Am J Blood Res 2021;11(3):279-285
www.AJBlood.us /ISSN:2160-1992/AJBR0133849

Original Article

Evaluation of clinical characteristics of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab in Turkey: a multicenter retrospective analysis

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Received April 2, 2021; Accepted June 4, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare X-linked genetic disorder. On the contrary to its name, it is a multisystemic disease and various symptoms other than hemoglobinuria could be occurred. It could be life threatening especially because of thromboembolic events. In the last decade, a terminal complement inhibition with eculizumab approved with promising results for PNH patients. We conducted this study to evaluate the long term experience of eculizumab therapy from Turkey for the first time. Our cohort included 138 patients with PNH treated with eculizumab between January 2008 and December 2018 at 28 centers in Turkey. Laboratory and clinical findings at the time of diagnosis and after eculizumab therapy were recorded retrospectively. The median age was 39 (range 18-84) years and median granulocyte PNH clone size was 74% (range 3.06-99.84%) at the time of diagnosis. PNH with bone marrow failure syndrome was detected in 49 patients and the rest of 89 patients had classical PNH. Overall 45 patients (32.6%) had a history of any prior thrombotic event before eculizumab therapy and only 2 thrombotic events were reported during the study period. Most common symptoms are fatigue (75.3%), hemoglobinuria (18.1%), abdominal pain (15.2%) and dysphagia (7.9%). Although PNH is commonly related with coombs negativity, we detected coombs positivity in 2.17% of patients. Seven months after the therapy, increased hemoglobin level was seen and remarkably improvement of lactate dehydrogenase level during the treatment was occurred. In addition to previous studies, our real life data support that eculizumab is well tolerated with no serious adverse events and improves the PNH related findings.

Keywords: PNH, eculizumab, LDH, hemolysis, coombs test

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is known as a rare acquired pluripotent hematopoietic stem cell disorder with the prevalence of 16 cases per million [1]. X-linked somatic mutation of phosphatidylinositol glycan class-A (PIG-A) gene which encodes an enzyme that is essential for the first step of biosynthesis of the glycosylphosphatidylinositol (GPI) anchor proteins is responsible for PNH, resulting in a deficiency of all GPI-linked proteins [2, 3]. The absence of CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) which are GPI-linked complement regulatory proteins on the surface of platelets, monocytes, granulocytes and red blood cells (RBC) cause complement mediated intravascular hemolysis [4]. Classically, a triad of acquired intravascular hemolysis, thrombophilia and a range of degrees of bone marrow failure is defined for PNH but the symptoms could be variable from one patient to another with anemia, hemoglobinuria, thrombosis, dysphagia, abdominal pain, dyspnea, renal impairment and erectile dysfunction [5]. Detection of deficient GPI-anchored proteins (such as CD59, CD55) or the GPI-anchor (flaer) by flow cytometry is a main principle in diagnosis of PNH which is defined clearly in the literature [6].

Treatment options are limited and currently consist of humanized anti-complement C5 monoclonal antibodies, new complement inhibitors and allogeneic hematopoietic stem cell transplantation [5, 7, 8]. United States Food and Drug Administration (FDA) allows the use of the eculizumab in the treatment of patients with PNH and introduced into clinical practice in 2007 [9]. Eculizumab is a humanized monoclonal antibody (mAb) derived from the murine anti-human C5 mAb; it binds to the complement component 5 (C5) and inhibits its further cleavage into C5a and C5b, disabling the progression to the terminal effector complement membrane attack complex [10]. It reduces hemolysis, the risk of thrombosis and transfusion requirements, improves symptoms like dyspnea, weakness, renal function, and improves survival and quality of life [11]. Although some of clinical trials have emphasized that the eculizumab has efficacy and safety in treatment of patients with PNH disease, there is still need to support these data by results obtained from real practice for the patients especially who get the chance of eculizumab therapy lately. Herein, we aimed to retrospectively analyze data from patients with PNH treated with eculizumab in Turkey in terms of efficacy and follow-up. This study has been designated as retrospective, multi-center and included data of patients for the last 7 years. In this study, our aim to describe the patients' baseline clinical and demographic characteristics, PNH symptoms at the time of diagnosis, PNH related findings, and more importantly laboratory and clinical outcomes after eculizumab therapy.

Material and methods

Study design and patients

We retrospectively evaluated 138 patients with PNH treated with Eculizumab between January 2008 and December 2018 from 28 different medical centers in Turkey. The patients who are adult (aged ≥18 years) and have confirmed diagnosis of PNH and treated with eculizumab are included in this study. All diagnostic procedures were performed by flow cytometry investigating GPI linked antigens on red cells and neutrophils. Data were collected from patients' hospital records from the time of diagnosis with PNH, including the start of eculizumab treatment and if available, until the last dose of therapy. Demographic and clinical data were collected through a paper case report form including information on age, gender, date of PNH diagnosis, clone size (%) at diagnosis, symptoms at the time of diagnosis such as fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia, dysphagia or erectile dysfunction, presence of a history of preceding aplastic anemia (AA) or myelodysplasia (MDS) and hematopoietic stem cell transplantation and treatments. The occurrence of thrombosis including vein and arterial thrombosis at any site before and during eculizumab treatment was recorded from the patients file. Laboratory data included: hemoglobin values, platelets, leucocyte and neutrophil count, lactate dehydrogenase (LDH) levels, absolute reticulocyte count, total bilirubin level at the time of diagnosis which are defined as baseline and the most recent value within 6 months prior to the last visit which is December 2018. Patients with classic PNH and PNH in association with another specified bone marrow disorder (BMD such as AA and MDS) were also included in the study.

Table 1. Demographic and clinical characteristics of patients

	Value
Gender	
Female n (%)	69 (50%)
Male n (%)	69 (50%)
Median age, year (range)	39 (18-84)
PNH clone size at diagnosis	
Granulocyte clone size, %, median (range)	74 (3.06-99.84)
Monocyte, clone size, %, median (range)	75.06 (3.1-99.78)
Erythrocyte Type I clone size, %, median (range)	53 (0-99)
Erythrocyte Type II clone size, %, median (range)	2.15 (0-99.53)
Erythrocyte Type III clone size, %, median (range)	21.6 (0.10-97.8)
Erythrocyte Type II+III clone size, %, median (range)	28.4 (1.9-85.2)
Laboratory data, median (range)	
Hb, g/dL	8.6 (3.6-13)
WBC, ×10e9/L	4225 (800-27200)
ANC, ×10e9/L	2030 (180-8200)
PLT, ×10e9/L	80000 (8000-727000)
Reticulocytes (%)	3.5 (0.2-19)
LDH normal range n (%)	31 (22.4%)
LDH >X1. 5 of upper limit n (%)	107 (77.5%)

Abbreviations: ANC (Absolute neutrophil count), Hb (hemoglobin) LDH (lactate dehydrogenase).

The approval from ethical committee has been obtained before study from Ege University Medical Faculty Ethical Committee (nr: 15-9.1/8).

Eculizumab therapy

Eculizumab treatment characteristics (prescription date, posology, duration, and discontinuation) were collected from the patients' medical charts. Eculizumab was initiated at the approved dosing schedule of 600-mg intravenous infusions each week for the first 4 doses. One week after the last 4th dose of 600 mg, a maintenance dose of 900-mg was then started every 14 days (±2 days) indefinitely. All patients were vaccinated with a tetravalent meningococcal vaccine as indicated.

Statistical analysis

Categorical variables were described using subject number and absolute frequency. Continuous variables were described with mean, standard deviation, median, minimum and maximum, and total valid values. Different groups were compared using Student's *t* test or ANOVA or with Mann-Whitney or Kruskal-Wallis tests in cases of parametric or non-parametric quantitative variables. For qualitative variables, chi-squared or Fisher's exact test were used to compare different groups.

In all cases, statistical significance was defined as a *P* value of less than 0.05 and the SAS® (Statistical Analysis System, version 9.3) statistical software package was used.

Results

Patient characterics and features at diagnosis

This study included 138 patients from 28 different centers. Equal number of male and female patients (69 male and 69 female of 138 patients) were reviewed. The median age was 39 (range 18-84) years. PNH clone sizes at diagnosis in granulocytes, monocytes, and erythrocytes were, 74, 75, and 53% respectively, (**Table 1**). At baseline, mean hemoglobin (Hb) level was 8.75±2.13 gr/dL (range 3.6-15); Platelet (plt) level was 123×10^9/L (range 80000-727000). 107 (77.5%) patients had LDH levels higher than 1.5 times the upper limit of normal value. Higher GPI-deficient granulocyte and monocyte clone size correlated with higher LDH level (P=0.033 and 0.002; respectively) (**Figure 1**). Three of all patients had

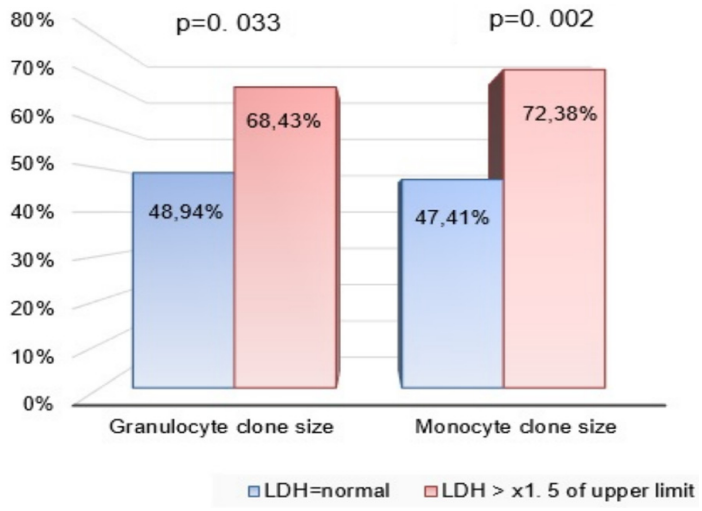

Figure 1. Corelation between LDH level and clone size *P-values* are shown in the graphs. Abbreviations: LDH (lactate dehydrogenase).

coombs positive hemolysis at baseline of diagnosis.

Fatigue is the most commonly reported PNH symptom at the time of diagnosis with 75.3% (104/138). The patients who presented with fatigue had significantly higher LDH level (P= 0.021). Pulmonary hypertension and abdominal pain were seen in 9.4% (13/138) and 15.2% (20/138), respectively. Other clinical manifestations were reported as hemoglobinuria 18.1% (25/138), hemorrhage 15.9% (22/138), hypertension 8.7% (12/138), dysphagia 7.97% (11/138). Organomegaly (hepatomegaly and/or splenomegaly) occured in 22.4% (31/138) of patients. A history of any prior thrombotic event before eculizumab therapy was reported in 45 patients (32.6%). All of these patients with thrombosis were also on therapeutic anticoagulation (aspirin, warfarin, heparin derivatives). Portal and hepatic vein thrombosis are common sites with 60% (27/45) of patients who experience thrombosis. Clone size, hb, plt, LDH levels at the time of diagnosis were not different between the patients with a history of thrombosis and no thrombosis.

Patients with PNH/BMD

Eighty nine (64.5%) patients had a diagnosis of classic PNH, and 49 patients had PNH/BMD (35.5%), including 31 PNH patients with concomitant AA or hypoplastic anemia (PNH/AA) and 18 patients with MDS (PNH/MDS). When we compare the Hb, plt and WBC levels between classic PNH and PNH/BMF groups, WBC levels were significantly lower in PNH/BMF group (mean WBC level is 4761×10^9/L compared to classic PNH and 3683×10^9/L for PNH/BMF P=0.043). However, there was not any differences between defined groups in terms of hb and plt levels.

Four of 31 patients with AA underwent allogeneic HSCT and 2 of 31 PNH/AA patients switched to immunsupressive therapy (cyclosporin A) due to no improvement with eculizumab treatment. One of PNH/MDS patients was treated with hypomethylating agent (decitabine) due to excess blast in bone marrow. All of PNH/AA patients had been treated with cyclosporine and/or ATG before eculizumab and 38.4% (53/138) patients had experienced steroid therapy before eculizumab. Two patients stopped eculizumab; one had PNH/MDS and required transfusions during the treatment and she refused to continue and the second one gave up eculizumab therapy with no reason.

Patient features after eculizumab therapy

The mean length of time between PNH diagnosis and starting eculizumab therapy was 2.54±4.59 years (range, 0-22 years). LDH was significantly decreased during treatment with eculizumab (P < 0.001). Mean Hb level improved significantly from 8.75±2.13 (range 3.6-15) prior to starting treatment with eculizumab to 10.83±2.46 gr/dL (range 4.7-15.8) (P < 0.001) while on treatment with eculizumab (**Table 2**). The median time for normalization of Hb (no requirement of transfusion) and LDH (defined as LDH became within normal range) level were 7 and 14.6 months, respectively. No difference was detected between platelet counts before or after eculizumab treatment, with the mean platelet count being 123×10^9/L and 143×10^9/L at the begining of eculizumab therapy and after eculizumab treatment at the last time of visit, respectively. Two thrombotic events occured while the patients were under eculizumab therapy; one is cutaneous thrombosis and the other one is deep vein thrombosis.

Survival and cause of death

Three patients (2.1%) died during follow-up. Two of them died due to PNH related complications;

Table 2. Laboratory findings of before and after eculizumab therapy

	Pretreatment	After eculizumab therapy	P
Hemoglobin level, mean, (range) g/dL	8.75±2.13 (3.6-15)	10.83±2.46 (4.7-15.8)	P < 0.001
MCV	95.53±10.46 (77.2-123)	99. 87±10.42 (70.9-130)	
Leukocyte count, mean, (range) $\times 10^9$/L	4.56±2.9 (0.8-27.2)	4.84±1.9 (1-11.2)	
Neutrophil count, mean, (range) $\times 10^9$/L	2.4±1.6 (0.18-8.2)	2.7±1.4 (0.22-8.4)	
Platelet count, mean, (range) $\times 10^9$/L	123±126 (8-727)	143±102 (7-704)	
LDH (range) IU/L	1234 (136-10314)	409 (146-4087)	P < 0.001
Total billirubin level, mean, (range)	1.59±1.3 (0.19-11.07)	1.63±1.2 (0.19-7.6)	

Abbreviations: MCV (mean corpuscular volume), LDH (lactate dehydrogenase).

56-year-old lady had classical PNH with multiple comorbidities (diabetes mellitus, arterial hypertension and obesity). She had severe pulmonary hypertension when started eculizumab therapy after 4 years from the diagnosis and died of pulmonary hypertension within the first year of eculizumab treatment. The other one who was 25-year-old female diagnosed with PNH when she was evaluated for cerebrovascular thrombosis and Budd-chiari syndrome and unfortunately she was died 2 months after starting eculizumab therapy. The third one, female patient was 60 years old and died due to a brain tumor.

No proven meningococcal infection was reported in our study group during the eculizumab therapy.

Discussion

Historically, a 35% mortality rate has been reported in patients with PNH at 5 years after PNH diagnosis, with patients dying due to PNH complications [1]. Nowadays, it can fairly be stated that eculizumab has transformed the life of patients with PNH [12]. To our review of the literature, this study is the first and largest study conducted in Turkey to evaluate patients with PNH under treatment with eculizumab therapy from many centers.

Patients are usually diagnosed with PNH in the third or fourth decade of their lives, consistent with previous studies as median age was 39 years in our study group [13]. Anemia and fatigue have been the most frequently reported signs and symptoms in our cohort confirming the literature [12, 14, 15]. At the time of diagnosis, median GPI-deficient granulocyte clone size was 74% and that is relatively high compared to 68% and 31.8% reported in International PNH Registry at different times [16, 17]. We demonstrated GPI-deficient granulocyte and monocyte clone size were correlated to high LDH level. However, it has been described that GPI-deficient granulocyte clone size has been directly related to high disease burden, thrombotic events and poor outcomes previously [18, 19], we could not describe the association of clone size and LDH level during the follow-up because of limitation of retrospective study.

Although, coombs negative hemolytic anemia is a common rule in PNH, one should consider that coombs positivity might be seen at baseline in small numbers of patients and we reported 2.17% of patients with coombs test positivity at baseline. Höchsmann et all reported the frequency of coombs positivity at baseline in PNH is 2.8% (1 of 35 patients) [20] and this positivity may disappear during eculizumab therapy as shown in previous studies [20, 21]. However, none of our patients had any coombs test positivity during the eculizumab therapy.

The main life-threatening complication is thromboembolism in PNH, and accounting between 40% to 67% of deaths related to PNH; the cause of thromboembolism is multifactorial and nearly half of patients with PNH would develop at least one thromboembolic event during the entire course of their disease [22]. Based on this information, the proportion of patients with a history of thromboembolic events in our study was 32.6%, which is quite similar with existing literature. One of three deaths in our study causes from thromboembolism. It seems resonable to use eculizumab and anticoagulation therapy concomitantly especially in patients who had experienced at least one thrombosis in order to prevent any further thrombotic events [12]. It was noteworthy that

only 2 new thrombotic events were recorded under the therapy with eculizumab. However, the cessation of anticoagulation in patients on eculizumab with no prior history of thrombosis is recommended due to the risk of bleeding complications of anticoagulation. All of the patients who had a prior thrombosis were on anticoagulation (warfarin or low molecule weight heparine or acetylsalicylic acid) and no bleeding events were reported in our study group.

Although an increase in plt levels in thrombocytopenic PNH patient as a direct result of eculizumab treatment has been reported previously in a study [23, 24], no increase in plt count was observed in our cohort after treatment with eculizumab as indicated in another study [12]. Kelly et all. reported that nearly two-thirds of patients do not need transfusion 12 months after starting eculizumab therapy [12] as well as, in TRIUMPH and SHEPHERD study declared that 51% of patients in clinical trials have been transfusion independent for 6 month and 12 mont period, respectively [7, 25]. However, we were not able to document transfusion requirements because of the limitation of our retrospective source. We demonstrated significantly increased Hb levels in 7 months after treatment with eculizumab with no transfusion requirement, by controlling the terminal complement activity and decreasing intravascular hemolysis. It is well known that the patients treated with eculizumab have an increased risk for developing meningococcal infections and vaccination and close monitoring are highly recommended to reduce meningococcal infection [26, 27]. However, we did not observed any infectional complications during the treatment.

In conclusion, the analysis of our relatively large and real life study demonstrated that eculizumab improves laboratory findings of PNH patients and PNH related complications with well tolerated and no serious adverse events by inhibiting terminal complement activation. Furthermore, results of our study confirm the benefits of eculizumab similar to previous well established clinical trials.

Acknowledgements

We thank to Alexion Ilac Tic. Sti., Istanbul, Turkey for statistical and editorial support and collecting the data.

Disclosure of conflict of interest

None.

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