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Management of factor VIII inhibitors

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The development of inhibitory alloantibodies to factor VIII is arguably one of the most severe and important complications of clotting factor concentrate exposure in haemophilia A. The development of an inhibitor compromises the ability to effectively manage haemorrhage, resulting in a greater rate of disability, complications and costs of therapy. This chapter briefly reviews the epidemiology, immunobiology, and laboratory evaluation of inhibitors. It discusses the therapeutic approach and management of inhibitors in various clinical settings and also focuses on inhibitor eradication practices (immune tolerance) and newer experimental strategies with potential clinical application for inhibitor prevention.

Key words: haemophilia A; immune tolerance; inhibitors; prothrombin complex concentrates; recombinant factor VIIa.

Haemophilia A is a bleeding disorder caused by a functional absence, or reduced levels, of factor VIII (FVIII). In the developed world, prophylaxis for haemophilia A uses infusions of virus-attenuated plasma-derived (pdFVIII) or recombinant (rFVIII) clotting factor replacement. Such treatment has substantially improved the quality of life of persons with severe (FVIII $<$ 1%) and moderately severe (FVIII 1–5%) haemophilia A by avoiding bleeding episodes and their long-term consequences, particularly in the joints.[1] However, we are still grappling with issues of cost-effective care of the disease and its other complications. The most serious of these complications is the development of a neutralizing antibody, or inhibitor, to FVIII. This chapter discusses the problem of FVIII inhibitor development, therapeutic management of minor and major haemorrhage in the presence of antibodies, current inhibitor eradication (immune tolerance) practices

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and experimental concepts that could result in the ultimate inhibitor prevention strategies of the future.

INHIBITOR DEVELOPMENT IN HAEMOPHILIA A

Epidemiology

In up to 30% of patients with severe haemophilia A, therapeutically administered exogenous FVIII is recognized as a foreign antigen and stimulates the production of polyclonal IgG antibodies (inhibitors).[2] These inhibitors usually neutralize and inactivate residual endogenous as well as exogenous FVIII, which is cleared rapidly from the circulation. Mechanisms for FVIII neutralization include: (i) steric hindrance; (ii) immune complex formation and clearance; and (iii) neo-epitope recognition and protein hydrolysis.[3–7]

Most inhibitors develop during early childhood.[8] Studies conducted in previously untreated children with severe haemophilia receiving only rFVIII suggest a trend towards inhibitor development at younger ages (with a median of age 9–12 years) and before 200 factor exposure days.[9–11] However, a 1–2% per year incidence of de novo antibody development occurs throughout the lifetime of a person with haemophilia.[12] Inhibitor formation is detected by routine laboratory surveillance for antibodies, which is performed at least every 3–12 months, and more rigorous monitoring for children during their first 50–200 factor exposure days.[13]

Inhibitor assay and characterization

FVIII inhibitors are detected by the Nijmegen modification of the clotting Bethesda assay, in which the ability of the patient's plasma to inactivate FVIII in normal plasma is tested[14,15]; 1 Bethesda unit (BU) is defined as the amount of antibody that neutralizes 50% of plasma FVIII activity and titres of 0.6 BU or greater suggest the presence of antibody.[16]

Inhibitors are generally classified as low titre if the level is <5 BU and high titre if ≥ 5 BU.[17] Further, patients can be categorized as low or high responders, depending on the immune (anaemnestic) response they exhibit when re-exposed to FVIII:

- Low responders have antibody titres <5 BU, demonstrate lack of anaemnestic response on exposure to FVIII and can be treated with specific factor replacement.
- High responders have antibody titres ≥ 5 BU, demonstrate a brisk anaemnestic response to FVIII and are not treatable with specific factor replacement.

Although the FVIII epitopes most frequently targeted by antibodies are well described[18–21] (Figure 1), the epitope specificities of these antibodies do not explain or predict the immunological characteristics of anti-FVIII antibodies.

Immunology of factor VIII inhibitor development

The mature host immune response to a foreign antigen is complex and involves antigen processing (MHC class 1 or 2) and T- and B-cell cross-talk that leads to B cell synthesis of antibodies, which in case of FVIII can function as inhibitors (Figure 2).[22,23]