Received: 16 April 2024 | Revised: 4 November 2024 | Accepted: 7 November 2024

https://doi.org/10.1016/j.rpth.2024.102637

CASE REPORT

Immune tolerance induction for inhibitor eradication in nonsevere hemophilia A: a case series

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Handling Editor: Suely Meireles Rezende

Abstract

Background: Persons with hemophilia A are at risk of inhibitor development with repeated exposures to factor (F)VIII concentrates. When persons with nonsevere hemophilia A (NSHA) develop inhibitors, they are at risk of developing severe bleeding manifestations like persons with severe hemophilia A (SHA). Evidence to guide inhibitor eradication in this population is limited as opposed to persons with SHA who develop inhibitors. Hence, inhibitor eradication strategies in NSHA are based on observational and retrospective data and are largely adopted from evidence derived from SHA with inhibitors.

Key Clinical Question: Can immune tolerance induction be used for patients with NSHA who develop inhibitors?

Clinical Approach: In this case series, we describe our single institutional experience with the management of 5 persons with NSHA who developed FVIII inhibitors, leading to significant bleeding complications, and underwent successful immune tolerance induction with eradication of FVIII inhibitor.

Conclusion: More research specific to persons with NSHA with inhibitors is warranted to develop guidelines regarding indications and strategies for inhibitor eradication therapy.

KEYWORDS
immune tolerance induction, inhibitor, mild hemophilia A, moderate hemophilia A, nonsevere hemophilia A

Essentials

- Evidence to guide inhibitor eradication in persons with nonsevere hemophilia A is limited.
- Five cases of nonsevere hemophilia A with inhibitors were diagnosed between 2006 and 2020.
- Immune tolerance induction was successfully used for management in these patients.
- We acknowledge that more research is warranted to develop evidence-based guidelines.

1 | INTRODUCTION

Hemophilia A (factor [F]VIII deficiency) is an X-linked recessive disorder with clinical manifestations ranging from asymptomatic disease to life-threatening bleeding. Nonsevere hemophilia A (NSHA) comprises mild (FVIII activity [FVIII:C] > 0.05 and <0.40 IU/mL) and moderate (FVIII:C ≥ 0.01 and ≤0.05 IU/mL) hemophilia A and has not gained significant research interest due to presumed low bleeding risk compared with severe hemophilia A (SHA; FVIII:C < 0.01 IU/mL) [1]. Prophylaxis or on-demand treatment of hemophilia A with plasma-

derived or recombinant FVIII concentrates can lead to the development of alloantibodies or inhibitors that neutralize exogenous FVIII:C, rendering FVIII infusions less effective. The cumulative incidence of inhibitor development in NSHA is as high as 13.3%, resulting in an almost 10-fold increase in annualized bleeding rate, necessitating the use of bypassing agents [2,3]. Although there have been significant advances in inhibitor eradication therapy for persons with SHA, evidence for optimal strategies for NSHA remains scarce, and practice patterns vary between institutions. Options for inhibitor eradication include immune tolerance induction (ITI), immunosuppressive (IS) agents, and watchful waiting without reexposure to the product [4].

Here, we present a cohort of 5 persons with NSHA who developed FVIII inhibitors leading to undetectable FVIII levels and severe bleeding symptoms. Informed patient consent has been obtained without any identifiable patient specifics that may jeapordize patient anonymity. Our single-center experience regarding the successful use of ITI for inhibitor eradication in these patients is highlighted here.

2 | CASE SERIES

The cases were diagnosed between 2006 and 2020 when 92 persons with NSHA were seen at our center. All patients were White and non-Hispanic in ethnicity. Initial diagnostic FVIII and inhibitor testing were done with 1-stage assays. For those started on emicizumab, subsequent testing was done by chromogenic assays. The Table gives an overview of patient demographics, clinical manifestations, and ITI regimens.

2.1 | Patient 1

A 6-year-old male child with moderate hemophilia A (baseline FVIII:C 3% to 5%, missense mutation c.6265T>C), after 30 prior exposure days (EDs) tomoroctocog alfa (Xyntha), developed a high titer inhibitor (24 BU) resulting in undetectable FVIII:C levels, initially diagnosed on routine annual testing with no provoking factor and subsequently manifested by severe epistaxis and bruising. He was started on weekly emicizumab for bleeding control. ITI was initiated with Xyntha 50 U/kg every alternate day for 12 months with suboptimal response (inhibitor 4.5 BU) and switched to efmoroctocog alfa (Eloctate), an extended half-life (EHL) recombinant FVIII concentrate, 100 U/kg daily for 6 months, leading to successful tolerance to ITI (defined as negative inhibitor titer, FVIII recovery ≥ 66% of expected, and FVIII half-life ≥6 hours) [5]. The patient is doing well on prophylactic emicizumab and elected to continue a weekly Eloctate dose to maintain FVIII tolerance. His inhibitor levels remain undetectable at 3 years post-ITI.

2.2 | Patient 2

An 8-year-old male child with mild hemophilia A (baseline FVIII:C 6% to 17%, missense mutation c.1106T>C), after ED with 1 dose of antihemophilic FVIII/von Willebrand factor complex Alphanate and 6 doses of Xyntha with no provocation, developed a high titer inhibitor (16 BU), resulting in undetectable FVIII:C levels manifested by left

TABLE Overview of patient demographics, clinical manifestations, and immune tolerance induction regimens.

Patient factors	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age[a] (y)	6	8	3	20	41
Baseline FVIII[b] (%)	3-5	6-17	3-8	11-19	3-7
FVIII variant	Missense variant c.6265T>C in exon 21	Missense mutation c.1106T>C	Missense mutation c.5895G>C	Unknown	Unknown
Bleeding manifestations with inhibitor development	Severe epistaxis, bruising	Left flank hematoma, gingival bleeding	Compartment syndrome of the arm	Compartment syndrome of the calf, left palm pseudoaneurysm	Left elbow hemarthrosis
Exogenous FVIII exposures prior to inhibitor development	30 doses of Xyntha	1 dose of Alphanate; 6 doses of Xyntha	5 doses of Advate; 55 doses of Xyntha	15-20 doses of Advate	Multiple doses of Kogenate
ITI regimen	Xyntha 50 U/kg every 2 d (12 mo); Eloctate 100 U/kg daily (6 mo)	Helixate 200 U/kg daily (3 mo), then 50 U/kg every 2 d (3 mo)	Kogenate 100 U/kg daily (2 mo); then 50 U/kg every 2 d (2 mo)	Advate 50 U/kg every 2 d (12 mo); Eloctate 100 U/kg every 2 d (12 mo)	Kogenate 100 U/kg 3 times/wk (12 mo)

FVIII, factor VIII; ITI, immune tolerance induction.
[a]Age of the patient at the time of inhibitor development.
[b]Range indicates the different laboratory values of FVIII levels on various occasions prior to inhibitor development.

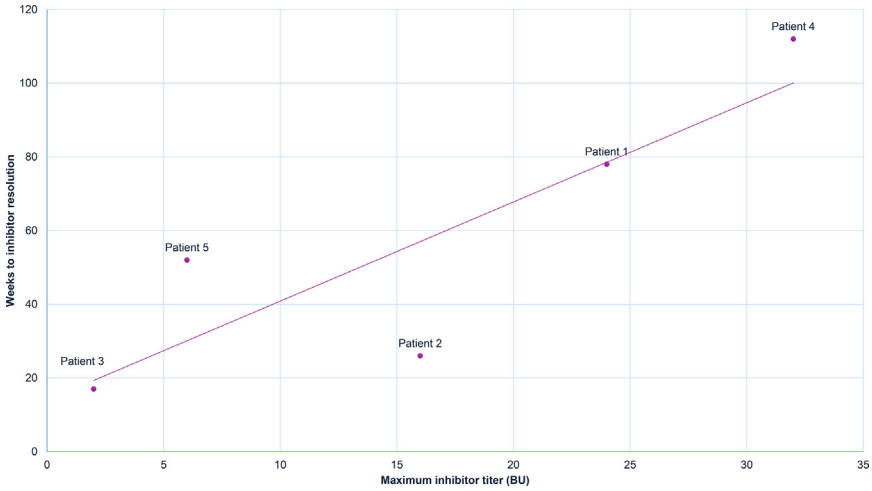

FIGURE Scatter plot describing the linear relationship between the strength of the inhibitor (in BU) and the time to successful inhibitor resolution (in weeks) with immune tolerance induction in persons with nonsevere hemophilia A.

flank hematoma and gingival bleeding. He completed ITI with recombinant antihemophilic FVIII Helixate (standard half-life [SHL]) 200 U/kg daily, followed by a taper over 6 months, leading to successful ITI. He is currently doing well on prophylactic emicizumab, and his inhibitor levels remain undetectable at 11 years post-ITI.

2.3 | Patient 3

A 3-year-old child with moderate hemophilia A (baseline FVIII:C 3% to 8%, missense mutation c.5895G>C) developed low titer inhibitor (2 BU), resulting in undetectable FVIII:C levels manifested by left arm compartment syndrome. He had significant on-demand factor exposure due to multiple traumatic bleeds prior to inhibitor development (5 doses of Advate and 55 doses of Xyntha). He completed ITI with Kogenate (SHL recombinant FVIII) 100 U/kg daily, followed by a taper over 4 months, which led to successful ITI. Post-ITI, he started prophylactic emicizumab, and his inhibitor levels remained undetectable at 7 years post-ITI.

2.4 | Patient 4

A 20-year-old male with mild hemophilia A (baseline FVIII:C 11% to 19%) sustained 2 traumatic hematomas requiring 7 doses of FVIII exposure over 10 days, followed by worsening of right calf hematoma and development of left palm pseudoaneurysm, leading to the diagnosis of high titer inhibitor (32 BU) and FVIII:C < 1%. After hemostatic management, he was started on ITI with Advate (SHL recombinant FVIII) 50 U/kg every alternate day for 12 months, resulting in a suboptimal response (inhibitor 9 BU). He was then switched to Eloctate (EHL recombinant FVIII) 100 U/kg every 2 days for 14 months, resulting in a successful ITI. He received prophylactic emicizumab during ITI and is currently being managed with on-demand Eloctate. His inhibitor levels remain undetectable at 3 years.

2.5 | Patient 5

A 41-year-old male with mild hemophilia A (baseline FVIII:C 3% to 7%) developed a high titer inhibitor (6 BU), resulting in undetectable FVIII:C levels manifested by left elbow hemarthrosis. He was treated with Kogenate (SHL recombinant FVIII) 100 U/kg 3 times per week for 12 months, resulting in successful ITI, and his inhibitor levels remain undetectable at 14 years. He currently self-infuses Kogenate as needed for bleeding episodes or prior to invasive procedures.

3 | DISCUSSION

NSHA accounts for more than half of all hemophilia cases and carries a significant bleeding risk with the development of inhibitors [6]. Risk factors for inhibitor development in NSHA include age at initial factor exposure, African ancestry, Hispanic ethnicity, intensity and type of previous factor therapy, and underlying genetic mutations [7]. The risk for inhibitor development in NSHA increases with age, likely because the frequency of surgical interventions increases, thereby resulting in greater factor exposure [8]. The age of inhibitor diagnosis varied in our cohort, from 3 to 41 years, but was roughly in line with the median age of 13 years indicated by the recent American Thrombosis and Hemostasis Network dataset analysis [4]. Each ED is defined as a day during which a patient receives 1 or more factor infusions. Cumulative EDs carry a strong correlation with the risk of inhibitor development in SHA, with the highest risk for inhibitor development being around 10 to 15 EDs [7]. Persons with NSHA carry a lifetime risk for inhibitor development as opposed to SHA, where the risk for inhibitor development is negligible after 50 EDs [2,9].

The Internation STudy on Etiology of Inhibitors in Patients with Moderate or Mild Form of Hemophilia A, Influence of Immuno-Gnetic & Hemophilia Treatment Factor study is a large retrospective study that reported 19 FVIII mutations associated with an increased risk of

inhibitor development [10]. Our cohort had 3 new mutations not previously identified in the INSIGHT study: missense mutations c.6265T>C (p.Trp2089Arg), c.1106T>C (p. Leu369Pro), and c.5895G>C (p.Trp1889Cys) in patients 1 to 3, respectively.

Despite representing a milder phenotype, bleeding complications in the presence of an inhibitor for NSHA are similar to persons with SHA [6]. In our cohort, all patients presented with severe bleeding complications, and 4 out of 5 developed high titer inhibitors. Treatment of acute bleeding episodes in patients with high titer inhibitors can be achieved with FVIII bypassing agents, such as activated prothrombin complex concentrates and recombinant FVIIa [11]. Emicizumab is a bispecific monoclonal antibody approved for prophylaxis to reduce bleeding episodes in persons with SHA with inhibitors [12] and was effectively utilized for bleeding control in 2 of our 5 patients. Initiation of emicizumab improved acute bleeding and was continued for hemostatic prophylaxis.

Long-term management of inhibitors involves ITI, IS, and close observation. ITI involves repeated administration of FVIII at higher doses, resulting in downregulation of the established antibody response. Various protocols have been used around the world, and most of the data are derived from persons with SHA [5,13,14]. An ATHN dataset study of persons with NSHA who developed inhibitors between 2010 and 2018 reported that only 17.5% of these patients received inhibitor eradication therapy, out of which 76.7% received ITI, 20% with IS, and 3.3% with both ITI and IS [4]. In our cohort, all 5 patients were successfully tolerized, with 3 out of 5 demonstrating resolution of inhibitor with SHL FVIII ITI, whereas 2 patients had suboptimal response to SHL ITI but responded to EHL Eloctate ITI. Patients with a higher titer inhibitor tended to require a longer period of ITI therapy for inhibitor clearance (See Figure). For titers that do not decline appropriately with initial ITI, experts recommend changing therapy by intensifying ITI dose and frequency, changing the FVIII product, or adding an IS agent. The dose may be tapered once the inhibitor is negative on 2 consecutive occasions and the postfactor infusion trough is detectable.

The advent of emicizumab has allowed for safe management without initiation of inhibitor eradication therapy. In patients managed without eradication therapy, while 70% of inhibitors cleared spontaneously, 40% of those rechallenged with FVIII developed an amnestic response [15]. All our 5 tolerized patients remain inhibitor-free and amnestic response-free at 3 to 14 years post-ITI despite multiple additional EDs.

Based on our single-institution experience, we conclude that ITI is a successful strategy that can be explored in NSHA with inhibitors, especially in patients with severe bleeding complications and/or high titer inhibitors. We acknowledge that more research specific to persons with NSHA with inhibitors is warranted to develop guidelines regarding indications and strategies for inhibitor eradication therapy.

FUNDING

The authors received no funding for this study.

AUTHOR CONTRIBUTIONS

S.N. has been involved in the identification of patients, data collection, interpretation of results, and manuscript preparation. N.P. and V.N. have been involved in manuscript preparation. O.K. was involved in the study conception and identification of patients. Furthermore, he provided valuable feedback on the manuscript.

RELATIONSHIPS DISCLOSURE

O.K. has been a consultant on the advisory board for BioMarin, Sanofi, Pfizer, and Genentech. All other authors have no funding or other relationship disclosures.

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