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Case Report

Recurrence of proteinuria after cessation of tocilizumab in patients with AA amyloidosis secondary to FMF

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Abstract

There is no established treatment protocol for amyloid-A (AA) amyloidosis secondary to Familial Mediterranean Fever (FMF). Recently, we reported the efficacy of tocilizumab in 11 amyloidosis cases associated with FMF. In 2 patients of 11, we discontinued the tocilizumab administeration owing to the normalization of amyloidosis-related symptoms, but proteinuria re-occurred eventually. Fortunately, the patients responded to tocilizumab re-treatment. This led us to conclude that physicians should not stop the treatment, even in patients with normalized proteinuria levels.

Keywords: Tocilizumab, AA amyloidosis, familial mediterranean fever

Introduction

Secondary or amyloid-A (AA) amyloidosis can be defined as deposition of fibrils mainly constituted of the fragments of an acute phase reactant serum amyloid-A (SAA) protein. Although the autopsy incidence was reported to be as high as 0.86% in the general population, in clinical practice, the rate of symptomatic or diagnosed cases is much lower (1). As the definition comprises the term *secondary*, there must be certain engendering factors involved, and the leading causes of AA amyloidosis are chronic inflammatory diseases such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) that account for almost half of the patients (2). On the contrary, Familial Mediterranean Fever (FMF) is responsible for over 60% of AA amyloidosis cases in Turkey, where the disease is prevalent (3).

Colchicine is the drug of choice in the prevention of both acute attacks and amyloidosis in these patients; however, once amyloidosis develops, colchicine has little effect, if any, on renal function or progression of the end-stage renal disease (4). No treatment protocol has been widely accepted for AA amyloidosis, although colchicine, azathioprine, anti-TNF agents, and IL-1 and IL-6 antagonists are used increasingly with variable effectiveness. Tocilizumab (TCZ) is a fully-humanized monoclonal antibody that inhibits IL-6 functions. This agent has been approved and used for various inflammatory diseases including RA, JIA, and Castleman's disease. Besides, it has beneficial effects on AA amyloidosis, which has been shown in several case reports. Recently, we reported a considerable efficacy of TCZ in 11 amyloidosis cases due to FMF (5). Here, we report the disease course in 2 of them, in whom we discontinued the TCZ administration owing to the normalization of proteinuria and other amyloidosis-related symptoms. Unfortunately, proteinuria re-occurred eventually. The patients were treated with the previous therapy and responded well.

Case Presentations

Case 1

A 34-year-old woman was treated with TCZ for 16 months. The *MEFV* gene mutation was homozygous for *M694V*. Her initial proteinuria of 6,810 mg/d decreased to 84 mg/d. Then the TCZ administration was discontinued, and the patient was administered oral colchicine. During the follow-up period, the patient was almost attack free (1 attack/year), and the level of proteinuria was always within the normal range (<150 mg/24 hours). Approximately 3 years from the cessation of TCZ, she was admitted to the hospital, complaining of the swelling in legs. During the physical examination, bilateral pretibial edema was detected. However, the level of proteinuria had begun to increase almost 3 months before the admission to our clinic (380 mg, 674 mg, and 770 mg, respectively, in consecutive months). In addition, she complained about an increased frequency of FMF attacks (2-3 attacks per month) during the past year. There was no other cause that could potentially deteriorate her clinical condition. In laboratory tests, proteinuria was found to be increased to 1,450 mg/24 hours. Albumin level was decreased (2.4 g/dL), and other biochemistry tests were

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within the normal limits, including the renal function. Repeated 24-hour urine test revealed similar results (1,612 mg). We considered this to indicate the recurrence of amyloidosis and decided to use TCZ again and follow the same protocol. The patient had only 6 cycles of TCZ, and proteinuria decreased to 548 mg/day, while albumin increased to normal values (3.6 g/dL). In addition, she was using losartan 100 mg/day during the tocilizumab treatment and at the time of AA recurrence.

Case 2

A 76-year-old man was treated with TCZ for 24 months with a diagnosis of AA amyloidosis secondary to FMF. The *MEFV* gene mutation was heterozygous for the *M694V/M680I* compound. His initial proteinuria was 4,368 mg/d and decreased to 180 mg/d, while the creatine level decreased from 4.22 to 2.1 mg/dl at the end of the 24-month treatment. At the time of initial diagnosis, AA amyloidosis had been confirmed by both rectal and renal biopsy. Therefore, we performed a follow-up rectal biopsy, and no evidence of amyloidosis could be seen. Then the TCZ application was discontinued, and the patient was prescribed oral colchicine. After 9 months, the patient was hospitalized due to generalized edema, diarrhea, nephrotic syndrome, and increased creatine levels. He had suffered from the FMF attacks for the last 3 months and experienced almost 4-5 attacks per month. There was no other cause that could potentially deteriorate his clinical condition. In laboratory tests, serum albumin was decreased to 2.1 g/dL, serum creatine levels increased (3.4 mg/dL), and proteinuria in a 24-hour urine test was detected to be within the nephrotic ranges (3,400 mg/day). We decided to administer TCZ, and after 9 cycles of the treatment, the patient's creatine levels decreased to his basal values (1.9 mg/dL), and proteinuria decreased dramatically (380 mg/day). In addition, he was using valsartan 80 mg/day during the tocilizumab treatment and at the time of AA recurrence.

Discussion

Amyloid-A amyloidosis is mostly associated with chronic inflammatory conditions such as RA and JIA, while FMF is the most prominent cause in countries where the prevalence of the disease is higher. A recent study from Turkey reported that 8.6% of patients with FMF have concomitant amyloidosis (6). The importance of this rate might be better recognized when the high prevalence of the disease itself is taken into account. Amyloidosis can cause significant morbidity and even mortality, and before the biological era, its ultimate outcome was renal failure, necessitating dialysis or transplantation. There has been a growing body of evidence demonstrating its reversible nature with convenient and timely treatment. However, there is no consensus about the treatment of AA amyloidosis.

Approximately, 5%-15% of patients with amyloidosis associated with FMF have been reported to benefit from colchicine, while the compliance seems to be major problem. Once amyloidosis occurs, the role of colchicine is controversial. Even though there is evidence suggesting that colchicine can stabilize or decrease proteinuria, this effect seems to be limited to those with earlier phases defined as non-nephrotic proteinuria and normal serum creatinine levels (7). In addition to colchicine, there is little experience with azathioprine, which has showed beneficial effects in a limited number of patients with amyloidosis secondary to FMF (8, 9). Fortunately, in the last decade, in other words during the biological era, there were case reports indicating varying degrees of effectiveness with different biological agents in patients with amyloidosis secondary to FMF. The first biological agent was a TNF antagonist, infliximab, which was shown to be effective by means of decreasing proteinuria in several cases (10). After recognizing the role of IL-1 in auto-inflammatory diseases, the blockade of this cytokine has got more attention. There is more evidence about the effectiveness of IL-1 antagonists, especially anakinra, as compared to other biological agents since the first report in 2006. The evidence for the use of TCZ in AA amyloidosis comes from the reported cases with RA and JIA complicated with amyloidosis. Observing its effectiveness on the disease itself and associated amyloidosis, physicians were encouraged to use it in other forms of AA amyloidosis, such as inflammatory bowel disease and Behcet's disease (11-14). Depending on the previous reports, we have decided to use TCZ in our patients with AA amyloidosis secondary to FMF, and we observed good responses in general (5). Recently, Ugurlu et al. (15) from Turkey have reported similar results in 12 patients with FMF. Taken together, these results suggest that TCZ might have a role in the treatment of this major FMF complication. Recommending its use based on these observations among a limited number of patients with a relatively short follow-up may not be justified. However, given the lack of clinical trials to answer this clinical problem and the limited data about the treatment of this complication with any drug, these results should be taken into account.

In 2 of our patients, we stopped the TCZ treatment due to normalization of proteinuria in 1, and stabilization of renal function in the other. The disappearance of amyloidosis in a follow-up rectal biopsy also encouraged us to cease TCZ. Unfortunately, almost the whole clinical picture reversed to the very beginning. Regarding the optimal treatment duration in AA amyloidosis with any treatment agent, there is no information available in the literature. This decision should be made by the attending physician. However, it seems that its better not to be in a hurry when ending the TCZ treatment in patients with AA amyloidosis, even in the case of complete remission. To stop a given drug in a patient who benefit from it is challenging in general. This is also true for the cessation of TCZ in patients with AA amyloidosis who responded well to treatment. Currently, to make a recommendation for the right time for TCZ discontinuation seems to be impossible. Larger studies with prolonged follow-up are needed to determine the timing of drug cessation in this group of patients.

In conclusion, TCZ seems to be an effective and safe alternative in cases of AA amyloidosis secondary to FMF. However, even in patients with favorable response, the treatment duration should be long. Determining an ideal treatment duration, or markers for ceasing the treatment, needs to be studied in larger cohorts. Until then, these decisions will continue to be made by physicians, but it is important to remember a potential recurrence of AA amyloidosis, and the patients should be monitored closely.

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