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1 **Reappearance of inhibitor in a tolerized patient with severe hemophilia A during**
2 **FVIII-free emicizumab therapy**

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22 **RUNNING TITLE:** FVIII inhibitor reappearance on emicizumab therapy

23 **KEYWORDS:** hemophilia A, FVIII inhibitor, emicizumab, immune tolerance induction

24 **Word count: 1393**

25 **ABSTRACT**

26 **Introduction:** The recent approval of emicizumab has significantly changed the
27 management of severe hemophilia A. It also raises several questions, particularly
28 concerning the need to maintain FVIII infusion in emicizumab-treated patients after
29 successful ITI. Indeed, the possible reappearance of the inhibitor is a major concern,
30 while, to date, no recurrence of the inhibitor has been observed in successfully tolerized
31 patients.

32 **Aim:** To describe the reappearance of an inhibitor in a successfully tolerized patient with
33 severe hemophilia A during emicizumab therapy alone (in the absence of any exposure
34 to FVIII), and to discuss the benefit in maintaining FVIII infusion.

35 **Methods:** Case report

36 **Results:** We report on a case in which inhibitor production spontaneously reappeared
37 more than 7 years after successful ITI and 4 months after emicizumab initiation and FVIII
38 withdrawal. Indeed, the patient was inhibitor-negative one month after emicizumab
39 initiation and despite the absence of any FVIII infusions, a low positive titer was
40 observed 4 months later together with reemergence of both anti-FVIII IgG1 and IgG4.

41 **Conclusion:** Our observation supports the hypothesis whereby regular exposure to FVIII
42 may be necessary to maintain successful, specific immune tolerance. Therefore,
43 emicizumab-treated patients with a history of inhibitor, even those not exposed to FVIII,
44 should be regularly screened for the presence of an inhibitor.

45

46 Severe hemophilia A is a severe bleeding disorder caused by factor (F) VIII deficiency.
47 The conventional treatment for hemophilia A is FVIII replacement. However, around
48 30% of patients develop neutralizing antibodies against FVIII (also known as
49 “inhibitors”), and those with high inhibitor titers become resistant to FVIII replacement
50 therapy. Inhibitors may be eradicated using immune tolerance induction (ITI), i.e.
51 frequent administration of high doses of FVIII for months or even years. Successful ITI is
52 defined as the fulfilment of three criteria after 33 months of treatment: inhibitor titer
53 <0.6 BU/mL, FVIII recovery >66%, and FVIII half-life >7 h.¹ ITI success is considered partial
54 when the recovery or half-life criteria are not fulfilled.

55 The recent approval of emicizumab (a humanized bispecific monoclonal antibody
56 against FIXa and FX that mimics FVIIIa’s activity in the tenase complex) has drastically
57 changed the management of severe hemophilia A. Yet, FVIII can still be used for
58 hemostatic management of bleeding or surgery in emicizumab-treated, inhibitor-
59 negative patients. In high-titer inhibitor-positive patients, however, the cautious use of
60 FVIII bypassing agents in conjunction with emicizumab therapy is the only option.²

61 The availability of emicizumab raises several questions, particularly concerning FVIII
62 prophylaxis after successful ITI. Should FVIII be maintained, administered less frequently
63 or even withdrawn when patients successfully tolerized are switched to emicizumab?³

64 The possible reappearance of the inhibitor is a major concern. Recently, Batsuli et al
65 reported the inhibitor status of 12 tolerized patients with severe hemophilia A during
66 emicizumab therapy.⁴ While they described the reappearance of a FVIII inhibitor in one

67 partially tolerized patient, no recurrence of the inhibitor was observed in successfully
68 tolerized patients.

69 At Necker Children's Hospital (Paris, France), the improved quality of life reportedly
70 associated with emicizumab prompted several patients with complete or partial
71 response to ITI to switch to emicizumab prophylaxis and to discontinue FVIII. Here, we
72 report on a case in which inhibitor production spontaneously reappeared more than 7
73 years after successful ITI and 4 months after emicizumab initiation and FVIII withdrawal.
74 The case, a 25-year-old male with severe hemophilia A, had initiated an ITI protocol at
75 the age of 32 months (peak inhibitor level: 7.6 BU/mL) and ultimately became inhibitor-
76 negative at the age of 17 years. During this time, ITI had been impaired by the regular
77 resurgence of the inhibitor: the inhibitor titer (measured using a one-stage clotting
78 assay) rose whenever the frequency of FVIII infusions was reduced (Figure 1). After
79 successful ITI, as attested by a negative inhibitor titer, a factor VIII recovery >66% and
80 half-life >6 hours since July 2013, the frequency of FVIII infusion was reduced to 26 IU/kg
81 three times a week, and the inhibitor had not reappeared. While the anti-FVIII antibody
82 response was mostly mediated by the IgG4 subclass prior to ITI success, IgG1
83 predominated and progressively disappeared during the inhibitor-free years (Figure 1).
84 When the patient turned 24, he switched from FVIII to emicizumab alone (3 mg/kg/week
85 for 4 weeks, and then 1.5 mg/kg/week) while anti-FVIII inhibitor was undetectable in a
86 Bethesda assay (measured using a chromogenic assay with bovine reagents). Although
87 the patient was inhibitor-negative one month after emicizumab initiation and despite
88 the absence of any FVIII infusions, a low positive titer (0.7 BU/mL) was observed, for the
89 first time, 4 months later together with reemergence of both anti-FVIII IgG1 and IgG4.

90 Presence of the inhibitor (same titer) was confirmed on second sample, more than 2
91 months later (figure 1). Reappearance of the inhibitor was not associated with any
92 notable clinical events.

93 Emicizumab is becoming a drug of choice for the prophylactic treatment of both
94 inhibitor-positive and inhibitor-negative patients with hemophilia A. In emicizumab-
95 treated inhibitor-positive patients, the need to initiate ITI, complete ITI or even maintain
96 FVIII administration after successful ITI is still subject to debate.³ The mechanisms
97 underlying successful ITI have not been elucidated. Neutralizing anti-FVIII IgG⁵ and FVIII-
98 specific CD4+ T cells⁶ have been detected in some patients after successful ITI; this
99 suggests that active FVIII-specific tolerance is mediated by anti-idiotypic antibodies⁵ and
100 probably regulatory T cells, rather than resulting from the mere elimination of FVIII-
101 specific immune effectors. Here, we reported on the reappearance of an inhibitor
102 shortly after the initiation of emicizumab prophylaxis and the concomitant interruption
103 of FVIII prophylaxis in a patient having achieved successful ITI more than 7 years
104 previously. Recurrence of the FVIII inhibitor was accompanied by an increase in levels of
105 both anti-FVIII IgG1 and IgG4, which parallels the situation in previously untreated
106 patients who develop FVIII inhibitors during FVIII prophylaxis.⁷ Interestingly, in our
107 patient, IgG1 were very low, but still detectable, before emicizumab initiation while the
108 inhibitor was undetectable for several years before. This may explain the difference with
109 patients reported by Batsuli *et al* who remained negative both in Bethesda and ELISA for
110 the IgG1 isotype.⁴ Our observation supports the hypothesis whereby regular exposure
111 to FVIII may be necessary to maintain successful, specific immune tolerance. However,
112 the optimal frequency and dose level of FVIII administration is unknown.

113 Even though the present case report proves that inhibitor can reappear and suggests
114 that the maintenance of immune tolerance requires the concomitant administration of
115 FVIII and emicizumab, it also raises many questions. The first question is whether the
116 reappearance of an inhibitor in emicizumab-treated patients with severe hemophilia A
117 has harmful consequences. It is known that in inhibitor-negative emicizumab-treated
118 patients, FVIII (rather than bypassing agents) can be used to manage emergency
119 situations or surgery.² However, the significant reduction in the number of bleeding
120 episodes associated with emicizumab treatment reduces the need for haemostatic
121 treatments.⁸ Moreover, the low-level reappearance of inhibitor (as observed in the
122 present case) does not preclude FVIII administration, although the latter may result in a
123 marked increase in the inhibitor titer. Lastly, bleeding episodes or surgery in patients
124 with high titers of inhibitor (>5 BU/mL) may still be managed using bypassing agents
125 such as recombinant activated FVII, that presents with a lower thrombotic risk than
126 activated prothrombin complex concentrates.⁸

127 In addition to providing superior bleeding control,⁸ subcutaneous administration of
128 emicizumab and reduction in the frequency of injections significantly improves the
129 patient's quality of life (relative to intravenously administered FVIII).⁹ Indeed, in order
130 to capitalize on the benefits of emicizumab prophylaxis (particularly after successful ITI),
131 it is questionable whether repeated intravenous injections of therapeutic FVIII should
132 be maintained.

133 Lastly, the economic cost of combining the two treatments must also be considered.
134 Several studies have modelled the future relative cost of hemophilia A treatment as the
135 use of emicizumab increases. It has been reported that relative to FVIII prophylaxis,

136 emicizumab might result in cost savings in the treatment of inhibitor-negative patients
137 with severe hemophilia A (including patients with successful ITI).¹⁰ However, the
138 modelling studies are based on a shift from FVIII to emicizumab prophylaxis, and not
139 concomitant administration of the two molecules. In fact, both drugs are very expensive
140 - making it difficult to justify concomitant administration unless this results in major
141 benefits for the patient.

142 On the basis of these elements, we suggest that emicizumab-treated patients with a
143 history of inhibitor (even those not exposed to FVIII) should be regularly screened for
144 the presence of an inhibitor. This would help to plan for patient management in
145 emergency situations, during surgery, if the inhibitor reappears.²

146 Several questions remain; further research should seek to determine the frequency of
147 inhibitor reappearance and identify risk factors for inhibitor reactivation in this context.

148 We are now closely monitoring 18 other patients who initiated emicizumab prophylaxis
149 after successful ITI. Moreover, longer-term follow-up of the present case is likely to
150 provide more information about changes over time in inhibitor levels.

151 As the use of emicizumab grows, the reappearance of FVIII inhibitor after successful ITI
152 and the withdrawal of FVIII might become more frequent and must be monitored
153 closely. Patients should receive information about the risk of reappearance of his
154 inhibitor and all therapeutical options should be discussed.

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167

168 **Authorship Contributions**

169 **LF, AH** and **CB** were in charge of the patient and provided the clinical samples. **LC, DB**
170 **DL, MD, SLD** and **SD** performed the coagulation tests. All authors contributed to the
171 interpretation of the data. **DB, LC, AH** and **SLD** wrote the first draft of the manuscript,
172 and all authors contributed to the editing of the final manuscript.

173

174 **Disclosure of Conflicts of Interest**

175 **AH** received fees for consultancy and board expert membership for Roche, Takeda, LFB,
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181 Roche for attending congresses. All other authors declare no conflict of interest.

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185 **FIGURE LEGEND**

186 **Figure 1: Changes over time in the inhibitor titer in a patient with severe hemophilia**

187 **A.** The patient had a period of prophylaxis with FVIII and achieved complete ITI before
188 the initiation of prophylaxis with emicizumab and concomitant interruption of FVIII
189 prophylaxis (depicted by the grey area). The patient was free of his inhibitor at the time
190 of initiation of emicizumab prophylaxis. Inhibitory titers (full circles) were measured
191 over a 24-year period in the patient's plasma (approved by a hospital ethics committee)
192 by the Bethesda method, using a one-stage clotting assay during the pre-emicizumab
193 period, and until January 2020, or using the chromogenic assay with bovine components
194 since this date. Thus, the last inhibitor control before treatment with emicizumab for
195 this patient was carried out on June 2020 using the chromogenic assay, and was <0.4
196 UB/mL. The patient's peak inhibitor titer is mentioned (7.6 BU/ml in November 1997).
197 The cross (x) symbols indicate inhibitory titers below the detection limit (<0.4 BU/ml)
198 and the dotted line depicts the cut-off for a negative inhibitor (0.6 BU/ml).¹ Mean levels
199 of anti-FVIII IgG1 (green line) and IgG4 (red line) were measure with an in-house ELISA,¹¹
200 using Advate® (coated at 2 µg/ml) as a source of FVIII and pools of 3 human monoclonal
201 anti-FVIII IgG1 or IgG4 (specific for the A2, C1 and C2 domains of FVIII) as standards,
202 respectively. The green and red dotted lines indicate the cut-off value for anti-FVIII IgG1
203 and IgG4 ELISA assays respectively; mean + 2SD obtained using plasma from 20 healthy
204 blood donors ([reference EFS: 13/CABANEL/008](#)). Anti-FVIII IgG levels are expressed as

205 arbitrary units (AU) and were measured from December 2008 (oldest plasma sample still
206 available) until February 2021.
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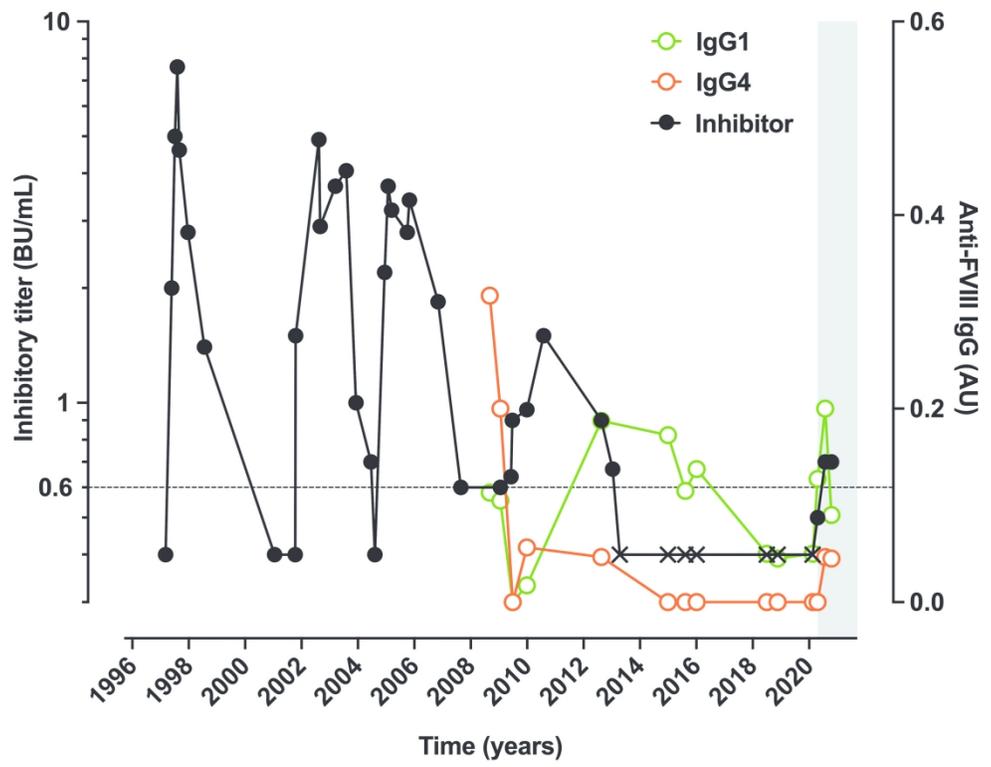
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