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ORIGINAL RESEARCH ARTICLE

Inhibitors in non-severe hemophilia A: a case report

Inhibidores en hemofilia A no grave: a propósito de un caso

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Abstract

Introduction: *The development of inhibitory antibodies against factor VIII (FVIII) is a complication in approximately 30% of patients with severe hemophilia A, increasing bleeding frequency and resistance to treatment.* **Objective:** *To report the experience of a tertiary care center in the management of an inhibitor or neutralizing antibody against FVIII in a patient with mild hemophilia A and to provide a brief critical review of the topic.* **Material and methods:** *The identified mutation was c.6301 C > G in exon 22 of the F8 gene, not among the missense variants previously associated with the highest inhibitor risk. In the absence of DDAVP response, the acute bleeding episode was managed with recombinant factor VIIa, and immunosuppression with prednisone was initiated. On day 7, as the inhibitor titre rose to 17 BU, rituximab (anti-CD20) was added at the standard dose of 375 mg/m² weekly for four weeks.* **Results:** *The inhibitor became undetectable at 2.5 months, and baseline FVIII: C levels were restored at 3.5 months, with a positive DDAVP challenge. At 12 months, the patient remains in complete remission.* **Conclusions:** *This case highlights the heterogeneity in managing inhibitors in non-severe haemophilia A, the lack of standardised guidelines, and the need for an individualised therapeutic approach. The complementary role of emicizumab is discussed, along with modifiable risk factors — FVIII dose, treatment duration, and surgical exposure — for inhibitor prevention.*

Keywords: *Non-severe Haemophilia A. Inhibitors AntiFVIII. Immunosuppression. Erradication.*

Resumen

Introducción: *El desarrollo de anticuerpos inhibidores frente al factor VIII (F8) es una complicación en cerca del 30% de los pacientes con hemofilia A grave, aumentando la frecuencia de sangrados y la resistencia al tratamiento.* **Objetivo:** *Reportar la experiencia en el manejo de un inhibidor o anticuerpo neutralizante frente al F8 en un paciente con hemofilia A leve en un centro de tercer nivel y hacer una breve revisión crítica del tema.* **Material y métodos:** *La mutación identificada fue c.6301 C > G en el exón 22 del gen F8, sin correspondencia con las variantes missense de mayor riesgo conocidas. Ante la ausencia de respuesta a desmopresina, se trató el episodio hemorrágico con factor VIIa recombinante y se inició inmunosupresión con prednisona. Al séptimo día, ante la elevación del título a 17 UB, se añadió rituximab (anti-CD20) en pauta estándar de 4 dosis semanales.* **Resultados:** *El inhibidor se negativizó a los 2,5 meses y el FVIII: C recuperó valores basales a los 3,5 meses, con respuesta positiva al test de DDAVP. A los 12 meses el paciente permanece en remisión completa.* **Conclusiones:** *El caso ilustra la heterogeneidad en el manejo de los inhibidores en hemofilia A no grave, la ausencia de guías estandarizadas y la necesidad de individualizar la estrategia terapéutica. Se discute el papel complementario del emicizumab y se destacan los factores de riesgo modificables (dosis de FVIII, duración del tratamiento, tipo de cirugía) para prevenir esta complicación.*

Palabras clave: *Hemofilia A no grave. Inhibidor AntiF8. Inmunosupresion. Erradicacion.*

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Introduction

The development of inhibitory antibodies against factor VIII (FVIII) is a complication in approximately 30% of patients with severe hemophilia A, increasing bleeding frequency and resistance to treatment. In mild hemophilia A (FVIII:C > 5%), desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin) is the first-line therapy.[1] This depends on response, bleeding severity, and treatment duration.[1,2] If DDAVP fails, which occurs in 40%–50% of cases, FVIII concentrates (FVIIIC) are the treatment of choice. The incidence rate of inhibitors in these patients is variable (3%–13%), but certain FVIII genotypes are associated with higher rates.[3,4] Eckhardt et al.[4] identified, among the 250–300 missense mutations described, 19 particularly high-risk mutations located in the A2 domain of the heavy chain and in the A3, C1, and C2 domains of the FVIII light chain, some with a risk of inhibitor development > 20%–40%. In addition, the risk remains elevated throughout life and, unlike in severe hemophilia A, does not decrease after the first 50 exposure days (> 50 exposure days [ED]).[5]

The aim of the present study was to report the experience of a tertiary care center in the management of an inhibitor or neutralizing antibody against FVIII in a patient with mild hemophilia A and to provide a brief critical review of the topic.

Method

We describe the case report of a patient with mild hemophilia A who developed a high-titer inhibitor (> 5 Bethesda units [BU]) after intensive treatment for an apparently spontaneous dorsal spinal hematoma. The strategy used for inhibitor eradication is described.

Description and results

The patient was a 20-year-old man diagnosed with mild hemophilia A (FVIII:C 14%, chromogenic FVIII 12%) with no inhibitor at 13 years of age, in the context of a rupture of the right lateral meniscus and secondary traumatic hemarthrosis of the right knee. At that time, he had no known family history of hemophilia, but genetic testing performed subsequently showed a c.6301 C > G mutation, according to the NM_000132.3 reference sequence, in exon 22 of the FVIII gene. He received intensive treatment with recombinant FVIII concentrate (moroctocog alfa) for 6 days, completed treatment with DDAVP, and began secondary prophylaxis for 4 weeks with alternating moroctocog alfa and DDAVP, 3 days per week, until completion of physiotherapy. FVIII inhibitor screening at 30 and 60 days was negative (< 0.4 BU). He received occasional care for dental procedures, which were managed with DDAVP and tranexamic acid. Five years later, he presented to the emergency department of our center with a 3-week history of central, radiating back pain of progressive onset, with no apparent relationship to any activity. Computed tomography showed an image compatible with a dorsal epidural spinal hematoma. Hospital admission was decided, and intensive treatment with moroctocog alfa was started for 2 weeks, followed by prophylaxis alternating moroctocog alfa and DDAVP until completing 1 month of treatment. At the first post-treatment assessment, 1 month later, the anti-FVIII inhibitor tested negative (< 0.4 BU). Three weeks later, he again presented to the emergency department with spontaneous pain in the right iliac fossa radiating to the testicle. Abdominal ultrasound showed a 2 × 3-cm perireteral hematoma. The spontaneous development of the hematoma, together with the recent intensive treatment, alerted us to the possible development of an inhibitory antibody. The Bethesda assay was performed and showed the presence of a high-titer antibody against FVIII (12.8 BU) (FVIII:C 5.6%), an adverse event that has already been reported to the *Agencia Española de Medicamentos y Productos Sanitarios*. Given the absence of response to DDAVP, treatment with recombinant activated factor VII (rFVIIa) was started, with a good response and resolution of the clinical picture in approximately 7 days. Simultaneously, immunosuppressive treatment with corticosteroids (prednisone, 1 mg/kg per day) was started. Seven days later, because of the increase in antibody titer (17 BU), an anti-CD20 monoclonal antibody was added at the usual dose (375 mg/m^2 weekly for 4 weeks). After 14 days, corticosteroid therapy was tapered over approximately 2 months, maintaining a dose of 5 mg for 2 additional weeks and then 5 mg every other day for another 2 weeks, until completing 3 months of immunosuppressive therapy. The inhibitor titer gradually decreased (Table 1) until becoming negative 2.5 months after the start of immunosuppression. FVIII:C levels reached the patient's normal value at 3.5 months, at which time the DDAVP test was repeated and showed response (FVIII:C > 50% at 4 hours). A pharmacokinetic study was performed using WAPPS-Hemo after administration of a 40 IU/kg dose of combined von Willebrand factor and factor VIII (Fanhdi®). The results confirmed treatment success (recovery, 82%; terminal half-life, 9 hours). Currently, more than 12 months later, he remains in complete

Table 1. Treatment and course of the inhibitor

Days	Inhibitor titer	Treatment	Additional treatment
Day 1	12.8 BU	PDN 1 mg/kg/day	
Day 7	17 BU	PDN 1 mg/kg/day	Anti-CD20 375 mg/m^2/week
Day 14	13 BU	Progressive PDN tapering started	2nd anti-CD20 dose
Day 21	10 BU		3rd anti-CD20 dose
Day 28	5.6 BU		4th anti-CD20 dose
Day 35	4 BU	Continued PDN tapering	
Day 75	< 0.4 BU	PDN 5 mg every other day	
Day 90	< 0.4 BU	PDN discontinued	
Day 105	< 0.4 BU; FVIII 14.6%; DDAVP response test: responder		

DDAVP: desmopressin; PDN: prednisone; S/D: solvent/detergent.

remission and has only required treatment for a mild traumatic hematoma in the right biceps brachii, which resolved with DDAVP and antifibrinolytics.

Discussion

Unlike inhibitors in severe forms of hemophilia A, patients with mild or moderate forms who develop a neutralizing antibody face the absence of guidelines standardizing the management of this complication, as well as substantial heterogeneity in the recommendations reported in the scientific literature. This is a serious problem with a very negative impact on all aspects of the patient's life, from clinical status to psychological well-being. The bleeding phenotype is up to 10 times more severe than that of patients without inhibitors, with an annual bleeding rate of 1.1 (IQR, 0.1–2.5).[6] It often resembles the hemorrhagic phenotype of patients with acquired hemophilia A (40%).[6] The intensity of treatment received,[1,3,7] as well as treatment duration longer than 10 days, influences the risk of developing an inhibitor in these patients. Our patient received treatment for almost 10 days, with FVIII concentrate doses > 40–45 IU/kg per day. Regarding the mutation,[4] some mutations are associated with a higher risk of inhibitor development. The mutation present in our patient has been reported in 3 cases in the database of the European Association for Haemophilia and Allied Disorders (https://dbs.eahad.org/; accessed November 9, 2024). It is a missense mutation that entails an amino acid change (p.[His2101Asp]), although it does not correspond to any of the missense mutations associated with a higher risk of inhibitor development, such as Trp2229Cys (risk, 41.7%) or Asp2074Gly (risk, 21.25%). Regarding the eradication strategy, there are no clinical practice guidelines on its exact management.[1] Experience is limited and ranges from simple observation to immune tolerance induction strategies similar to those used in patients with severe congenital hemophilia A, as well as immunosuppression, similar to that used in the management of acquired hemophilia. Emicizumab is indicated for bleeding prophylaxis in these patients and has shown efficacy both in clinical trials[8] and in real-world practice[9]; therefore, it may complement any of the previously mentioned approaches. The literature includes reports on the outcomes of the different strategies. The INSIGHT Study Group[3] included 101 patients with nonsevere hemophilia A (FVIII:C, 2%–40%) and a median age of 37 years (IQR, 15–60). The median maximum inhibitor titer was 7 BU (IQR, 2–30). Spontaneous disappearance of the inhibitor occurred in 51 of 73 patients, whereas success was achieved in 21 of 28 patients who underwent an eradication strategy. Overall, 64% of patients in whom the antibody became negative remained antibody-free after reexposure to FVIII concentrate. Kempton et al.[10], in a study of 36 patients, evaluated different treatment strategies for eliminating FVIII inhibitors in patients with mild or moderate hemophilia A. In the analyzed sample, rituximab-based treatments and other immune-modulating approaches showed a higher probability of successful inhibitor elimination than immune tolerance

induction, although without statistical significance. They noted that patients with low inhibitor titers appear to have a higher probability of spontaneous remission without requiring any type of treatment. The conclusions of Van Velzen et al.[3] are along the same lines and support the theory that patients with high-titer inhibitors, such as our patient, appear to benefit more from eradication treatment to prevent future relapses than patients with low-titer inhibitors. It should be noted that patients with certain specific FVIII genotypes, such as R2150H, may have a greater tendency toward inhibitor persistence.[10] In patients with high-titer inhibitors, sustained success was associated with eradication treatment (unadjusted RR, 2.3; 95%CI, 1.3–4.3) compared with no treatment. Nevertheless, the need for an individualized approach to this problem is emphasized,[3] especially now that highly effective therapeutic options are available.[8,9] In our opinion, 2 aspects are key when considering immune-modulating strategies: 1) the increase in patient life expectancy will probably lead to a greater need for surgeries or procedures, with the consequent risk of intensive exposure to FVIII:C and an increased risk of inhibitor development at later ages[2] (Table 2); and 2) immune-modulating or even immunosuppressive strategies entail increased infectious mortality in elderly patients, as can be inferred from studies performed in acquired hemophilia A.[11] In this disease, in which immunosuppressive regimens such as the one received by our patient are used, the main causes of death are hemorrhagic complications and infections. Mortality reaches 9%–33% of cases within the first 2 months, and up to 40% of these deaths are attributable to infections resulting from immunosuppressive treatment.

In our case, given the patient's age and the "alarm" generated in the family, an aggressive immune-modulating strategy and bleeding management with bypassing agents (rFVIIa) were chosen in the presence of a high-titer inhibitor. The option of simple observation associated with bleeding prophylaxis with emicizumab – similar to what is currently advocated in some acquired hemophilia A protocols[12] – was ruled out because we considered that it could take longer to achieve natural tolerance, because there was a risk that tolerance would not be achieved given the high-titer inhibitor, and because of the described risk of relapse. Van Velzen et al.[3], in patients with high-titer inhibitors who received eradication treatment, reported a sustained success rate, with no relapse, of 100%, whereas patients with low-titer inhibitors showed greater variability in response. Some experienced relapses even without eradication treatment; specifically, 35% relapsed after reintroduction of FVIII concentrate following initial disappearance of the inhibitor. In our case, the patient's assessments within the first year after eradication have been negative (< 0.4 BU), although he has not been reexposed to FVIII concentrate beyond the pharmacokinetic study performed to confirm the success of immunosuppression. Regarding the type of product, in patients with mild forms of hemophilia there does not appear to be a relationship between the first product used and the risk of inhibitor development.[13]

Table 2. Main risk factors for inhibitor development in patients with mild hemophilia A

Surgery (OR, 4.2; 95%CI, 1.7–10.3)
FVIII dose > 45 IU/kg (OR, 7.5; 95%CI, 1.36–35.6)
Treatment duration ≥ 10 days (OR, 3.8)

95%CI: 95% confidence interval; OR: odds ratio.
Adapted from Van Velzen et al.[7]

Conclusions

The incidence rate of inhibitor development in non-severe hemophilia A increases progressively with the cumulative number of exposure days to FVIII concentrate, apparently without reaching a plateau,[2,3] unlike what is observed in severe hemophilia A. Inhibitors in this group of patients are a relevant problem, and it is important to establish strategies to reduce risk.[1,4] Knowledge of the causative mutation, maximization of the use of DDAVP or antifibrinolytics, and, when necessary, use of FVIII concentrate doses < 45 IU/kg for the shortest possible time are among the measures cited to reduce the risk of inhibitor development. It is imperative to learn more about the treatment regimens used for eradication and to try to determine the best strategy for achieving immune tolerance.

Immunosuppression appears to be a valid option for the management of high-titer inhibitors,[5] although, with the advent of emicizumab,[8,9,12] the urgency to initiate it is lower, making it possible to defer initiation and choose simple observation, as in the case of low-titer inhibitors. The problem with this second strategy is that, although it makes it possible to confirm inhibitor elimination, confirmation of eradication will also depend on clinical behavior. Further work is needed in the recording and modeling of simple and effective therapeutic

strategies to manage this problem. Finally, individualization is key, as in other areas of care for these patients. Treatment of patients requiring eradication should be decided on a case-by-case basis, because a single approach is unlikely to be appropriate for all.

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Conflicts of interest

None declared.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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