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Successful immune tolerance induction with von Willebrand factor containing concentrate in an adult with haemophilia A and chronic inhibitor – a case study

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Haemophilia A (HA) is a rare, X-linked recessive disorder resulting from a deficiency in factor VIII (FVIII). Treatment of the disease involves intravenous infusions of recombinant or plasma-derived FVIII protein. In up to approximately 30% of patients with severe HA, the immune response to the infused FVIII leads to the development of antibodies (inhibitors) against FVIII [1]. The development of inhibitors remains the most serious treatment complication for patients with HA. Inhibitor eradication is critical, as it allows for a haemostatically effective FVIII replacement therapy and the continuation of FVIII prophylactic care.

Inhibitor eradication is achieved for a large proportion of patients deemed, low-risk, through immune tolerance induction (ITI), which is characterized by the prolonged administration of regular high dose FVIII concentrate. Low-risk patients have typically been described by the following: age <8 years, peak historical inhibitor titer ≥5 and ≤200 BU mL^{-1}, and a titer at start of ITI ≤10 BU mL^{-1} [2]. Adult patients with long-standing inhibitors are therefore often considered to have a poor prognosis with regards to ITI response [3]. Furthermore, adult patients often have poor venous access, higher risk of bleeding, and require more factor concentrate over a longer duration – increasing the risk of complications, and potential cost associated with ITI. For these reasons, risks and benefits of inhibitor eradication by ITI is carefully and individually weighed in adult patients. The eradication of inhibitors in the adult patient however is an increasingly important issue given improvements in haemophilia-related care resulting in a life expectancy that approaches the general population [4]. Therefore, mitigation of bleed risk in the adult patient is essential as age-related comorbidities, and the need for general and/or orthopaedic surgery increases.

Recent reports from the international ITI study and the Bonn centre show that adult patients with long-standing inhibitors achieve similar overall success rates as children, but these data are limited [1]. Furthermore, a decision analysis model suggests that ITI therapy has an economic advantage when compared with prophylactic or on-demand therapy, lowering drug and hospitalization costs, reducing the number of bleeding events, extending life expectancy, and increasing reported quality of life [1].

Here, we present the first-described case of successful ITI in an adult patient with long-standing inhibitors using a high-purity, 1:1 ratio, von Willebrand factor (VWF)/FVIII concentrate, Wilate® (Octapharma, Toronto, ON, Canada).

Born in China, the male patient was delivered vaginally with no bleeding complications. At six months of age, he developed a febrile illness and experienced a seizure. The treating physician suspected meningitis, and a lumbar puncture was performed. The patient had no evidence of meningitis, but developed right hemiplegia thereafter, thought secondary to an intracranial haemorrhage. From birth to age 6, the recurrent seizures were managed with an anti-epileptic drug and over this time period, a global development delay became apparent. At age 3, in the context of recurrent gingival bleeding and easy bruising, the diagnosis of HA was made. Family history was remarkable for haemophilia in the patient's maternal grandfather. The patient was treated with cryoprecipitate on-demand to manage recurrent musculoskeletal and mucocutaneous bleeding episodes. Over the course of treatment course with cryoprecipitate, the patient was told that he had developed antibodies, rendering this blood product haemostatically ineffective.

When the patient was 11 years old, he and his family immigrated to Canada where his care was assumed by the Hemophilia Treatment Center of the Hospital for Sick Children (Toronto, Canada). The diagnosis of severe HA was made with a baseline residual FVIII activity of <1% and the mutation responsible was found to be a donor splice site mutation at the exon/intron boundary of exon 9 in the FVIII gene. He was

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managed with on-demand therapy with Kogenate® FS for intermittent musculoskeletal bleeds. There was no evidence of an inhibitor on testing conducted at this time. Given clinical responsiveness to factor concentrate during this time period, pharmacokinetic (PK) studies were not performed. By the age of 13, the patient had end-stage haemophilic arthropathy, and avascular necrosis from recurrent hip haemarthroses. At this time, the patient was started on prophylactic Kogenate® FS at 40 U kg^{-1}, 3 days per week – a recombinant factor VIII (rFVIII) concentrate, (Bayer Corporation, Berkley, CA, USA). Within 6 months, the patient required surgical intervention due to a subtrochanteric fracture of the femur. A few weeks postoperatively, FVIII-targeted inhibitors were detected on Bethesda assay, and quickly reached a peak titer of 70 BU mL^{-1}. At age 14, his inhibitor titer was 30 BU mL^{-1} and primary ITI was initiated with Kogenate® FS at a daily dose of 50 U kg^{-1}.

During ITI, the patient experienced ongoing bleeding into the hips. Prophylactic haemostatic treatment with activated prothrombin complex concentrate (FEIBA; Baxter Healthcare, Westlake Village, CA, USA) was initiated at a daily dose of 75 U kg^{-1}. Over the next 6 months, inhibitor titers diminished, and FVIII activity rose, allowing for gradual lowering of the FEIBA dose, and eventual cessation of FEIBA prophylaxis. The inhibitor titer became undetectable by Bethesda assay 1.5 years postoperatively – after 14 months of Kogenate® FS ITI.

At 16 years of age, the patient underwent an uncomplicated bilateral hip arthroplasty under continuous infusion of rFVIII. Despite undetectable levels of inhibitor, at 6 months postsurgery, PK analysis revealed diminished recovery at 25% suggesting the persistence of a low titer inhibitor. At 18 years of age, the patient was transferred to St. Michael's Hospital (SMH). At this time, the patient had been on ITI for 3.5 years with presumed low titer inhibitor, undetectable by Bethesda assay, but resulting in diminished PK recovery. However, the patient had experienced no breakthrough bleeding (Fig. 1).

Shortly after transfer to SMH, the patient developed repeated upper gastrointestinal bleeding necessitating reinstitution of FEIBA prophylaxis (50 U kg^{-1} every other day). Following the second gastrointestinal bleed, inhibitor titers were detected (16 BU mL^{-1}) prompting cessation of Kogenate® FS ITI therapy. The patient remained on FEIBA prophylaxis for over 2 years with inhibitor titers remaining below 10 BU mL^{-1}. With stable low titer inhibitors and the absence of bleeding episodes, at age 20.5, FEIBA prophylaxis therapy was discontinued. Shortly thereafter, the patient experienced a haematoma of the right calf, and the decision was made to reinstitute the FEIBA prophylaxis therapy (50 U kg^{-1} every other day).

At this time, the treating team at SMH decided to attempt ITI with a VWF containing FVIII product (Wilate®; Octapharma). Several groups have reported the successful use of VWF:FVIII products for primary, or rescue ITI in patients with severe HA [5,6]. When used for primary or rescue ITI, VWF:FVIII complexes have been shown to increase both thrombin generation [7] and FVIII recovery [8]. Through direct binding to FVIII, the presence of VWF in FVIII concentrates has been shown to protect FVIII from proteolytic cleavage, thereby increasing the half-life of FVIII [9]. Furthermore, *in vitro* studies have demonstrated reduced inhibitor activity against VWF:FVIII complexes compared to purified rFVIII, suggesting a role for VWF in modulating antigenicity [10].

At the age of 21, the patient was started on Wilate® for ITI at a daily dose of 100 U kg^{-1}. Prophylaxis FEIBA was continued during Wilate® ITI. Despite a previous ITI attempt lasting 3.5 years, within 6 months, the inhibitor titers fell below the detectable limit, at

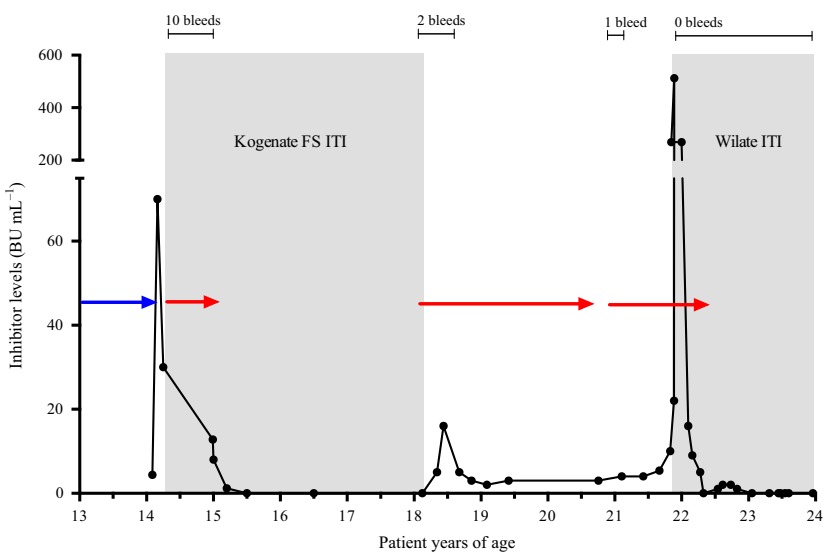

Fig. 1. Patient inhibitor titers measured overtime with corresponding treatment, and occurrence of bleeding episodes. Shaded boxes indicate primary and secondary immune tolerance induction (ITI) treatment (Kogenate FS at a daily dose of 50 U kg^{-1} for 3.5 years, and Wilate at a daily dose of 100 U kg^{-1} for 17 months, and 50 U kg^{-1} for 10 months). The blue arrow indicates prophylaxis Kogenate FS (40 U kg^{-1} 3 days per week) and red arrows indicate prophylaxis FEIBA (50 U kg^{-1} every other day).

which point FEIBA prophylaxis was discontinued. Within 8 months of commencing Wilate® ITI, the recovery levels at two consecutive follow-up appointments were found to be greater than 66% of predicted with an estimated terminal half-life of 6 hours. After 17 months of daily Wilate® at 100 U kg^{-1}, and 10 months at daily doses of 50 U kg^{-1}, inhibitor titers have remained below detectable limits, and the patient has not experienced any treatment-related adverse effects or any major or minor bleeding episodes. Wilate® ITI has therefore been declared a success in this patient. He remains on daily Wilate® prophylaxis to this date.

In conclusion, Wilate® ITI was found to be a safe and effective treatment approach for this high-risk, adult patient with severe HA complicated by long-standing FVIII inhibiting alloantibody. Eradication of the inhibitor was achieved with Wilate® ITI despite the presence of several risk factors associated with poor ITI outcome, i.e. previous ITI failures, onset of ITI after 6 years of age, and ITI initiation more than 12 months from inhibitor detection. The patient has not experienced further breakthrough bleeding or reappearance of the inhibitor despite discontinuation of prophylactic bypassing therapy and reduction in the Wilate® dose. We conclude that VWF containing products, such as Wilate® may be considered as an ITI alternative for adults with HA complicated by inhibitor.

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The utility of VWF multimer analysis in response to the desmopressin administration for the diagnosis of severe type 1 von Willebrand disease

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von Willebrand disease (VWD), the most common of the inherited bleeding disorders, is caused by a deficiency or defect of von Willebrand factor (VWF). VWD is classified into three major types based on a partial (type 1) or complete (type 3) quantitative deficiency or qualitative defect of VWF (type 2) [1]. Type 2 VWD is further classified into four subgroups.

