REAL FUNDACIÓN VICTORIA EUGENIA

SETH
SOCIEDAD ESPAÑOLA DE TROMBOSIS Y HEMOSTASIA

GENE THERAPY IN HEMOPHILIA

QUESTIONS AND ANSWERS ABOUT GENE THERAPY IN HEMOPHILIA

REAL
FUNDACIÓN
VICTORIA
EUGENIA

Coordination

Dr. MARÍA TERESA ÁLVAREZ ROMÁN
Chair of the Scientific Commission of the Real Fundación Victoria Eugenia (RFVE). Hemostasis Section. Hematology Service of the University Hospital La Paz, Madrid. Associate Professor at the Autonomous University of Madrid.

Mr. DANIEL ANÍBAL GARCÍA DIEGO
Chair of FEDHEMO and Board Member of the RFVE.

Authors

Dr. RAMIRO NÚÑEZ VÁZQUEZ
Hematology Service. Head of the Hemostasis section at the Virgen del Rocío University Hospital, Seville. Vice-chair of the Scientific Commission of the Real Fundación Victoria Eugenia (RFVE).

Mrs. LOURDES PÉREZ GONZÁLEZ
Social worker and Manager of the Spanish Federation of Hemophilia (FEDHEMO).

Dr. MANUEL RODRÍGUEZ LÓPEZ
Hematology Service. Álvaro Cunqueiro University Hospital of Vigo, Pontevedra. Member of the Scientific Commission of the Real Fundación Victoria Eugenia (RFVE).

Ms. MARÍA SÁNCHEZ RUIZ
Health Psychologist at the Spanish Federation of Hemophilia (FEDHEMO).

ISBN: 978-84-09-60007-6

Translator: **Emma Barraclough**

Layout maker: **E. C. V. Patricia Joga**

INTRODUCTION

In recent years, the therapeutic approach to patients with hemophilia has changed completely. New strategies have emerged attempting, on the one hand, to reduce the burden of the disease by reducing the number of bleeds and, on the other, to reduce the burden of treatment by requiring fewer infusions or with a simpler route of administration such as subcutaneous delivery.

These new treatments, include, in particular, gene therapy, whereby a single infusion is able to achieve a "functional cure" of the disease in most patients.

Hemophilia has always been considered as an ideal candidate for gene therapy based on a number of reasons: it is a monogenic disease; the causative genes and genetic defects are well characterized; the expression of small amounts of protein (FVIII and FIX) is sufficient, since inconspicuous increases in the missing protein are capable of changing the hemorrhagic phenotype of the disease. In addition, we have the appropriate methodology to measure treatment results and animal models are available.

After many years of research, gene therapy has become a reality. Currently, there are already two treatments that use adeno-associated viruses approved by the European Medicines Agency (EMA): one of them from the company BioMarin, Roctavian® is indicated in hemophilia A, while the other, Hemgenix® by CSL Behring, is for hemophilia B. The latter has also been approved by the Federal Drug Administration (FDA). The close implementation of this disruptive treatment means that the patient needs to be properly informed as this therapeutic approach differs greatly from those used previously.

Patients should know if, based on their specific characteristics, they can be good candidates for gene therapy. They should also be aware of the effectiveness and safety of the treatment, both in the short and long term; the most frequent adverse events not only during, but also after infusion; any precautions or restrictions; and how they may be forced to change their habits with treatment. Finally, they need to know where the procedure will be carried out and where the subsequent follow-ups will take place.

This monograph arises as an initiative of the Scientific Committee of the Real Fundación Victoria Eugenia (RFVE) and the Spanish Federation of Hemophilia (Fedhemo), aimed to provide information, using plain language, to people with hemophilia on the implications of gene therapy and everything related to it. This will help them to decide, in a duly informed manner, if it is a suitable option for them.

A close and accessible language used to inform both patients and their families can minimize communication errors and facilitate conversations and decision-making about possible opportunities and treatment options. The monograph has been designed with a "questions and answers" format. The team involved is formed by patients, and by professionals such as social workers, psychologists and hematologists who have strived to collect information considered essential for the patient before undergoing the procedure.

Shared decision making (SDM) in the field of medicine is becoming the most commonly accepted approach in societies such as ours.

This approach, however, is not new in the world of hemophilia and coagulopathies, where this approach has been promoted for some time, with very high levels of trust, transparency and responsibility in the doctor-healthcare team/patient relationship. However, promoting healthy shared decision-making requires, among other things, information and deliberation.

We are facing an unexplored horizon such as gene therapy for hemophilia (hopefully we can also add "other coagulopathies") and we trust that this guide will serve to clear the way towards a better understanding of gene therapy, clarifying doubts, doing away with myths and misunderstandings.

This guide cannot, and should not, replace the clear, frank and constructive dialogue between patients and health professionals; on the contrary, it should serve as an auxiliary element in this dialogue, which by definition should be adapted to each of the various potential scenarios. This work may not answer all questions, but we be-

lieve that it will allow the patient to better pose the questions that will be discussed in this dialogue.

This guide has been prepared by many hands, involving various professional profiles, and scientific and patient entities; we hope that in addition to serving to improve shared decision-making in terms of therapeutic choice for hemophilia, it will serve as an example of how we can collaborate and work together, from various professional perspectives and different views, in improving the approach to health-related issues.

Mª Teresa Álvarez Román
Chair of the Scientific Committee of the RFVE

Daniel-Aníbal García Diego
Chair of FEDHEMO

CONTENTS

WHAT DO I NEED TO KNOW ABOUT GENE THERAPY

1. WHAT DO I NEED TO KNOW ABOUT GENE THERAPY?

1. WHAT DO I NEED TO KNOW ABOUT GENE THERAPY?

1.1. What treatment options are currently available for my disease?

Currently, for both hemophilia A (HA) and hemophilia B (HB), we have extremely efficient and very safe therapeutic alternatives, both in terms of immunogenicity and viral safety; this allows for prophylaxis regimens with few infusions and even the possibility, in HA, of an effective prophylaxis with the subcutaneous delivery of a factor FVIII replacement product with barely 12 administrations per year.

1.2. What is gene therapy?

It is a new method of treatment that makes the patient's liver capable of producing the missing factor, FVIII in the case of patients with hemophilia A and FIX in the case of patients with hemophilia B.

1.3. How is it carried out?

Genetic material is inserted through a "vehicle" known as a vector, an adeno-associated virus (AAV), which, while not having the ability to infect, carries the genetic material required to synthesize the missing protein, FVIII or FIX. It is considered a "functional cure of the disease".

It involves a single intravenous infusion.

This "functional correction or cure" of the disease only benefits the patient undergoing gene therapy, but not the patient's offspring, since the patient continues to transmit the disease.

1.4. Is it currently available in Spain?

At the moment there are a number of approved gene therapy strategies and others at very advanced stages of development.

¿AM I A CANDIDA FOR THE PROCEDU

2. AM I A GOOD CANDIDATE FOR THE PROCEDURE?

2. AM I A GOOD CANDIDATE FOR THE PROCEDURE?

2.1. Am I a good candidate for gene therapy?

At this time, not all patients are candidates. Patients under 18 years of age, those with liver disease secondary to active hepatitis C or B virus infection, or with antibodies against the adeno-associated virus, have been systematically excluded from most gene therapy clinical trials (CTs). So, if you are in any of these groups, you are not a candidate. Further, those patients who present -or who have presented it in the past- inhibitors against clotting factor FVIII or FIX, as well as patients not previously treated or minimally treated (2 to 5 days of exposure), are not candidates, although the possibility of including them in the future is not ruled out.

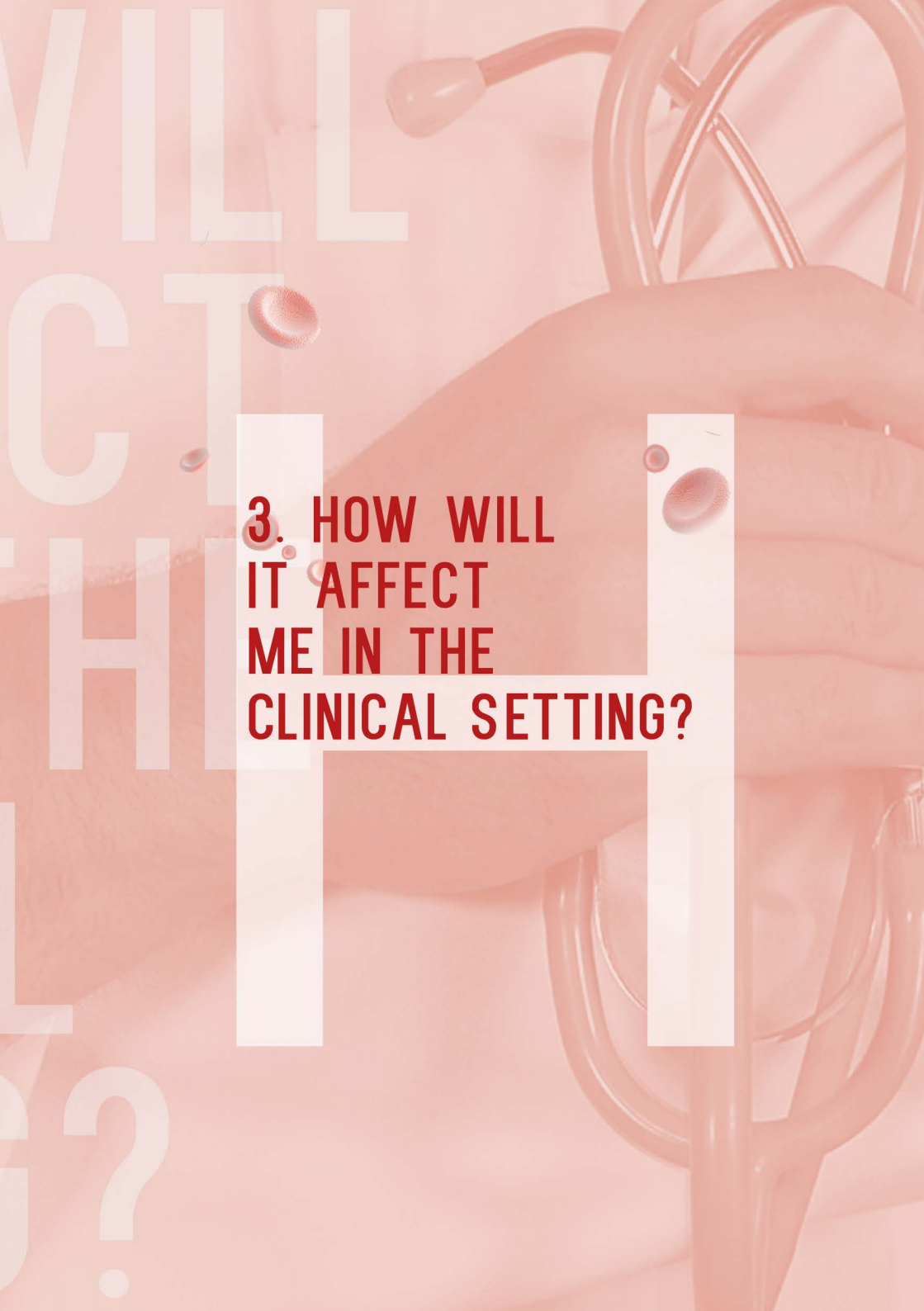
Likewise, the pediatric population and patients with mild or moderate forms of the disease are also not considered eligible for gene therapy at this time (except in hemophilia B, having included patients with levels between 1-2%).

2.2. Which patients are ideal candidates for gene therapy according to hematologists?

Currently, even without being an absolute rule, the first patients would be those in whom an adequate control of the disease is not achieved (basically of bleeding) with the currently available treatments, or who present bad venous accesses that make it difficult to administer regular prophylaxis, or patients with poor adherence to traditional treatment. Another group of patients with a high burden associated with the treatment of the disease or with advanced arthropathy could also be considered as suitable candidates.

Even so, it is a highly promising therapy that may become an option to consider for a large group of patients, once some of the current uncertainties are clarified.

HOW W
IT AFFE
ME IN T
CLINICA
SETTING



3. HOW WILL IT AFFECT ME IN THE CLINICAL SETTING?

3. HOW WILL IT AFFECT ME IN THE CLINICAL SETTING?

3.1. What are the results of the various CTs?

With regard to hemophilia B, the results of the only therapy approved so far in humans show a short-term response, with normalization or practical normalization of FIX levels without needing further FIX concentrates and without further bleeding events in practically 100 % of patients.
For hemophilia A, although the results in terms of increased plasma levels of FVIII are more modest, the clinical results are good both because of the reduction in the number of bleeds, which almost disappear in 100% of cases, and because no additional FVIII concentrate treatment is needed in the vast majority.

3.2. Will I feel better after therapy?

If the response (factor production) is achieved and maintained, we can say that not only will you feel better, but much better, reducing the number of bleeds very significantly, as well as the need for intravenous treatment.

3.3. Am I at risk of other diseases by undergoing this procedure?

Based on current knowledge, there is no risk of disease in the strict sense of the word; however, in a variable percentage of patients, higher in the case of hemophilia A than in hemophilia B, there may be liver problems, in the form of increased transaminases, which may require treatment with corticosteroids for a given time, which in some patients has been associated with a loss of response, forcing them to resume prophylaxis.

In addition, the use of these corticosteroids or other immunosuppressive agents is associated with potential side effects, such as hyperglycemia, high blood pressure... which are usually manageable and reversible. In any case,

any such liver problems are more common in gene therapy in hemophilia A than in hemophilia B, where they only affect about 1 in 5 patients, at least, with regard to the only gene therapy approved so far in hemophilia B.
Importantly, we should also be reminded that, although there have been no deaths directly related to gene therapy, a few cases -4 patients- of thrombosis and cancer have been described; after the studies carried out, any relationship with gene therapy has been reasonably ruled out. In addition, it should be noted that, to date, the AVVs used to transport the FVIII or FIX gene have not caused any known diseases in humans.

3.4. What uncertainties ("issues") does gene therapy present today?

The greatest uncertainty is related, on the one hand, to the progressive loss of factor production and, therefore, the potential decrease of its levels in the plasma over time, which will lead, in the long run, to a probable loss of the effect.

In some patients, an immune reaction occurs after the infusion that destroys the liver cells that are producing the missing factor, thus the therapeutic response is lost. This is because the transgene of the currently approved therapies is located at the episomal level, outside the nucleus.
Interestingly, this effect is less marked in hemophilia B than in hemophilia A, to the point that mathematical simulations estimate that 8 out of 10 infused patients will have FIX levels >5% (i.e., values considered as mild hemophilia B), 25 years after gene therapy infusion.

On the other hand, a key aspect has to do with the vector or "carrier" that we use to introduce the gene; currently adeno-associated viruses (AAVs) -against which we could have antibodies in the event of previous contact with them- are used. That is why currently for most of the gene therapies under study, only people who do not have antibodies against these AAVs are candidates for gene therapy, since they will not reject that gene transporter, i.e., the AAV. Once infused, the patient's immune system will generate antibodies against that AAV, the same thing that happens when we have a cold

or the flu; if in the future, a loss of factor production occurs for any reason, the patient, in the light of current knowledge, could not receive gene therapy with that vector again.

To date, gene therapy clinical trials have excluded patients with the presence of previous antibodies to the AAVs used, except for Hemgenix® (Etranacogene Dezaparvovec, gene therapy approved in hemophilia B) where patients with an amount -what is known as antibody titer- below 1/700 were included, without this affecting the effectiveness of treatment. This is likely to change in the future, since there are already studies in hemophilia A in patients with pre-existing antibodies against AAV. On the other hand, possible strategies are being studied to attempt to overcome this barrier, so that the presence of these antibodies is not a limitation when selecting candidate patients.

3.5. Can I develop inhibitors?

In relation to inhibitors, so far, none have been reported in any of the studies carried out, so, with the logical reservations due to the novelty of this treatment, we can affirm that the risk of developing an inhibitory antibody is practically zero. On the other hand, if you do not respond adequately to therapy or its effect is lost, you should resume prophylaxis with factor concentrates or with non-replacement therapies, as the most appropriate treatment strategy, deciding with your hematologist which is the most suited product in your case.

3.6. What if it doesn't work for me?

If not sufficiently effective and protective levels are not reached, you will need to resume prophylactic treatment.

3.7. What if the effect is too strong? What will happen to me?

In the event that "the therapy has an overly strong effect", in principle, this will be addressed like any other case with similar levels, while it is expected that the levels will gradually decrease to normal values. So far, only one case of venous thrombosis has been described in a patient undergoing gene therapy diagnosed with hemophilia B and who, in addition, presented other thrombosis-related risk factors; the patient was treated like any other patient who develops this complication.

3.8. And if I have to undergo surgery or I suffer a major trauma, will I need factor concentrates?

Currently and in light of the experience reported from clinical trials, factor infusion may be necessary in the case of severe trauma or before certain types of surgery, especially major surgery, such as the implantation of prostheses.

Both minor and major surgery has been documented in clinical trials; in some cases of minor surgery, the prior administration of a single dose of factor concentrate has been required; for major surgery, treatment has needed to be administered regularly, to strengthen protection against bleeding, immediately before and in the first days after surgery.

3.9. ¿What questions should I ask my hematologist? ¿What should I know before DECIDING on gene therapy? And if at the last moment I change my mind and decide not to go ahead, what will happen?

- It is very important to learn all about gene therapy and understand how it works.
- Requirements to be a candidate for gene therapy and commitments acquired.
- I need to know that it is a single infusion and be aware of the adverse events both at the time of the infusion and in the long term.
- Place where the infusion will take place and whether the center has previous experience.
- Understanding that the currently approved gene therapy uses AAV and that it provides a functional cure for the disease, but it is still transmitted to the offspring.
- I must be informed of the clinical results, factor levels, annualized bleeding rate, factor consumption, adverse effects and observation time for patients who have received this gene therapy. Changes it will mean in my lifestyle such as drinking alcohol, sexual relations or physical activity.
- Being aware of other treatments under development that I could benefit from perhaps the same or even more than gene therapy.

- Tests needed before and after the infusion, frequency of visits and place where those tests will be done.
- I need to know, that before deciding on gene therapy, there is currently an international recommendation that the patient be evaluated and informed independently by two different medical teams, who will work together: on the one hand, the Center in charge of administering the product and of the initial follow-up; and on the other, the patient's own Center of origin. These teams will work in a coordinated manner to ensure maximum patient information and safety. In addition, after having been informed and being able to start certain tests, the patient has a time "for reflection" being able to think over step he or she is going to take. Patients must consider that it is an important decision, that will change their way of living in the short-medium term, that will require on their part, a commitment to proper compliance with medical orders, that will change their relationship with family and environment, in short, a decision that will completely change their life.
- The high economic cost, not inconsiderable for society, also deserves much thought, so that time for "reflection" is essential, during which the staff of the medical teams involved in the procedure will be available to clarify each and every one of the doubts that may arise in order to guarantee the success of this treatment.

3.10. Can the procedure be repeated if the response wears off?

Not at this time; after the first infusion, as a result of the immune response that is generated, antibodies against the infused adeno-associated virus will develop.

Currently, different strategies are being developed in order to solve this problem and allow eventual reinfusion, if not with the same AAV vector, with another one.

3.11 What will I feel and what problems will I have during the infusion? Is it risky? Does it hurt? Can I die?

The infusion is continuous infusion, is not given as a bolus as factor concentrates are administered, but lasts longer and must be monitored at a day hospital.

During infusion only 15 % of patients develop adverse events. Hypersensitivity reactions and anaphylaxis may occur. Symptoms may include chest tightness, headache, abdominal pain, lightheadedness, flu-like symptoms, chills, flushing, rash, and hypertension. For this reason, you should stay at the center where the infusion is performed at least three hours after completion. If a reaction occurs during administration, the infusion may be slowed down or interrupted. If the infusion is stopped, it will restart at a slower rate when the reaction has disappeared. The patient may even require treatment with corticosteroids or antihistamines to control the reaction. Generally, they are mild and controllable reactions, in addition to the fact that the infusion is carried out in a hospital environment with easy and immediate access to any measure that may be required, and to date, no fatal reaction has been reported, so, in this regard, the medical team and the patient should be at ease.
In relation to pain, although this is something subjective and that varies depending on the person, pain has not been reported in the context of clinical trials.

3.12. Will I have to do many tests after gene therapy?

Diagnostic tests after follow-up are:

- Periodic analysis of liver enzymes to detect any increase, which may indicate liver toxicity (hepatotoxicity). These should be done weekly for 3 months after infusion. If liver function tests reveal increased values, mainly of the ALT parameter, above normal limits or to twice the patient's baseline value in the first three months after administration, possible treatment with corticosteroids should be considered and, in this case, the controls could continue beyond three months post-infusion.
- Monitoring the activity of the missing factor (weekly for three months), mainly in patients who are receiving factor as a treatment; this should be done for the first weeks following infusion, before

the therapy is effective, in order to decide when to discontinue administration.

In the case of developing hepatotoxicity, it may be advisable to follow up in reference centers that have specialized resources to carry out an adequate follow-up. On the other hand, factor determination will be done using the recommended technique according to the infused gene therapy and it should be taken into account that this may not be available in all centers.

3.13. Where will the procedure be carried out?

At this time and given that it is a very novel therapy, every precaution should be taken. Think that, for one thing, hemophilia is a rare disease and affects few people; also, this is not a treatment for all patients, so this therapy will not be performed on a large number of people, at least in this initial phase and with these vectors.

Currently, the literature all over the world is consistent - in the drafting of which specialists and patient groups have participated - and insists on the relevance of this first gene therapy being carried out at centers with previous experience in this type of therapy or that have participated in gene therapy clinical trials. Accordingly, a model of referral centers and smaller and closer centers is necessary and, therefore, more suitable for patient follow-up, at least in the first months or the first year after administration of the therapy, with the aim of guaranteeing success.

This will further allow treatment centers to generate and acquire more experience in this type of therapy, resulting in a greater benefit for everyone, for the centers themselves and for the patient community.

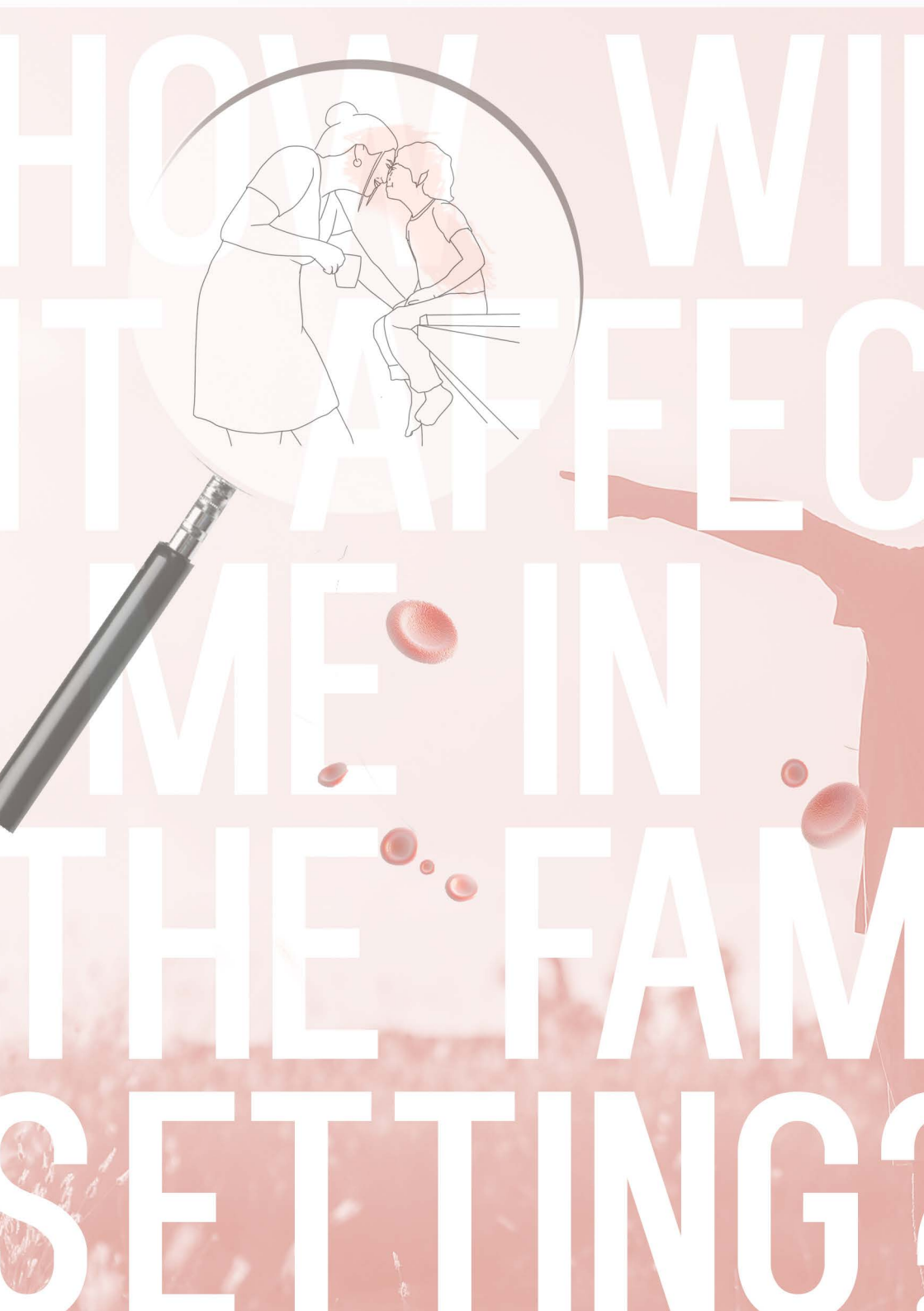
Obviously, it is in everyone's interest that the process interferes as little as possible with your life routine and that of your family, as well as with your job and social life. However, as explained above, frequent visits to the hospital center, either where the infusion was performed, or to the one closest to the patient's home, will be necessary at least during the first three to six months after administration of the therapy.

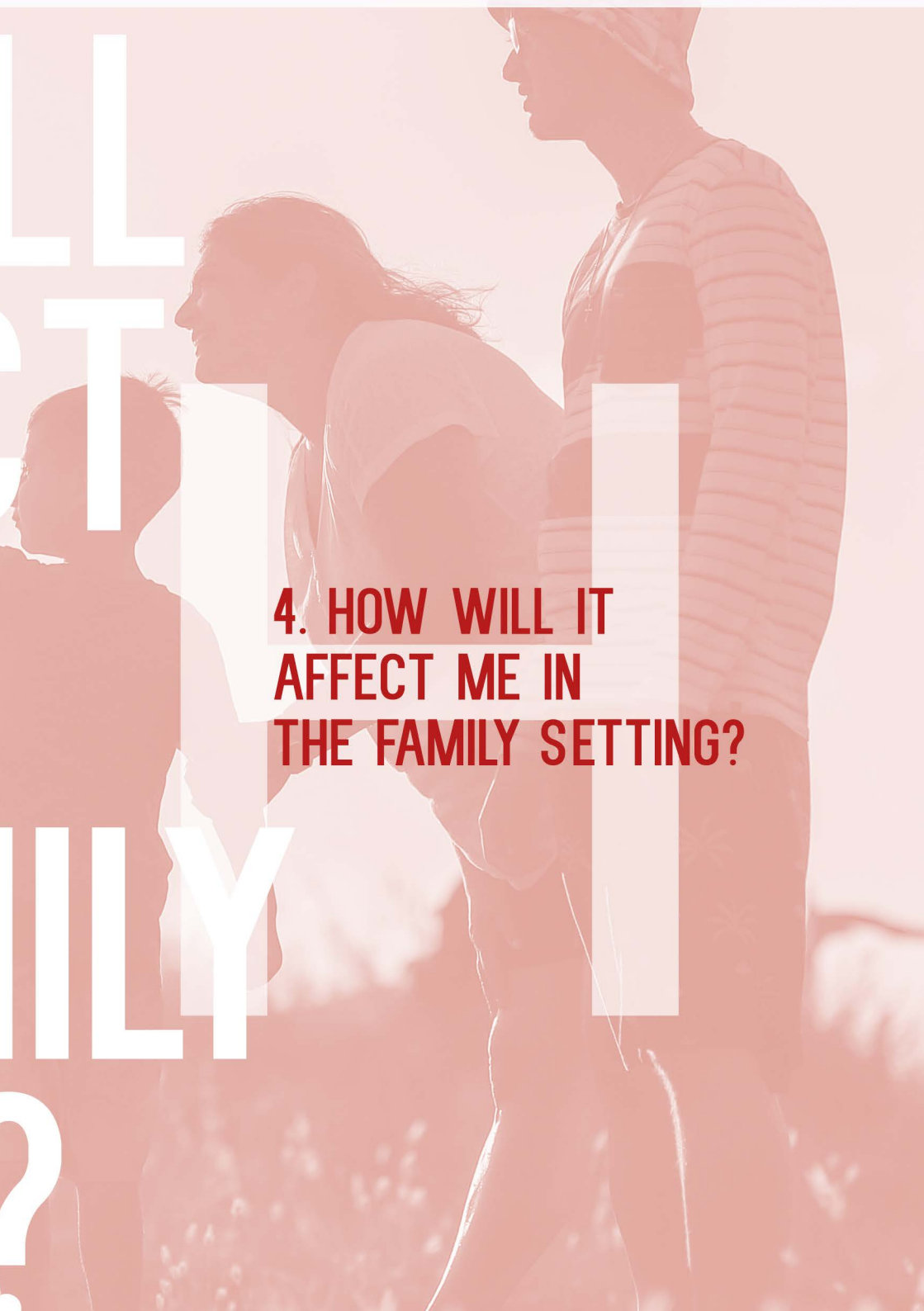
3.14. Will my current pain (arthropathy) disappear? What is going to happen to my target joints (elbows, knees and ankles)? Will they get better?

Arthropathy, once developed, does not disappear, however, if you respond to treatment, the increased plasma level of the factor will imply the disappearance of subclinical bleeding, not only spontaneous bleeding, including joint bleeding. This means, on the one hand, that pain will disappear, partially or completely, in a great majority of cases (it also depends on joint condition at the time of infusion), an improvement that will become more evident the longer the time elapsed since the infusion; an improvement in the target joints - that is, those joints where bleeding usually occurs- and also a slowdown in the progression of the arthropathy already established. Consequently, there will be a reduced need for painkillers and all this will be associated with an obvious improvement of the patient's quality of life.

The results regarding gene therapy in hemophilia A with Valactocogene Roxaparvovec were recently reported at the Congress of the International Society of Thrombosis and Hemostasis in July 2023.

Mark Skinner reported the results at two years in terms of health improvement and quality of life, with a frank and maintained improvement, regardless of the scale used, evaluating aspects such as pain, employment, education, mobility or family life.


HOW WI
IT AFFEC
ME IN
THE FAM
SETTING?



4. HOW WILL IT AFFECT ME IN THE FAMILY SETTING?

4. HOW WILL IT AFFECT ME IN THE FAMILY SETTING?

In the field of chronic diseases, the ability to make decisions involves and affects the family unit. In this context, it needs to be understood as a process of adaptation and adjustment to the important change involved in undergoing gene therapy treatment to improve health. This process of adaptation will differ, for example, depending on the severity of the disease, how it is lived in the family unit, whether it brings an improvement or a relapse.

Deciding whether or not to undergo gene therapy treatment is difficult. Fear and uncertainty, family effort, feelings and emotions are at stake. All changes are complex; in families in which there is a member with hemophilia, the latter's decisions affect the whole family, since patients rely on their families to help them face everyday problems. People with hemophilia are subjected to a lifelong journey through hospitals. Their families need to be a basic support network.

To cope with the change, it is essential to be well informed; this will allow you to reorganize and reschedule. Good communication is essential; the hemophilia patients should be able to express their needs and ideas which should be respected, strengthening this support network that will help to solve in a collaborative way everyday problems.

In the same way, this process of change depends on factors related to culture, gender, socioeconomic status, social context and family history over the generations, and on the life cycle of the family itself and of each of its members (Falicov, 1995, 2007; McGoldrick, 2005; Masten, 2009); also the family beliefs system, the organizational patterns which govern the family, and the type of communication and problem solving adopted (Walsh, 2003).

The family should not take decisions for the person with hemophilia, rather the patient, based on his or her needs and all the information that will be offered, is to ultimately decide. But it is important to make the decision taking into account everything that it entails. Therefore, all the information needs to be collected to be able to gauge the change, only in this way the process of family adaptation and adjustment will be easier.

Ultimately, the person who decides is the person with hemophilia. However, the above observations serve to make visible the importance of a support network such as the family.

HOW WILL IT AFFECT M FINANCIAL

5. HOW WILL IT AFFECT ME FINANCIALLY?

5. HOW WILL IT AFFECT ME FINANCIALLY?

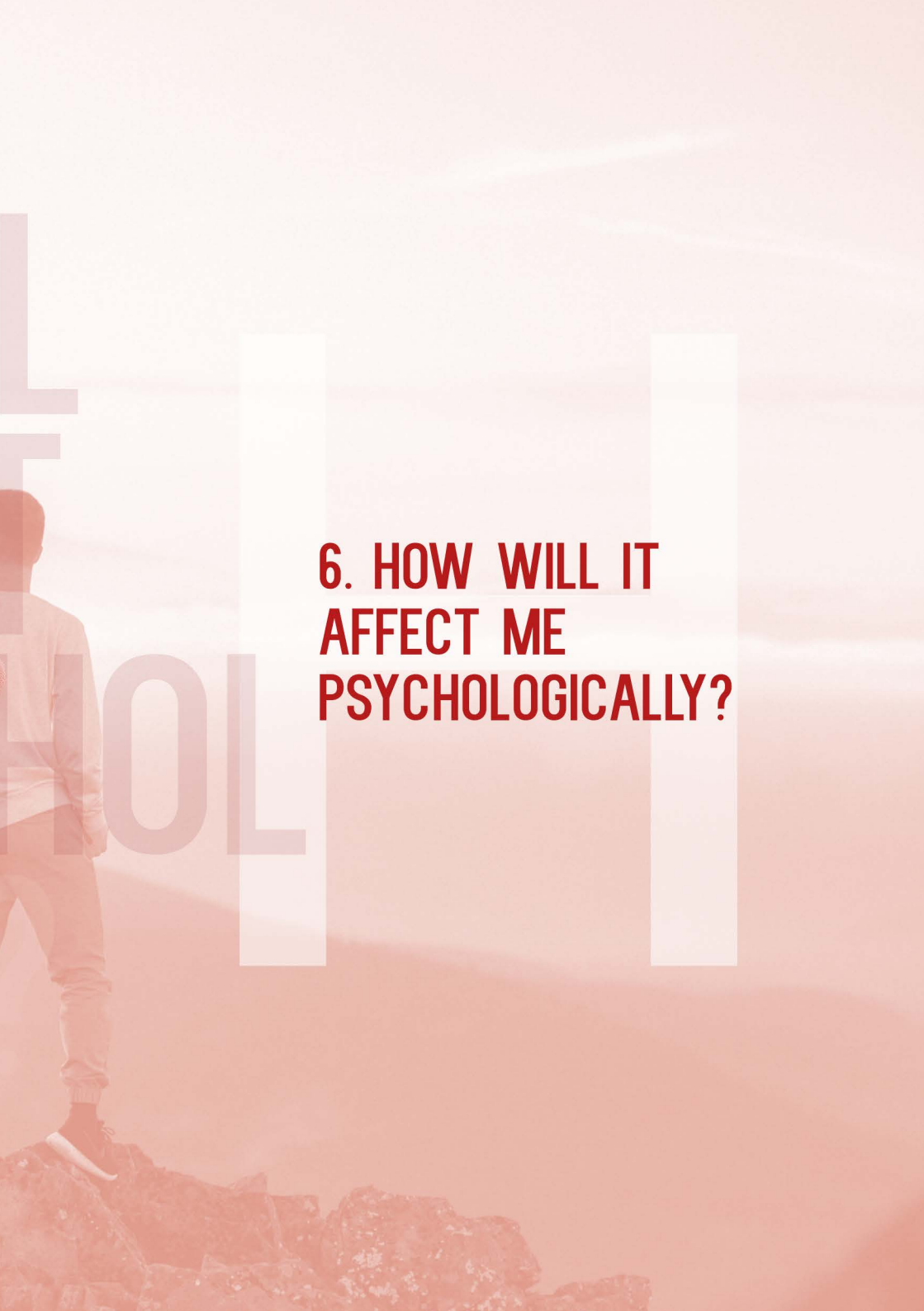
This treatment is funded by the Public Health System, however, to establish if undergoing gene therapy may affect you economically, you need account, on an individual basis, for travel to the treatment center (infusion center, where the procedure will be performed and follow-up center closest to your home).

Before undergoing gene therapy, the patient must assess dependence on the hospital, commuting to the hospital (in your own car or using public transport, the cost of parking, if any, if you will need to miss work, etc.)

Subsequently, travel should be assessed when visiting the center for the first infusion (in your own car or public transport, the cost of parking, if any, will you miss work, etc.), taking into account that it is a one-off appointment. Normally, once the person has been infused, subsequent periodic reviews and controls will be at their usual center, so any economic impact should quantified, as said before, individually. Based on the patient's evolution, at first, these visits will expectedly be monthly, then being spaced every two or three months (depending on the cases) once six months have elapsed and for approximately two years thereafter.

Once this has been assessed, if everything goes well, it will undoubtedly benefit the patient, who will no longer be dependent on hospitals.


HOW WIL
IT AFFECT
ME PSYCH
OGICALLY



6. HOW WILL IT AFFECT ME PSYCHOLOGICALLY?

6. HOW WILL IT AFFECT ME PSYCHOLOGICALLY?

We all agree that hematologists are the experts in pathophysiological processes, however, it is you, as a patient, who knows infinitely more about your intimate experiences with hemophilia and about your vital values and goals, which greatly nuance your attitude towards treatment and the decisions you are going to make. The experience of hemophilia is individual, personal and non-transferable. The meaning of the hemophilia experience for each person undoubtedly has an importance in any decision that is made about their life, marking vital choices such as, for example, profession.

Hemophilia is a chronic disease, with all that this entails. It has been with us throughout our life, and at each stage, in a different way. Therefore, as far as the disease is concerned, we are rarely faced with static situations and the meaning is constantly changing. In the case of chronic illness, uncertainty is always present.

Another part of our life that is non-transferable for each individual is quality of life. Quality of life is the individual's perception about his or her life situation, considering the cultural context and values, in addition to goals and interests. It is important to understand this, so that you can assess what it is, as you perceive it, "to have a good quality of life". Quality of life also depends on the effect of the pathology, and on the effect achieved with treatment. Thus quality of life cannot be defined based on the opinion of any other person or professional, but according to your own perception and based on your life expectations.

In order to reach a suitable decision, you need to be aware of all the information about gene therapy, expected sensations, desirable behavior and management of side effects.

If you eventually decide to undergo treatment, you may reorganize these expectations. Hemophilia has occupied an important place in your life from the moment of diagnosis, close to birth, and often it will have occupied so much space, that you have forgotten about other parts of yourself. Any reorganization, on an emotional level, involves energy, which if not controlled, can increase anxiety levels.

Anxiety is present when we are faced with a situation which we do not feel capable of dealing with. This occurs, above all, in the face of unknown situations, or imagined situations that can be catastrophic. If you feel that uncertainty causes anxious thoughts or physical symptoms, such as rapid breathing and tachycardia, you may need help to guide you in this journey. Such help will mainly involve providing you with tools to be able to cope with a situation that is new for you. The first step to reducing an anxiogenic situation is information.

It is normal that your emotions will change throughout the entire process of treatment. Be vigilant and pay attention not only to symptoms in relation to hemophilia, but also signs at the emotional level. Not paying attention to our emotional part deprives us of any reference about ourselves and others. Moreover, making sense of our emotions reduces uncertainty and gives meaning to who and how we are.

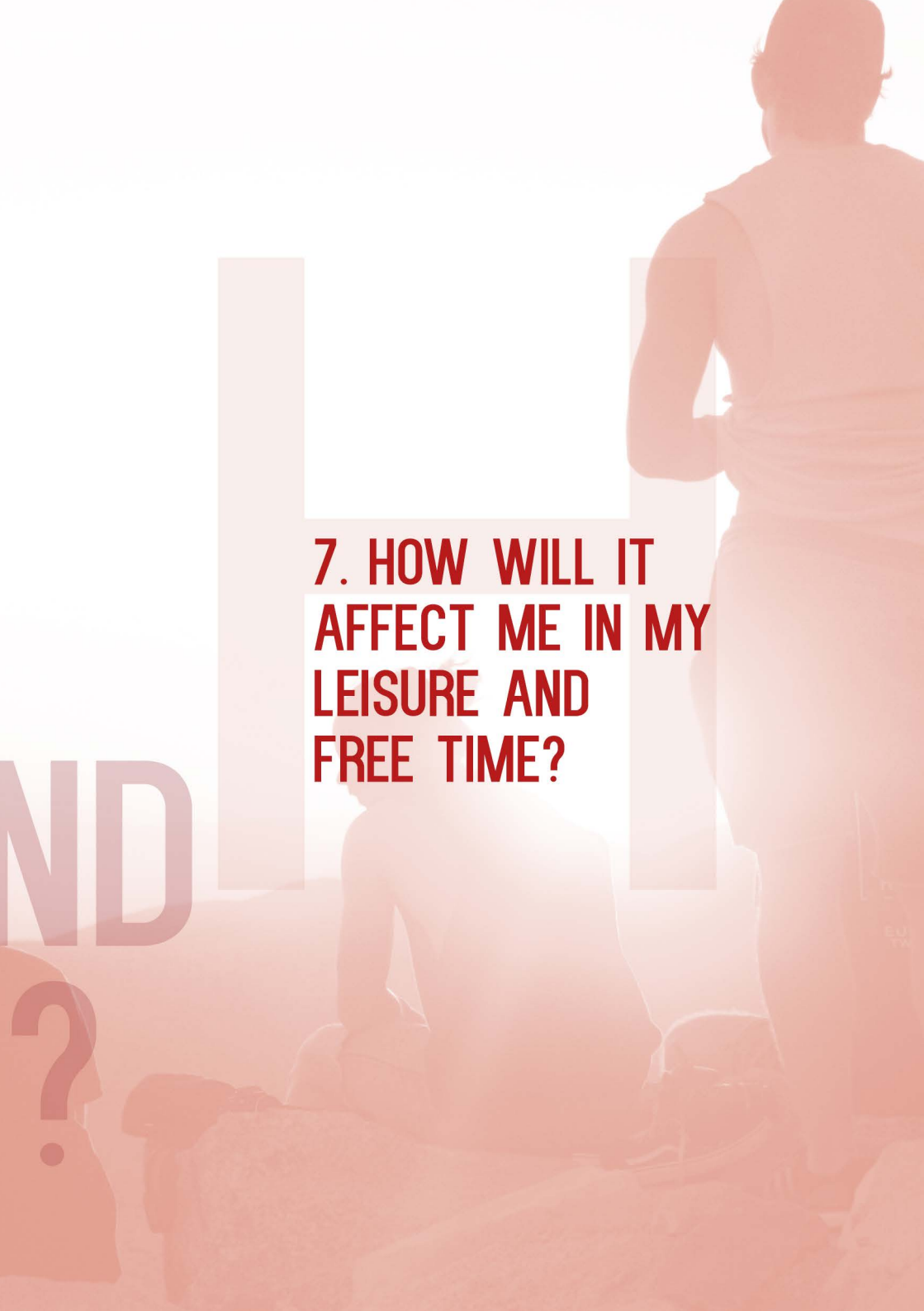
When considering how you are and how you feel, look for help if you detect any of the following signs:

- Insomnia.
- Lack of appetite.
- Negative thoughts about myself.
- Feeling of choking, tachycardia or undue nervousness.

The psychologist's role is crucial from the moment the patient decides to learn about gene therapy. Psychological support is recommended in

combination with assistance from your association, in order to receive a multidisciplinary approach. The objective of this guidance process will be to provide you with tools and discover your own resources, in complex situations, such as decision-making, managing the effects of treatment and changes regarding your relationship with hemophilia.

HOW WILL IT AFFECT ME IN MY LEISURE AT FREE TIME



7. HOW WILL IT AFFECT ME IN MY LEISURE AND FREE TIME?

7. HOW WILL IT AFFECT ME IN MY LEISURE AND FREE TIME?

Will my life change after gene therapy? Will I be able to work? Will I be able to have children? Will I pass the disease on to my children? Will I be able to travel, have a beer, and eat anything?

Obviously it will change and a lot, to the point that you might even need the support of the psychosocial team to guide you through the process of change. Just imagine the emotional impact that for a blind person it would be to suddenly be able to see... because something similar - all differences considered - will happen to you; your relationship with yourself, with your closest environment, with the world in general, will change to the point that, sometimes, this might be stressful when managing your emotions. Gene therapy will change many of your lifelong routines; many of your fears and anxieties related to the disease will disappear, but other doubts may arise, but rest assured that in that process of change you will not be alone either, you will be accompanied at all times and whenever you need it. As already discussed, gene therapy does not prevent the transmission of the disease to offspring, as it is a simply functional cure. As for your lifestyle, you will not be able to drink alcohol at least for the first two years after the infusion, and overall, you will have to maintain healthy lifestyle habits, including a varied and balanced diet. On the other hand, with regard to your sexual life, you will need to use barrier methods to prevent the transmission of the vector through sexual fluids.

As for sport, your professional of reference should be consulted in all cases. On the whole, the patient needs to be especially careful, so sport in a controlled manner is recommended, avoiding risky sports that can lead to serious traumatic injury. Controlled sport is essential; ideally you should

design an activity plan with the help of the health professional of reference and, of course, inform them of any injury immediately.

GLOSSARY

8. Glossary

Adherence to treatment: the degree of compliance with a treatment depending on the dose, the frequency of administration and the persistence or maintenance of the treatment over time. In addition, it refers to how the patient gets involved and collaborates with the prescriber in the decision to take the drug and accept the treatment.

The European Medicines Agency (EMA): European body that ensures the scientific evaluation, supervision and monitoring of the safety of medicinal products for human and veterinary use in the European Union.

Food and Drug Administration (FDA) Federal Drug Administration: equivalent body to the EMA in the United States.

Antibodies: proteins produced by the immune system whose function is to detect foreign elements that may enter the body. They usually detect specific parts of these elements, for example bacterial or viral surface proteins, which are called "antigens". When antibodies bind to these antigens, a series of reactions occur that will block and destroy the pathogen.

Target joint: in plain language, a target joint is one that has joint damage. In hemophilia, the joints that usually experience a larger number of bleeds are the ankles, knees and elbows. The scientific literature considers joints that have three or more spontaneous bleeds in a single joint in a period of six months.

Arthropathy: it can be defined as the pathology that affects the joints. Hemophilic arthropathy is a consequence of repeated bleeding in the joints and can trigger a degenerative process characterized by changes in the articular cartilage and other joint structures. It presents different clinical manifestations such as pain, decreased range of motion and functional disorders that can cause serious sequelae.

Corticoids: are drugs with a chemical structure similar to natural hormones that are produced in the adrenal glands. These drugs are important for the treatment of multiple inflammatory and allergic processes, among others. Although they are very useful medicines, as their downside they have certain

side effects, especially when they are used at high doses and for prolonged periods of time.

Monogenic disease: one that has been originated as a result of a mutation or alteration in the sequence of a single gene. More than 6,000 monogenic hereditary diseases are known. Hemophilia is one of them.

Clinical trial: research carried out in healthy or unhealthy people, which allows to check the effects of a new drug or therapeutic strategy, in order to define its efficacy and safety. Clinical trials are subject to the evaluation and approval of the health authorities following ethical and legal standards, both nationally and internationally, and in accordance with the provisions of a protocol, which must be strictly followed.

Episomal: in gene therapy it refers to the characteristic of adeno-associated virus-based vectors whereby they remain inside cells, producing the protein of interest (FVIII or FIX), with a very small probability of being integrated into the genome of the host cell.

Hyperglycemia: a term that refers to abnormally high levels of sugar or glucose in the blood. It can occur for different reasons. For example, as an adverse effect of certain medications such as corticosteroids.

High blood pressure or hypertension: increased blood pressure values in the arteries of the blood circulating through them. The risk of developing hypertension is higher in patients taking corticosteroids daily for more than three months. Hypertension is predominantly systolic (known as “maximum” pressure, although diastolic or “minimum” pressure can also be affected).

Inhibitor: they are immunoglobulin G (IgG) type antibodies created by the immune system which neutralize the clotting factor concentrates, reducing the effectiveness of treatment and preventing the factor from doing its job of preventing bleeding.

Cell nucleus: is a small spherical or oval-looking structure that is (usually) located in the center of the cells and that contains all the genetic material of the organism.

Subclinical bleeding: bleeds with no apparent clinical expression, in the form of joint pain or swelling, but which can repeatedly affect the joint over the years.

Gene therapy: any procedure whereby a patient's cells are genetically modified for the purpose of treating or alleviating a disease. In the case of hemophilia, by triggering the production by the own cells of clotting factor VIII or factor IX.

Transaminases: a set of enzymes that are found inside cells of organs such as the heart, liver, muscles and kidneys. The most relevant include alanine aminotransferase (ALT or GPT) and aspartate aminotransferase (AST or GOT) that are inside the liver cells (hepatocytes). An abnormal increase in their values is usually indicative of liver damage.

Viral vector: in gene therapy, the system used to introduce genetic material into the cell nucleus is known as a vector, that is, it is a vehicle for microscopic delivery of genetic material to specific targets, i.e., the target cells (hepatocytes in the case of hemophilia). Adeno-associated viruses (AAVs) are the most widely used viral vector in gene therapy.

Virus: a very small infectious microorganism consisting of genetic material (DNA or RNA) surrounded by a protein shell. A virus cannot replicate itself; on the contrary, it must infect cells and use components of the host cell to make copies of itself. There are a huge number of viruses, but only a small number of them can infect humans. Some well-known examples of viruses that cause illness in humans include HIV, COVID-19, measles, and smallpox.

Adeno-associated viruses (AAVs): they are DNA viruses belonging to the parvovirus family, very simple, which reproduce only in the presence of an auxiliary virus. They are widespread in the human population but are not associated with any known disease. They present multiple advantages for use in gene therapy and recombinant adeno-associated viruses (rAAVs) containing the therapeutic transgene are used for this purpose.

Bibliographic References

Aguiar-Palacios, Luis Horacio, González-Arratia López-Fuentes, Norma Ivonne, Ruíz Martínez, Ana Olivia, Domínguez Espinosa, Alejandra del Carmen, Martínez-Alvarado, Julio Román, Padilla-Bautista, Joaquín Alberto, & Torres Muñoz, Martha Adelina. (2022). Self-esteem and coping skills: predictors of quality of life in patients with hemophilia. Revista Cubana de Hematología, Inmunología y Hemoterapia, 38(2), e1503. Epub 1 June 2022. Retrieved on September 27, 2023, from http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0864-02892022000200006&lng=es&tlng=en

Isidro de Pedro. Afrontamiento y mejora de la calidad de vida en afectados de hemofilia. Intervención Psicosocial, 2002. Vol 11 (3) 333-347

Hart DP, Branchford BR, Hendry S, et al. Optimizing language for effective communication of gene therapy concepts with hemophilia patients: a qualitative study. Orphanet J Rare Dis. 2021 Apr 28;16(1):189. doi: 10.1186/s13023-020-01555-w. PMID: 33910590; PMCID: PMC8082836.

Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. Blood. 2021 Sep 16;138(11):923-931. doi: 10.1182/blood.2019003777. PMID: 34232980

Ozelo MC, Mahlangu J, Pasi et al. GENEr8-1 Trial Group. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. N Engl J Med. 2022 Mar 17;386(11):1013-1025. doi: 10.1056/NEJMoa2113708. PMID: 35294811.

Nathwani AC. Gene therapy for hemophilia. Hematology Am Soc

Hematol Educ Program. 2022 Dec 9;2022(1):569-578. doi: 10.1182/hematology.2022000388. PMID: 36485127; PMCID: PMC9821304.

Hermans C. Haemophilia gene therapy: experiences and lessons from treated patients. Orphanet J Rare Dis. 2022 Apr 4;17(1):154. doi: 10.1186/s13023-022-02313-w. PMID: 35379279; PMCID: PMC8981926.

Pipe SW, Gonen-Yaacovi G, Segurado OG. Hemophilia A gene therapy: current and next-generation approaches. Expert Opin Biol Ther. 2022 Sep;22(9):1099-1115. doi: 10.1080/14712598.2022.2002842. Epub 2022 Jan 6. PMID: 34781798.

Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective. Haemophilia. 2019 Jul;25(4):545-557. doi: 10.1111/hae.13769. Epub 2019 May 21. PMID: 31115117; PMCID: PMC6852207.

Pipe SW, Reddy KR, Chowdary P. Gene therapy: Practical aspects of implementation. Haemophilia. 2022 May;28 Suppl 4(Suppl 4):44-52. doi: 10.1111/hae.14545. PMID: 35521727; PMCID: PMC9324089.

Pipe SW, Leebeek FWG, Recht M et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. N Engl J Med. 2023 Feb 23;388(8):706-718. doi: 10.1056/NEJMoa2211644. PMID: 36812434.

Hermans C, Gruel Y, Frenzel L, Krumb E. How to translate and implement the current science of gene therapy into haemophilia care? Ther Adv Hematol. 2023 Jan 12;14:20406207221145627. doi: 10.1177/20406207221145627.

PMID: 36654740; PMCID: PMC9841832.

Noone D, Astermark J, O'Mahony B, Peyvandi F, Khair K, Pembroke L, Jenner K. The journey of gene therapy in haemophilia – putting the patient at the centre of the hub and spoke model. J Haem Pract 2022; 9(1): 156-166. doi: 10.2478/jhp-2022-0021.

Ten Ham RMT, Walker SM, Soares MO, Frederix GWJ, Leebeek FWG, Fischer K, Coppens M, Palmer SJ. Modeling Benefits, Costs, and Affordability of a Novel Gene Therapy in Hemophilia A. Hemasphere. 2022 Jan 28;6(2):e679. doi: 10.1097/HS9.0000000000000679. Erratum in: Hemasphere. 2022 Feb 15;6(3):e698. PMID: 35141470; PMCID: PMC8820916.

O'Mahony B, Dunn AL, Leavitt AD, Peyvandi F, Ozelo MC, Mahlangu J, Peerlinck K, Wang JD, Lowe GC, Tan CW, Giermasz A, Tran H, Khoo TL, Cockrell E, Pepperell D, Chambost H, López Fernández MF, Kazmi R, Majerus E, Skinner MW, Klamroth R, Quinn J, Yu H, Wong WY, Robinson TM, Pipe SW. Health-Related Quality of Life Following Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A in the Phase 3 Trial GENEr8-1. J Thromb Haemost. 2023 Sep 5:S1538-7836(23)00663-3. doi: 10.1016/j.jtha.2023.08.032. Epub ahead of print. PMID: 37678546.

Executive Board, 95. (1995). Maternal and child health and family planning: quality of care: family: quality of care Conceptual and strategic framework for reproductive health. World Health Organization.

González A. (2020). Lo bueno de tener un mal día. Editorial Planeta. Barcelona

J. Jay Miller, Joann Lianekhammy, Natalie Pope, Jacquelyn Lee & Erlene Grise-Owens (2017) Self-care among healthcare social workers: An exploratory study, Social Work in Health Care, 56:10, 865-883, DOI: 10.1080/00981389.2017.1371100

Rolland J.S. (2011). Familias, enfermedad y discapacidad. Editorial Gedisa. Barcelona

Walsh M, Macgregor D, Stuckless S, Barrett B, Kawaja M, Scully M-F. Health-

related quality of life in a cohort of adult patients with mild hemophilia A. J Thromb Haemost 2008; 6 755-61

WHO Quality of Life Assessment Group. (1996). What quality of life? / WHO Group on Quality of Life. World Health Forum 1996; 17 (4): 385-387

Claudia Grau Rubio. Revista Española de Discapacidad, 1 (1), 195-212. Fostering resilience in families with pediatric chronic diseases.

Alice Anderson PT, DPT, PCS and Angela Forsyth, PT, DPT. Playing it safe. Bleeding disorders, sports and exercise. National Hemophilia Foundation (NHF)

Sponsoring:

BIOMARIN CSL Behring Pfizer

Partner:

fedhemo
Federación Española de Hemofilia