Gene transfer in hemophilia A: not cogent yet

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The phase 3 clinical study of gene transfer in hemophilia A using the BioMarin vector AAV5-hFVIII-SQ (also identified as valoctocogene roxaparvovec) recently reported the results obtained in as many as 134 adult men with severe hemophilia A, so that it is at the moment the largest gene transfer study ever conducted in a rare monogenic disorder.[1] The relevance of the study is witnessed by its publication in a leading medical journal such as the New England Journal of Medicine,[1] with an accompanying editorial.[2] The article and related editorial provide information on the many positive results obtained but also on the limitations and still unanswered questions. Among them, the pre-existing antibodies against the viral vector, the high between-patients variability of the factor VIII response and its downward trend during the limited follow-up period. Yet, it is expected that this publication will accelerate the regulatory approval within 2022 of this gene transfer products for clinical use, at least by the Food and Drug Administration in the USA.

With this preamble on the monument of ingenuity represented by this hallmark study that demonstrates the feasibility of transfer to patients of such a huge gene as *F8*, I shall try to convey my views on the real-life impact of this approach in the context of the currently blooming scenario of the care of persons with hemophilia (PWH). My personal views are those of a senior insider who is also an innocent bystander, because I am not personally involved in any of the many ongoing trials of gene transfer in hemophilia A and B.

I shall also try to first convey the opinions of a few PWH. When at joint meetings and/or in the frame of my clinical practice I meet them and I happen to explain to them and their next-of-kin the outstanding progresses witnessed in the management of this disease, particularly in the last 10 miraculous years,[3] their comment is almost always the same "OK, doc, fantastic!, but when are we going to be ultimately cured from this scourge?" This eager question is made in the context of a scenario characterized by a life expectancy of PWH that is practically identical to that of their male peers without the disease and by a quality of life that, notwithstanding a lifelong chronic ailment, is made good by the fact that currently available intravenous and subcutaneous therapeutic products succeed to avoid almost completely spontaneous bleeding episodes (the so called zero bleeding rate).

In this frame, which expectations but also uncertainties on gene therapy do I gather from PWH? Their motivations and exigencies for this novel therapeutic approach are to skip forever the need of repeated intravenous infusions or subcutaneous punctures, the desire to live a new a life without hemophilia with the related mental freedom, as well as the ability to freely travel to countries or regions where treatment is not available or less than optimal. By the same token, patients are cognizant of barriers that still make them hesitant. Beside concerns about potential, very rare and thus still unknown long-term side effects that may emerge only post marketing in real life use, as well as the limited evidence that the attained factor VIII plasma levels will be sufficient to obtain and maintain the goal of zero bleeding, PWH mention the burden of gene therapy in terms of costs for them and the community, as well as the uncertainty regarding the need and feasibility of repeating the first gene transfer. On the whole, my impression is that, notwithstanding the positive current scenario of their care they are happy about the forthcoming availability of this new weapon, but also fully aware of existing and potential limitations.

With this preamble on the opinions recorded from

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PWH, in the second part of this commentary I shall share with you my own concerns and hesitancies, notwithstanding my enthusiasm for this milestone that will hopefully come soon to a climax with the regulatory approval.[1] In addition to the unanswered question on whether or not a single intravenous injection of the vector carrying the transgene will be able to offer life-long bleeding prevention, it is a fact and deed that at the time being and also when approved gene therapy will be applicable only to adults but not to children with hemophilia, obviously and definitely the main and ideal target of any curative strategy in any inherited disease. Furthermore, I am concerned not only by the potential of DNA integration of the transgene but much more so by the observed high rate of serum transaminases increase, that means unequivocally that some degree of hepatocyte necrosis occurred after the transgene reached the liver. This frequent adverse effect did need for its control high doses of corticosteroids for at least two months, but even longer for many cases.[1,2] Incidentally, the term transaminitis, frequently used to describe this biochemical abnormality, is not only inaccurate but also misleading, because it gives the undue impression of a benign phenomenon, which remains to be demonstrated in the absence of liver biopsies and a long follow-up.

An obvious and additional snag is that there is still no information of the costs and models of payment for gene therapy in hemophilia. The early voices and hints are worrisome. BioMarin, the Californian-based company that developed valoctocogene roxaparvovec and conducted so far all the experimental and pivotal clinical studies, did declare to the Wall Street Journal that after approval for clinical use they planned to look for a price between 2 and 3 million dollars per dose and patient. This would make this pharmaceutical product the most expensive in the history of medicine! A comprehensive cost-effectiveness analysis is still not available in the absence of approval. My hope of an uncurable optimist is that in Italy and perhaps other countries the national drug agencies will be able to negotiate a reasonable price with the manufactures, taking as example the antiviral drugs for hepatitis C that are much less costly than in other countries such as the USA.

All in all, my comments on the article Ozelo *et al.*[1] are that the reported findings are still unsettled in terms of the broad application of this therapy in real life, at a time when drugs such as emicizumab and FVIII products with a truly extended plasma half-life are offering further promising weapons to the already rich array.[4,5] My perusal of the article and accompanying editorial tells me that both authors and editorialist are aware of the preliminary value to their findings, because there is clear emphasis on the need of a more prolonged patient follow-up. Moreover, I strongly hope that strict post-marketing surveillance will be implemented transparently and independently from manufacturers.[6]

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