

# Hemophilia A and Incidence of Inhibitors

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## Abstract

Factor VIII has always been the standard of care in the prophylactic and on demand treatment of hemophilia A. Development of inhibitors (antibodies) against factor VIII remains the most challenging event in this treatment. Current review of data revisits the etiology and management of such an outcome, as well as reviewing current and emerging therapeutic modalities.

**Key Words:** Hemophilia - Recombinant Factor VIII – hemophilia with inhibitors – prophylaxis – on demand – rFVIII - plasma-derived factor VIII – pdFVIII - activated Prothrombin Complex Concentrates - aPCC – rFVIIa - von Willebrand Factor – vWF – Rituximab – ITI.

## INTRODUCTION

Hemophilia A is an x-linked genetic disorder characterized by deficiency of factor VIII. Current epidemiology estimates an incidence of 1 in every 5000 males. Prevalence varies among different areas of the world, with a range of 5.4 - 14.5 cases per 100,000 males. In the United States, prevalence of hemophilia A is estimated to be 20.6 cases per 100,000 males [1]. Basic treatment of hemophilia A includes replacement of the missing factor VIII, unfortunately, presence of inhibitors to that factor (primarily IgG antibodies), poses as a threat and challenge to such an effective therapy [2].

## Incidence

It has been proposed in some studies that the risk of development of inhibitors is higher (36% after 2 weeks) with severe disease than with low to moderate hemophilia. In the study carried out by Bray et al. in 1994, 23.9% of the subjects (who all had severe hemophilia A) were found to develop inhibitors upon receiving recombinant factor VIII, the majority of the reactions identified were low in titer [3].

The CDC inhibitor Surveillance Working Group meeting in 2012 has emphasized the importance of reporting and scanning for new cases, since this has a massive impact on future prevention and management of these cases [4].

## Pathogenesis

Factor VIII contains three A domains (A1, A2 and A3), one B domain, and 2 C domains (C1 and C2). Inhibitors are antibodies that are found targeted mainly against A2, A3 and C2 epitopes [5]. Inhibitors are restricted polyclonal IgG antibodies, different subclasses have been identified with different degrees of factor VIII polypeptide cross-reactivity [6]. Formation of factor VIII inhibitors is found to be a T-cell dependent immune reaction that involves B and T-lymphocytes together with antigen presenting cells [7]. Antibodies to factor VIII were found to vary in their pathogenicity, and the response varies in patients with congenital hemophilia from patients with acquired hemophilia; where antibodies in congenital cases tend to form against multiple epitopes, blocking their function. In acquired cases, single antibodies to a single domain tends to be the case [8]. Antibodies formed might also cause proteolysis of factor VIII [9].

## Possible risk factors and Role of genetics

The development of inhibitors in about one-third of previously un-treated patients (PUPs) with hemophilia A raised the possibility of genetic and/or environmental factors being the determinants of such a reaction. The SIPPET randomized controlled trial evaluated the development of inhibitors in 251 PUPs or minimally-treated patients with hemophilia A, it

compared the results of treatment with either plasma-derived (pdFVIII) or recombinant factor VIII (rFVIII). The study has concluded that an 87% higher rate of development of inhibitors took place in patients treated with rFVIII during the first 50 days post-exposure [10]. Upon genetic risk stratification of these results, it was found that the frequency of occurrence of inhibitors was significantly higher in genetically high-risk patients where the number needed to harm was found to be 6.3 versus only 2.3 in genetically low-risk patients [11]. In another French study, 3 factor VIII products were assessed, one of them is plasma-derived, and 2 recombinant products. The study concluded that lower inhibitor incidence occurred with the use of the plasma-derived product [12]. High-risk mutations are found to be more associated with inhibitors formation. In the PROFIT study that included 86 Italian patients, 81% rate of development of inhibitors was detected in patients with high-risk mutations (large deletions, inversions, nonsense and splice site mutations), while the incidence was found to be only 19% in patients with low-risk mutations (small insertions/deletions, nonsense mutations) [13]. A possible explanation for such a genetic observation is that with severe hemophilia A, there is complete absence of fetal induction of tolerance to factor VIII, whereas in milder forms, some form of tolerance to self-factor VIII, even if altered, may be encountered [14]. Higher incidence of inhibitors development was found with stop mutations, non-sense mutations, large deletions and intra-chromosomal intron 22 inversions [15]. The CANAL study (included 332 patients) proposed a scoring system for risk stratification as follows:

- Family history of inhibitors development: 2 points
- High-risk gene mutation presence: 2 points
- High dose treatment of first bleeding episode: 3 points

The incidence was 6%, 23%, and 57% for those with a risk score of zero, 2, or  $\geq 3$  points, respectively [16].

Specific mutations such as Trp2229  $\rightarrow$  Cys substitution in C2 epitope [17], or Arg593  $\rightarrow$  Cys substitution in A2 epitope [18] have been associated with more incidence of inhibitor development.

## Diagnosis

There are generally two categories for response to factor VIII transfers, response is quantified by Bethesda units (BU) [19]:

**1) Low-responders:** These patients have low titer of inhibitors (less than 5 BU) [20], the level of response tends to be stationary throughout repeated factor VIII transfusions [21]. In this type of response, continued treatment with factor VIII may be attempted [13].

**2) High-responders:** High titers (above 5 BU) are detected, response begins in the first week post-transfusion, peaks in the second week and usually persists even without re-treatment with factor VIII, this type needs alternative methods of treatment other than factor VIII transfusions [22].

#### Proposed treatment strategies

In cases of low-titer of inhibitors, treatment may be attempted using high doses of factor VIII (immune tolerance induction or desensitization), other possible alternatives include treatment with agents that bypass factor VIII (such as recombinant activated factor VII “rFVIIa”) [13]. Treatment of high-responders, though, remains a challenge. Comprehensive Hemophilia Treatment Centers should be consulted for management of such cases. Treatment options include porcine factor VIII, rFVIIa, and plasma-derived activated Prothrombin Complex Concentrates (aPCCs) that are virally inactivated. These treatment strategies may still lack the presence of complete profiling of their efficacy, safety, dosing frequency and possible adverse effects development [23]. Elimination of inhibitors is the target of long-term management plans [22]. Immune-Tolerance Induction (ITI) is the mainstay of such management. Several factors may impact the success of ITI therapy;

- Level of titer at initiation of management, with better responses at titers less than 10 BU.
- Age of patient and duration since onset of inhibitor occurrence, where better outcomes are noticed in younger patients and shorter durations
- Success rate of ITI appear to be lower in patients with color (such as Blacks, Hispanics and Asian/Indians); ITI should still be, however, attempted in these patients with careful balancing of risks versus benefits.

An initial rise in antibody titer may be expected at the beginning of ITI, the level should be monitored continuously for future tapering with maintenance of treatment. Various protocols have been proposed for ITI therapy as regards to dosing regimens, spacing intervals, concurrent use of immunosuppressive therapy or use of bypassing agents [24]. The initial product the patient received is generally used for ITI. However, if response is not good enough, switching to a product containing von Willebrand Factor (vWF) may be attempted. Presence of vWF as a carrier protein for factor VIII has been suggested to attenuate the effect of inhibitors, this was further supported by the SIPPET trial where plasma-derived vWF-containing products were used [10]. The success of ITI has also been correlated with genetic risk, where high-risk mutations have been associated less success rate (41%) of ITI versus low-risk mutations (81%) [13].

#### Role of Immunosuppressive medications

Use of Rituximab as a concurrent immunosuppressive therapy with ITI has been evaluated in various studies. Rituximab is an anti-CD20 monoclonal antibody that targets B lymphocytes, hence decreases antibody production in various autoimmune disorders [25]. This combined treatment strategy has been successfully implemented in the case study carried out by Chuansumrit et al. published in 2008 [26]. The consecutive cohort study carried by Collins et al. in 2009 has further supported this combination treatment method [27]. A treatment protocol that involved the use of Rituximab alone has been proposed by Dunkley et al. in 2006 [28]. Other studies have shown better outcome using immunosuppressive agents alone than using ITI therapy alone in achieving inhibitor clearance [29]. The study by Lim et al. in 2014 proposed the use of Rituximab as a first-line treatment for non-severe hemophilia A with inhibitors [30].

#### CONCLUSION

Development of factor VIII inhibitors is a serious outcome that might develop upon treatment of hemophilia A patients. It has variable presentations ranging from continuous resistant bleeding up to serious complications and death. Treatment with alternative agents such as rVIIa has been proposed, yet control of bleeding with such agents may be challenging [31]. Desensitization with ITI has been proposed as a management plan, with more efficacy in treatment of low-responders than high-responders [24]. The current review of literature has found promising results using combined management with ITI and immunosuppressives (such as Rituximab), yet more studies are needed to evaluate risk/benefit ratio of such combination therapy, as well as to assess the efficacy of alternative therapies such as bypass agents in both treatment and prophylaxis in hemophilia A patients [32].

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