

# Remission of nephrotic syndrome due to AA-amyloidosis, complicating familial Mediterranean fever, with tocilizumab

Sirs,

Reactive systemic amyloid alpha (AA)-amyloidosis complicates familial Mediterranean fever (FMF) and is secondary to the deposition of amyloid A protein in the kidney. The precursor of the deposited amyloid A protein is serum amyloid A (SAA), an acute phase reactant, produced by interplay of proinflammatory signals Interleukin-1 (IL-1), Tumour necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6). Tocilizumab is a monoclonal antibody that binds to soluble and membrane-bound IL-6 receptors and inhibits IL-6 receptor mediated signalling. We attempted tocilizumab use, since treatment options for established AA-amyloidosis are limited and IL-6 plays a critical role in the synergistic induction of human SAA gene (1). Amyloid deposits are in dynamic turnover and interventions aiming to decrease the supply of amyloid precursor proteins may improve the prognosis of the condition (2).

A 32-year-old woman of Turkish-Georgian origin was diagnosed as FMF, based on clinical manifestations (fever, diarrhoea, arthritis and serositis), since 1982 and genetic screening with mutation in exon 10 of the *MEFV* gene (3). She presented with refractory nephrotic syndrome on September during her second pregnancy (2009). She was admitted on the 28<sup>th</sup> week of gestation with nephrotic syndrome (proteinuria of >8 g/24 h and serum albumin <1.5 mg/dL). She underwent a caesarean section on June 2010, due to intrauterine growth retardation of the fetus. A renal biopsy showed strong diffuse positivity for amyloid-A on the glomeruli and vascular wall.

We administered monthly tocilizumab infusions 8 mg/kg, since November 2010 (6 months after delivery) with rapid improvement. Sense of wellbeing was the first to change, and over the next 2 months peripheral oedemas disappeared and diuretics were discontinued. She has been stable since then. Her laboratory results are shown in Table I. Currently, she remains in an excellent condition, on colchicine 1 mg daily, lisinopril 5 mg twice daily and monthly tocilizumab infusions 8 mg/kg. She continues to undergo milder arthralgia crises twice a year.

**Table I.** Laboratory results of the patient during 4 years of follow-up.

|                       | 10/2010 | 10/2011 | 10/2012 | 10/2013 | 09/2014 |
|-----------------------|---------|---------|---------|---------|---------|
| Creatinine (mg/dL)    | 2       | 1.3     | 1.1     | 1.3     | 1.2     |
| Serum albumin (mg/dL) | 2.1     | 2.4     | 2.9     | 3.4     | 3.9     |
| 24-hour urine (g)     | 9       | 5.6     | 3.9     | 2.7     | 3.6     |

Our patient had established amyloidosis before conception (proteinuria 2 g/24 h), which deteriorated during pregnancy. The effect of pregnancy on kidney function was studied in 29 pregnancies of 17 patients with FMF and amyloidosis. Pregnancy associated deterioration of renal function occurred in seven patients, who had advanced renal disease at conception, marked by serum creatinine  $\geq 1.5$  mg/dL or urine protein  $\geq 2$  g/24 h (4).

In the era of biologic treatments anti-TNF- $\alpha$  and anti-IL-1-receptor antagonists have been used. Infliximab was used on a series of paediatric patients, FMF and established nephrotic syndrome and manifestations of arthritis and diarrhoea improved. Partial remission of the proteinuria lasting from 2.5 to 3.5 years was noted (5). IL-1-receptor antagonists have been tried on patients with FMF and renal amyloidosis, however, most of the case reports refer to patients who are dialysis-dependent (6, 7).

Tocilizumab has been used for treatment of AA-amyloidosis complicating mainly different inflammatory diseases. Recently, case reports of patients suffering from AA-amyloidosis treated effectively with tocilizumab, have been summarised (8). In addition, a study on a series of 40 rheumatoid arthritis patients with AA-amyloidosis has been published, divided to tocilizumab versus anti-TNF- $\alpha$  treatment with variable follow-up. Tocilizumab treatment was of greater utility (9). Tocilizumab treatment of FMF patients with AA-amyloidosis has been recently reported on a series of 10 patients with favourable response after a mean follow-up period of  $7.2 \pm 2.2$  months (10).

To our knowledge, this is the case with the longest follow-up in the literature, which demonstrates sustained long-term remission of nephrotic range proteinuria with tocilizumab infusions in a patient with renal AA-amyloidosis due to FMF.

J. SERELIS  
S. CHRISTAKI  
F.N. SKOPOULI

Department of Internal Medicine and  
Clinical Immunology, Euroclinic Hospital,  
Athens, Greece.

Address correspondence to:

Prof. F.N. Skopouli, Department of Internal  
Medicine, Athens Euroclinic, 7-9 Athanasiadou  
Str, Athens 11521, Greece.

E-mail: fskopouli@euroclinic.gr

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