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Efficacy and safety of eculizumab in adult patients with atypical hemolytic uremic syndrome: A single center experience from Turkey

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ABSTRACT

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy, which develops as a result of defective activity of the alternative complement pathway and excessive complement activation due to genetic or acquired factors. No satisfactory responses were obtained by plasmapheresis, corticosteroids and fresh frozen plasma (FFP) transfusion. However, promising results are obtained in recent years by eculuzimab treatment, which inhibits C5 activation.
Objective: To evaluate the efficacy, safety and effect of eculizumab on quality of life of adult aHUS patients followed in our center.
Materials and Methods: Seven patients who received eculizumab treatment in single center between the years 2012 and 2016 due to aHUS diagnosis were retrospectively evaluated. Patients were diagnosed with aHUS in accordance with certain criteria, after eliminating all the other factors caused by thrombotic microangiopathy. Complement gene mutations were completed in six patients. All patients received eculizumab as recommended (900 mg/per two weeks) following plasmapheresis, FFP, corticosteroid and hemodialysis (HD) treatments.
Results: Four out of seven patients were men and three were women; average patient age was 51.1 (26–69) years and average duration of disease was 25.3 (2–45) months. Average period from the initial complaints of the patients up to aHUS diagnosis was 4.2 (2–13) months. Tests were implemented on six patients for complement gene mutations, and complement factor H (CFH) homozygous mutation was identified in three patients. Complete remission was observed in four patients and partial remission in two patients after eculizumab; however, one patient died. Plasmapheresis was discontinued in patients with complete remission, whereas two patients with partial remission continued the HD program, despite normalization in hematologic parameters. Significant improvement was observed in post-treatment quality of life in all six patients who currently continue eculuzimab treatment. No transfusion reaction and/or no serious infections were observed in any of the patients, while URTI (upper respiratory tract infection) was observed in one patient.
Discussion: Eculizumab is an effective and safety treatment option in adult aHUS patients. Early diagnosis and initializing eculizumab therapy at an early stage may decrease mortality and morbidity in patients with aHUS. New studies are required on this topic.

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1. Introduction

Atypical hemolytic uremic syndrome (aHUS) is a disease which develops as a result of uncontrolled complement dysregulation, and may result in leukocyte and thrombocyte activation, thrombotic microangiopathy and multiple organ injury [1]. Mutations are detected (e.g.. complement factor H (CFH), factor I (CFI), membrane cofactor protein (MCP), factor B (CFB), thrombomodulin (THBD), C3) in genes encoding complement proteins in 60–70% of the patients [2]. Yet complement factor H antibodies exist in a small part of patients. Microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure are typical findings of the disease [3]. Different than typical HUS, concomitance of Shiga-toxin synthesizing *Escherichia coli* (STEC) and/or *Streptococcus pneumoniae* does not occur in the cases with aHUS [4]. Thrombotic thrombocytopenic purpura (TTP) must be considered in differential diagnosis, with decrease in the activity and the level of ADAMTS13 [5]. aHUS is a rare disease, with a high rate of morbidity and mortality [6]. In the untreated cases, permanent renal dysfunction (RD), high recurrence rate and high mortality are observed. The studies revealed that final stage RD or death may occur in 30–40% of the patients, when the first clinical symptoms appear [7]. Again, it results with irreversible renal damage, end-stage renal disease (ESRD) or death in 65% of the patients within 1 year after diagnosis, despite plasmapheresis therapy. Eculizumab, which is a recombinant humanized anti-C5 monoclonal antibody, has opened a new era in aHUS therapy [8]. It inhibits membrane attack complex (MAC) formation and overactivation of alternative complement pathway by blocking the activation of terminal complement cascade. Efficacy of eculizumab was demonstrated first in paroxysmal nocturnal hemoglobinuria (PNH) then in aHUS cases [9]. It has been emphasized in a few publications that long term treatment was necessary in order to prevent recurrence; even lifelong therapy was necessary according to the European Medicines Agency (EMA) [10].

The aim of this study was to retrospectively evaluate the efficacy, safety and effects on quality of life of eculizumab in adult aHUS patients' follow-up in our center.

2. Materials and methods

Seven aHUS patients who were followed between June 2012and August 2016 in our Hematology Clinic were retrospectively evaluated. aHUS diagnosis was considered in presence of the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and acute renal failure. Renal biopsy for histopathological verification was implemented in case of necessity. ADAMTS13 activity and level were checked in all patients and TTP was eliminated in case of 10% increase. Also, other factors that may cause secondary MAHA and thrombocytopenia (DIC, systemic autoimmune disease, lupus anticoagulant, metastatic cancer, Shiga toxin) were eliminated. Mutation of the complement proteins encoding genes (complement factor H (CFH), complement factor I (CFI), complement factor B (CFB), C3, C5, CFH antibodies) were checked by PCR method. Laboratory tests (total blood count, peripheral smear, LDH, haptoglobin, liver function tests, renal function tests (RFT), C-reactive protein, erythrocyte sedimentation rate, C3, C4, C4, ANA, ANCA, dsDNA) of all the patients were performed. All patients received plasmapheresis, corticosteroid, and HD treatments. Seven patients who failed to respond to these treatments were given eculizumab loading dose of 900 mg i.v. per week for 4 weeks and 1200 mg i.v. per two weeks. Before treatment, all patients were injected meningococcal vaccine and the informed consents were obtained. The conditions with normalized hematological parameters (thrombocyte count, LDH and haptoglobin levels, absence of schistocytes) and renal function tests were accepted as full clinical remission, whereas any of them without normalization as partial remission. The quality of life of the patients was evaluated before and after treatment, by means of health related quality of life (HRQL) forms (the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) and the 36-Item Short Form Health Survey (SF-36) questionnaires) [11,12]. Ethics committee approval was obtained and informed consent forms were taken from all patients.

3. Results

Approximately 4 years of monitoring data of seven aHUS patients and their responses to eculizumab treatment were retrospectively evaluated. Four of the seven patients were men and three were women; average patient age was 51.1 (26–69) years and average duration of disease was 25.3 (2–45) months. Average time period from the initial complaints of the patients to their aHUS diagnosis was 4.2 (2–13) months. Demographical, clinical (Table 1) and laboratory data (Table 2), presenting complaints at admission and treatment strategies of the patients were recorded. One patient has pulmo-renal syndrome and was diagnosed as Wegener granulomatosis coexisting with aHUS. Five patients were implemented renal biopsy; some changes were observed suggesting thrombotic microangiopathy. As the result of molecular analysis, we determined CFH homozygous mutation in 3 patients (case 1,2,3), CFI homozygous mutation in 4 patients (case 1,3,6,7), and C5 homozygous mutation in 2 patients (case 1,7). Besides, we determined CFH heterozygous mutation in 3 patients (case 5,6,7), CFB heterozygous mutation in 2 patients (case 1,4), and C3 heterozygous mutation in 1 patient (case 3) (Table 3). TTP diagnosis was eliminated by plasma ADAMTS13 level and activity evaluation. On laboratory analysis during admission, renal dysfunction was also present in addition to MAHA, thrombocytopenia, high levels of LDH and low levels of haptoglobin. All patients received plasmapheresis, corticosteroid and HD treatments prior to eculizumab administration. All patients received plasmapheresis treatments of average 28 sessions (range 7–67) before eculizumab, but no improvement was observed in hematological and renal parameters. Except, slightly higher level of thrombocyte and lower level of LDH were observed temporarily in patient #3 and patient #5, respectively. Hematological parameters of all patients displayed a progressive recovery in the 12th and 16th weeks following the initial infusion of eculizumab. Four patients were observed to normalize completely in renal function tests, while dialysis dependence remained in 2 patients