High efficacy of eculizumab treatment for fulminant hemolytic anemia in primary cold agglutinin disease

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LETTER

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Running title: High efficacy of eculizumab for cold agglutinin disease

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Dear Editor:

Cold agglutinin disease (CAD) is characterized by immunoglobulin M (IgM)-mediated hemagglutination in cold conditions and complement activation leading to extra- and intravascular hemolysis [1, 2]. Under conditions like infection, complement activation persists and intravascular hemolysis occurs by the formation of membrane attack complex (MAC). Therefore, eculizumab, an anti-C5 antibody is expected to be effective in suppressing hemolytic attacks in CAD.

Herein, we report a case of fulminant type primary CAD treated with eculizumab.

A 39-year-old man was diagnosed with bacterial pneumonia by a family doctor and treated with antibiotics. Five days after the diagnosis, he was referred to our hospital on account of hemoglobinuria, malaise, hemolytic anemia, and acute kidney injury. He had severe anemia (Hb 5.2 g/dL), increased indirect bilirubin (3.6 mg/dL) and lactate dehydrogenase (LDH, 4347 IU/L) levels, decreased haptoglobin (<10 mg/dL) concentration, renal dysfunction (serum creatinine 2.99 mg/dL), and hemoglobinuria. Due to severe hemolysis and clotting of blood, red blood cell and reticulocyte counts could not accurately be assessed. In a direct Coombs test, only complement Coombs test yielded positive results. Paroxysmal nocturnal hemoglobinuria (PNH)-type cells were not detected. Serum cold agglutinin titers were markedly elevated (> 8192 folds).

Based on the diagnosis of fulminant hemolytic crisis in CAD caused by bacterial pneumonia, we initiated heat retention, blood transfusion, and steroid administration, but the

hemolysis did not improve. Due to the worsening renal function, further increasing LDH level (>7000 IU/L), and rapidly deteriorating general condition in a few days, the decision was made to commence eculizumab at 900 mg once a week (Fig. 1). After the initial administration, rapid reduction in the LDH level and improvement in hemolysis were observed, and most of the laboratory data were normalized including serum creatinine levels one month after initiation of eculizumab. Although there were no decreases in agglutinin titers, eculizumab treatment was terminated after the fourth shot because of the stabilization of hemolysis and the marked improvement in general condition. Since then, the observation period has been more than ten months; cold agglutinin titers were decreased, and hemolysis has not recurred.

Recently, the effectiveness of combination therapy using rituximab and bendamustine for the treatment of CAD has been reported [3]. However, a period of several months is required before the effect is noticeable, and immediate changes cannot be expected. Eculizumab is an antibody that specifically binds to the C5 complement protein and prevents intravascular hemolysis [4-6]. Theoretically, eculizumab is also expected to be effective for the treatment of hemolytic attacks in CAD. Although there are no clinical trials, its potential efficacy has been suggested in some case reports [7-9]. In the current case, complement activation triggered by pneumonia led to fulminant hemolytic anemia. Because renal failure and hemolysis progressed rapidly in our case, eculizumab was administered instead of rituximab. Suppression of complement activity by eculizumab was clear, which resulted in the reversal of the patient's critical condition and rapid clinical remission. It is likely that hemolytic attacks in CAD are a good target of eculizumab, as anticipated.

Figure Legend

Fig.1 Effect of eculizumab in a patient with fulminant hemolytic anemia of primary cold agglutinin disease. PSL, prednisolone; LDH, lactate dehydrogenase; RBC, red blood cell; sCre, serum creatinine; ∗, Cold aggulutinin titers were saturated over 8192-fold.

Notes

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

Written informed consent was obtained from the patient.

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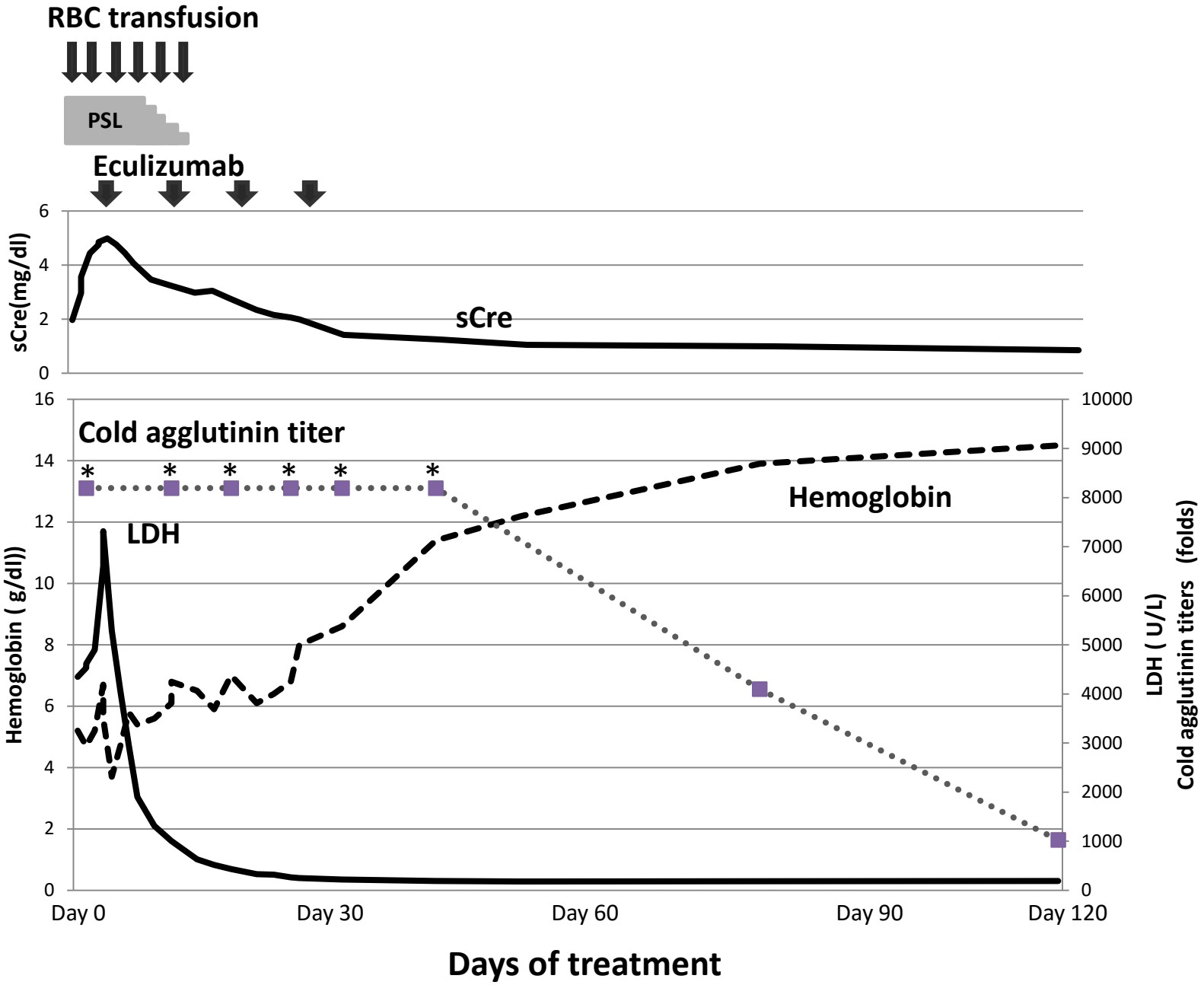
Figure 1


RBC transfusion
PSL
Eculizumab
sCre(mg/dl)
sCre
Cold agglutinin titer
Hemoglobin
LDH
Hemoglobin (g/dl))
LDH (U/L)
Cold agglutinin titers (folds)
Day 0
Day 30
Day 60
Day 90
Day 120
Days of treatment