LETTER TO THE EDITORS

Transplantation within the era of anti-IL-1 therapy: case series of five patients with familial Mediterranean fever-related amyloidosis

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Dear Editors,

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease [1]. Amyloidosis still continues to occur during the colchicine era, with a rate of 11.4%, in untreated and noncompliant FMF patients [2]. Long-term outcomes of patients with FMF-related amyloidosis who had received kidney transplantation were controversial [3–6]. In recent years, interleukin (IL)-1 inhibitors have been used in the treatment of FMF patients [7]. Very little data exist about the use of these agents in amyloidosis, especially in renal transplant recipients. Accordingly, the aim of this study was to present the clinical findings and treatment responses of renal transplant patients with amyloidosis who were treated with anti-IL-1 therapies. This report will be one of the largest series reported from a single center including patients with long-term follow-up.

All patients with FMF-related amyloidosis who had received a kidney transplant in our center between 2008 and 2018 were included. Patients fulfilled the clinical criteria for the diagnosis of FMF [8] and had two exon 10 Mediterranean fever gene mutations and biopsy-proven AA amyloidosis. Informed consent was obtained from the parents of each patient. The study was approved by the Ethics Committee of Ankara University School of Medicine (20-1253-17).

Among 68 transplantations, five had received a kidney (four living related) because of FMF-related amyloidosis. Detailed information about the patients is given in Table 1. All patients were on colchicine therapy (1–1.5 mg/day) and had maintenance immunosuppression with prednisolone, tacrolimus, and mycophenolate sodium. The patient who had received a deceased donor had induction therapy with basiliximab. Patients were followed on anti-IL-1 therapy with a duration of 18–81 months. Three patients who were on anti-IL-1 therapy before transplantation continued this therapy within the first week of transplantation. Patient 1 had an attack of FMF on the fourth day of transplantation, anakinra was started at the seventh day, and he had no attacks thereafter. The two other patients had not been on anti-IL-1 therapy prior to transplantation. Patient 3 had recurrent attacks (a total of 10) in the first 10 months after transplantation. At the post-transplant 10th month, she had chest pain and myocardial ischemia probably related with cardiac amyloidosis was diagnosed. Anakinra was started. Thereafter, she had three mild attacks and no cardiac problems after 81 months of follow-up. Patient 5 had mild attacks in the first 1.5 years of transplantation; however, thereafter recurrent severe attacks per month set in. With every attack her oral intake was deteriorated, creatinine levels increased and she needed hospitalization in majority of those attacks. Anakinra was started at the 32nd month of transplantation, attacks disappeared with only one attack in the 18 months of follow-up. Anakinra (1 mg/kg/day s.c.) was switched to canakinumab (2 mg/kg or 150 mg/4–8 weeks s.c) for ease of administration in all patients except one. One of the patients developed steroid-responsive acute cellular rejection during anti-IL-1 therapy, and anakinra was maintained at that time. None had anti-IL-1-related side effects nor cytomegalovirus, Epstein–Barr virus and BK virus infection. Three of the five patients required hospitalization because of infection only once. None of the patients had proteinuria in the last visit. Acute phase reactants (AFRs) were normal during anti-IL-1 therapy beyond the periods of infection and attacks.

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Table 1. Clinical findings of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Female	Male	Female
Age (years)	19	17	23.5	24	23.5
Age at amyloidosis diagnosis (years)	6	9	13.5	11	12
Age at ESRD (years)	11.5	14.5	14	19	19
Age at transplantation (years)	16.5	15.5	16	19	19.5
Time from transplantation (months)	28	23	91	56	50
Post-transplant Anti-IL-1 onset	Within the 1st week	Within the 1st week	At 10th month	Within the 1st week	At 32nd month
Anti-IL-1 duration (months)	28	23	81	56	18
Anti-IL-1 type duration (months)	Anakinra (12) Canakinumab (16)	Anakinra (1) Canakinumab (22)	Anakinra (63) Canakinumab (18)	Anakinra (40) Canakinumab (16)	Anakinra (18)
Number of attacks during anti-IL-1 therapy	0	0	3	2	1
Number of infection requiring hospitalization cause	1 Acute tonsillitis	1 Pneumonia	0	1 Otitis media	0
Number of rejection (time)	0	0	1 (at 8.5th month)	1 (at 4th month)	0
Attack					
ESR (mm/h)	–	–	40	58	54
CRP (mg/L)	–	–	40	5.5	225
Attack free					
ESR (mm/h)	6	2	16	2	13
CRP (mg/L)	0.1	0.1	0.1	0.5	0.5
Last creatinine (mg/dl)	0.7	0.8	0.9	1.53	1.3
Last GFR (ml/min/1.73 m^2)	158	126	75	84	60
Last proteinuria (mg/day)	91	107	50	116	85

ESRD, end-stage renal disease; IL: interleukin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein (N: 0-3 mg/L); GFR: glomerular filtration rate.

Recently published studies found that overall survival is significantly reduced in patients with FMF-related amyloidosis after transplantation [5,6]. Green *et al.* [6] reported death rates of 55%, most of them within the first 7 years after transplantation. Pathogenesis of FMF has been associated with increased activation of IL-1β through a dysregulated inflammasome complex [9]. Previously, five single adult cases who received anakinra after renal transplantation were presented in the literature [10–14]. Moser *et al.* [10] reported the first patient in 2009. Anakinra had been started prior to transplantation because of recurrent attacks despite colchicine therapy in that patient and he was followed approximately 20 months after the transplantation. He had an acute rejection episode and central venous catheter infection. Thereafter, four additional patients were reported. Two of them similarly started anakinra prior to transplantation and the drug was continued 6 and 10 months after the transplantation. Anakinra was commenced 4 months and 3 years after transplantation in two other patients and was continued for about 8 and 2 months, respectively. In this report, we present five patients with renal transplantation with a minimum follow-up of 18 months with the longest follow-up of 81 months on anti-IL-1 therapy. Our three patients had already been on anakinra prior to transplantation and proceeded with this therapy within the first week of transplantation. One of them had an attack in the postoperative day 4, and anakinra was started on the 7th day. Similarly, Moser *et al.* [10] described attacks in their patient perioperatively even at the doses of 100 mg/three times weekly and they increased the dose to standard regimen of 100 mg daily to control attacks and inflammatory markers. As all previously described cases, our patients had no or mild few attacks during anti-IL-1 therapy and AFRs were completely normal.

Infections and related fatal consequences were reported to be high in patients with AA amyloidosis both under dialysis and after kidney transplantation [3,6]. The increased risk of infection is a major concern while using these drugs in the context of immunosuppression. Interestingly, according to previous cases and our results, anti-IL-1 therapy seems not to be related with increased serious infection frequency in renal transplant patients. Only one of the five patients reported previously had pneumonia requiring hospitalization. Three of our patients required hospitalization because of infection only once during these long follow-up periods.

Suggested colchicine dose is maximum tolerated dose —up to 2 mg/day in patients with amyloidosis [15]. However, generally patients cannot tolerate this dosage due to exacerbation of diarrhea by gastrointestinal system amyloidosis. Accordingly, more liberal colchicine administration can be offered in renal transplant recipients together with anti-IL-1 therapy.

As a conclusion, in light of our preliminary results, we imply that anti-IL-1 therapies seem to be the emerging effective and safe treatment options in patients with FMF-related amyloidosis after renal transplantation.

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Conflict of interest

The authors declare that they have no conflict of interest.

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