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ORIGINAL ARTICLE

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Perspectives and perception of haemophilia gene therapy by French patients

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Abstract

Introduction and aim: A national survey was initiated by representatives of French patients with haemophilia (AFH) and the French reference centre for haemophilia, in order to appreciate the awareness and knowledge of these patients regarding haemophilia gene therapy (HGT) and understand better their position about this innovative treatment that will soon become available.

Results: Of 143 answers received, 137 could be analysed, representing about 3.5% of patients with severe or moderate haemophilia over 16year-old. They were 80.3% with haemophilia A and 19.7 % with haemophilia B, with a severe form of the disease for 80.3 % of them. Curiosity for HGT was formulated by 64.2% of the participants, 33.6 % being interested by this approach as soon as it will be available and 38.7 % preferring to wait until more patients have been treated. Only 3.6 % of the participants would never consider receiving HGT. The level of awareness and knowledge was estimated to be limited by 39.5 % of the patients. More than 60 % of them declared having never or almost never discussed HGT with the team of their haemophilia centre. Before deciding to get HGT, 54.4 % of the participants considered that it will be very important to compare it with their current treatment and 53.7 % would like to be better informed by their care providers.

Conclusions: These results highlight the need for training and education for patients, but also for professionals at haemophilia centres, about HGT and the shared decision-making process. Objective, unbiased and transparent information must be available for patients about this very promising therapy which nonetheless carries more uncertainty and unknowns compared to other haemophilia treatments.

KEYWORDS
gene therapy, haemophilia, perspectives, preference, questionnaire, survey

1 | INTRODUCTION

Haemophilia is a hereditary X-linked bleeding disorder related to a deficiency in coagulation factor VIII (FVIII, haemophilia A [HA]) or FIX (haemophilia B [HB]). Three levels of severity are considered, depending on the level of circulating FVIII or FIX. Severe haemophilia is characterised by FVIII or FIX levels below 1% while the activity of these factors is between 1% and 5% in moderate haemophilia and between 5% and 40% in mild haemophilia.[1] Bleedings correlate with factor plasma levels. For decades, the principle of treatment for haemophilia was replacement therapy with intravenous injections of factor VIII or IX. Patients with severe haemophilia and/or severe bleedings benefit from prophylaxis, in order to prevent bleeding, especially joint bleeds that lead to disabling arthropathies[2]

Prophylaxis is thus the current 'gold standard' of haemophilia management.[3] Recent progresses have reduced the burden of this prevention, lowering the number of intravenous injections of factors, thanks to recombinants with extended half-life.[4] Moreover, non-factor therapies have been developed, mimicking factor VIII and allowing for subcutaneous prophylaxis.[5] These pharmacological progresses have already greatly improved the quality of life (QOL) of patients with hemophilia.[6] New innovative advances are ongoing. For instance, rebalancing agents modify hemostasis and aim at correcting hypocoagulability by inducing a 'controlled' hypercoagulability through the inhibition of such natural anticoagulants as antithrombin, tissue factor pathway inhibitor (TFPI) or activated Protein C.[7] Some of these molecules are already authorized in some countries and others are currently evaluated in clinical trials. All allow for a remarkable reduction of bleeding accidents and are administered subcutaneously.[8] Yet, although symptomatic joint bleeds are significantly reduced, no current therapy is able to suppress the risk of haemophilic arthropathy which persists and appears to be related to sub-clinical micro-bleeds.[9]

Hemophilia gene therapy (HGT) has been designed with the aim of getting the patient's hepatocytes to produce of the missing clotting factor. It is however emerging in an environment where health professionals and patients with haemophilia will have to choose between several options including personalized therapy.[10]

Two HGT constructs, valoctocogene roxaparvovec (Roctavian, Biomarin) and etranacogene dezaparvovec (Hemgenix, CSL Behring) have recently been authorized in the USA and Europe. Hemgenix is also approved in Canada.

Considering that eligible recipients of HGT might have knowledge gaps about this innovative approach, this survey was designed to understand the awareness of patients with haemophilia about these advances. It also investigated the ways through which patients get knowledge about HGT and how they position themselves in view of potentially benefiting from these therapies in France.

2 | MATERIALS AND METHODS

2.1 | Study design

This survey relied on an online questionnaire that was made available on the websites of the Association Française des Hémophiles (AFH) and of the French reference centre for hemophilia (CRH) between 20 Oct 2022 and 20 Mar 2023. All the patients who answered volunteered, did not receive any fee and provided consent for their participation. The study was conducted in accordance with French and European data protection laws.

2.2 | Questionnaire format

The survey was built by French patients' representatives (AFH) in a collaboration with healthcare providers of the French National Reference Centre for Hemophilia (CRH) and the support of MoiPatient, a web-based research platform. Demographic and epidemiological information collected included patient age, gender, area of residence, distance from their home to their usual haemophilia care centre, AFH membership or not, education level, profession, type and severity of haemophilia, current treatment (prophylaxis or on-demand) and satisfaction level regarding their current haemophilia therapy (Supplemental Data).

Participants then had to answer questions to appreciate their level of knowledge and perception of HGT (positive beliefs, eligibility, safety, information needs, negative expectations, patient involvement, access to gene therapy including financial barriers and reimbursement). There were 55 questions in the questionnaire. Thirty-six (65.45%) questions had a drop-list where patients could select one answer, twelve were scaling questions ranging from 1 to 5 points and 4 required free-text answers. The questionnaire was available in French only. Several questions aimed to evaluate the level of patient awareness on precise points.

The questionnaire was associated to resources based on the essential knowledge needed for patients to reach a decision about HGT. Patients completing the survey had access to proper answers to the survey questions (whenever available), additional information and documentation on HGT.

2.3 | Participants

The target population was men and women with severe or moderate haemophilia, over 16 years of age, in a position of possibly being candidates for HGT. AFH and healthcare providers from all comprehensive haemophilia care centres in France informed their patients about the survey and encouraged their participation.

2.4 | Data collection and analysis

Only questionnaires with complete data were analysed. Patients below 16 years of age, those with minor haemophilia or another inherited/acquired bleeding diseases (von Willebrand disease, platelet disorder, rare bleeding disorder) who answered the questionnaire were excluded from the analysis as well as patients who partially completed the survey.

In partnership with Cemka's statisticians, descriptive statistics were used to report on participant characteristics and answers. A subgroup analysis was performed in three age-groups, respectively young adults < 40 years old (yo), middle-aged adults 40–55 yo and senior adults > 55 yo.

3 | RESULTS

3.1 | Patients

Overall, 143 individuals participated in the survey and 137 questionnaires could be analysed. Patient characteristics are summarized in Table 1.

This population represented about 3.5% of French patients with severe/moderate haemophilia over 16-year-old. They were issued from 14 French regions with a strong participation of patients from Rhône Alpes (13.1%), Ile de France (13.1%) and Brittany (10.2%). All participants knew about AFH and 66.4 % were members.

3.2 | Interest for gene therapy

Choosing HGT to treat their haemophilia was an option for 64.2% of the patients. Among them, 33.6% would be willing to benefit from it as soon as available and 38.7% would like to wait for a while. Some (24.1%) were undecided and only 3.6% declared that they will never consider this option.

In terms of knowledge, only 5.1% of participants declared being well-informed on HGT, 55.5% considered having little information and 39.5% did not net feel to be informed. The three major sources of information mentioned were AFH (73%), health professionals (45.3%) and media (44.5%). It was surprising to find out that more than 60% of participants considered they seldom or never discuss HGT with hematologists at their haemophilia centre. To the question of what they felt was the major advantage of gene therapy, most (56.1%) answered '*increase my coagulation capacity thus avoiding prophylactic injections*'.

3.3 | Patient perception of gene therapy

The duration of HGT was considered as very important for 42.6% of the participants with, for 41.9% of them, an acceptable minimal expression duration of more than 6 years. HGT safety was considered by 56.8% of the participants as presenting short-term risks (liver lesions, allergy or intolerance) and by 66.2% as carrying potential long-term risks (cancer, liver lesions). That an immunosuppressive therapy might be needed after HGT was known by 32.4% of participants.

TABLE 1 Patients characteristics.

Characteristics	Value
Gender Male/female/binary (*n* =)	129/7/1
Age in years, mean, SD (range)	46.8± 15.8 (17 –73)
Haemophilia A/B (%)	80.3%/19.7%
Severe haemophilia (%)	80.3%
Prophylaxis/on demand Factors (%)	72.3%/27.7%
About their current treatment (%)	
Satisfied	44.5%
Moderately satisfied	51.8%
Not satisfied	3.7%
Education level (%)	
Baccalaureate (A level) +2 or more	46%
Baccalaureate (A level) +2	23.4%
Baccalaureate (A level)	10.9%
Youth training (NVQ)	11.7%
High school or lower	8%
Employment (%)	
Employed	46%
Retired	21.9%
Unemployed	9.5%
Students or on probation	11.6%
Handicapped or self-employed	9.5%
Distance from haemophilia care centre (%)	
Less than 30 min	24.8%
30 min to 1 h	46.7%
1 to 2 h	23.4%
More than 2 h	5.1%

3.4 | For several important questions such as

- do all patients receiving HGT have a satisfactory expression of FVIII or FIX?
- can FVIII or FIX decrease or disappear with time after HGT?
- can treatment be stopped after HGT?
- is it possible to have a second HGT injection?

most patients answered that they did not know (42.3%, 47.4%, 41.6% et 58.4%, respectively).

Questions about eligibility to HGT allowed to recognize that only 50% of patients knew that not all patients with haemophilia are eligible for this innovative approach since gene therapy is not yet approved for use in children and women (1.5% and 22.1% respectively).

TABLE 2 Main results of the survey.

WHAT IS IMPORTANT FOR YOU TO DECIDE RECEIVING GENE THERAPY?		
1	Comparing with my current treatment	54.4%
2	Being informed by the team of the treatment centre about benefits and risks	53.7%
3	Knowing short-term treatment-related side effects	45.6%
4	Knowing long-term treatment-related side effects	41.9%
5	Knowing about the short-term thorough medical follow-up involved	24.3%
6	Knowing about the long-term thorough medical follow-up involved	23.5%
7	Sharing the experience of patients having received gene therapy	17.6%
8	Having access to information produced by the AFH with health professionals: brochures, videos…	11.0%
9	Discussing with my relatives, caregivers, patients…	9.6%
10	Taking time to consider the option	7.4%
11	Knowing about costs involved	5.1%

Abbreviation: AFH, association française des Haemophiles.

3.5 | Why would patients choose gene therapy?

Table 2 ranks the importance of criteria considered for the choice of HGT by patients. The major points are comparison of this new opportunity with their current treatment and information and counsel provided by their haematologist at the haemophilia centre.

For 65.4% of the patients, it appears to be very important to understand the mechanisms of action of HGT. There is no concern for 44.1% of them to go to a centre hub for HGT injection and 36% consider acceptable to go there several times each year for follow-up. For 34.8%, daily QoL would be greatly improved by HGT while 24.4% consider that this will change their identity of a person with haemophilia.

3.6 | Age-related results

Three age-groups were considered, respectively < 40 years old (yo), 40–55 yo and > 55 yo with respectively 47. 44 and 46 individuals in each group. This disclosed that patients most interested in HGT belong to the 40–55 yo group, half of them willing to move to HGT as soon as it will be available. Patients below 40 years of age are those who know best about eligibility criteria and do not consider as important the potential short-term side effects such as hepatic toxicity. A focus on a subgroup of 20 very young participants below 25 years of age showed that they are less optimistic and less willing to benefit from HGT when available, also being more worried about side effects. At variance from middle-aged and senior-adult patients, most of young adult participants did not agree with the proposal « *I think it is acceptable to have access to gene therapy even if some issues remain unknown after clinical trials* » and 60% of them ask for psychological support whenever they will opt for HGT. Moreover, although 55% of participants did not believe that their daily life will improve after HGT, still about one third (34%) believe their QoL will be improved after HGT and 48% say that they are aware of the advantages of HGT.

3.7 | Financial concerns about access to gene therapy

The majority of participants, that is, 72%, felt concerned about the price of HGT and 87% worried whether HGT could pose problems with reimbursement and access to treatment.

4 | DISCUSSION

This study evaluated the awareness and choice parameters of French patients with haemophilia about HGT. A survey conducted among Canadian patients with haemophilia had reported that 52.8% of respondents had heard about 'gene therapy' but only 19.6% of them believed that this would soon become available.[4] Fourteen years later, haemophilia B gene therapy is available in Europe, USA and Canada and haemophilia A gene therapy is authorized in the USA and in Europe. In spite of this, 60% of the 137 participants to the present survey declared having never discussed this opportunity with their haematologist and more than a third (39.5%) admitted that they do not know much about it. These figures illustrate the knowledge gap of the patients with regard to this innovative therapy and perhaps also that of healthcare personnel who may not yet feel at ease to discuss it with their patients. Of note, most of the participants were well-educated and more than 66%, members of the AFH, had access to some information. These results show how important it is to communicate with patients and inform them. The educational responsibility of professionals in comprehensive haemophilia care centres is major. Because the needs for information and education are important for patients as well as health professionals, AFH and CRH have decided to produce objective and transparent information tools on a web-based platform to provide to all French speaking patients and health professionals an access to industry independent shared decision-making tools for all haemophilia therapies including HGT.

The multidisciplinary teams of haemophilia care centres must provide objective information for these irreversible treatments that cannot be stopped once administered. Patient education and the development of shared decision-making tools will be mandatory to allow patients to reach a decision liable to 'change their life' after being well aware of transparent information about efficacy, safety, uncertainties and unknowns of HGT.[11–14] The World Federation of Haemophilia has developed a shared decision-making tool to guide patients and caregivers in discussing treatment options (https://sdm.wfh.org/).

A survey about the preferences and priorities of American patients with haemophilia[15] has previously indicated that efficacy (i.e., number of bleeding episodes) was their first concern (31%) for treatment choice, followed by the frequency of injections (26%) and safety issues (17%). This was confirmed in a more recent publication.[16] Similarly, here, 54.4% of the French patients were found to first want to compare their current treatment with HGT before making a decision.

Many patients explain that the disease impacts their life all day long and see in HGT the hope of a definitive cure. However, is it the current reality?

The phase 3 trials that led to approval of the two available molecules are not similar in terms of efficacy nor safety. Patients with HB can expect to achieve mean endogenous FIX levels of approximately 35%, with a prolonged durability of FIX expression of at least 10 years.[17,18] Yet, 17% of the patients who received etranacogene dezaparvovec required corticosteroids to control the increase of alanine aminotransferase (ALT) and preserve FIX-expressing hepatocytes. In patients with severe HA treated with valoctogene roxaparvovec, outcome measures at 2 years post-treatment showed a mean of 22 IU/dL increase of FVIII activity compared to baseline and a 84.5% decrease of annualised treated bleeding rate.[19] In contrast to etranacogene dezaparvovec, treatment-related increase of ALT was common in HA, occurring in 86% of the patients and leading to corticosteroid therapy for 79.1% of them, with a median treatment duration of 230 days. Moreover, 23% of the patients treated with valoctogene roxaparvovec had a median FVIII activity of less than 5% as measured with a chromogenic assay.[20] These results clearly indicate that the current technology does not yet provide the cure hoped for.

In addition, a number of uncertainties[21] and unknowns remain regarding the individual response of each patient, still unpredictable, the long-term efficacy and risks, notably the potential oncogenicity of these drugs.[22] Gene therapy for haemophilia is completely different from that applied in other indications such as spinal muscular atrophy (SMA) which represents the most frequent monogenic cause of childhood mortality[23] or Duchenne muscular dystrophy, diseases without any alternative treatment where vital prognosis is conditioned by the efficacy of the gene therapy. Patients with haemophilia who live in high-income countries can opt for a variety of efficient solutions, and this justifies them being more demanding on the efficacy and safety of HGT, at variance from diseases without alternative therapies. Recent results of a phase 3 trial with a new FVIII molecule indeed show a FVIII activity of more than 40 IU/dL for most of the week and of 15 IU/dL at day 7 with a weekly intravenous injection.[24] This molecule and other non-factor therapies reduce annual bleeding rates to between 0 and 1 and do not require the immunosuppressants likely to generate important side-effects.

As demonstrated in the present survey, patients with haemophilia are highly interested by the idea of a single injection allowing them to stop prophylaxis. The two main benefits mentioned are the arrest of prophylaxis and improved plasma FVIII/FIX levels. However, these patients, for whom other therapeutic alternatives exist, are more demanding compared to patients with other serious diseases for which gene therapy is the only treatment option, and they have reservations regarding the uncertainties and safety of current HGT. More than half of patients think there may be risks in using HGT and prefer to wait until there is more experience.

Patients expect substantial improvement before a wider use of this promising therapy. Indeed, HGTcan change the life of good responders. Beyond the hemostatic efficacy usually measured by the ABR, HGT may bring multiple benefits non captured by the trials through lack of appropriate assessment tools. Neither the usual criteria of clinical or biological efficacy, nor QoL questionnaires translate the radical change brought by HGT to patients and their entourage no longer preoccupied by the disease and the burden of conventional treatment. When HGT is efficient, the constant expression of FVIII or FIX suppress bleeding episodes allowing for less school absenteeism, a better socio-professional insertion, a more satisfactory personal life and finally the bliss of an « haemophilia-free mind»,[25] all highly motivating prospects.

Only a part of the patients reaches these goals with the current molecules of HGT. Moreover, many patients will not be eligible for HGT with the criteria applied nowadays[26] such as pre-immunization to adeno-associated viruses (AAV) which concerns about 30%–35% of French patients,[27] the presence of inhibitors, women, children and adolescents with haemophilia, or the presence of certain comorbidities. This was the first time that the question of eligibility occurred for a population of patients who has access to all available treatments whatever their age, gender or disease severity, in a community attentive to the concept of equity. It is important not to neglect the psychological support that will have to be brought to disappointed patients found ineligible, in spite of their motivation and aspiration to a better health.

As noticed in the survey reported here, younger (less than 25-year-old) patients with haemophilia, who benefited from primary prophylaxis limiting joint bleeds, arthropathy and joint pain, mostly treated by subcutaneous molecules or extended half-life products, are more cautious about the side effects of HGT and will not choose it as soon as it will be available.

Finally, some survey participants wondered about access to HGT owing to its high cost, positioning of payers and public instances about reimbursement. HB gene therapy was approved by the Food and Drug Administration (FDA) at a cost of 3.5 million USD but, according to a recent clinical trial, it avoids the use of 250,000 IU of FIX concentrates per year.[18] According to French tariffs, this would save every year between 200,000 and 425,000 euros per patient, depending on FIX concentrates price. Discussions between authorities and manufacturers are ongoing to develop new reimbursement approaches for HGT in haemophilia, based on its efficacy and durability with regard to current uncertainties on its short- and long-term efficacy.[28]

The main limitation of this study is the relatively small number of participants who represent only approximately 3% of French adult patients with severe haemophilia. A bias may exist linked to recruitment by the patients' association because their members are usually more informed and involved in their care. Finally, in the population of participants, men had a higher level of education than the general population of patients with severe haemophilia.

While these exciting discussions are ongoing, it is important to remember that 85% of patients with haemophilia worldwide still have no access to therapy[29] and that HGT in its current form is unlikely to be the ultimate solution, owing to the intensive medical follow-up required at least during the first year, hard to implement in countries with limited medical, laboratory and imaging resources.

HGT is, at the moment, a major scientific advance, liable to considerably improve the QoL of many patients through a single injection. It could allow patients to go through their daily activities without worrying about their last prophylactic injection, without regularly getting their medication in hospital pharmacies, without getting to a dentist appointment worrying about their haemophilia and a prophylactic injection. They would be able to practice sport activities good for their joints without worrying about bleeding. They could thus lead an « almost normal » life even if it is not a total cure. French patients are however still looking for more information on HGT. Some are ready to benefit from this innovative therapy but many need to compare it to their current treatment to find out whether HGT can be truly beneficial for them. Finally, they have some concerns given the uncertainties and unknowns surrounding this very innovative treatment.

Medics, patient associations and payers should get through all possible moves to allow as many as possible patients with haemophilia to benefit from this major therapeutic advance. Yet, all others, not yet eligible or who would develop liver reactions leading to the loss of transgene expression, or who, despite corticosteroids, would see the efficacy of HGT decrease with time, with unpredictable individual expression variability may rightly become disappointed.

For all these patients, research must go on for a better understanding of the mechanisms responsible for expression variability, for the identification of technological advances targeting more physiological cells such as endothelial cells for HA, for the design of new vectors improving efficacy or reducing the toxicity of AAV, for gene editing and other strategies liable to provide patients with haemophilia with a more efficient gene therapy, safer and with less uncertainties, which is so much expected by most of them.

AUTHOR CONTRIBUTIONS

Geneviève Pietu, Nicolas Giraud, Gaétan Duport and Yesim Dargaud conceived and designed the project, analysed the results; Yesim Dargaud produced the first draft of the manuscript which was subsequently finalised by all authors. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

This manuscript reports patient perspectives and reflects the positions of French haemophilia patient representatives (AFH) and French reference centres for haemophilia. Nicolas Giraud is the president of AFH and Yesim Dargaud is the coordinator of the reference centre of haemophilia in France. The authors have no other relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Research ethics committee (REC) approval was not required for the preparation of this manuscript.

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SUPPORTING INFORMATION

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

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