-up (Table 5). During clinical trials, it occurred between weeks 7 and 14 after infusion of GT and is believed to happen through an immune-mediated process [48]. Fortunately, ALT elevation is transitory but can be associated with a reduction of transgene expression and a decrease in the efficacy of the therapy [48]. In Table 5, the timeline of follow-up monitoring of FIX, ALT, aspartate aminotransferase, and creatine phosphokinase is depicted. Even if no direct comparisons were made, it has been shown that corticosteroid treatment duration for transaminases increase was also shorter for etranacogene dezaparvovec (median, 74 days, and all the patients were off treatment by week 26) compared with HA GT (median, 230 days) [26,62]. This is particularly important due to the potential for patients to experience glucocorticoid-related side effects [64]. In the HOPE-B clinical trial, no glucocorticoid-related side effects requiring treatment were reported [31]. However, in the same clinical trial, a serious AE of hepatocellular carcinoma (HCC) occurred in 1 patient 12 months after GT infusion [26,65]. The patient had multiple risk factors for HCC, and this AE was highly unlikely linked to GT since no integration of the viral vector was found, and a direct carcinogenesis event was ruled out [66]. Notwithstanding, it is recommended that patients with preexisting risk factors for HCC undergo annual liver ultrasound screenings and alpha-fetoprotein analysis for at least 5 years after GT administration [25]. In general, even in the absence of risk factors, authors believe that it is advisable to perform abdominal ultrasound annually.

3.4 | Needs of Italian centers

3.4.1 | The Hub and Spoke organizational model

Due to the need to have good knowledge and experience with GT for patient selection, treatment, and monitoring, the panelists agreed that the organizational Hub and Spoke model with a long-term safety and efficacy monitoring system should be followed [33]. The centers are designated as Hubs by the Regions following approval from the Italian Regulatory Agency.

In Italy, AICE has long since started a process of developing a professional accreditation system for centers that treat hemophilia and rare hereditary and acquired hemorrhagic diseases. The project aims to achieve high professional standards, as well as to adopt continuous improvement policies and best practices by rigorously and independently evaluating processes to ensure maximum transparency on guaranteed quality levels [61,67]. AICE has also set up a working group dedicated to GT [61]. The first fundamental objectives of the group are i) the establishment of an Italian Hub and Spoke model for the management of GT in HA and HB; ii) the construction of a dedicated registry; iii) the planning of training courses for centers and collaborating figures. In addition, Italian Regions will identify Hub centers based on the expertise, services, and geographical distribution of the centers.

From the discussion of the panelists, it emerged that, to draw a realistic pathway for HB treatment with GT in Italy, there is a need for increasing the interaction between the Hub and Spoke centers. They also think that information about the delivery of GT, patient journey, follow-up, and AEs should be shared among centers by presenting data and experiences at national congresses, webinars, and international meetings supported by the scientific societies and through publications of newsletters and case reports about HB GT updates. Moreover, it is of paramount importance that the Hub and Spoke centers build a fruitful dialogue in compiling the monitoring registry with long-term efficacy and safety data that could also be useful for the Italian Regulatory Agency to carry out analysis on the durability of efficacy and the safety of GTs. Data collection should be made in accordance with the Gene Therapy Minimum Data Set identified by the International Society on Thrombosis and Haemostasis. The use of the Gene Therapy Minimum Data Set standard would allow the collection of sufficient data for inclusion in national registries and the World Federation of Haemophilia Gene Therapy Registry [68]. Furthermore, if the provisions of the State-Regions agreement of 13 March 2013 (which listed the essential due services for hemophilia care) were implemented, there would be a homogeneous organization and availability of basic care services among all the hemophilia centers. This would enable the creation of a real network with a well-defined role and responsibility of the Hub and Spoke centers in GT for HB. Through the establishment of a network among centers and by having a common model at the national level applied to all regions, it would be possible to minimize the differences among centers and support PWH in having equal access to therapy. In addition, the role of patient associations in supporting an adequate organization at a territorial level and identifying solutions to avoid discrepancies among regions in patient access to HB GT has been highlighted. Moreover, there is a need to provide a centralized (eg, scientific societies and patient associations) and unbiased source of information about HB GT that must be easily accessible and understandable for patients, as also previously stated [46]. This would also ensure that consistent information is given to patients by HCPs of the different centers.

Another important aspect discussed is how to deal with possible emergencies such as spontaneous or injury-related hemorrhages or any other situation that could compromise the patient's health and that needs prompt medical intervention. Therefore, both the Hub and Spoke centers need to be prepared to deal with those emergencies. Additionally, it could be useful to have an emergency phone line that would identify the center in which the patient should be managed. In this scenario, the authors' perception is that continuous communication between the Hub and the Spoke is essential in all the phases of the therapy.

3.4.2 | Patient engagement, management, and retention: role of the multidisciplinary team

The authors have highlighted that the multidisciplinary team plays an essential role in all the phases of GT. During the selection of patients, the role of the psychologist is essential to evaluate familiar and psychosocial issues and, hence, to identify the candidates who will receive GT. Moreover, the psychologist will help make the patients confident to discuss GT with the new physician at the Hub if arriving from a Spoke center. Indeed, the psychological support to patients, from selection to follow-up monitoring, will help provide patients with the best care and enhance patient engagement and retention. In line with this, it is of paramount importance that all members of the multidisciplinary team facilitate the mental transition of patients from therapy adherence to follow-up adherence. To receive the GT, the patient must be fully aware of the importance of having and maintaining liver health to minimize possible hepatotoxicity. In this context, the role of the hepatologist and his collaboration with the specialized hemophilia treater is crucial to rigorously select patients, considering lifestyle and diet, and detecting potential risk factors [48]. In addition, to support patients carefully, the logistics and costs should also be considered. It has also been stressed that, whenever possible, patients should be provided with a nursing service that will be responsible for collecting blood samples at home. During the follow-up, remote monitoring should be available through phone calls and, whenever possible, through telemedicine. Also, the important role of a dedicated nurse/case manager in the care delivery model for HB GT has been highlighted by considering the patient journey and logistics [34].

The authors have drawn attention to the availability of a multidisciplinary team that must be carefully evaluated in the Italian centers. Moreover, in order to improve patient and physician engagement, a shared decision-making strategy is advisable [43]. The value of treatment decision discussions will be influenced by the

language adopted by HCPs because it should be accessible and tailored to PWH. HCPs and PWH should share common questions and uncertainties as they progress together along the patient journey [69]. Concerning the outcome of the patients, there is an agreement that QoL is an essential endpoint to be observed and that a specific hemophilia GT QoL questionnaire should be adopted.

3.4.3 | Laboratory surveillance, patient follow-up, and outcomes

The authors agree that it is important to guarantee the same analytical quality between Hub and Spoke and alongside the phases of the treatment by performing an external quality assessment of the laboratories, as currently in place by AICE in Italy. The external quality assessment will provide information about accuracy and precision by comparing the results obtained by the specific laboratory with the mean results of other laboratories [70,71].

3.4.4 | Challenges in HB GT in Italy

The panelists have envisioned that the communication between the Hub and Spoke could represent a challenge to the delivery of HB GT. Also, regional differences and the need to travel to the Hub center could hamper equal access to HB GT. Moreover, to follow the General Data Protection Regulation, the centers will need an informatic system that is able to anonymize patients' data. Regarding the multidisciplinary team, not all the professional figures will be staffed at the Spoke center, and therefore, the Hub center should assist in the evaluation of patients and give the necessary support. The panelists have also drawn attention to the difficulties in maintaining patient retention and suggested that the patient is checked once a year by the Hub or, as an alternative, the Hub center can review patient data sent by the Spoke. With this regard, telemedicine would facilitate the visits of patients by the Hub center and promote a close collaboration with the Spoke center. Furthermore, panelists envisioned that continuous formative pathways would be needed if new healthcare providers were hired.

4 | CONCLUSION

The approval by the European Medicines Agency of HB GT poses attention to the need for Italian centers to establish a care delivery model in the country. Therefore, the importance of the Hub and Spoke Italian Regional Organization emerged, and in order to enhance the efficiency of this model, a close collaboration between the Hub and the Spoke and between all the HCPs that compose the multidisciplinary teams coordinated by the specialized hemophilia treater was suggested.

The Hub and Spoke model in various Italian regions could foster the generation of evidence about GT in hemophilia. This model may improve the GT experience by creating expertise, sharing know-how on a network, generating evidence, helping scientific societies to draw up guidelines that correspond to clinical practice, and constantly updating them.

Critical factors to the implementation of the model could be having clear roles, coordination mechanisms among hospitals and multidisciplinary team members, shared information technologies facilities, and the ability to engage the patient.

Given the change of treatment paradigm introduced by GT for HB, there is a strong need to guarantee that centers are equipped and trained and that patients are educated on GT. The multidisciplinary team would ensure an efficient selection of patients and maximize patient engagement, management, and retention. It is also crucial to have a shared responsibility between the Hub and the Spoke to recall the patient to follow-up, particularly if the Hub and Spoke are from different regions.

Moreover, quality checks of the laboratories that will perform the analysis to determine short- and long-term safety issues and outcomes would be crucial.

It is, therefore, clear that all the aspects discussed in the present work should be carefully evaluated to ensure HB GT's success in Italy. This document could also help in updating the diagnostic and therapeutic care pathways that are not yet designed for GTs.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF COMPETING INTERESTS

G.C. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, BIOVIIIx, CSL Behring, BioMarin, Sanofi, Novo Nordisk, Takeda, Kedrion, LFB, Grifols, Roche, Sobi, and uniQure and reports participation on data safety monitoring board or advisory board for Bayer, CSL Behring, BioMarin, Sanofi, Novo Nordisk, Takeda, Kedrion, LFB, Grifols, Pfizer, Roche, and uniQure. G.D.M. reports being a speaker or a member of a speaker bureau for BioMarin, Bayer, CSL Behring, Roche, Takeda, and Viatris Pharmaceuticals and consultant or ad hoc speaker/consultant for BioMarin, Bayer, Pfizer, Takeda, and Viatris Pharmaceuticals. P.S. reports being a speaker for Bayer, CSL Behring, Stago, uniQure, Werfen, and Pfizer. S.S. has acted as a consultant for CSL Behring, Amgen, Novartis, Novo Nordisk, Sobi, and

Bayer. E.B. participated in advisory boards for Amgen, Novartis, CSL Behring, Bayer, Roche, and Sobi. V.L.M. is a member of the advisory board of Pfizer, CSL Behring, and BioMarin; is a speaker for Gore and Alfasigma; and received research grants from Gilead and travel grants from Sobi, Sanofi, and Takeda. A.L. has participated in speaker bureaus for BioMarin and CSL Behring. F.P. reports consulting for and being a member of advisory boards of CSL Behring, BioMarin, Roche, Sanofi, and Sobi and is a member of the speaker's bureau or educational programs/symposia for Takeda/Spark. E.F.G. has participated in speaker bureaus and advisory boards for BioMarin, Sobi, and Roche e Novo Nordisk. A.C.M. declares that they have no conflict of interest.

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SUPPLEMENTARY METHODS

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