VIA MEDICA

REPORT

Journal of Transfusion Medicine
2022, vol. 15, no. 1, 67–68
DOI: 10.5603/JTM.2022.0007

ISSN 1689-6017
eISSN 2080-1505

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

Jerzy Windyga

Department of Disorders of Hemostasis and Internal Diseases, Department of Hemostasis and Metabolic Disorders, Institute of Hematology anf Transfusion Medicine, Warsaw, Poland

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].

Conflict of interest: none declared

References

1. Nishimura JI, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine (Baltimore). 2004; 83(3): 193–207, doi: 10.1097/01.md.0000126763.68170.46, indexed in Pubmed: 15118546.
2. Socié G, Mary JY, Gramont Ade, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. The Lancet. 1996; 348(9027): 573–577, doi: 10.1016/s0140-6736(95)12360-1.
3. Hillmen P, Lewis SM, Bessler M, et al. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995; 333(19): 1253–1258, doi: 10.1056/nejm199511093331904, indexed in Pubmed: 7566002.
4. Rother RP, Bell L, Hillmen P, et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel

Correspondence address: prof. dr hab. n. med. Jerzy Windyga, Department of Disorders of Hemostasis and Internal Diseases, Department of Hemostasis and Metabolic Disorders, Institute of Hematology anf Transfusion Medicine, Gandhi Street 14, 02–776 Warsaw, e-mail: jwindyga@ihit.waw.pl

Translation: mgr Krystyna Dudziak

mechanism of human disease. JAMA. 2005; 293(13): 1653–1662, doi: 10.1001/jama.293.13.1653, indexed in Pubmed: 15811985.
5. Lee J, Jang J, Kim J, et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. Int J Hematol. 2013; 97(6): 749–757, doi: 10.1007/s12185-013-1346-4, indexed in Pubmed: 23636668.
6. Hillmen P, Muus P, Dührsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007; 110(12): 4123–4128, doi: 10.1182/blood-2007-06-095646, indexed in Pubmed: 17702897.
7. Sharma VR. Paroxysmal nocturnal hemoglobinuria: pathogenesis, testing, and diagnosis. Clin Adv Hematol Oncol. 2013; 13(9): 2–8, indexed in Pubmed: 25856267.
8. Connell NT. Ravulizumab: a complementaary option for PNH. Blood. 2019; 133(6): 503–504, doi: 10.1182/blood-2018-12-891499, indexed in Pubmed: 30733201.
9. Roth A, Rottinghaus ST, Hill A, et al. et al. Ravulizumab (ALXN1210) in patients with paroxysmal nocturnal hemoglobinuria: results of 2 phase 1b/2 studies. Blood Adv. 2018; 2(17): 2176–2185, doi: 10.1182/bloodadvances.2018020644, indexed in Pubmed: 30171081.
10. Lee J, Fontbrune FS, Lee LW, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019; 133(6): 530–539, doi: 10.1182/blood-2018-09-876136, indexed in Pubmed: 30510080.
11. Kulasekararaj A, Hill A, Rottinghaus S, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019; 133(6): 540–549, doi: 10.1182/blood-2018-09-876805, indexed in Pubmed: 30510079.
12. Brodsky R. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2021; 137(10): 1304–1309, doi: 10.1182/blood.2019003812, indexed in Pubmed: 33512400.