Thromboembolic events in paroxysmal nocturnal hemoglobinuria — pathophysiology and new therapeutic options

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Paroxysmal nocturnal hemoglobinuria (PNH) is a life-threatening disorder of hematopoietic stem cells related to mutations in the gene encoding PIGA required for glycosylphosphatidylinositol (GPI) anchor biosynthesis [1–4]. GPI deficiency leads to partial or complete absence of GPI-associated proteins (GPI-AP). The deficient proteins include those that inhibit the functions of the complement system. Erythrocytes of a PNH patient are devoid of CD55 (decay-accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL), which leads to chronic, uncontrolled complement activation and to hemolysis [4].

Intravascular hemolysis results in the release of free hemoglobin, secondary deficiency of nitric oxide with hemoglobin-induced vasoconstriction, endothelial activation and activation of leukocytes and platelets. These are the main mechanisms of thromboembolic events in PNH patients [5]. PNH is considered the most severe form of acquired thrombophilia [6].

PNH usually develops about the age of 30 [3]. The clinical presentation includes hemolysis with negative Coombs’ test and high lactate dehydrogenase level (LDH), bone marrow failure (one-, two- or three-cell line cytopenia), as well as venous and arterial thrombosis. Characteristic for PNH thrombosis is atypical location (usually varicose veins), and no response to anticoagulants [6, 7].

The greatest advancement in the management of PNH patients was recorded with the implementation of eculizumab — a C-5-blocking monoclonal antibody [8, 9]. This complement blocking drug stops intravascular haemolysis in PNH patients, significantly reduces the rate of thromboembolic events and contributes to marked improvement of health-related quality of life. Ravulizumab is another C-5-blocking monoclonal antibody currently registered in the European Union [9–12]. It is an “improved” version of eculizumab molecule, modified in the Fab and Fc antibody fragments. The half-life is longer and there is no loss in C-5 blocking effectiveness. Ravulizumab can be administered every 8 weeks, unlike eculizumab (every 2 weeks) [10, 11].

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References


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