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Low-dose prednisolone in patients with paroxysmal nocturnal hemoglobinuria and inadequate response to eculizumab

TO THE EDITOR: Corticosteroids have been widely used in patients with paroxysmal nocturnal hemoglobinuria (PNH), based on the notion that administration may ameliorate hemolysis. However, there is no strong evidence of clinical benefit in the inhibition of complement-mediated hemolysis associated with corticosteroids. The short-term use of prednisolone (Pd) may be beneficial in some situations, but long-term use is generally not recommended because of concerns regarding complications [1, 2]. Eculizumab is a humanized monoclonal antibody that blocks terminal complement by binding to C5. This antibody is a standard therapeutic modality for PNH and has altered the natural history of the disease [3, 4]. A subpopulation of patients placed on eculizumab, however, still require red blood cell (RBC) transfusion [5], and standard salvage therapies for these patients have yet to be determined. We retrospectively analyzed the therapeutic effects of low-dose Pd in patients with PNH who show inadequate responses to eculizumab treatment.

Seven patients were treated with eculizumab between February 2012 and April 2016 at Chungnam National University Hospital. All patients were men and the median duration of the disease was 19.1 years (range, 5.1–24.5 yr). At the time of analysis, all patients were still taking eculizumab, and the median duration of eculizumab treatment was 36.3 months (range, 6.9–39.1 mo). After 6 months of eculizumab treatment, all patients showed improvement of anemia and hemolysis. Four (57.1%) patients showed an optimal response, one (14.2%) showed a major response and 2 (28.5%) showed a partial response, according to a modification of a previously reported stratification [6, 7]. During the first 12 months of eculizumab treatment, 4 patients no longer required RBC transfusion; however, 3 patients continued to require transfusion, although the transfusion requirements were reduced. Low-dose Pd (5 mg/day) was additionally administered to these 3 patients.

Of the 3 patients requiring transfusion, patient 1 was previously diagnosed with aplastic anemia (AA) and patient 2 had concurrent chronic kidney disease. At the time of initiation of low-dose Pd therapy, the hemoglobin (Hb) levels were 8.9, 8.9, and 8.3 g/dL, respectively, and the lactate dehydrogenase (LDH) levels were 418, 655, and 1,069 IU/L, respectively, in these 3 patients. The direct Coombs test was positive in all 3 patients, and the CH50 levels after 6 months of eculizumab treatment were 4.4 U/mL, <2.0 U/mL, and 20.9 U/mL, respectively (<2.0 U/mL, 10.3 U/mL, 5.4 U/mL, and 5.2 U/mL, respectively, in patients with optimal response). Low-dose Pd (5 mg/day) was administered to these 3 patients, and the Hb levels gradually increased over 12 months. The LDH levels were maintained or modestly decreased. Patient 3 experienced 2 infection episodes (upper respiratory infection with fever and tenosynovitis of the right wrist). Decreases in the Hb level and increases in the LDH level were observed during each event. During the 12 months of additional low-dose Pd therapy, the requirements for RBC transfusion in these 3 patients were modestly decreased. While a total of 26 packs of RBC transfusion were needed before Pd therapy, only 10 packs were needed after 12 months, indicating that low-dose Pd induced a favorable effect of about 60% reduction in RBC transfusion requirements (Table 1). There were no severe adverse events related to low-dose Pd therapy. Patient 1 experienced a mild upper respiratory infection after 1 month of Pd, and this spontaneously resolved. As mentioned above, patient 3 experienced 2 mild infections that were manageable with oral antibiotics.

In the present analysis, 3 of 7 patients required RBC transfusion, even after long-term eculizumab treatment. Inadequate hematologic benefit in some patients may be related to complement protein C3. Because eculizumab inhibits the terminal complement cascade and has no effect on proximal components, C3 and its fragments accumulate on RBCs in PNH patients. This phenomenon leads to destruction of RBCs in the spleen and liver. As a result, extravascular hemolysis is increased and might result in dependence on RBC transfusion [7]. Considering such a mecha-

Table 1. Characteristics of patients with inadequate response to eculizumab.

	Patient No.		
	1	2	3
Age (yr)[a]	46	74	70
Prior hematologic disorder	Aplastic anemia	None	None
Concurrent illness	Chronic mucositis	CKD	Variant angina CI
Duration of eculizumab treatment (mo)	34.4	22.5	15.4
Laboratory values[a]			
Hemoglobin (g/dL)	8.9	8.9	8.3
Corrected reticulocyte (%)	8.3	9.0	2.2
RPI	4.1	4.5	1.1
LDH (IU/L)	418	655	1,069
CH50 (U/mL)[b]	4.4	<2	20.9
Serum ferritin (ng/mL)[c]	1,568	2,845	2,628
Serum erythropoietin (mIU/mL)[d]	NT	56.8	NT
PNH clonal size (%)[a, e]			
Granulocyte	79.1/16.6	79.8/15.0	77.8/15.8
RBC	6.9/8.6	7.5/49.3	5.7/7.2
Coombs test			
Direct	Positive	Positive	Positive
Indirect	Negative	Negative	Negative
Laboratory values after 12 mo of Pd			
Hemoglobin (g/dL)	10.8	9.4	10.5
LDH (IU/L)	399	513	821
CH50 (U/mL)	3.9	<2	6.7
Units of RBC transfusion			
In the 12 mo before Pd	6	2	18
In the 12 mo after Pd	2	0	8

[a]At the time additional prednisolone was started. [b]Reference range: 23.0–46.0 U/mL. [c]Reference range: 50–200 ng/mL. [d]Reference range: 3.7–31.5 mIU/mL. [e]CD55-negative cells/CD59-negative cells.
Abbreviations: CI, cerebral infarction; CKD, chronic kidney disease; LDH, lactate dehydrogenase; NT, not tested; Pd, low-dose prednisolone treatment (5 mg/day); RPI, red cell production index.

nism, corticosteroids and splenectomy may be a treatment option for patients demonstrating enhanced extravascular hemolysis following eculizumab therapy [7, 8]. Bone marrow function affects erythropoiesis and thus the outcome of eculizumab treatment. A red cell production index (RPI) >2.5 in anemia suggests sufficient erythropoiesis. In a previous report, patients with low RPI did not respond well to eculizumab [6]. Interestingly, Peffault de Latour *et al.* reported that CH50 activity is a simple biomarker related to intravascular hemolysis and circulating free eculizumab levels. In this study, low CH50 activity (CH50 ≤10% of normal) was significantly associated with low LDH levels. Furthermore, low circulating free eculizumab correlated with CH50 >10% and the need for transfusions [9].

In the present analysis, patient 3 showed a low (1.1) RPI and a very high (1,069 IU/L) LDH level at the time of initiation of Pd therapy. Furthermore, the patient showed a slightly higher level of CH50 compared with other patients. Considering these findings, this patient might have had components of both ineffective erythropoiesis and extravascular hemolysis. After 12 months of Pd therapy, the level of CH50 decreased from 20.9 to 6.7 U/mL, and both the need for RBC transfusion and the LDH level also decreased. Patient No. 1 had AA prior to the diagnosis of PNH, and thus defective bone marrow function might have led, at least in part, to the inadequate response to eculizumab. Patient 2 showed a serum erythropoietin (EPO) level of 56.8 mIU/mL (reference range, 3.7–31.5 mIU/mL), just above the normal range, suggesting the presence of an inadequate EPO response to anemia since EPO levels tend to be very high in PNH patients [10]. Taken together, factors other than enhanced extravascular hemolysis appeared to have a role in these 3 patients.

These results indicates that low-dose Pd might be helpful in patients who continue to be dependent on RBC transfusion despite long-term eculizumab, although its mechanisms of action remain unclear. There has been little information on the use of corticosteroid therapy to control extravascular hemolysis occurring after eculizumab treatment. Furthermore, the results of the small series conducted to date have not been consistent. Berzuini *et al.* [11] reported that prednisolone at an initial dose of 75 mg

per day led to satisfactory results in one patient. In contrast, Risitano *et al.* [12] reported unsatisfactory results in 14 patients. Notably, long-term use of high-dose corticosteroid is always accompanied by concerns related to its well-known complications. That is the reason why we used low-dose Pd in this study. The results of the current study suggest that low-dose Pd might be helpful in patients who remain dependent on RBC transfusion despite long-term eculizumab treatment.

In summary, we suggest that low-dose Pd reduces red cell transfusion requirements in some PNH patients with inadequate response to eculizumab. However, the long-term efficacy and adverse effects of the low-dose Pd treatment need to be determined.

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