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FVIII tolerance in the Emicizumab era: Why yes?

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Introduction

The development of neutralizing antibodies (inhibitors) against factor VIII (FVIII) continues to be the main unresolved iatrogenic complication in relation to the classic treatment with FVIII concentrates (CFVIII) of patients with hemophilia A (AH), neutralizing their action, reducing their efficacy, increasing the morbidity and mortality of patients and worsening their quality of life. As indicated in the latest World Federation of Hemophilia Guidelines (2020).[1]

Although there is no complete consensus, it is considered that prophylaxis, by controlled and regular exposure to CFVIII, could reduce this risk, especially when initiated early,[2] a relevant fact if we take into account that the mutation responsible for the disease is key when estimating the risk of inhibitor development[3] and more than 70% of mutations responsible for severe forms of HA are associated with a high risk of developing it.[2] This fact is supported by other subsequent observations such as that of Jonker et al.[4] which cite 3 factors especially associated with the risk of inhibitor development: a positive family history of inhibitors, a high-risk F8 genotype, and intensive treatment at first exposure.

New treatments such as Emicizumab®, a mimetic agent of FVIII, allow prophylaxis in AH by routes and mechanisms of action different from those of classic prophylaxis, and can be started at younger ages with very satisfactory results, without the need to administer CFVIII, as shown by the HAVEN-7 study (NCT04431726). However, this therapy has limitations, because, although its use is not associated with the development of inhibitors against FVIII, this absence of risk is not due to the direct effect of the drug, but due to less or no need for exposure to FVIII. Prophylaxis with emicizumab® decreases spontaneous and severe bleeding, but the risk of bleeding is not zero, with mean annual bleeding rates (ABS) of between 2.6 and 4.5/year reported (HAVEN-3 NCT02847637, HAVEN-4 NCT03020160 studies). These bleeds may require administration of CFVIII. The need for intensive treatment in these first exposures to FVIII due to intercurrent bleeding that may occur while the patient is on emicizumab® prophylaxis confers a high risk of inhibitor development.[4] In fact, in the HAVEN-7 study, which evaluates the efficacy and safety of emicizumab® prophylaxis in patients with severe AH, aged ≤12 months, 2 patients developed inhibitors against FVIII in the context of bleeding that required co-administration of CFVIII for resolution.[5]

The risk of inhibitor development in PUPs (previously untreated patients) with severe AH[1] is about 30%; 79% appear in the first 20 exposures (SD) to CFVIII, although the risk persists until at least 75 SD.[2] Prophylaxis with Emicizumab monotherapy could alter the "natural" history of inhibitor development since, with classical prophylaxis, neonates with severe AH take an average of 1.2 years to reach 75 SD and using Emicizumab®® alone it could take years before reaching 50-75 SD.[6] Studies in non-severe AH[7] in which the 1st administration of CFVIII ranged from 2.5 to 9.7 years, estimated that for patients with baseline FVIII of 5-15 IU/dl, 20 SD would be reached at 9.0 years of age and although age does not seem to be a key aspect in terms of the risk of developing inhibitors, it does seem that the older the age, the economic impact of Immune Tolerance Induction (ITI) is considerably greater. Therefore, there are many uncertainties surrounding the non-regular exposure to FVIII in patients who start prophylaxis with Emicizumab without regular exposure to CFVIII, so that ongoing studies such as the Atlanta Study (NCT04030052) or the EMI-PUPs study (NCT04030052)) will try to provide information on this issue, combining prophylaxis with Emicizumab®® and the administration of low doses of CFVIII up to 20-50 SD. However, there is no unanimity in the scientific community on how to act in this scenario. Recently, in 2022, Ranfa et al.[8] published the results of an electronic survey carried out in 32 centers belonging to the PedNet, a survey that was answered by 28 centers and, in relation to their clinical practice, in 20 of 25 centers, Emicizumab® was the preferred option for prophylaxis in PUP or MTP (minimally treated patients), the majority (80%) without concomitant FVIII.

At the same time, in those cases where the concomitant administration of FVIII is decided, no recommendations can be made as to which product to use although it seems to be It is logical to opt for potentially less immunogenic products such as CFVIII of plasma origin or recombinant 4th generation CFVIII, obtained from human cell lines, such as Efmoroctocog Alfa® - its study in PUPs[9] reports an incidence of high-titer inhibitors of 15.6% - or Simoctocog Alfa®, with an incidence of high-titer inhibitors in PUPs of 16.2%. Although 0% for patients with non-null mutations.[10] Nor can recommendations be issued on how to continue after, once these 50 SDs have been reached, although, taking as a reference the latest British recommendations regarding ITI in patients with AH with inhibitor, they recommend that once toleration has been achieved, if prophylaxis with emicizumab® is chosen, even in the absence of evidence to support this recommendation, weekly administration with CFVIII (≤30 IU/kg) should be maintained, although there is no established minimum dose.[11] In addition, in favor of toleration, it can be said that currently, among the exclusion criteria for gene therapy, PUPs or minimally treated patients are included, as well as those with a present or past inhibitor against FVIII.[12] For all these reasons, it is understood that, even in the absence of consensus at present, it may be a priority in patients on emicizumab® prophylaxis, although only routine clinical practice and ongoing clinical studies will shed light on what and how the most appropriate approach to this dilemma.

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Conflicts of interest

The author declares that there is no conflict of interest.

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