Berardino Pollio
Pediatric Hemophilia Center, Regina Margherita Children Hospital of Turin, Turin, (Italy)

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Editor: G. Sottilotta
Director: D. Greco Malara

e-mail: ojhm@hemonline.it
https://www.hemonline.it

B. Pollio

NON-REPLACEMENT THERAPY IN HEMOPHILIA: PRESENT AND FUTURE

In 2007 Manco Johnson's pivotal randomized trials established that primary prophylaxis is the standard of care for people with hemophilia. In just 15 years, hemophilia has seen an extraordinary development of increasingly innovative molecules. By the end of 2021, an extraordinary therapeutic arsenal of at least a dozen factors designed to reduce immunogenicity and modify clearance in order to increase protection and shorten dosing intervals is available for treatment of hemophilia. The non-factor replacement therapies are novel approaches restoring generation of thrombin by means of monoclonal antibodies mimicking FVIII, antithrombin interference RNA therapy and monoclonal antibodies directed against the tissue factor pathway inhibitor (anti-TFPI). The advent of emicizumab, a subcutaneously administered bispecific humanized monoclonal antibody is a FVIII mimetic, resulting in a dramatic

improvement of quality of patient-life with inhibitors. Moreover, emicizumab is now an alternative form of prophylaxis for patients with severe hemophilia A without inhibitors. The 2021 study of Callaghan et al. demonstrated that 82% of patients treated with emicizumab were free from bleeding during a follow-up of 144 weeks. The real-world data also confirm the efficacy data of the pivotal studies and are reassuring on safety. Hemorrhagic phenotype changes to mild and bleeding episodes are almost exclusively secondary to significant trauma; drug-related thrombotic events remain confined to those of patients enrolled in the first pivotal Haven-1 study and are related to the association with prolonged therapy with FEIBA. Phase III Haven 6 study investigates the efficacy and safety of emicizumab in patients with mild and moderate hemophilia A of any age. Phase III Haven-7 study and the observational study of the Italian association of hemophilia centers (AICE) are under way to collect data on the management of previously untreated patients and children <12 years without inhibitors. Another monoclonal antibody called Mim-8 is a FVIII mimetic under investigation also in children between 1 and 11 years old. Fitusiran is a small interfering RNA (siRNA) that acts by targeting and binding Antithrombin (AT) messenger RNA. It is given subcutaneously and is under investigation in hemophilia A and hemophilia B with and without inhibitors. Patients treated with fitusiran experienced an almost 80% reduction in AT levels. ABR was 1 in patients without inhibitors and 0 in patients with inhibitors Unfortunately, a Hemophilia A patient suffered a cerebral sinus vein thrombosis following FVIII therapy for breakthrough bleeding that was ultimately fatal. After a clinical hold on the trial, a risk-mitigation strategy was developed and the clinical trial program has restarted. Concizumab and marstacimab are two humanized monoclonal antibodies against TFPI which is a natural inhibitor of extrinsic pathway. Hemostasis rebalancing strategies are particularly interesting because they are potentially useful even in rare disorders of hemostasis. Furthermore, they may represent a valid therapeutic option for the neglected category of patients with factor IX inhibitors. In this amazing scenario of innovative therapies, however, some points remain unchanged regarding the management of patients with hemophilia: the need for careful monitoring of the joint health, the need for adequate adherence to therapy and finally a constant attitude to pharmacovigilance.