Abstract 036

NON-FACTOR APPROACHES AND NEW HORIZONS

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Hemophilia is an X-linked recessive disorder. It is divided into two different subtypes; hemophilia A (HA) and B (HB), which result from the deficiency or complete absence of clotting factors VIII (FVIII) and IX (FIX) respectively. Current management of HA and HB includes prophylactic factor replacement[1]. Neutralising antibodies, as inhibitors, can develop against the infused factor and that can complicate the management of hemophilia patients. If inhibitors develop, immune tolerance induction can potentially promote tolerance to exogenous FVIII or FIX, and bypassing agents (BPAs) such as recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates (aPCC) can be used to circumvent factor use[2]. Inhibitor development impacts negatively upon quality of life and treatment compliance, highlighting the need for improved therapies. Several novel pharmacological therapies developed for hemophilia aim to rebalance the clotting cascade. These therapies utilise a range of different mechanisms, namely: the extension of the circulating half-life of standard recombinant factors; the mimicking of factor VIII cofactor activity; rebalancing of coagulation through targeting of natural anticoagulants such as antithrombin and tissue factor pathway inhibitor; and inducing the production of endogenous factors with gene therapy. **Discussion:** Extended half−life products involves fusing FVIII or FIX to a protein with a long half-life[3]. Albumin and the constant region (Fc) of IgG have long plasma half-lives as they bind to the neonatal Fc receptor, which is critical for the endogenous recycling of both IgG and albumin. Another method is PEGylation, where one or more PEG chains are covalently linked to rFVIII or rFIX. PEG chains interfere with the recombinant factors binding to their clearance receptors, thereby prolonging circulating half-life. Emicizumab, a recombinant humanised bispecific IgG antibody, mimics the cofactor function of the missing FVIII in HA. It simultaneously binds activated FIX (FIXa) and factor X (FX), bringing them into spatial proximity to promote FIXa-catalysed FX activation, thereby restoring haemostasis[4]. Fitusiran, a novel therapy applicable to both HA and HB, consists of the amino acid, N-Acetyl- galactosamine, the ligand of the hepatic asialo-glycoprotein receptors, conjugated to a synthetic siRNA. It targets and degrades a region of the SERPINC1 gene mRNA, preventing antithrombin production and enhancing thrombin generation. Antithrombin is a potent anticoagulant which inactivates FIXa, activated factor X (FXa) and activated factor II (FIIa/thrombin). Therefore, fitusiran can correct the coagulation imbalance and prevent the bleeding phenotype[5]. Concizumab is an IgG4 monoclonal antibody targeting tissue factor pathway inhibitor (TFPI). It presents an alternative therapy for HA and HB patients, both with and without inhibitors. TFPI is a coagulation inhibitor. It limits coagulation during the initiation of the coagulation cascade through inhibition of the tissue factor-activated factor VII (TF-FVIIa) complex and through FXa inhibition[6]. Gene therapy presents a novel and effective treatment modality for hemophilia, potentially bypassing complications of other therapies. Gene therapy regimens consist of single infusions of a viral vector, which result in transduction of a gene coding for the deficient factor into patient hepatocytes. Current gene therapy regimens for hemophilia predominantly utilise adeno-associated virus (AAV) vectors to deliver the required gene[7]. **Conclusion:** Current factor replacement poses numerous issues, resulting in poor adherence and reduced QoL. Inhibitor development presents a key limitation to factor replacement. EHL products, emicizumab, fitusiran, and concizumab (summarised in appear effective in patients with and without inhibitors, and their longer half-lives enable less frequent injections.

Keywords: Hemophilia A, Hemophilia B, Extended half-life, Emicizumab, Fitusiran, Concizumab, Gene therapy.

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Abstract 037

IMMUNE THROMBOCYTOPENİA: PATHOPHYSIOLOGY AND MOLECULAR BIOLOGY

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Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia. While traditionally explained by antibody-mediated platelet destruction, recent studies reveal a broader syndrome of immune dysregulation involving both platelet destruction and impaired thrombopoiesis. The best-established mechanism involves autoantibodies, primarily IgG1 and IgG3, against platelet glycoproteins GPIIb/IIIa and GPIb/IX. Antibody-coated platelets are phagocytosed by macrophages via Fcγ receptors in the spleen and liver. Anti-GPIb antibodies cause platelet desialylation and clearance by the hepatic Ashwell−Morell receptor. Autoantibodies also trigger complement activation, enhancing destruction through C3b deposition. Beyond humoral immunity, T-cell dysregulation is central. Th1 polarization, characterized by elevated IFN-γ, TNF-α, and IL-2, stimulates macrophage activation and autoreactive B-cell differentiation. In contrast, Th2 cytokines (IL-4, IL-10) are reduced, impairing tolerance. Increased Th17 cells and IL-17 further amplify inflammation and suppress regulatory T-cell (Treg) activity. Indeed, $CD4^+CD25^+FoxP3^+$ Tregs are both reduced in number and function, with diminished production of IL-10 and TGF-β. This promotes unchecked autoreactive B- and T-cell activity. $CD8^+$ cytotoxic T cells have emerged as key players. These cells directly induce apoptosis of platelets and bone marrow megakaryocytes through perforin−granzyme and Fas/FasL pathways, representing antibody-independent platelet destruction. Their expansion is particularly evident in refractory or chronic ITP. B-cell activation is driven by cytokines from Th1 and follicular helper T cells. The B-cell survival factors BAFF (B-cell activating factor) and APRIL (A proliferation-inducing ligand) are elevated in