

CASE REPORT

Anticoagulant therapy with rivaroxaban in a young patient with paroxysmal nocturnal hemoglobinuria

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Key Clinical Message

The new direct oral anticoagulants such as rivaroxaban, could play an important role in the anticoagulant treatment of patients with paroxysmal nocturnal hemoglobinuria where anticoagulant treatment is complex to run, since they have shown a reduction in serious bleeding complications compared to antithrombotic therapy with classical vitamin K antagonist.

Keywords

Anticoagulant therapy, bleeding complication, paroxysmal nocturnal hemoglobinuria, rivaroxaban, thrombosis.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder of hematopoietic cells characterized by a defect in the glycosylphosphatidylinositol (GPI) anchored molecules due to a somatic mutation in the X-linked PIG-A gene [1]. This leads to a partial or complete absence of two complement inhibitor GPI-linked proteins, particularly CD59 and CD55, from the membrane of the circulating cells, causing the activation of the complement system on red cells surface and intravascular hemolysis. In addition to intravascular hemolytic anemia, PNH is characterized by hypercoagulable state and bone marrow aplasia.

The hypercoagulable state is responsible for life-threatening venous thrombosis generally arising in hepatic, intra-abdominal, cerebral, and extremity veins and these thrombotic complications represent the most common cause of death in patients with PNH [2]. Prophylactic anticoagulant treatment (AT) seems capable of improving survival and morbidity. Since 2000 a major advance has been obtained with the introduction of eculizumab, a monoclonal antibody that targets the C5 protein of the complement system. Eculizumab is able to reduce complement-mediated hemolysis, improving anemia and

fatigue. Besides, eculizumab seems able to prevent thrombosis, probably, as an indirect effect of intravascular hemolysis [3].

We report the case of a 42-year-old female patient with paroxysmal nocturnal hemoglobinuria diagnosed in 1998 by a positive HAM test and flow cytometry analysis (PNH type III circulating cells: 97% granulocytes, 96% monocytes, 75% erythrocytes). At diagnosis, the patients showed severe hemolytic anemia, abdominal pain, and the presence of thrombosis in the superior sagittal sinus. In light of this severe thrombosis, AT with vitamin K antagonist (warfarin) was started to get the Prothrombin Time/International Normalized Ratio (PT/INR) target value of 2.5 (Range: 2.00–3.00).

Indeed, 1 month after the beginning of AT with warfarin, the patient showed a major bleeding due to the occurrence of menorrhagia that required red blood cell (RBC) concentrates transfusion, even if the PT/INR value was in the range. The patient underwent multiple gynecological assessments but no specific pathologies were found. The menses-related anemia required recurrent RBC transfusion that was by one unit each month. This determined an important decrease in the quality of life.

In 2007, with the aim to reduce transfusion requirement, the patient underwent therapy with eculizumab. Since 2000 a major advance in the treatment of patients with PNH has been obtained with the introduction of eculizumab a monoclonal antibody that targets the C5 protein of the complement system. Eculizumab is able to reduce complement-mediated hemolysis, improving anemia and fatigue. Besides, eculizumab seems able to prevent thrombosis, probably, as an indirect effect of intravascular hemolysis reduction.

The principal common side effects include headache, tiredness, nausea, and muscle pain. Moreover, meningococcal infections are the most important adverse reactions experienced by patients receiving eculizumab due to the interference of eculizumab with complement cascade.

In our patient, eculizumab treatment obtained a significant both reduction in lactate dehydrogenase (Mean value of nine controls before eculizumab treatment = 1206.0 ± 104.1 IU/L versus the mean value of nine controls after the beginning of eculizumab treatment 259.8 ± 34.5 IU/L; Grouped *T*-Test, $P < 0.0001$) and unconjugated bilirubin (2.9 ± 0.54 versus 1.28 ± 0.35 mg/dL; Grouped *T*-Test, $P = 0.0001$) but the hemoglobin level did not change (8.2 ± 1.2 versus 7.4 ± 0.7 ; Grouped *T*-Test, $P =$ not significant) since the menses-related bleeding persisted. As to side effect due to the infusion of monoclonal antibody in our patient with PNH, we observed the occurrence of mild headache, fever and itch but these symptoms disappeared after the second infusion of monoclonal antibody and the treatment was generally well tolerated. Our patient received meningococcal vaccination before the beginning of eculizumab treatment.

The patient remained strongly transfusion dependent and for this reason the physicians used the bridging therapy with low-molecular-weight heparin (LMWH) to stop the menses-related bleeding.

On the 1st July 2014, the AT with warfarin was changed in order to reduce bleeding events associated with menses and the patient started a new AT with rivaroxaban (15 mg/day); the patient gave informed consensus to rivaroxaban therapy.

Rivaroxaban is an orally active direct Factor Xa inhibitor, which demonstrated to be effective in the prevention of venous thromboembolism after orthopedic surgery [4]. In addition, this drug has been shown to be an effective single-drug approach to the short-term and continued treatment of venous thrombosis with a major bleeding rate lower than that observed in standard therapy [5]. In addition to it, for people with nonvalvular atrial fibrillation rivaroxaban was noninferior to warfarin to prevent stroke or embolism, with significant reductions in intracranial hemorrhage and fatal bleeding. Rivaroxaban can be given in fixed doses and without routine anticoagulant

monitoring offering a less complex therapeutic regimen for patients.

The anticoagulant therapy in patients with PNH is particularly complex since these patients can develop the aplastic anemia and the consequent thrombocytopenia contributes to bleeding complication especially in patients under antithrombotic treatment. In addition, the pharmacological interference with other drugs administered in patients with PNH, complicates the management of antithrombotic therapy. Moreover, considering that the thrombotic complications represent the most common cause of death in patients affected by PNH, prophylaxis and treatment of thrombosis is mandatory in these patients.

For these reasons, since the direct oral anticoagulant drugs (rivaroxaban, apixaban, and dabigatran) demonstrated to be effective in the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism with a reduction in severe hemorrhagic complications respect to classical vitamin k antagonist, we decided to start rivaroxaban treatment in our patient with PNH, thrombotic complication, and severe bleeding related to treatment with vitamin K antagonist.

Table 1. Hematological and clinical parameters during 9 months of the anticoagulant treatment with warfarin and rivaroxaban in the patient with paroxysmal nocturnal hemoglobinuria.

	Warfarin	Rivaroxaban	<i>P</i> *
Hemoglobin (g/dL)	7.7 ± 0.4	8.5 ± 0.6	0.006
Hematocrit (%)	22.7 ± 2	26.1 ± 1.9	0.003
Platelets ($\times 10^3/\mu\text{L}$)	78.3 ± 7.7	76.5 ± 10.4	n. s.
Lactate dehydrogenase (IU/L)	327.0 ± 15.0	311.6 ± 11.5	n. s.
Bleeding Days	6.0 ± 0.9	3.7 ± 0.8	0.0008
Low-Molecular-Weight Heparin (Days of bridging therapy)	8.1 ± 0.7	1.7 ± 1	<0.0001
Red Blood Cell Units transfused	9	3	0.03
Diapers (number)	15.0 ± 0.6	10.2 ± 0.7	<0.0001
WHOQOL-BREF ¹			
Total (26 items)	67	76	
QOL rate (one item)	25	75	
Satisfaction (one item)	50	75	
Physical (seven items)	64	71	
Psychological (six items)	71	83	
Social relationships (three items)	83	83	
Environment (eight items)	69	72	

Data reported are the mean values and standard deviations of the evaluated parameters performed every month for 9 months during the treatment with warfarin and rivaroxaban.

n. s., not significant.

*Grouped *T*-Test.

¹WHOQOL-BREF: The World Health Organization Quality of Life.

We reported the hematological parameters, days of menses-related bleeding, diapers used to stop bleeding, days of bridging therapy with LMWH, and number of RBC units transfused during the 9 months before and after rivaroxaban therapy (Table 1). The quality of life (QOL) total score, and the QOL scores for each domain was determined according to WHOQOL-BREF questionnaire [6]. The WHOQOL is a quality of life evaluation performed by the WHOQOL Group with 15 international field centers, simultaneously, in order to develop a quality of life standardized assessment applicable cross-culturally.

The treatment with rivaroxaban led to a significant reduction in both intensity and frequency of bleeding events with a significant increase in hemoglobin levels and reduction in bridging therapy with LMWH. Moreover, there was a significant reduction in RBC units requirement. As for as the quality of life, the total WHOQOL score was higher after rivaroxaban therapy than before it, similarly scores for both the physical (seven items) and the psychological (six items) domains were higher after rivaroxaban therapy.

In our case rivaroxaban was administered in a patient affected by PNH and with moderate thrombocytopenia treated at the same time with the monoclonal antibody eculizumab. In conclusion, the anticoagulant treatment with rivaroxaban respect to warfarin was able to reduce bleeding complication, transfusion requirement and to ameliorate the quality of life in the patient with PNH.

However, further studies are needed to confirm the effectiveness and safety of rivaroxaban treatment in patients with PNH.

Conflict of Interest

None declared.

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