Do Biological Agents be Useful in the Treatment of Amyloidosis Related FMF?

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Abstract

Familial Mediterranean Fever (FMF), is an autosomal recessive disease associated with mutations in the MEFV gene. A 13-year-old female patient was admitted to hospital with vomiting and increasing abdominal pain. Her physical examination showed generalized edema. Laboratory examination revealed proteinuria, hypoalbuminemia, hypercholesterolemia. Renal biopsy showed AA-type amyloidosis and homozygous M694V mutation was detected. Colchicine was started. However, heavy proteinuria persisted despite colchicine treatment and infliximab treatment was administered. Since patient developed edema, proteinuria, hypoalbuminemia, after tenth dose of infliximab therapy, resistance was considered and treatment was discontinued. Anakinra therapy was initiated. Anakinra treatment was stopped after six months due to the patient was rejected any more using that treatment and end stage renal failure was developed. Although biological agents may be useful in the treatment of amyloidosis caused by FMF, the progression of illness despite treatment with these agents has been reported in many patients.

Key words: Familial mediterranean fever, amyloidosis, biological agents

Introduction

Familial Mediterranean Fever (FMF), is an autosomal recessive disease associated with mutations in the MEFV gene, affecting mostly Mediterranean populations (Armenians, Arabs, Jewsand, Turks). It is characterized by self-limited recurrent attacks of fever and serositis [1]. Since 1972, colchicine is the standard treatment in FMF patients and majority of the patients achieve complete or partial remission together with colchicine therapy [2,3]. The most serious complication of FMF is AA-type amyloidosis, which can result in end-stage renal disease (ESRD) [4]. There is limited data on the treatment of amyloidosis caused by FMF in children.
Herein, we present a patient who progressed to ESRD with FMF related amyloidosis despite being used biological agents.

**Case Report**

A 13-year-old female patient with a history of recurrent abdominal pain, and fever periods for eight years, was admitted to hospital with edema, vomiting and increasing abdominal pain in the last five days. Her blood pressure was 100/60 mm/Hg. Height was height:143 cm (<3p) and body weight was 33 kg (<3 p). Physical examination revealed that generalized edema. Laboratory examination revealed proteinuria (330mg/m2/h), hypoalbuminemia (<1g/dl), and hypercholesterolemia. Serum complement levels were normal and ANA was negative. According to those findings such as older presentation age and normal levels of the complements (C3 and C4), FSGS or secondary causes of nephrotic syndrome were thought and kidney biopsy was performed. Renal biopsy showed AA-type amyloidosis (Figure 1) and homozygous M694V mutation was detected. After detected amyloidosis, her medical history was detailed and we learnt that she had recurrent fever attacks and abdominal pain for about ten years. Her parents didn’t have complaint such as recurrent fever attacks, joint swelling and abdominal pain.

Two mg per day colchicine was started for treatment in addition to dipyridamole, ACE inhibitors and atorvastatin. However, growth retardation, generalized edema and heavy proteinuria persisted despite after one year of colchicine treatment and a TNF-alpha antagonist infliximab treatment was administered (3 mg/kg at time 0, 2, 6 weeks, then every 8 weeks). Following six dose of infliximab therapy partially improvement was observed. Serum total protein was increased to 5.2 g/dl, and albumin 1.9 g/dl. Patient received a total of 10 doses of infliximab therapy. But generalized edema, massive proteinuria, and hypoalbuminemia (<1 g/dl) developed after tenth dose of infliximab therapy, resistance was considered and treatment was discontinued. After then, interleukin receptor antagonist (anakinra) therapy was initiated (1 mg/kg/day). During anakinra treatment, proteinuria was decreased and acute phase reactants improved (Graphic 1, 2). Anakinra treatment was stopped after six months due to non-response, and serum creatinine began to increase. ESRD was developed after one year and peritoneal dialysis was started. Two years later, she received kidney transplant from her mother. After successful renal transplantation she is on two mg/day of colchicine and there is no proteinuria and acute phase reactants were normal.

**Discussion**

The major complication of FMF is the development of secondary (AA) amyloidosis. Amyloidosis is primarily manifests as a nephropathy characterized by proteinuria, nephrotic syndrome, uremia and finally ESRD necessitating chronic dialysis and renal transplantation [4]. Daily colchicine prevents
both attack recurrence and amyloidosis in most patients affected with FMF and remains so far the first-line treatment of FMF [2]. Colchicine also has benefits of treatment of the patients with amyloidosis due to FMF Oner et al have followed 38 children with amyloidosis secondary to FMF mean 30.5 months. They used colchicine 1.5-2 mg/day. They reported that proteinuria improved in 13 patients, it remained stable in 5 patients and in one patient it deteriorated. These patients were all compliant to treatment. In contrast, none of 14 non-compliant patients improved. They thought that the presence of renal failure or tubulointerstitial injury at presentation and non-compliance to colchicine affect negatively on renal survival [5].

In patients who do not tolerate colchicine or fail to respond, second-line agents, as interferon-alpha, and tumor necrosis factor inhibitors, IL-1 receptor antagonists have been used with limited response on preventing inflammatory flares, and there is no much data on their effects to prevent the occurrence of amyloidosis [6]. Our patients’ growth retardation, generalized edema and heavy proteinuria persisted despite after one year of colchicine treatment and a TNF-alpha antagonist infliximab treatment was administered. In the literature, there are reports of patients with FMF, who were successfully treated with anti-TNF agents mainly for abdominal and arthritic attacks [7,8,9]. Ozçakar et al presented four patients with FMF-related amyloidosis whom were treated with long term infliximab therapy with the longest duration (2-6.5 years) of follow-up, together with the literature review. They have thought that infliximab was very effective in controlling gastrointestinal system findings and protracted arthritis, and it also had a favorable impact on the clinical findings of nephrotic syndrome in their patients [10]. Our patient received a total of 10 doses of infliximab therapy in 16 months. Since generalized edema, massive proteinuria, and hypoalbuminemia developed after tenth dose of infliximab therapy, resistance was considered and treatment was discontinued. Interleukin receptor antagonist (anakinra) therapy was initiated.

Anakinra is an analogue of the natural interleukin (IL)-1-receptor antagonist that targets type I IL-1-receptor and thus blocks the effect of IL-1β, which is thought to be activated in FMF [11]. It was used for the first time in a child who had frequent severe FMF attacks despite colchicine therapy in 2007 [12]. In the literature, there are reports of patients with FMF related renal amyloidosis, who were successfully treated with anti-IL 1 agents [13-15]. Cetin and Stovanovic reported beneficial effect of anakinra to FMF related amyloidosis on their adult patients [13,14]. To date, a small number of children with FMF related amyloidosis have been treated with anakinra. Ozçakar et al used to anti-IL-1 agents (anakinra or canakinumab) their colchicine resistant patients with FMF. There were seven children and median attack frequencies, erythrocyte sedimentation rate and CRP levels were decreased significantly with treatment biological agents. Ozçakar et al followed six children with renal amyloidosis secondary to FMF. However, their four patients used infliximab (one also etanercept) before and three patient were ended ESRD, only one patient had partial remission of nephrotic syndrome. The other two patients who did not use infliximab before were resulted chronic renal failure and ESRD [15]. Recently Topaloğlu et al demonstrated that progression of renal tissue damage after the improvement of proteinuria with anti-IL 1 in auto-inflammatory associated amyloidosis [16]. So, we thought that anakinra was not very effective on renal survival in patients with renal amyloidosis related FMF. Likewise, during anakinra treatment, our patient’s proteinuria was decreased and acute phase reactants improved at the beginning. But, anakinra treatment was stopped after six months due to non-response; and chronic renal failure occurred. Peritoneal dialysis was begun after one year. She received kidney transplant from her mother. After renal transplantation her renal function was normal and she hadn’t FMF attacks. She used 2 mg/day of colchicine and gave good response. Thus we didn’t start any biological agents.

In conclusion, biological agents are used safely in colchicine resistance and maybe FMF-associated gastrointestinal amyloidosis. But majority of patients with renal amyloidosis will be resistant to these agents eventually and frequently progress to ESRD. Further data with larger number of patients, longer follow-up, and ideally randomized controlled studies are needed to establish the efficacy and safety of these drugs in FMF related renal amyloidosis patients. Early diagnosis and proper treatment of FMF are the most important points for not development of amyloidosis.
Disclosures
The authors declare no conflicts of interest.

References