Long-term tocilizumab efficacy in a patient with psoriatic arthritis and AA amyloidosis

Sirs,

We have read with great interest the manuscript by Lane *et al*. describing the efficacy and safety of the humanised anti-interleukin (IL)-6 receptor antibody Tocilizumab (TCZ) in twenty adults with refractory chronic inflammatory conditions complicated, in fourteen cases, by AA amyloidosis (1). Six patients had unclassified inflammatory disorders, two hyper-immunoglobulin D and periodic fever syndrome, seven rheumatoid arthritis (RA), four systemic juvenile idiopathic arthritis and one localised Castleman's disease. The authors reported that TCZ was effective in suppressing inflammation and that, in those patients with AA amyloidosis, TCZ therapy determined the regression of amyloid deposits.

The capability of TCZ in suppressing the hepatic acute phase response enables to speculate TCZ as one of the most viable treatment options in patients affected with chronic inflammatory diseases with already developed AA-amyloidosis or in subjects who are at high risk of developing it. Indeed, inhibiting the hepatic acute phase response may prevent the progressive amyloid deposition, thus dramatically improving the patients' outcome.

Nevertheless, data supporting TCZ use in these subjects are still scarce and providing additional evidence with longitudinal randomised clinical trials and with longer follow-up is needed. In the meanwhile, also data from case reports and case series should be welcome to sustain the role of IL-6 blocking. In this regard, a patient with psoriatic arthritis (PsA) and AA-amyloidosis refractory to tumour necrosis factor (TNF)-α inhibitors, in whom TCZ treatment determined a sustained remission of arthritis and a striking improvement of proteinuria is herein reported.

In April 2008, a 46-year-old woman affected with PsA since the age of 29, was admitted in our Unit for overall active disease. Over the past years, she had been treated with conventional disease-modifying anti-rheumatic drugs (DMARDs) (methotrexate 15 mg/week; sulfasalazine 2 gr/day), non-steroidal anti-inflammatory drugs (NSAIDs) (etoricoxib 90 mg/day) and glucocorticoids (GCs) (methylprednisolone up to 16 mg/day) without achieving good disease control. A combination therapy with infliximab (5 mg/kg every 8 weeks), methotrexate (10 mg/week) and prednisone (5 mg/day) was then started, obtaining a partial response. Indeed, despite an amelioration of arthritis, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), checked routinely every two months, were elevated over time. In March 2012, the patient had a clinical flare: Disease Activity Score 28 (DAS28) and Disease Activity Index for Psoriatic Arthritis (DAPSA) were 4.72 and 127.27 respectively; moreover a synovitis with power Doppler signal was detected in the patient's knees by ultrasonography. Therefore, infliximab was suspended and etanercept was then started (50 mg/week) in combination with methotrexate (15 mg/week). Three months later, she was hospitalised for the occurrence of pitting oedema of the lower limbs and arterial hypertension. Upon admission, proteinuria was 3.75g/24h, whereas serum creatinine level was normal. A nephrotic syndrome was diagnosed and kidney needle biopsy was performed revealing an extensive amyloid deposition in renal arterial wall, mesangial matrix and interstitial peritubular space (Fig. 1). Therefore, etanercept treatment was interrupted. One month later, laboratory analysis showed CRP 5.9 mg/dl (n.v <0.5), ESR 104 mm/h (n.v <35), serum amyloid-A (SAA) 68 mg/L (n.v <10) and proteinuria 5 g/24h. TCZ at a dose of 8 mg/kg every four weeks was given in combination with methotrexate (15 mg/week) and prednisone (12.5 mg/day). After the second TCZ infusion, proteinuria rapidly decreased to 2 g/24h and inflammatory parameters dropped to normal values. Prednisone was gradually tapered to 5 mg/day. At 24 months follow-up the patient was symptom free, inflammatory parameters were persistently within normal values and proteinuria was 0.48 g/24h. The treatment was well tolerated and no adverse events occurred.

SAA is an acute phase response protein synthesised by the liver upon the stimulus of different proinflammatory cytokines, such as interleukin (IL)-6, tumour necrosis

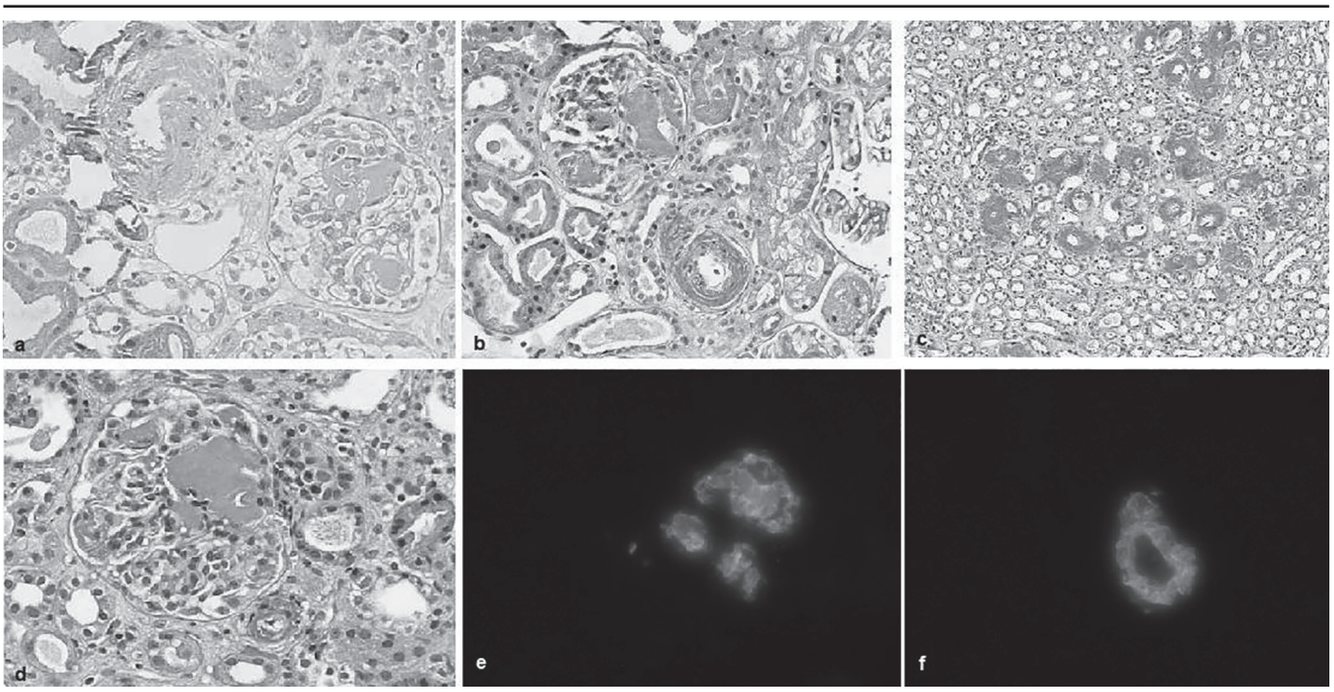

Fig.1. a: Accumulation of amorphous, acellular, eosinophilic material in the mesangium of a glomerulus with nodular appearance. This material is also present within the wall of a small artery (Haematoxylin and Eosin, x 200); **b**: Congo red positive material (amyloid) within mesangial areas of a glomerulus with nodular appearance and within the wall of a small artery (Congo Red, x 200); **c**: Congo red positive material (amyloid) is also focally present within the tubular basement membranes (Congo Red, x 100); **d**: Congo red positive material (amyloid) within mesangial areas of a glomerulus with nodular appearance (Congo Red, x 200); **e**: immunofluorescence with antisera for AA protein shows deposits of AA protein in the glomerulus in the mesangium and along the capillary walls (anti AA, x 200); **f**: immunofluorescence with antisera for AA protein shows deposits of AA protein in the wall of a small artery (anti AA, x 200).

factor (TNF)-α and IL-1 (2, 3). Reactive amyloidosis is a life-threatening long-term complication of systemic inflammatory disorders caused by abnormal deposition of SAA in various organs and causing a rapid deterioration of renal function that manifests with proteinuria and kidney failure.

PsA is rarely complicated by AA amyloidosis, since markers of inflammation are only slightly increased in most subjects. Despite treating with anti-TNF-α drugs, the patient we reported herein had persistently elevated acute phase reactants that might have favoured amyloidosis development. To the best of our knowledge, Moise *et al*. first described a case of amyloidosis complicating PsA in a 34-year-old man who died of renal failure (4). Subsequently, only a few subjects with PsA-related amyloidosis have been described (5, 6). More recently, a retrospective study has been focused on the frequency of amyloidosis in patients with spondyloarthropathies. The medical records of 1.125 patients with spondyloarthropathies were reviewed and 15 patients with a histological diagnosis of amyloidosis AA were identified; four out of 15 (26.7%) were affected with PsA (7).

The management of patients with reactive amyloidosis is challenging: the aim of vast majority of therapeutic aids are directed on reducing acute-phase proteins in order to control the underlying disease and to preserve renal function in patients with kidney involvement. In this regard, TNF-α inhibitors have proven to be a compelling therapeutic strategy for treating reactive amyloidosis complicating PsA by halting the inflammatory response, albeit their failure has been also described (8). Two recently reported case series, including patients with different rheumatologic disorders, have shown that also other biological drugs, especially those neutralising IL-6, might reduce AA-amyloid deposition in patients unresponsive to anti-TNF drugs, thus pointing out the usefulness of TCZ in countering amyloidosis development (1, 9). Until today, only a few case reports describing TCZ efficacy in the treatment of PsA-related amyloidosis has been previously published (10). In conclusion, our case corroborates the efficacy of IL-6 blocking in stemming the progression of renal disease in patients with PsA and reactive amyloidosis, in particular in those patients with sustained systemic inflammation and refractory to conventional DMARDs and to TNF-α inhibitors. Looking into the future, these encouraging observations need to be confirmed by longitudinal controlled studies, specifically aimed at assessing TCZ long-term effects in the management of PsA-associated amyloidosis.

L. Dinoia[1]
G. Lopalco[1]
L. Cantarini[2]
L. Gesualdo[3]
M. Rossini[3]
F. Iannone[1]

[1]Interdisciplinary Department of Medicine, Rheumatology Unit, University of Bari Aldo Moro, Bari, Italy;
[2]Research Center of Systemic Autoinflammatory Diseases and Behcet's Disease Clinic, Rheumatology Unit, Policlinico Le Scotte, University of Siena, Italy;
[3]Department of Emergency and Organ Transplantation, Nephrology Unit, University of Bari Aldo Moro, Bari, Italy.

Address correspondence to:
Luca Cantarini, MD, PhD,
Department of Medical Sciences, Surgery and Neurosciences, Rheumatology Unit, University of Siena, Policlinico Le Scotte, Viale Bracci 1, 53100 Siena, Italy.
E-mail: cantariniluca@hotmail.com

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