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Unexpected Beneficial Response to Etanercept Therapy in a Hemodialysis Patient with Ankylosing Spondylitis

Ankilozan Spondilitli Bir Hemodiyaliz Hastasında Etanersept Tedavisine Beklenmeyen Olumlu Yanıt

ABSTRACT

Erythropoietin (EPO) deficiency is the main cause of renal anemia. However, chronic inflammation may be one of the important causes for EPO resistance in patients with renal anemia. Inhibition of erythropoiesis by cytokines such as tumour necrosis factor alpha (TNF-α) may play an important role. Etanercept, a recombinant dimeric fusion protein consisting of a TNF-α receptor ligand-binding region linked to the Fc portion of human IgG, is approved for use in the treatment of ankylosing spondylitis. Here, we present an end-stage renal failure patient with ankylosing spondylitis treated by etanercept and observed no need for erythropoietin during etanercept treatment.

KEY WORDS: Renal anemia, Tumour necrosis factor-alpha, Etanercept, Erythropoietin

ÖZ

Eritropoietin (EPO) eksikliği renal aneminin başlıca nedenidir. Bununla birlikte, kronik inflamasyon renal anemili hastalarda EPO tedavisine karşı dirence yol açabilir. Tümör nekrozis faktör alfa (TNF-α) gibi sitokinlerle eritropoezin inhibisyonu önemli rol oynayabilir. Bir TNF-α blokörü olan etanersept ankilozan spondilit tedavisinde kullanılmaktadır. Biz bu raporda ankilozan spondilitli, etanersept ile tedavi edilen ve bu tedavi süresince eritropoietin tedavisine gereksinim duymayan bir son dönem böbrek yetmezlikli hastayı sunuyoruz.

ANAHTAR SÖZCÜKLER: Renal anemi, Tümör nekrozis faktör-alfa, Etanersept, Eritropoietin

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INTRODUCTION

Inflammation is implicated in the pathogenesis of EPO resistance in patients with end-stage renal disease. Inhibition of erythropoiesis by cytokines such as tumour necrosis factor alpha (TNF-a) may play an important role (1). Well-responders to erythropoietin treatment generally have normal expression of pro-inflammatory cytokines. Patients who are not well-responders, however, express abnormally elevated levels of these cytokines such as tumour necrosis factor-alpha (TNF-alpha), which is also known to hamper erythropoiesis (2).

Ankylosing spondylitis (AS) is a common inflammatory joint disorder affecting the axial skeleton, peripheral large joints, certain entheses (attachments of tendons and ligaments to bone) and extra-articular sites such as the anterior uvea.

Etanercept is a recombinant dimeric fusion protein consisting of a tumor necrosis factor-alpha receptor ligand-binding region linked to the Fc portion of human IgG. It is approved for use in the treatment of rheumatoid arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis, psoriasis, and psoriatic arthritis (3). Extensive use of the soluble receptor fusion protein etanercept in patients with rheumatoid arthritis has shown a good safety profile and clinical benefit including increases in hemoglobin levels. It has been shown that the pharmacokinetics of etanercept in patients with chronic renal failure on hemodialysis (HD) is similar to patients with normal renal function. It was

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found, therefore, feasible to administer etanercept to HD patients without adjusting the dose (4). Thus, based on these data, we treated an end-stage renal failure patient with ankylosing spondylitis by etanercept and observed no need erythropoietin during etanercept treatment.

CASE REPORT

Our patient was a 43-year-old male. When he was 21 years old, he has been diagnosed with ankylosing spondylitis. He received many kinds of non-steroidal anti-inflammatory drugs (NSAID) thereafter. In February 2004, he was diagnosed with chronic renal failure and four months later he was started on hemodialysis. His kidneys were small and hyperechogenic on ultrasound. So he was accepted to have analgesic nephropathy. In September 2007, his symptoms relapsed under NSAID treatment. He had lower back pain, especially at nights. He also had morning stiffness about two hours, arthralgias in his knees and ankles. He was examined by a rheumatologist (MS) and his AS was accepted as active (Bath Ankylosing Spondylitis Disease Activity Index= BASDAI was 6.2). His C-reactive protein (CRP) was 43 mg/L, his albumin was 3.2 g/dL and hemoglobin was 10.0 g/dL under EPO alpha 150 IU/kg/week. Before etanercept treatment started, his serum iron concentration was 84 mg/dL, total iron binding capacity was 132 mcg/dL, ferritin was 965 ng/mL. He did not have any other obvious cause of EPO resistance. Then he started taking etanercept subcutaneous 25 mg twice a week. One month later he was quite good symptomatically (BASDAI 3.0) and his hemoglobin was 13.8 g/dL. Therefore EPO was stopped. After this he never needed EPO during one year of etanercept treatment. His hemoglobin was at least 13 g/dL or more (Figure 1). His CRP decreased to 4.3 mg/L at six months but then increased slightly again. Also his serum albumin level increased slowly from 3.2 g/dL baseline to 4.2 g /dL at twelve month (Figure 2). He did not experience any side effect due to etanercept.

DISCUSSION

In this case report, we presented a maintenance HD patient with AS who did not need EPO after anti-TNF-α (etanercept) treatment of one month.

Chronic inflammation may be one of the important factors for EPO resistance in patients with renal anemia. Well-responders to erythropoietin treatment generally have normal expression of pro-inflammatory cytokines. Patients who are not well-responders, however, express abnormally increased levels of these pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF-alpha), which is also known to hamper erythropoiesis (2). Our patient did not have EPO resistance. He had acceptable hemoglobin levels under EPO treatment. Nonetheless, he did not need EPO after etanercept treatment started. AS is a common inflammatory joint disorder. The first large, multicenter trial to indicate the efficacy of etanercept in patients with AS showed that etanercept was superior to placebo, significant improvements being apparent as soon as 2-weeks and ASAS (ASsessment in Ankylosing spondylitis) 20 responses being observed in 57% of etanercept treated patients as compared to 22% of those on placebo in 24-week (5).

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In a non-inflamed patients group, etanercept (25 mg) was administered subcutaneously twice a week immediately after dialysis for 13-16 weeks. Albumin and CRP levels did not change during the study period. However, four patients had increases in hemoglobin by 1–1.5 g/dL (3 patients) or decreased transfusion requirements (1 patient). (4). Thus, it can be said that etanercept treatment deserves to be evaluated in HD patients with inflammation. On the other hand, these drugs are not free from adverse events. Especially reactivation of

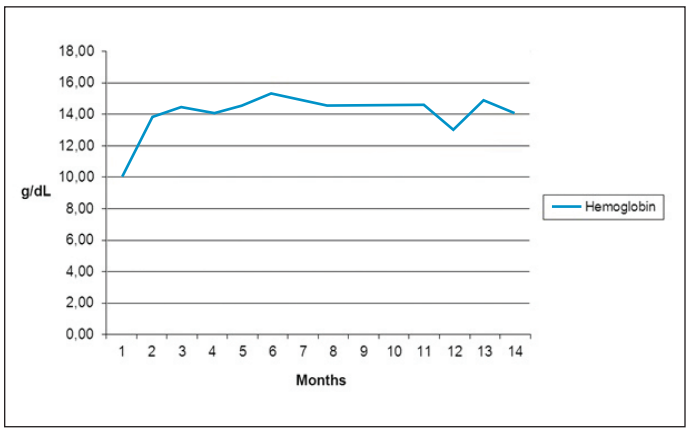

Figure 1: *The patient's hemoglobin levels during etanercept treatment without erythropoietin.*

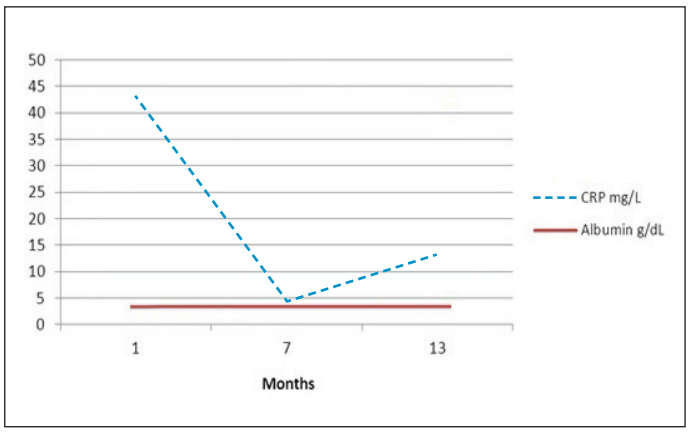

Figure 2: *The patient's C-reactive protein (CRP) and albumin levels after etanercept treatment.*

latent tuberculosis is an important problem. Detection of latent tuberculosis may be a daunting task in HD patients who are relatively immunocompromised and most of the time anergic. Moreover the cost of anti-TNF therapies may not be warrant their routine use in anemia management in HD patients.

CFU-E colony formation is inhibited by soluble factors present in the sera of uremic patients with or without inflammatory disease. These soluble factors stimulate the production of IFN-γ and TNF-α, which directly inhibit erythropoiesis at a local level in the bone marrow (6). Yuen et al tested the hypothesis that augmentation of uremia clearance by nocturnal hemodialysis (NHD) results in a reduction of proinflammatory cytokine levels, thereby enhancing EPO responsiveness. EPO requirement was significantly lower in the NHD cohort [90.5 +/- 22.1 U/kg/week (NHD) vs. 167.2 +/- 25.4 U/kg/week (HD), p = 0.04]. Augmentation of uremic clearance by NHD improves EPO responsiveness in end-stage renal disease. A possible mechanism for this improvement is through better control of inflammation, as manifested by lowering of plasma IL-6 levels (1).

In addition, the phosphodiesterase inhibitör, pentoxifylline has been used to deal with the problem of chronic inflammation in patients with renal anemia. Pentoxifylline can downgrade T-cell expression of TNF-α and, can also regenerate the response to EPO and ameliorate hemoglobin levels (2). Blockade of TNF-α significantly increases hemopoietic colony formation from MDS marrow in vitro (7).

In the light of this putative role of pro-inflammatory cytokines, we think that anti-cytokine agents deserve to be investigated for their roles on anemia treatment of patients with end stage renal failure, at least in patients with inflammation of undetermined origin.

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