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REVIEW ARTICLE

Laying the foundations for gene therapy in Italy for patients with haemophilia A: A Delphi consensus study

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Abstract

Introduction: Current treatment for haemophilia A involves factor VIII replacement or non-replacement (emicizumab) therapies, neither of which permanently normalise factor VIII levels. Gene therapy using adeno-associated viral (AAV) vectors is an emerging long-term treatment strategy for people with severe haemophilia A (PwSHA) that is likely to be available for clinical use in the near future.

Aim: This article proposes practical guidelines for the assessment, treatment, and follow-up of potential PwSHA candidates for AAV-based gene therapy.

Method: Using the Delphi method, a working group of Italian stakeholders with expertise in and knowledge of the care of adults with haemophilia A analysed literature for AAV-based gene therapy and drafted a list of statements that were circulated to a panel of Italian peers. During two rounds of voting, panel members voted on their agreement with each statement to reach a consensus.

Results: The Delphi process yielded 40 statements regarding haemophilia A gene therapy, across five topics: (1) organisational model; (2) multidisciplinary team; (3) patient engagement; (4) laboratory surveillance; and (5) patient follow-up and gene therapy outcomes. The consensus was reached for all 40 statements, with the second round of voting needed for five statements.

Conclusion: Use of the hub-and-spoke organisational model and multidisciplinary teams are expected to optimise patient selection for gene therapy, as well as the management of dosing and patient follow-up, patient engagement, laboratory surveillance, and patient expectations regarding outcomes. This approach should allow the benefits of AAV-based gene therapy for haemophilia A to be maximised.

KEYWORDS
consensus, Delphi technique, genetic therapy, haemophilia A, Italy, patient care team, patient selection

1 | INTRODUCTION

Haemophilia A is an X-linked inherited haemorrhagic disorder, characterised by factor VIII (FVIII) deficiency due to mutations in the encoding gene.[1,2] Disease severity is classified according to plasma FVIII residual activity levels, with levels <1% of normal defined as severe, 1%–5% as moderate, and >5% to <40% as mild.[3] People with severe haemophilia A (PwSHA) are at increased risk of spontaneous and trauma-related bleeding events, including bleeding into the joints that lead to haemophilic arthropathy and associated severe disability.[4]

Intravenous administration of exogenous FVIII, as either prophylaxis or 'on demand' treatment for bleeding events, trauma or surgery, represents the cornerstone of treatment for PwSHA.[5–7] However, FVIII replacement therapy has several limitations, including the need for frequent dosing[6] and the development of neutralising antibodies to FVIII that can reduce therapeutic efficacy.[8,9] Advances have been made to improve the efficacy of and reduce the burden associated with treatments for haemophilia A, with the development of extended-half-life FVIII concentrates[10] and non-replacement subcutaneous therapy.[11] However, none of the currently available therapeutic approaches provide sustained normalisation of FVIII levels.

Gene therapy that employs adeno-associated viral (AAV) vectors represent an emerging long-term effective treatment strategy for PwSHA that may bypass the need for continuous therapy with exogenous FVIII or other haemostatic products, and avoid the associated treatment burden and complications, thereby significantly improving quality of life (QoL).[12] Several AAV-based gene therapies for haemophilia A are being evaluated in clinical trials.[13–23]

Gene therapy is a complex treatment process and will likely first be offered at comprehensive care centres with significant expertise in haemophilia management. A recent joint publication from the European Association for Haemophilia and Allied Disorders (EAHAD) and the European Haemophilia Consortium (EHC) suggested that a modified 'hub-and-spoke' model, incorporating a long-term surveillance system, be introduced to ensure appropriate prescription, administration and monitoring of gene therapy in PwSHA.[24] Given the imminent first approval of gene therapy for haemophilia A in Italy,[25] there is a need to determine how this treatment service will be organised on a national and local level, and how patients who are candidates for gene therapy in Italy will be assessed, treated and managed. In Italy, there are 52 haemophilia centres, which are members of the Italian Association of Haemophilia Centres (AICE). These centres provide care to approximately 1800 patients with severe haemophilia A. However, there are only a few comprehensive care centres that provide multidisciplinary clinical management, and the availability and quality of haemophilia care are not homogeneous across different regions of Italy.

To address these concerns, a Delphi consensus process was undertaken to develop clinically relevant statements that will lay the foundations for haemophilia A gene therapy in Italy, including patient management during gene therapy, and its monitoring pre- and post-infusion and during follow-up.

2 | MATERIALS AND METHODS

A Delphi consensus study was conducted between 16 September 2020 and 30 November 2021. A multidisciplinary, working group composed of 16 professionals involved in the care of people with haemophilia, other specialists, and representatives from patient associations was created. The group analysed the literature for AAV-based gene therapy in PwSHA (see Table S1 for literature search strategy), determined

areas that required investigation, and identified five topics of interest: (1) organisational model; (2) multidisciplinary team; (3) patient engagement; (4) laboratory surveillance; and (5) patient follow-up and gene therapy outcomes. Statements for each of these topics were then formulated.

The statements were circulated to a panel of national experts in haemophilia A (Table S2) across two successive rounds of voting. After Round 1, the committee reviewed the results of the Delphi questionnaire to gauge the level of consensus and discussed the expert panel's opinion on each statement. Although a consensus was reached after the first voting, some statements were re-evaluated due to inconsistencies between the experts' opinions and the statements' intended meaning. These statements were reworded to remove ambiguity or include missing content. The experts voted on each statement using a 5-point Likert scale, ranging from 1 = 'absolutely disagree' to 5 = 'absolutely agree'. For each statement, the consensus was defined as ≥66.6% of respondents answering 4 or 5. The group combined the data from the two rounds of voting and discussed the results.

3 | RESULTS AND DISCUSSION

The Delphi process yielded 40 statements for Round 1 of voting, of which five (2, 17, 23, 24 and 27) were revised for Round 2. For Round 1, 78 experts were contacted and 75 agreed to participate, while for Round 2, 75 individuals were contacted and 72 agreed to participate. Thirty-seven panel experts completed the questionnaire in Round 1 (all voted on Statements 1–10, 36 voted on Statements 11–25 and 35 voted on Statements 26–40), and 35 experts responded to Round 2 (all of whom voted on all five statements). The consensus was reached for all 40 statements. The statements are discussed below according to the five main topics identified by the working group.

3.1 | Topic A: Organisational model (Statements 1–11)

The statements regarding the organisational model for gene therapy in haemophilia A showed high levels of agreement, with consensus ranging from 81.1% to 100.0% (**Table 1**).

Of interest, despite this general consensus, not all members of the expert panel agreed with the use of the hub-and-spoke model (Statement 1). However, this model was suggested by the working group and is recommended by EAHAD and EHC.[26] Further, the almost 95% consensus for Statement 1 does indicate that there is strong support for the adoption of the hub-and-spoke model for the management of A gene therapy in Italy.

The aim of the hub-and-spoke model is to provide coordinated patient care, including patient counselling and informed consent regarding gene therapy, close monitoring immediately after infusion, and individualised long-term follow-up monitoring.[24] 'Hub' centres are expert national haemophilia treatment centres that have experience with comprehensive care and/or gene therapy.[24] The Hubs will engage all specific staff who are necessary for the management of AAV-based gene therapy (Statement 7) and will be responsible for all aspects of its delivery (Statement 2). Hub centres will also collect relevant data for submission to appointed national authorities or official registries (Statement 3), be experienced in gene therapy clinical trials (Statement 8)[24] and where possible, have available a 24-h laboratory enrolled in dedicated quality control programs (Statement 9).

Local 'Spoke centres' will be responsible for pre-screening laboratory tests and the selection of potential candidates for gene therapy (Statement 4). It is highly likely that all haemophilia clinics will be considered Spoke centres, but not all will be Hub centres. Staff at Spoke centres should include at least one physician experienced in the management of patients with congenital bleeding disorders (Statement 10). Spokes will also conduct follow-up monitoring of patients after the infusion (Statement 5). The suggested timing for the patient transition from Hub to Spoke for follow-up is 2 months; however, clinical experience will establish the most appropriate timing for shifting the responsibility of follow-up from the Hub to the Spoke centre. There was consensus that Spoke centres should be equipped with a laboratory for pre-screening and follow-up testing (Statement 11). However, many Spoke centres in Italy do not have access to all necessary laboratory testing. For these centres, tests should be performed by an accredited external laboratory that is used consistently for patient screening and follow-up.

Given the complexity of gene therapy, close collaboration between the Hub and Spoke centres will be mandatory (Statement 6), and this is particularly important with regard to the assessment of patient eligibility, as the final decision on gene therapy will be made by the Hub centre, which is usually not where the patient is routinely managed.

3.2 | Topic B: Multidisciplinary team (Statements 12–17)

The statements regarding the multidisciplinary team approach for the management of haemophilia A gene therapy showed agreement levels of 80.6%–97.2% (**Table 2**).

According to the World Federation of Hemophilia 2020 guidelines, optimal haemophilia care requires comprehensive management from a multidisciplinary team.[27] It is important that all members of the multidisciplinary team are provided with up-to-date information and trained on all relevant facets of gene therapy so that each patient receives consistent information.[24]

In the context of the consensus statements, the development of multidisciplinary teams within both the Hub and Spoke centres was considered vital, and such teams as a whole are considered responsible for the selection and management of patients (Statement 12). The teams must understand that each patient's circumstances and unique characteristics are the fundamental drivers of patient selection and should be used to tailor patient education on gene therapy (Statement 13). As a result, the teams must be provided with specific education programs to allow them to develop the necessary skills to take full responsibility for the needs of patients and caregivers (Statement 16).

An appointed member of the multidisciplinary team at the Hub centre should be available to act as an intermediary for any of the

TABLE 1 Consensus statements regarding the organisational model for gene therapy in patients with haemophilia A (Topic A)

Statement	Level of consensus, %	
	Round 1	Round 2
Topic A: Organisational model		
1. Gene therapy for haemophilia A using AAVs should be managed by engaging easily accessible expert centres, geographically distributed throughout the country and organised by a hub-and-spoke model, in compliance with the 'EAHAD-EHC Joint Statement on promoting hub-and-spoke model for the treatment of haemophilia and rare bleeding disorders using gene therapies'	94.6	–
2. (Round 1) Expert comprehensive haemophilia care centres, operating as national hubs (hereafter 'Hub centres'), should be in charge of: (1) preparing a standard checklist to be used by referring Spoke centres for patient screening; (2) verifying whether patients who are candidates according to Spoke centres meet the requirements for AAV-based gene therapy for haemophilia A; (3) prescribing and managing the gene therapy; and (4) conducting part of the follow-up examinations	89.2	–
(Round 2) Expert comprehensive haemophilia care centres, operating as national hubs (hereafter 'Hub centres'), should be in charge of: (1) preparing a standard checklist to be used by referring Spoke centres for patient screening; (2) verifying whether patients who are candidates according to Spoke centres meet the requirements for AAV-based gene therapy for haemophilia A; (3) informing patients and obtaining informed consent before gene therapy infusion; (4) prescribing and managing the gene therapy; and (5) conducting part of the follow-up examinations	–	88.6
3. Hub centres are responsible for: (1) collecting all relevant data of patients treated with AAV-based gene therapy for haemophilia A; and (2) submitting those data to any appointed national authorities or officially recognised registries when required	91.9	–
4. Haemophilia treatment centres operating as spokes (hereafter 'Spoke centres'), in close communication with national Hubs (which can also operate as Spoke centres), should be in charge of: (1) selecting candidates for AAV-based gene therapy for haemophilia A; (2) pre-screening patient candidates for the therapy with relevant tests if required; and (3) preparing a clinical report to submit candidate patients to Hubs, including screening checklists	94.6	–
5. Spoke centres, in close communication with national Hubs, should be in charge of conducting some of the follow-up examinations and laboratory tests, especially after month 2 from the gene therapy infusion	81.1	–
6. Hub and Spoke centres must collaborate closely to ensure safety, therapy efficacy and monitoring of long-term outcomes of the patients	100.0	–
7. Hub centres should engage specific staff for the management of AAV-based gene therapy for haemophilia A, including physicians experienced in the management of patients with congenital haemorrhagic disorders, dedicated nurses, emergency staff and data managers for collection and treatment of patient data	89.2	–
8. Hub centres should preferably be designated among those with experience in gene therapy clinical trials and must have obtained approvals for the use of GMOs by regulatory authorities	81.1	–
9. The laboratory of a Hub centre should possibly be an internal laboratory, able to operate 24 h/7 days-a-week, and to take part in AICE, WFH, NEQAS or other dedicated quality control programs	86.5	–
10. Spoke centre staff should include at least one physician experienced in the management of patients with congenital bleeding disorders	97.3	–
11. Spoke centres should: (1) be equipped with a laboratory for coagulation assays participating in dedicated quality control programs; (2) be in charge of ordering the companion diagnostic test for the detection of anti-AAV antibodies (CDx-Companion Diagnostic) if required; (3) inform patients and obtain informed consent before testing; (4) prepare and ship samples to a central laboratory if required; and (5) receive test results, inform and manage patients accordingly	88.9	–

Abbreviations: AAV, adeno-associated virus; AICE, Italian Association of Haemophilia Centres; EAHAD, European Association for Haemophilia and Allied Disorders; EHC, European Haemophilia Consortium; GMO, genetically modified organism; NEQAS, National External Quality Assessment Service; WFH, World Federation of Hemophilia.

patient's needs regarding gene therapy (Statement 15). This individual is appointed by the team members and plays an important role because most patients will be referred to the Hub by the Spoke centres and they will need to have a single point of contact during initial treatment and follow-up. One important aspect of the appointed team member's role is to provide patients with information on the advantages and disadvantages of gene therapy and obtain a declaration of awareness and acceptance from the patient (Statement 14).

The multidisciplinary team should include one orthopaedic and one physiotherapy consultant who is responsible for evaluating the musculoskeletal status of candidate patients for gene therapy and providing individualised recommendations for physical activity, rehabilitation (as needed) and follow-up visits (Statement 17).

TABLE 2 Consensus statements regarding the multidisciplinary team for gene therapy in patients with haemophilia A (Topic B)

Statement	Level of consensus, %	
	Round 1	Round 2
Topic B: Multidisciplinary team		
12. The multidisciplinary team as a whole is in charge of the selection and management of patients from the beginning of the AAV-based gene therapy for haemophilia A program, and takes charge of the engagement of more specialists, including a general practitioner, when needed	94.4	–
13. For the multidisciplinary team, understanding the individual circumstances and unique characteristics of each person (culture, personality, resources, individual and environmental behaviour) must be a fundamental driver when selecting patients, and when tailoring information on AAV-based gene therapy for haemophilia A to patients, based on their expectations and socio-cultural context	94.4	–
14. The multidisciplinary team works from the beginning to identify which patients are the optimal and most realistic candidates for AAV-based gene therapy for haemophilia A treatment, and provides them with a fact sheet about the most up-to-date information on advantages and disadvantages of the treatment. After having provided all the required information to patients on AAV-based gene therapy and their own musculoskeletal status, it is necessary to obtain a declaration of awareness and acceptance, and informed consent from patients	97.2	–
15. Patients should be able to rely on an appointed member of the multidisciplinary team to act as an intermediary for any of their needs related to the AAV-based gene therapy for haemophilia A, and to accompany them through the most important stages of treatment such as the infusion	80.6	–
16. Specific educational programs should be delivered to the multidisciplinary team in order to develop the necessary skills to take full responsibility for the needs of patients and caregivers	97.2	–
17. (Round 1) From the very beginning of the AAV-based gene therapy for haemophilia A treatment, all specialists in the multidisciplinary team must agree with patients on their musculoskeletal status and the need for physical maintenance and personalised rehabilitation programs, which must include all contextual details	88.9	–
(Round 2) When proposing an AAV-based gene therapy for haemophilia A treatment, the multidisciplinary team should evaluate the musculoskeletal status of candidate patients and recommend personalised actions required for physical maintenance, rehabilitation programs if needed and appropriate follow-up visits over time, including regular ultrasound assessment of the joints	–	85.7

Abbreviation: AAV, adeno-associated virus.

3.3 | Topic C: Patient engagement (Statements 18–23)

The statements regarding patient engagement in haemophilia A gene therapy showed agreement levels ranging from 72.2% to 97.2% (**Table 3**).

Active involvement of the patient is an important aspect of shared decision-making in haemophilia A management[28]; however, maintaining patient engagement is one of the major challenges.[24] Patients should be provided with adequate information regarding the risks and benefits of treatment so they can make autonomous decisions, in addition to the availability of a support network that can guide them through the complex treatment process.[28] Shared decision-making should be based on close communication between gene therapy experts, patients and patients' families or caregivers.[29] It is likely that such an approach will increase patient compliance with treatment, which is considered vital for a successful outcome (Statement 18). Optimal engagement and compliance may be enhanced by a pre-treatment discussion with patients around their priorities for treatment, including requirements related to QoL issues (Statement 19).

Support from a psychologist or counsellor may be required so that patients and their families/caregivers are fully aware of the risks and benefits of gene therapy and receive appropriate support during follow-up (Statement 20).[29] A psychologist or counsellor may also help with the identification of motivated patients who will be compliant with treatment and the follow-up process. However, the level of agreement for Statement 20 was relatively low (72.2%), although it did reach the threshold for consensus. This may be because some centres do not have a psychologist or counsellor available, and the statement was expressed as if the patient selection was dependent on psychologist/counsellor involvement. Therefore, the committee suggested that psychologist/counsellor involvement in patient selection should be considered 'advisable' rather than 'essential', with patients made aware that this optional resource is available to them. It should be noted that every member of the multidisciplinary team shares responsibility for maintaining patient engagement and, therefore, patient selection for gene therapy is not dependent on the availability of a psychologist or counsellor. In addition, psychosocial support may be needed in patients who have joint involvement in order to manage their expectations, since gene therapy is not expected to provide improvement in severe arthropathy symptoms. Patient support programs will

TABLE 3 Consensus statements regarding patient engagement in haemophilia A gene therapy (Topic C)

Statement	Level of consensus, %	
	Round 1	Round 2
Topic C: Patient engagement		
18. The ideal patient must be compliant with the entire therapeutic program, from the preparation phase to the AAV-based gene therapy for haemophilia A treatment, and post-infusion monitoring	94.4	–
19. The QoL parameters to be used for assessment should be shared with the patients, with attention to their priorities (e.g., including degree of pain, quality of sleep, sports participation and importance of intravenous administration)	91.7	–
20. A psychologist/counsellor evaluating probable patient compliance at the beginning of treatment is essential, as well as their support during the follow-up	72.2	–
21. The planning of the different stages of AAV-based gene therapy for haemophilia A should be managed within a PSP in order to consider all the logistical issues that could negatively affect the patient's QoL if ignored	91.7	–
22. Awareness-raising programs on AAV-based gene therapy in haemophilia A should be implemented in order to: (1) help and support the patient during the introduction of this form of therapy; (2) overcome resistance and understand the limitations of the new treatment; (3) facilitate communication between patients and multidisciplinary team; and (4) increase patient motivation as well as the motivation of the multidisciplinary team	97.2	–
23. (Round 1) The engagement of PAGs is essential both to inform and to provide logistical support to patients and their families	66.7	–
(Round 2) PAGs have a key role both in informing and providing logistical support to patients and their families; their engagement should be encouraged by the multidisciplinary team as much as possible	–	77.1

Abbreviations: AAV, adeno-associated virus; PAG, patient association group; PSP, patient support program; QoL, quality of life.

be needed to manage the different stages of gene therapy so that all aspects that could negatively impact patient QoL are considered (Statement 21). The high level of agreement for this statement (91.7%) confirms the importance of patient support programs. It is expected that these programs will be particularly important during the frequent follow-up visits. Programs that raise awareness of gene therapy will help to provide patient support, overcome patient resistance, increase understanding of the limitations of treatment, facilitate communication between patients and the multidisciplinary team, and increase the motivation of both patients and multidisciplinary teams (Statement 22).

Patient association groups may also play a role in providing logistical support and information to patients and their families/caregivers (Statement 23). The level of agreement for this statement was relatively low in Round 1 (66.7%) but increased to 77.1% in Round 2. In Round 2, the statement was modified to emphasise that the involvement of patient association groups should be 'encouraged by the multidisciplinary team', rather than stating that their involvement was 'essential'. The committee noted that patient associations are not available in many regions. This may represent an opportunity for improvement, whereby the centres work to establish patient support groups to help improve patient engagement and support.

3.4 | Topic D: Laboratory surveillance (Statements 24–32)

The statements regarding laboratory surveillance in patients undergoing haemophilia A gene therapy showed agreement levels of 75.0%–91.4% (**Table 4**).

Standardised laboratory testing will be required to monitor selection criteria for potential gene therapy candidates, including tests for pre-existing antibodies against AAV, which may reduce liver cell transduction of gene therapy and subsequent FVIII expression.[24] Only patients with undetectable neutralising and non-neutralising AAV antibodies will be eligible for gene therapy (Statement 24). The level of agreement for Statement 24 decreased between Round 1 (75.0%) and Round 2 (68.6%) after the statement was modified to clarify that total AAV antibodies included neutralising and non-neutralising antibodies. The committee suggested that the decrease in the agreement between rounds indicated that there is a need for training with regard to the clinical relevance of the AAV antibody test results.

As part of the patient eligibility process, all candidates for gene therapy will need to undergo testing for anti-AAV antibodies using an approved companion diagnostic test (Statement 25) that conforms to specified timing and compliance requirements (Statement 26). This testing should be conducted within 3 months prior to the gene therapy infusion, with retesting performed during follow-up as needed (Statement 27). Statement 27 was modified during Round 2 to state that the test is performed 1–3 months prior to infusion; however, the level of agreement decreased from 82.9% in Round 1 to 68.6% in Round 2. This decrease in the level of agreement may be due to some centres considering that the timeframe of 1 month prior to gene therapy infusion is too short. As noted in Statement 24, this may also indicate that there is a need for training concerning the results of AAV antibody testing.

In the follow-up period, further laboratory testing will be required, including monitoring of FVIII levels and liver function tests.[24] FVIII levels must be monitored using the chromogenic test (Statement 28). Traditionally, FVIII levels have been monitored by the one-stage clotting assay after infusion of the modified coagulation factor concentrates. However, discrepant results are reported between one-stage clotting and chromogenic assays when measuring FVIII levels in the

TABLE 4 Consensus statements regarding the laboratory surveillance for gene therapy in patients with haemophilia A (Topic D)

Statement	Level of consensus, %	
	Round 1	Round 2
Topic D: Laboratory tests		
24. (Round 1) Undetectable levels of total AAV antibodies are a necessary condition to patient enrolment for AAV-based gene therapy for haemophilia A	75.0	–
(Round 2) Undetectable levels of total (neutralising and non-neutralising) AAV antibodies are a necessary condition to patient enrolment for AAV-based gene therapy for haemophilia A	–	68.6
25. Anti-AAV antibodies should be tested in all candidates for AAV-based gene therapy for haemophilia A using an approved test equal to the one used in clinical trial patient selection	86.1	–
26. After collecting samples for CDx (companion diagnostic test for detection of anti-AAV antibodies), samples must be sent to the central laboratory – if required – as soon as possible, preferably not later than the third working day of the week, and in all cases, in compliance with central laboratory guidelines	91.4	–
27. (Round 1) Testing for AAV antibodies should be performed within 3 months prior to the date scheduled for the AAV-based gene therapy administration for haemophilia A, and retesting must be performed at a later stage when needed	82.9	–
(Round 2) Testing for AAV antibodies should be performed within 1–3 months prior to the date scheduled for the AAV-based gene therapy administration for haemophilia A, and retesting must be performed at a later stage when needed	–	68.6
28. Monitoring of FVIII levels must be performed with the chromogenic test during follow-up	82.9	–
29. FVIII levels should be assessed from week 2 after the AAV-based gene therapy infusion and then at least every 4 weeks for the first 6 months	80.0	–
30. After the first 6 months, FVIII levels should be assessed at least every 3 months	88.6	–
31. In order to monitor liver function, ALT should be measured after the infusion of AAV-based liver-directed gene therapy for haemophilia A every week from week 2 to week 8	88.6	–
32. ALT levels that exceed 1.5 times the ULN range require an evaluation by a specialist for specific management	82.9	–

Abbreviations: AAV, adeno-associated virus; ALT, alanine aminotransferase; FVIII, factor VIII; ULN, upper limit of normal.

same patient.[30] Both assay systems recognize the native FVIII present in the standard (pooled plasma from healthy human donors) and the modified FVIII in the patient plasma differently, which might explain the discrepancy.[30] Similarly, both assay systems gave discrepant results when measuring the FVIII expressed following AAV-based gene therapy, probably due to molecular differences between the native (standard) FVIII and the transgene-produced FVIII.[31] The committee agreed that chromogenic assays were better than the one-stage clotting assay and more amenable to standardisation. Therefore, the committee unanimously recommended chromogenic assays for monitoring FVIII levels during and after therapy. While pragmatic, this is an interim solution, that may need to change based on the development in the field.

While there was consensus that FVIII levels should be assessed from week 2 after the infusion and then at least every 4 weeks for the first 6 months (Statement 29) and every 3 months thereafter (Statement 30), shorter intervals were also suggested during the discussion. Nonetheless, it was agreed that the specific timeframe for testing will be clarified once the summary of product characteristics (SmPC) for the gene therapy is available.

Liver-specific gene therapy requires ongoing monitoring of liver enzymes due to the potential for liver toxicity and possible subsequent loss of transgene expression.[24] Liver function should be monitored by regular assessment of alanine aminotransferase (ALT) levels (Statement 31) and patients with ALT levels of >1.5 times the upper limit of normal (ULN) should be referred to a hepatologist for specialist treatment (Statement 32). The committee noted that the specific schedule for liver function tests and the duration of follow-up will likely be clarified in the SmPC. Although some respondents suggested an upper threshold of 2 × ULN for specialist referral, the threshold of 1.5 × ULN was maintained to ensure patient safety. Moreover, this value was used in the phase 1/2 valoctocogene roxaparvovec clinical trial.[17] The committee suggested that the multidisciplinary team should include a hepatologist to reduce the waiting period for specialist assessment. However, steroid treatment should be started by the haematologist-in-charge as soon as deemed necessary.

3.5 | Topic E: Patient follow-up and gene therapy outcomes (Statements 33–40)

The statements regarding patient follow-up and gene therapy outcomes showed agreement levels ranging from 71.4% to 97.1% (**Table 5**).

After the delivery of gene therapy, it will be important for the Hub and Spoke centres to provide regular patient follow-up (Statement 33), especially in the first year, using well-defined and structured protocols.[24]

TABLE 5 Consensus statements regarding follow-up and outcomes for gene therapy in patients with haemophilia A (Topic E)

Statement	Level of consensus, %	
	Round 1	Round 2
Topic E: Patient follow-up and gene therapy outcomes		
33. The schedule of post-infusion follow-up examinations and tests must be provided to the patients – and, with their consent, to their family/caregiver – in advance and with relevant details	97.1	–
34. Following AAV-based gene therapy infusion for haemophilia A, patients should attend at least the specified follow-up visits: weekly until month 2, at the Hub centre; then every 2 weeks until month 6, at the Hub or Spoke centre in shifts; then every 2 months until month 12, at the Spoke centre; then yearly, at the Hub centre	91.4	–
35. Follow-up visits at the haemophilia reference centre should be carried out routinely, and some visits might also be carried out using telemedicine, when necessary	82.9	–
36. Once the transgene is no longer expressed at an acceptable level, it is possible to go back to one of the standard treatments previously used	80.0	–
37. An absence of spontaneous bleeding events is the primary goal of haemophilia A gene therapy	71.4	–
38. AAV-based gene therapy for haemophilia A should induce a persistent production of FVIII and modify the severity of haemophilia from a severe into a mild or moderate form of the disease	82.9	–
39. The treatments currently available for haemophilia A target endpoints including zero spontaneous bleeding, low ABR, good joint health, no pain, improvements in QoL and reduction in FVIII consumption	82.9	–
40. ABR alone should not be used as the only parameter to assess the effectiveness of AAV-based gene therapy for haemophilia A treatment	91.4	–

Abbreviations: AAV, adeno-associated virus; ABR, annualised bleeding rate; FVIII, factor VIII; QoL, quality of life.

Patient follow-up visits after the gene therapy infusion will initially be conducted weekly at the Hub centre until Month 2, then every 2 weeks at the Hub or Spoke centre in shifts until Month 6, followed by every 2 months at the Spoke centre until Month 12, then annual Hub centre visits (Statement 34). Close collaboration between Hub and Spoke centres and within the multidisciplinary team will be essential, and it is expected that the optimal schedule of follow-up will be gradually determined with clinical practice. It should be remembered that visits may be carried out using telemedicine rather than in person, as necessary (Statement 35).

During follow-up, if transgene expression decreases below an acceptable level, patients may return to a previously used standard therapy (Statement 36). This statement implies that other therapeutic options are available for those patients in whom gene therapy fails. The 'acceptable level' for expression will need to be customised. Further, the haemorrhagic phenotype will need to be considered, given that some patients with low expression levels may not experience bleeding.

Standardised assessment of outcomes is needed for the management of each patient with haemophilia to monitor the quality of care and to aid in clinical research or patient support.[27] Treatment-related outcomes require monitoring with a prospective and systematic plan.[27] The frequency of bleeding events, especially those in the muscles or joints, is the main indicator for the efficacy of any haemostatic treatment and is a predictor of long-term musculoskeletal outcomes.[27] Absence of spontaneous bleeding events is the primary goal of gene therapy (Statement 37); however, this outcome does not consider silent bleeds or musculoskeletal involvement, which should also be included. Musculoskeletal data are not being collected in the valoctocogene roxaparvovec clinical trials,[13,14,17] but real-world data regarding musculoskeletal outcomes will eventually be collected by registries; these data will be important to analyse.

Gene therapy should also result in persistent FVIII production and reduce the severity of disease from severe to mild or moderate (Statement 38). However, it will be important for patients to understand that, while gene therapy is not a cure for haemophilia A, it may still be a good available treatment option. It should also be emphasised that the exact outcomes may be difficult to predict and, therefore, the purpose and limitations of treatment should be clearly explained to the patient in order to avoid disappointment. The role of a psychologist/counsellor will be very important for this aspect of patient care. Physicians at Spoke centres will also need to be trained in methods of communicating the expected outcomes of gene therapy with their patients.

The success of current treatment strategies for haemophilia A is measured by outcomes such as zero spontaneous bleeding, low annualised bleeding rate (ABR), good joint health, no pain, and reduced FVIII consumption (Statement 39). It is also important to measure patient QoL, using tools such as Haemophilia-specific Quality of Life questionnaire.[32] Point-of-care ultrasound and functional assessment should be used to measure joint health. There was a high level of agreement (91.4%) for Statement 40, which stated that the effectiveness of gene therapy should not be assessed by ABR alone.

4 | CONCLUSION

Haemophilia A gene therapy has moved beyond proof of concept, with the first licensed product expected to be available in 2022.[25] Using the Delphi method, consensus was reached on all statements relating to patient management and the organisation of haemophilia infusion centres for gene therapy delivery. The use of the hub-and-spoke model and multidisciplinary teams is expected to optimise patient selection, as

well as dosing management and patient follow-up, patient engagement, laboratory surveillance and patient expectations regarding outcomes. This will enable the benefits of gene therapy in haemophilia A to be maximised. It is anticipated that gene therapy will shortly enter the armamentarium of management options for patients with haemophilia A, with the potential to provide long-lasting protection in selected individuals.

AUTHOR CONTRIBUTION

All authors contributed to the development and review of the manuscript (read and approved all drafts) and approved the final version for submission.

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CONFLICTS OF INTEREST

G.C. has been on a speaker's bureau or participated in advisory boards for Sobi, Biomarin, Grifols, LFB, Takeda, Roche, Bayer, Kedrion, Novo Nordisk, Sanofi, CSL Behring and Uniqure. C.C. participated in advisory boards for Sobi, Biomarin, Kedrion and Novo Nordisk. R.D.C. received honoraria for advisory board participation from Bayer, Sobi, CSL Behring and Takeda. M.E.M. has acted as a paid consultant/advisor/speaker for Bayer, Biomarin, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark Therapeutics, Takeda and UniQure. C.S. has been on a speaker's bureau or participated in advisory boards for Sobi, Biomarin, Takeda, Roche, Bayer Kedrion, Novo Nordisk and CSL Behring. S.S. received fees from Amgen, Novartis, Novo Nordisk, SOBI, Bayer and CSL Behring. L.S. received speaker's fee from Novo, Sobi, Roche and Takeda. A.T. received speakers' fee from Werfen, Stago and Roche outside this work. E.Z. participated in advisory boards for Bayer and Biomarin. G.D.M. participated in advisory boards for Sanofi-Aventis, BioMarin, Novo Nordisk, Pfizer Takeda, CSL Behring. A.C.M., A.L., M.F., M.F.M., P.P. and R.C.S. have no interests which might be perceived as posing a conflict or bias. Medical writing assistance was funded by Biomarin, Italy.

DATA AVAILABILITY STATEMENT

Data generated during this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. *Haematologica*. 2019;104(9):1702-1709.
2. Pipe SW, Gonen-Yaacovi G, Segurado OG. Hemophilia A gene therapy: current and next-generation approaches. *Expert Opin Biol Ther*. 2022;22(9):1099-1115.
3. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.
4. Collins PW, Blanchette VS, Fischer K, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost*. 2009;7(3):413-420.
5. Berntorp E, Fischer K, Hart DP, et al. Haemophilia. *Nat Rev Dis Primers*. 2021;7(1):45.
6. Castaman G, Linari S. Prophylactic versus on-demand treatments for hemophilia: advantages and drawbacks. *Expert Rev Hematol*. 2018;11(7):567-576.
7. Mannucci PM, Cortesi PA, Di Minno MND, Sano M, Mantovani LG, Di Minno G. Comparative analysis of the pivotal studies of extended half-life recombinant FVIII products for treatment of haemophilia A. *Haemophilia*. 2021;27(4):e422-e433.
8. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397(10274):630-640.
9. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. *Ther Adv Hematol*. 2013;4(1):59-72.
10. Ar MC, Balkan C, Kavakli K. Extended half-life coagulation factors: a new era in the management of hemophilia patients. *Turk J Haematol*. 2019;36(3):141-154.
11. Franchini M, Marano G, Pati I, et al. Emicizumab for the treatment of haemophilia A: a narrative review. *Blood Transfus*. 2019;17(3):223-228.
12. Perrin GQ, Herzog RW, Markusic DM. Update on clinical gene therapy for hemophilia. *Blood*. 2019;133(5):407-414.
13. Ozelo M, Mahlangu J, Pasi K, et al. Efficacy and safety of valoctocogene roxaparvovec adeno-associated virus gene transfer for severe hemophilia A: results from the phase 3 GENEr8-1 trial. *Res Pract Thromb Haemost*. 2021;5(Suppl 2):89-90.
14. 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(6):947-956.
15. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med*. 2020;382(1):29-40.
16. Pasi KJ, Rangarajan S, Robinson TM, et al. Hemostatic response is maintained for up to 5 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A. *Res Pract Thromb Haemost*. 2021;5(Suppl 2):90-91. [abstract OC 67.1].
17. Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. *N Engl J Med*. 2017;377(26):2519-2530.

18. 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(21):1961-1973.
19. Sullivan S, Barrett J, Drelich D, et al. SPK-8016: preliminary results from a phase 1/2 clinical trial of gene therapy for hemophilia A. *Haemophilia*. 2021;136(Suppl 1):129-130. [abstract ABS199].
20. Chapin J, Allen G, Alvarez-Roman M, et al. Results from a phase 1/2 safety and dose escalation study of TAK-754, an AAV8 vector with a codon-optimized B-domain-deleted factor VIII transgene in severe hemophilia A. *Haemophilia*. 2021;27(Suppl 2):122. [abstract ABS185].
21. Pipe S, Hay C, Sheehan J, et al. First-in-human gene therapy study of AAVhu37 capsid vector technology in severe hemophilia A: safety and FVIII activity results. *Res Pract Thromb Haemost*. 2020;4(Suppl 1):27-28. [abstract OC 09.4].
22. Nathwani A, Tuddenham E, Chowdary P, et al. GO-8: preliminary results of a phase I/II dose escalation trial of gene therapy for haemophilia A using a novel human factor VIII variant. *Blood*. 2018;132(Suppl 1):489.
23. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. *N Engl J Med*. 2022;386(11):1013-1025.
24. 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(6):967-973.
25. Batty P, Lillicrap D. Hemophilia gene therapy: approaching the first licensed product. *HemaSphere*. 2021;5(3):e540.
26. European Association for Haemophilia and Allied Disorders, European Haemophilia Consortium. EAHAD-EHC joint statement on: Promoting hub-and-spoke model for the treatment of haemophlia and rare bleeding disorders using gene therapies. 2020. Accessed January 19, 2022 https://eahad.org/eahad-ehc-covid-19-joint-statement/
27. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1-158.
28. Nossair F, Thornburg CD. The role of patient and healthcare professionals in the era of new hemophilia treatments in developed and developing countries. *Ther Adv Hematol*. 2018;9(8):239-249.
29. Miesbach W, Pasi KJ, Pipe SW, et al. Evolution of haemophilia integrated care in the era of gene therapy: treatment centre's readiness in United States and EU. *Haemophilia*. 2021;27(4):511-514.
30. Tripodi A, Chantarangkul V, Novembrino C, Peyvandi F. Advances in the treatment of hemophilia: implications for laboratory testing. *Clin Chem*. 2019;65(2):254-262.
31. Rosen S, Tiefenbacher S, Robinson M, et al. Activity of transgene-produced B-domain-deleted factor VIII in human plasma following AAV5 gene therapy. *Blood*. 2020;136(22):2524-2534.
32. von Mackensen S, Gringeri A, Siboni SM, Mannucci PM, Italian Association Of Haemophilia C. Health-related quality of life and psychological well-being in elderly patients with haemophilia. *Haemophilia*. 2012;18(3):345-352.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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