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Review Article

An overview of FVIII inhibitors in Hemophilia A

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Abstract

Hemophilia A (HA) is a X-linked recessive bleeding disorder occurring due to the deficiency of factor VIII (FVIII). It is treated by transfusion of plasma-derived (pdFVIII) or recombinant FVIII (rFVIII) concentrates. In ~25% of patients with severe Hemophilia A (SHA) inhibitory antibodies may get produced against FVIII, causing shortening of the FVIII half-life and consequently in nullification of its function. These antibodies are known as inhibitors. Bleeding episodes now become refractory to the standard treatment, making alternative therapeutic approaches like costly inhibitor bypassing agents necessary; consequently, increasing the morbidity and shrinking the quality of life of patients with Hemophilia A (PwHA).

This review aimed to: (i) summarize the current knowledge on inhibitors in Hemophilia A and, (ii) enumerate the clinico-pathological variables related to inhibitor development.

Keywords: Inhibitors, Hemophilia, Hemophilia A, Factor VIII, Neutralizing antibodies, Risk factors, Prevalence.

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1. Introduction

The patients with hemophilia A are ideally managed with primary prophylaxis using regular FVIII infusions. The focus is to prevent joint damage, that gets started from the first joint bleed itself, or even earlier.[1] Most PwHA do not mount a clinically measurable immune response towards FVIII. However, in about 25-30% of patients, neutralizing antibodies emerge against FVIII, called as inhibitors.[2] These inhibitors render FVIII treatment ineffective and impair the functional status of patients, representing the most dangerous adverse effect after FVIII replacement therapy. Factor VIII Inhibitors are classically divided into Types I or II inhibitors. Types I inhibitors follow simple-first order kinetics, and are characterized by complete inhibition of FVIII that result due to alloantibodies formation against foreign FVIII concentrate used to treat PwHA. Type-II inhibitors follow complex-second order kinetics, and are characterized by incomplete FVIII inhibition that occurs due to the formation of autoantibodies seen in acquired Hemophilia A. This review was prompted by a series of researches conducted in our lab at a tertiary care institute in north India. All the research data has already been published.[3-5]

2. Materials and Methods

Electronic databases like PubMed and Google search were searched for articles using the key words 'inhibitors,' 'hemophilia,' and 'hemophilia A' from the years 1975 to 2023. Relevant key articles in English literature including original articles and systematic reviews pertaining to the development, prevalence and detection of inhibitors were selected. Additional references were gained by cross-referencing these articles. Irrelevant and duplicate articles were excluded. In total 34 relevant articles were selected, analysed in details and extracted data were arranged into the following sections: mechanism of development, risk factors for inhibitor development, prevalence and detection of inhibitors.

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3. Literature Review

3.1. Mechanism of development

The inhibitor development is a complex activity influenced by multiple aspects like cells, cytokines, and other immuno-regulatory elements, with their levels and actions determined by both genetic and non-genetic characteristics. Induction of an immune reaction and production of antibodies against FVIII, requires interaction between antigen presenting cells (APCs) and CD4+Tcells via HLA class-II molecules, with T-regulatory cells playing an important role.[6] In previously untreated patients (PUPs), the immune reaction probably occurs via dendritic cell mechanisms. However, in primed patients with a pre-devolved immune reaction, B cells are considered to enact antigen-presenting cells (APCs).[6]

Von Willebrand factor (VWF) has been purported as a potential immunoprotective chaperone by antigenic competition with/without diminishing dose-dependent endocytosis of FVIII. Thus, initiation of immune reaction is prevented.[7] Commoner inhibitor isoforms include immunoglobulin (Ig)-G1 and -G4, of which IgG4 is more prevalent.[5]

3.2. Risk factors for inhibitors development

Multiple risk factors linked with inhibitor development include:

3.2.1. Causative FVIII mutation

Siblings are at higher risk for inhibitor development, if there is family history of inhibitors positivity, suggesting a genetic predilection for inhibitor development. Significance of these mutations is quite accepted. In a meta-analysis, inhibitor production risk is higher in patients with large deletions and nonsense mutations, than in those with intron 22 inversions.[8] Hemophilia Inhibitor Genetics Study (HIGS) study reported more inhibitor development in other mutations like certain deletions/insertions, splice-site and missense mutations, also.[9]

3.2.2. HLA class II

HLA class-II alleles have been purported to be linked with FVIII polymorphisms and FVIII inhibitor development in H3/H4 haplotype-PwHA. This fact shows potential to advance our knowledge about the intricate immune response.[10] However, further studies are entailed to affirm these associations. Hosseini et al did a study in Iran reported that allele HLA-DRB1*01:01 is perhaps linked to protective effect; while HLA-DRB1*15:03 or HLA-DRB1*11 alleles are likely not associated with increased possibility of inhibitor development in SHA patients.[11]

3.2.3. Immune response genes

Various polymorphic candidate genes belonging to immune pathways have been implicated in inhibitor production, over the past years. Of these associated polymorphisms interleukin-10, interleukin-5, tumour necrosis factor-α, cytotoxic T-lymphocyte antigen 4, etc. are linked with higher chances, while interleukin-2, transforming growth factor-β, etc are linked with lower chances of inhibitor development.[12] Of these, the most persistently and commonly reported polymorphic gene is IL-10 gene.[6] However, these associations have been variable across the study cohorts, probably due to diverse analytical/technical methods & study designs, meagre statistical strength, impact of non-genetic determinants, and intricacy of the immune mechanisms.

3.2.4. Race and ethnicity

Risk of inhibitor development has been reported differently with respect to different racial, ethnic and regional groups across the world. Patients of African and Latino ancestry have been reported to have more chances of inhibitor production than Caucasians, similar to black PwHA who have inhibitor prevalence to be twice as that of white patients.[13]

3.2.5. Non-genetic risk factors

Several probable non-genetic risk factors have been implicated with inhibitor development, of which few factors have neither been evicted nor proved potentially with reverse effect, like young age initiation of FVIII replacement.

3.2.5.1. Intensity of FVIII treatment

The wide gamut of clinical applications causes large variation in the strength of FVIII treatment, ranging from lone prophylactic FVIII concentrate replacement (prophylactic therapy/PxT), to the administration of loads of FVIII concentrates for numerous days consecutively, in scenarios of severe bleeding episodes or surgeries known as peak treatment moments (on-demand therapy/ODT). Multiple studies reported inhibitor occurrence in PwHA on PxT. In the Concerted Action on Neutralizing Antibodies in severe Hemophilia A study (CANAL) and Research of Determinants of Inhibitor Development (RODIN) study, peak treatment moments for >5days as the preliminary treatment, were linked with higher chances of inhibitor development.[14,15] Two different meta-analysis, including PUPs with SHA and moderate HA (MHA), described more inhibitor development in SHA cases receiving rigorous FVIII replacement for surgical procedures at first requirement, than those treated strenuously for bleeding alone, reverberating the “danger model” of inhibitor development.[16] However, Oldenburg et.al. purported that prophylaxis with FVIII may potentially induce tolerance against FVIII.[17]

3.2.5.2. Prophylaxis

Multiple studies have analyzed the effectiveness of early application of prophylactic therapy in diminishing the chances of inhibitor development. However, this could not be reproduced in other studies, including RODIN and Early Prophylaxis Immunologic Challenge (EPIC) study.[15,18] Kurnik et.al. reported, standard prophylaxis started at/after

the first joint or other severe bleed, led to the production of inhibitors in 47% patients, compared with only 3.8% in patients given a low-dose prophylactic regimen started at manifested bleeding tendency, with no long or intensive treatment.[19] However, current findings provide no definite support to advise the correct timing to start the prophylaxis, for diminishing the risk of inhibitors.

Few studies suggest that PxT is related to lower risk of inhibitor development, compared to ones with ODT.[14,20] Studies conducted on the ODT basis, are relatively sparse, and are usually available in the setting of populations where free and ample supply of FVIII is yet unavailable.

3.2.5.3. Plasma-derived versus recombinant products

Wight and Paisley reported that the inhibitor formation rFVIII was more than that of pdFVIII.[21] Subsequent studies showed similar results.[22] This may be partly attributed to the VWF in present in the pdFVIII concentrates which may reduce the immunologic potential of the FVIII as stated above. RODIN study reported inhibitor formation is different across the three types of rFVIII, with second generation rFVIII appearing more immunogenic.[15] Other studies, including SIPPET (Study on Inhibitors in Plasma-Product Exposed Toddlers) study asserted the same.[23] Above data is important as our studies were conducted on north Indian PwHA homogenously receiving ODT with pdFVIII (not VWF-enriched) and, reported inhibitor prevalence of 9.67%. Moreover, we found that mean factor intake in inhibitor-positive PwHA was significantly higher than, in inhibitor-negative PwHA, again indicating that inhibitor development is linked to higher factor intake.[3]

Summing-up, literature analysis shows wide heterogeneity due to variable study design/populations, definitions of disease intensity, severity, diagnosis, therapy and follow-up of inhibitor positive patients, which leads-to a high-risk of biases and cause indirect relations dicey and, even precarious.

3.2.5.4. Blood group O protection

Franchini et.al. reported, inter-individual variations in the half-life of FVIII concentrate in HA patients owing to ABO-related different glycosylation patterns of VWF and, that blood-group O appears to independently protect against inhibitor development.[24] However, in our study we observed that the most common blood-group in inhibitor-positive PwHA was A-subtype, whereas in the whole study group it was B-subtype. We didn't find any significant disparity with respect to O-subtype.[3] Hence, associations of the blood groups with inhibitor development need further research and validation in larger studies from different geographic regions.

3.3. Prevalence of inhibitors

As per World Federation of Hemophilia and studies from different parts of the world the reported prevalence of inhibitors in PwHA is very variable ranging between 20% and 33%. This variation may be attributed to factors like ethnicity, different patterns, frequencies and dosage of FVIII treatment etc. in the different locations of the world. In terms of ethnicity, African-American, Latino, and Hispanic patients show more inhibitor prevalence than Caucasians. Few recent studies conducted in the past decade have been tabulated in **Table 1**.[3,25-33] Chinese study showed a lowest prevalence of 3.9% only while highest was reported in Japanese study (29.7%).[25,31] Our results were similar to another Indian study by Pinto et al (9.6% and 6.07%) respectively.[3,29]

Table 1: Reported prevalence around the world in the past decade.

Population	Reported prevalence	Study which reported
Japanese	29.7%	Shirahata A et al. 2011[25]
Saudi	22%	Owaidah T et al. 2011[26]
Iraqis	18.6%	Taresh AK et al. 2019[27]
Pakistani	15%	Borhany et al. 2012[28]
Indian	6.07%, 9.6%, 7.9%, 3.6%	Pinto P et al. 2014,[29] Our study (2018),[3] John et al (2018),[30] Kumar et al (2019)[31]
Tunisian	5%	Kraiem et al. 2012[32]
Chinese	3.9%	Wang XF et al. 2010[33]

3.4. Status of inhibitors in India

Indian PwHA are managed mostly with blood product transfusions, rather than recombinant FVIII etc.; and that too usually 'on-demand' basis because of the exorbitant costs involved. Facilities for screening and confirming the existence of inhibitors are extremely scarce, with few available laboratory facilities needing regular external quality assessment to improve their performance.

PwHA are still frequently managed with blood-derived transfusions, typically on an 'on-demand' manner, due to the exorbitant costs involved. The incidence of FVIII inhibitor development in India varies with location where PwHA resides. This may be attributed to quantitative and qualitative in the treatment in terms of amount and type of FVIII provided, along with the genetic predisposition of the PwHA. Pinto P et.al. conducted a study including PwHA from different regions of India and, reported overall incidence of FVIII Inhibitors as 6.07% in India, with highest incidence in South India (13.04%).[29] In northern India they mentioned the prevalence to be only 5.45%. Our study which too was conducted on North Indian PwHA, reported a prevalence of 9.6%.[3] This may be attributed to increased availability of FVIII therapy and facilities for screening and confirmation of inhibitors, which review inhibitors have upgraded, during the past few years. However, both of these still need improvement. After our study, John et al. and Kumar et al. reported the inhibitor prevalence to be 7.9% in Punjab and 3.6% in the north-eastern part of India.[30,31]

Acquired hemophilia A (AHA) is quite uncommon. In India too it is reported infrequently. Kumar et.al. reported

eight cases of acquired hemophilia A, over a period of 15 years, of which six cases tested showed inhibitor formation.[34]

3.4.1. Detection of inhibitors

Multiple techniques are available for the detection of inhibitors. Broadly these can be categorized into (1) clotting-based assays, (2) chromogenic factor assays and, (3) immunologic assays. The immunologic assays may be further divided into enzyme based- [e.g., enzyme-linked immunosorbent assay (ELISAs)] and fluorescence based-immunoassays.

The functional clotting-based detection techniques i.e., Classical Bethesda Assay (CBA) or Nijmegen-modified Bethesda Assay (NBA) form the trusted and standard methods, classically used for detecting FVIII inhibitors in PwHA. However, CBA has its disadvantages like less sensitivity, especially for detection of low-titer inhibitors and, its inability to detect non-inhibitory antibodies and isotypes of inhibitors. In our study too, those samples which had suspected low titers on CBA were confirmed and quantified by NBA, a more sensitive method of inhibitor detection.[4] Nonetheless, both CBA and NBA are technically challenging and expensive.

FVIII-inhibitor ELISAs can also be used for detecting FVIII inhibitors. These ELISAs hold promise as they display better sensitivity in evaluating low-titer inhibitors and detecting the inhibitor isotype. Moreover, the inhibitors are predominantly of immunoglobulin IgG1 and IgG4 subtypes, of which most inhibitors are of IgG4 subtype.[35] Considering this, we evaluated the efficacy of IgG4-ELISA in diagnosing functionally relevant inhibitors and found the metrics of diagnostic efficacy to be good (sensitivity, specificity, NPV and PPV of 93.3%, 97.0%, 97% and 93.3%, respectively).[5] Although, ELISAs hold advantage of swift large-scale screening of FVIII inhibitors, it lacks the ability to confirm or quantitate the inhibitors which requires Bethesda assays.

4. Conclusion

It is enigmatic that while availability of FVIII has helped PwHA by overcoming bleeding complications, it has introduced inhibitor development. We in this review summarize the current knowledge on inhibitors in hemophilia A in terms of mechanism and risk factors of inhibitor development, aiming to emphasize the need of both the clinical and laboratory professionals to acclimatize themselves about the same and bring about changes in the clinical and laboratory practices for preventing inhibitor development and manage them if they occur at all. In addition, we give a glimpse of prevalence of inhibitors in the world, India and its detection. Lastly, we will admit that even though insights about certain aspects of inhibitors are available now, but still more research is needed to fathom further mystifying aspects of the inhibitors.

4.1. Highlights

1. Hemophilia A treatment with plasma-derived (pdFVIII) or recombinant FVIII (rFVIII) concentrates can lead to inhibitor development.
2. Inhibitors reduce the half-life of infused FVIII and neutralize its coagulant activity
3. Review summarizes the current knowledge on inhibitors in hemophilia A in terms of mechanism and risk factors of inhibitor formation and its detection.
4. Organizes the prevalence of inhibitors in the world and India.

5. Ethical Approval

Not Applicable

6. Conflict of Interests

No conflicts to declare

7. Source of Funding

None.

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Not Applicable.

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