# Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature

T. Lane, J.D. Gillmore, A.D. Wechalekar, P.N. Hawkins, H.J. Lachmann

*National Amyloidosis Centre, University College London Division of Medicine, London, UK.*

*Thirusha Lane, MSc*
*Julian D. Gillmore, PhD*
*Ashutosh D. Wechalekar, MD*
*Philip N. Hawkins, FMedSci*
*Helen J. Lachmann, MD*

*Please address correspondence to:*
*Thirusha Lane,*
*National Amyloidosis Centre,*
*UCL Division of Medicine,*
*Rowland Hill Street,*
*London NW3 2PF, United Kingdom.*
*E-mail: t.lane@ucl.ac.uk*

*Reprints will not be available from the author.*

*Received on November 7, 2014; accepted in revised form on April 21, 2015.*

*Clin Exp Rheumatol 2015; 33 (Suppl. 94): S46-S53.*



**Key words:** amyloidosis, chronic inflammatory disease, systemic autoinflammatory disease, tocilizumab, interleukin-6.

*Competing interests: none declared.*

**ABSTRACT**

**Objective.** *AA amyloidosis is the most serious potential complication of chronic inflammatory disorders. The main aim of treatment is to suppress inflammation thereby inhibiting serum amyloid A protein (SAA), which is the precursor of AA amyloid fibrils, to prevent or halt amyloid deposition. Interleukin (IL)-6 blockade is frequently effective in inflammatory conditions, however, there are few published data on its use in AA amyloidosis or the systemic autoinflammatory diseases (SAIDs) or chronic inflammatory conditions. We assessed clinical and serological responses and adverse events associated with tocilizumab (TCZ) use in 20 adult patients with inflammatory disorders refractory to other treatments, including 70% with AA amyloidosis and four with renal transplants.*

**Methods.** *In addition to routine haematology and biochemistry (including SAA) blood panels, patients with AA amyloidosis underwent SAP scintigraphy to quantify amyloid load. Those with SAIDs underwent genetic analysis to identify mutations/variants in known associated genes. Quality of life (QoL) was surveyed using SF-36v2®.*

**Results.** *Whole-cohort median pre-treatment SAA fell from 70 to 4 mg/L within 10 days of the first dose; this response has been maintained over an on-treatment follow-up period of 23 months ($p<0.0001$). AA amyloid deposits either regressed or remained stable. QoL improved in several domains. Infections were the predominant adverse effect experienced, but none resulted in permanent discontinuation of therapy.*

**Conclusion.** *This small series shows that in patients with treatment-refractory chronic inflammatory conditions TCZ can be effective in suppressing inflammation, and in those with AA amyloidosis, can lead to regression of amyloid deposits. Longer follow-up is required to determined long-term safety and efficacy in these conditions.*

## Introduction

AA amyloidosis is the most serious potential complication of disorders associated with chronic inflammation and results in progressive renal insufficiency, poor quality of life (QoL) and substantial mortality (1, 2). The most important aim of treatment is to suppress inflammation thereby inhibiting production of the acute phase reactant, serum amyloid A protein (SAA), which is the precursor of AA amyloid fibrils. Sustained suppression of SAA not only prevents the risk of developing AA amyloidosis, but it is also known to be associated with regression of AA amyloid deposits, improvement in amyloidotic organ function and prolonged survival (3).

Treatment of the inflammatory arthritides, inflammatory bowel disease and systemic autoinflammatory disorders (SAIDs) has been revolutionised by the availability of biological agents that block specific cytokines. TNF blockade is now very widely used as an effective treatment for rheumatoid arthritis (RA) and some SAIDs; interleukin (IL)-1 blockade has dramatically improved management of several previously nigh on untreatable SAIDs, notably cryopyrin-associated periodic syndrome (CAPS), tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), colchicine-refractory familial Mediterranean fever (crFMF) and many cases of mevalonate kinase deficiency (MKD), also known as hyper-immunoglobulin D and periodic fever syndrome (HIDS) (4, 5). IL-1 inhibition by means of anakinra or canakinumab has also been effective in patients with AA amyloidosis complicating CAPS and TRAPS and, as a result, can reduce proteinuria and salvage renal function (1, 6). Block-

ade of IL-6 is frequently effective in RA and systemic onset juvenile idiopathic arthritis (SJIA), the anti-IL-6 receptor monoclonal antibody tocilizumab (TCZ) (RoActemra®) now licensed treatment for both conditions. There are very few published data on the use of TCZ in AA amyloidosis or the SAIDs or chronic inflammatory conditions.

The short- and long-term efficacy of TCZ has been established by means of several clinical trials in RA (7-21), as well as in a real life cohort (22), and in SJIA clinical trials (23-26). TCZ has also been successfully used within clinical trials in other diseases such as multicentric Castleman's disease (MCD) (27) and Crohn's disease (28).

Current knowledge of the safety profile of TCZ in adults with RA is derived from clinical trials involving 3577 patients who received treatment for at least six months, 3296 who were treated for at least one year, 2806 who received treatment for at least two years and 1222 treated for three years. The commonest reported adverse drug reactions (ADRs), *i.e*. those occurring in ≥5% of patients treated with TCZ monotherapy or in combination with sDMARDs were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased serum alanine aminotransferase. Preliminary safety data on TCZ in children with SJIA has been reported from an international phase 3 trial (TENDER) in 112 children, clinical trials in Japan involving 149 patients, and the Japanese post-marketing monitoring program which includes 366 cases. The authors concluded that TCZ was not associated with an increased risk of macrophage activation syndrome (MAS) (29). In TENDER 57% of patients had at least one episode of neutropenia. This was associated with an increased risk of infection compared to periods when the children were not neutropenic. MTX use and younger age were associated with increased risk for more severe neutropenia, but TCZ exposure was not (30).

The safety and efficacy of TCZ in renal impairment has been supported by a number of publications; three case reports document the safe and effective use of TCZ in patients with end stage renal failure and underlying RA (31) and MCD (32, 33). A Japanese registry study has reported on 102 patients with RA and renal insufficiency showing that the safety and efficacy profile is comparable with the group with independent renal function (n=279) (34). In a case series of five patients with AA amyloidosis secondary to RA, improvement in renal function was seen at one year (35) with no safety issues. To our knowledge there are no extant reports on the use of TCZ after renal transplantation.

We assessed clinical and serological responses and adverse reactions to TCZ in 20 adult patients with a variety of inflammatory disorders refractory to other treatments, 70% of whom had developed AA amyloidosis, including four patients who underwent renal transplantation.

## Methods

*Patients*

We identified 20 patients from the UK National Amyloidosis Centre clinic database who were given a therapeutic trial of TCZ between 2010 and 2014. This included 14 with AA amyloidosis. Disease activity and treatment response were monitored by patient-reported symptom scores and serial SAA and CRP measurements. Amyloid load was evaluated by whole body $^{123}$I-SAP scintigraphy. Renal function was measured by means of serum and urine chemistry. QoL was measured in 12 patients using the SF36v2® questionnaire.

*SAA assay*

SAA was measured in serum by latex nephelometry (BNII autoanalyser; Dade Behring, Marburg, Germany) (36). The lower limit of detection was 0.7 mg/l, with an inter-assay CV of 2.6% at 15 mg/l and 3.7% at 80mg/l. Standardisation of both CRP and SAA assays was based on the respective WHO International Reference Standards, 1987.

*Genetic analysis*

Genomic DNA was isolated from patients' peripheral blood as described by Talmud *et al*. (37). Sequence variants were identified by polymerase chain reaction (PCR) and direct sequencing of the appropriate exons of the gene in question. Genes and exons analysed were as follows: *MEFV* exons 2 and 10; *TNFRSF1A* exons 2-3 including intron 2, 4-5 including intron 4, and 6-7 including intron 6; *NLRP3* exon 3 and *MVK* exons 9 and 11. Analysis was extended to other exons where necessary. PCR was validated by gel electrophoresis. In six patients no sequence variants were identified by these methods, thereby rendering their inflammatory disorder as yet 'unclassified'.

*Renal function*

Renal function was measured by means of serum creatinine, calculated GFR, and creatinine clearance and proteinuria from 24-hour urine collections. Renal involvement by amyloid was defined as 24-hour urine protein leak >0.5 g/day, predominantly albumin, according to the International Consensus Criteria (38).

*Histology and immunohistochemistry*

The presence of amyloid in tissue sections was confirmed by a modified version of the alkaline-alcoholic Congo red method described by Puchtler *et al*. (39). Formalin-fixed deparaffinised tissue sections, 6-8 μm thick, were stained and then visualised under bright field and cross-polarised light. Positive controls, obtained from a known Congo red-positive composite block, were always processed in parallel. Immunohistochemical staining of formalin fixed de-paraffinised 2 μm sections of amyloidotic tissue were performed using commercial monoclonal antibodies against SAA protein (Euro-Diagnostica, Huntingdon, UK) and AL kappa and lambda (Dako Ltd, Denmark House, Ely, UK) to determine the amyloid fibril type (40). Positive and negative controls were used in each run. The diagnosis of AA amyloidosis was made histologically in thirteen of the 14 patients with this complication, whilst one child with JIA was diagnosed by non-invasive SAP scintigraphy.

*SAP scintigraphy*

This nuclear medicine technique involves the intravenous injection of highly purified serum amyloid P component (SAP) which has been radio-labelled

with the gamma emitting isotope $^{123}I$; radio-labelled SAP localises rapidly and specifically to visceral amyloid deposits in proportion to the amount of amyloid present (41). The technique has 100% diagnostic sensitivity in patients with systemic AA amyloidosis (42).

*QoL*

The QualityMetric SF36v2® Health Survey is designed to measure functional health and well-being from the patient's perspective. There are eight health domains (physical functioning, role physical, bodily pain, general health, social function, role emotional and mental health) which are scored individually, and the result expressed in comparison to American norms. The average score for healthy controls in each measure is 50, and higher scores represent a better QoL. A change of 10 points or more in a domain between administrations is considered clinically significant.

*Statistical analysis*

Mann-Whitney tests were performed using GraphPad Prism® to calculate differences between pre- and on-treatments groups. Graphs were produced using Microsoft® Excel®.

## Results

*Whole cohort characteristics*

Table I summarises the patient characteristics. Twelve (60%) were male. Six patients had unclassified inflammatory disorders, two had MKD, seven had RA, four SJIA and one unicentric Castleman's disease. All patients in the cohort had received at least one previous line of treatment with an anti-cytokine therapy or disease-modifying anti-rheumatic drug (DMARD), which had proved ineffective (including anakinra in two patients with MKD and one SJIA patient) or had intolerable side effects. Many patients were extensively pre-treated, one having tried more than ten different therapies over her disease course. Fourteen patients (70%) had developed AA amyloidosis. The total median follow-up time for the whole cohort was 56 months, with an interquartile range (IQR) of 18 to 86 months. Median follow-up of patients on TCZ was 23 months. All results are shown as median (IQR) unless otherwise stated.

*Serial monitoring of the acute phase response*

The whole cohort median pre-treatment SAA (the median of all available SAA measurements in the year prior to commencement of TCZ) was 70 mg/L (38–158). The first post-treatment SAA measurements were undertaken at 10 days (7–13) after the first dose of TCZ, and were significantly improved to a median of 4 mg/L (3–7); this excellent serological response has been maintained at median 5 mg/L (3–8) over an on-treatment follow-up period of 23 months (13–35) (Mann-Whitney $p<0.0001$) (Fig. 1).

*Change in renal function in AA amyloidosis cases*

Of 14 patients with AA amyloidosis, 12 had renal impairment. Four of the 12 had renal transplants and a further two were dialysis-dependent. The six patients with measurable native renal function showed a mean reduction in proteinuria of 3.4 g/24 hours over the on-treatment period when compared with the pre-treatment 24 hour urine collection.

**Table I.** Patient characteristics.

| Patient ID | Sex | Ethnicity | Inflammatory disorder | Age at onset (y) | Previous unsuccessful therapy | Renal impairment | Renal transplant | AA amyloidosis | Follow-up (y) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | N. European | RA | 36 | MTX, SSZ, ETC, RTX, G, LEF | 1 | 1 | 1 | 7 |
| 2 | F | N. European | RA | 28 | MTX, SSZ, ETC, RTX | 1 | 0 | 1 | 4 |
| 3 | F | N. European | RA | 49 | MTX, SSZ, ETC | 1 | 0 | 1 | 2 |
| 4 | M | N. European | RA | 19 | MTX, ETC, CMB | 1 | 0 | 1 | 7 |
| 5 | M | N. European | RA | 22 | MTX, ETC, RTX | 1 | Dialysis | 1 | 2 |
| 6 | F | N. European | RA | 40 | MTX, RTX, ADA, ETC | 1 | 0 | 1 | 8 |
| 7 | F | N. European | RA | 35 | MTX, RTX | 0 | 0 | 1 | 6 |
| 8 | M | N. European | SJIA | 12 | CMB, ETC, INF, ADA, RTX | 1 | 1 | 1 | 22 |
| 9 | F | N. European | SJIA | 14 | CSP, RTX, LEF, MMF, TAC, ANA, ABT, CMB, CSP, AZA, MTX | 1 | 1 | 1 | 6 |
| 10 | F | N. European | SJIA | 6 | MTX, ETC | 0 | 0 | 1 | 3 |
| 11 | F | N. European | SJIA | 19 | MTX, ETC, ADA | 1 | 0 | 1 | 5 |
| 12 | M | N. European | Castleman's | 38 | MTX | 1 | 0 | 1 | 4 |
| 13 | M | N. European | MKD | <0.5 | ANA, ETC | 1 | 1 | 1 | 11 |
| 14 | M | N. European | MKD | <0.5 | ANA | 0 | 0 | 0 | 2 |
| 15 | M | S. Asian | Unclassified | 41 | CSP, AZA, MTX, CAM, RTX, INF, ANA | 1 | Dialysis | 1 | 8 |
| 16 | M | S. European | Unclassified | 10 | ADA, ETC, ANA, MMF | 0 | 0 | 0 | 8 |
| 17 | M | S. Asian | Unclassified | 15 | MTX, SSZ, PCM, CSP, COL, INF | 0 | 0 | 0 | 18 |
| 18 | F | N. European | Unclassified | 16 | MTX, ANA | 0 | 0 | 0 | 4 |
| 19 | M | N. European | Unclassified | 55 | AZA, ANA, ETC | 0 | 0 | 0 | 1 |
| 20 | M | N. European | Unclassified | 19 | ANA | 0 | 0 | 0 | 2 |

Patients are described in terms of demographics, underlying disease, previous therapies and total follow-up period. ANA: anakinra; ADA: adalimumab; ETC: etanercept; MMF: mycophenolate mofetil; MTX: methotrexate; SSZ: sulphasalazine; PCM: penicillamine; CSP: cyclosporine; COL: colchicine; INF: infliximab; RTX: rituximab; G: gold; LEF: leflunamide; CMB: chlorambucil; CAM: CAMPATH; TAC: tacrolimus; ABT: abatacept; 1: present; 2: absent.

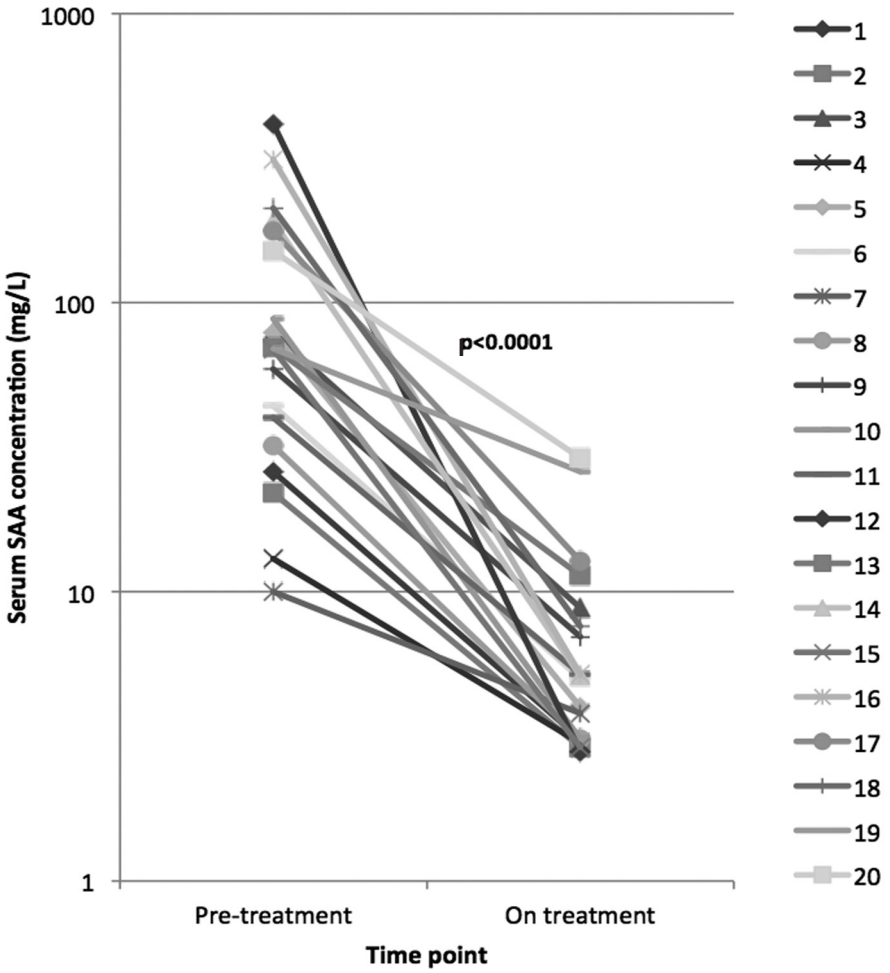


**Fig. 1.** Sustained suppression of serum SAA after IL-6 blockade by tocilizumab. Pre-treatment values are shown as the median of all pre-treatment SAA measurement up to 1 year prior to commencement of tocilizumab therapy. On-treatment values are shown as the median of all on-treatment SAA measurements to date. Mann-Whitney test revealed a statistically significant difference between the pre- and post-treatment measurements ($p$<0.0001). The on-treatment follow-up period (duration of treatment) was 23 months (13–35).

*Monitoring of amyloid deposits*

Thirteen of 14 patients with AA amyloidosis have had pre- and on-treatment serial SAP scans. Four patients showed stable amyloid deposits whilst nine showed regression of amyloid; none showed worsening amyloid deposition whilst on TCZ. The interval between commencement of TCZ therapy and the first improved SAP scan was 10 months (7–13). Figure 2 shows serial SAP scans of patient 4 who had regression of amyloid.

*QoL before and during treatment*

QoL was measured in 10 patients whilst treatment with TCZ was ongoing, and in three of these QoL was also measured prior to commencing therapy. Results are shown in Figure 3. A comparison of the mean scores in each domain before and after treatment were statistically significant (Mann-Whitney $p$=0.0354) whilst clinically significant changes were seen in all domains apart from mental health, in which the change was 9 points. The bodily pain domain showed the greatest improvement of 24 points, followed closely by the vitality and social functioning domains at 22 points each, and the physical functioning and role physical domains which showed a post-treatment improvement of 20 points each.

*Adverse events*

Adverse events (AEs) were reported in eight patients. Patient six developed two urinary tract infections (UTIs) and a respiratory tract infection within the first year of TCZ therapy; however, this patient had a long history of recurrent UTIs and was on a long term rotational antibiotic regimen of cephalexin and nitrofurantoin. Patient nine developed gallstone pancreatitis which resolved following endoscopic retrograde cholangiopancreatography. Neither of these patients had their TCZ therapy interrupted or stopped as a consequence of the AE.

Patient 20 has had an infusion delayed due to a transient drop in his white cell count. Patient one developed a subclinical Klebsiella ozaenae UTI, discovered coincidentally at a routine clinical review. Treatment was not stopped at that time; however, TCZ was temporarily discontinued just prior to renal transplantation. In view of ongoing inflammatory activity post-transplant TCZ was recommenced with excellent and dramatic anti-inflammatory effect, but was unfortunately complicated by a subcutaneous abscess around a peritoneal dialysis catheter cuff. TCZ treatment was temporarily halted whilst he was being treated for the infection, and has now recommenced. Patient eight had a four month break in treatment due to elevated LFTs; these have now normalised and he has resumed therapy at the same dose.

Patient 19 developed shingles two months after starting treatment, and bacterial pneumonia four months later; both episodes resulted in hospitalisation. Patient 13 developed EBV septicaemia after his renal transplant, detected on routine monitoring. His dose of TCZ was halved for six months until this resolved. Patient 10 was hospitalised for MAS; treatment with TCZ was temporarily halted during the acute period. Despite these complications, all three patients elected to continue with TCZ therapy.

Patient 14 has elected to have a 'treatment holiday'; however having had severe disease flares in the four months off TCZ he has restarted treatment. Patient 15 had a sudden cardiac death after over three years of successful treatment with TCZ; he had been on dialysis for six years at the time of his death.

## Discussion

The IL-6 gene is located on chromosome 7 (43). IL-6 is a 26-kDa glyco-

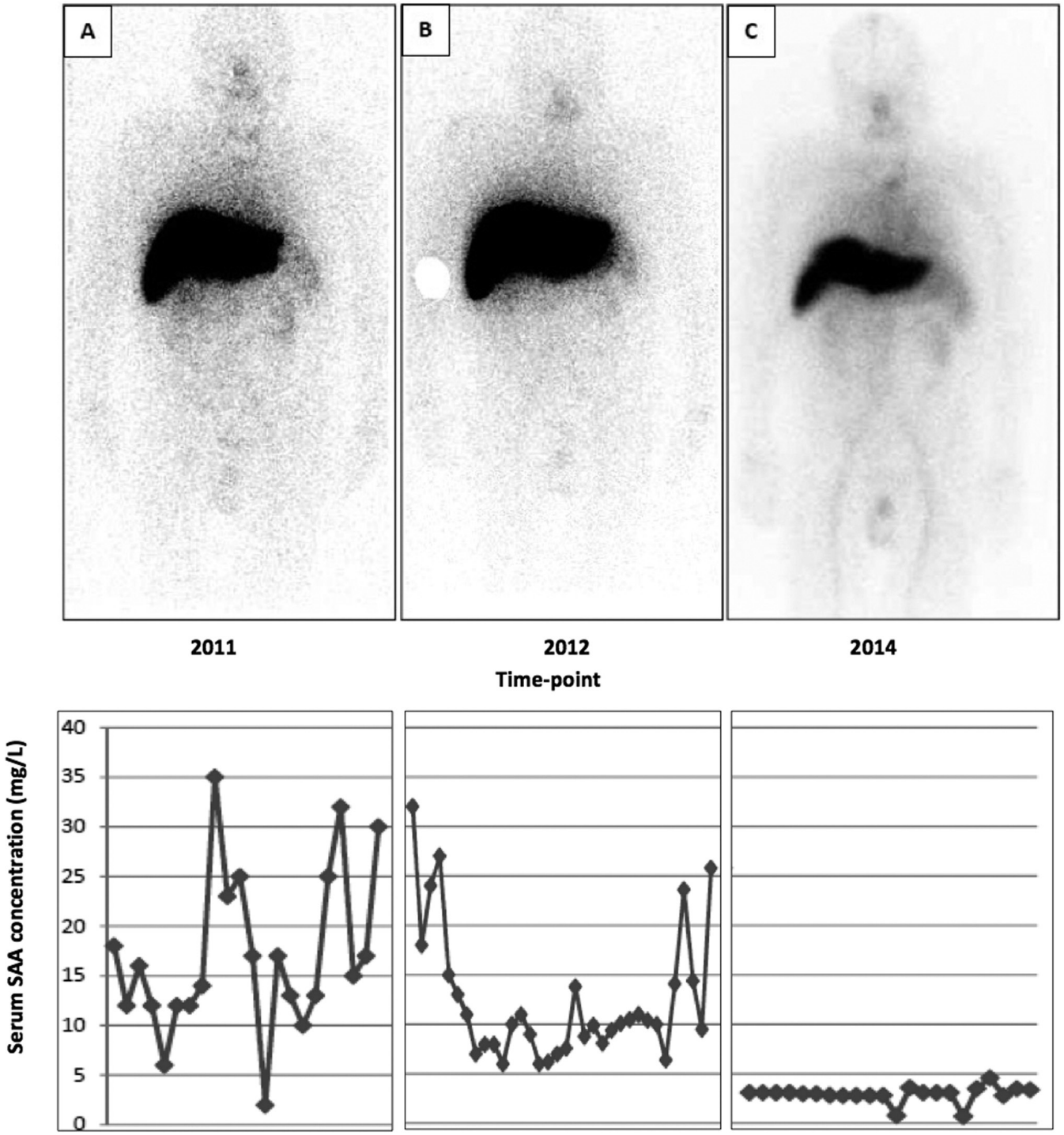


**Fig. 2.** Serial SAP scans showing regression of amyloid from the liver of patient 4 with corresponding serum SAA measurements over the time period. Previous treatment with MTX, ETC and CMB had little effect on the underlying inflammatory disease resulting in further accumulation of amyloid in the liver shown on the anterior SAP scan in 2012 (panel B) compared with the baseline scan in 2011 (panel A). Subsequent successful treatment with tocilizumab for two years resulted in regression of amyloid as shown in the 2014 SAP scan (panel C).

peptide produced by a variety of cell types including fibroblasts, osteoblasts, endothelial cells, monocytes, keratinocytes, T cells and B cells. IL-6 acts via two known signalling pathways; classic signalling through the membrane-bound IL-6 receptor (mIL-6R) via activation of glycoprotein gp130, or trans-signalling via soluble receptors (sIL-6R) (44). There is increasing evidence that classic signalling plays a role in tissue regeneration and trans-signalling is responsible for the majority of pro-inflammatory responses. Novel agents that specifically target soluble IL-6R are currently under investigation and may be advantageous in human disease (45). TCZ is a humanised anti-human IL-6R monoclonal antibody which binds both sIL-6R and mIL-6R, thereby inhibiting both signalling pathways (46). The rec-

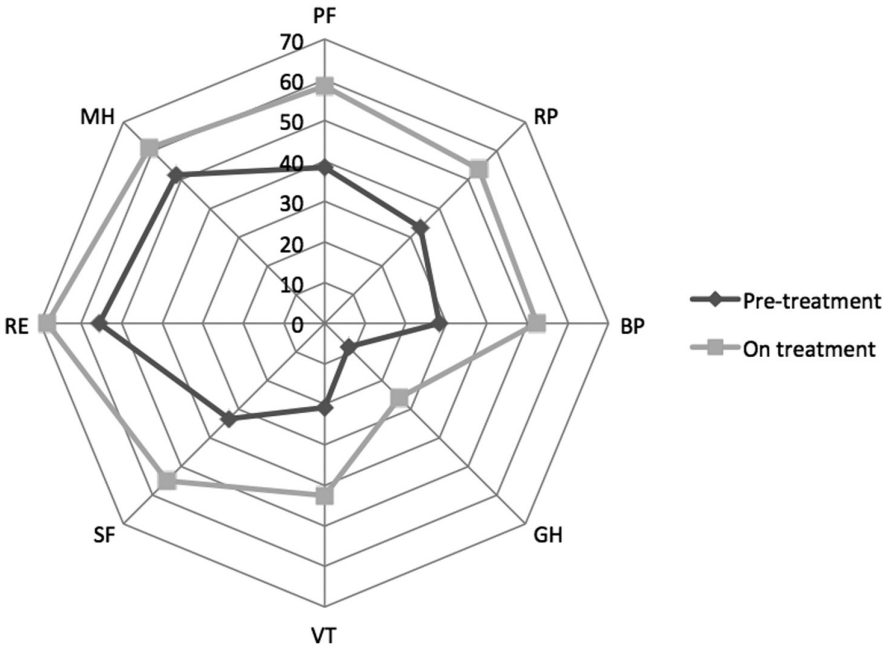


**Fig. 3.** Quality of life before and during treatment with tocilizumab. Patients were surveyed before and whilst on treatment. A comparison of the mean scores in each domain before and on-treatment were statistically significant (Mann-Whitney $p$=0.0354) whilst clinically significant changes were seen in all domains apart from mental health, in which the change was 9 points (a change of 10 points or more is considered clinically significant). PF: physical function; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: role emotional; MH: mental health.

ommended dosing for adults with RA is 8 mg/kg infused once every four weeks. Dose adjustments are recommended in cases of liver enzyme abnormalities, low absolute neutrophil count and low platelet count. Successful dose reduction in patients with low disease activity is possible, with dose escalation to treat occasional flare (47).

This small series shows that in patients with treatment-refractory chronic inflammatory conditions which have either already resulted in AA amyloidosis or which are a high risk of being complicated by it, TCZ can be effective in suppressing the hepatic acute phase response. In patients with AA amyloidosis suppression of SAA levels is the major goal of treatment as this is known to dramatically improve outcome. We had been optimistic that TCZ would reduce SAA levels as IL-6 is the most important cytokine driving the hepatic acute phase response. This property raises the theoretical possibility that IL-6 blockade could work at the level of hepatocytes to dissociate on-going symptomatic inflammatory disease from a measurable hepatic acute phase response. In AA amyloidosis such an outcome could effectively prevent progressive amyloid deposition without providing any relief from inflammatory symptoms, particularly in those patients with chronic joint damage from inflammatory arthritides. Somewhat to our

**Table II.** Details of tocilizumab treatment.

| Patient ID | Age at Onset of Therapy (y) | TCZ dose, frequency, route | Serological response to TCZ | Clinical response to TCZ | Duration of therapy (m) | Monotherapy/ with other agent | Continuing | Reason, if not continuing |
|---|---|---|---|---|---|---|---|---|
| 1 | 56 | 162 mg q2w sc | Complete | Partial | 3 | Pred 15 mg daily | Yes | |
| 2 | 65 | 8 mg/kg q4w iv | Complete | Partial | 20 | Pred 10 mg daily | Yes | |
| 3 | 54 | 8 mg/kg q4w iv | Complete | Partial | 12 | Monotherapy | Yes | |
| 4 | 56 | 8 mg/kg q6w iv | Complete | Partial | 23 | Monotherapy | Yes | |
| 5 | 57 | 8 mg/kg q4w iv | Complete | Complete | 14 | Pred 10 mg | Yes | |
| 6 | 53 | 8 mg/kg q4w iv | Complete | Partial | 34 | Pred 5 mg daily | Yes | |
| 7 | 64 | 8 mg/kg q4w iv | Complete | Partial | 30 | Monotherapy | Yes | |
| 8 | 35 | 8 mg/kg q6w iv | Complete | Partial | 28 | Pred 5 mg | Yes | |
| 9 | 39 | 8 mg/kg q4w iv | Complete | Partial | 44 | Monotherapy | Yes | |
| 10 | 6 | 8 mg/kg q3w iv | Complete | Partial | 9 | ETC 25 mg bi-weekly; MTX 20 mg weekly; Pred 4 mg daily | Yes | |
| 11 | 26 | 8 mg/kg q4w iv | Complete | Partial | 24 | Pred, LEF | Yes | |
| 12 | 51 | 8 mg/kg q4w iv | Complete | Complete | 38 | Monotherapy | Yes | |
| 13 | 28 | 8 mg/kg q4w iv | Complete | Complete | 24 | Pred 0.5 mg daily | Yes | |
| 14 | 24 | 8 mg/kg q4w iv | Complete | Complete | 13 | Monotherapy | Yes | |
| 15 | 52 | 8 mg/kg q4w iv | Complete | Partial | 39 | Monotherapy | No | Deceased |
| 16 | 15 | 8 mg/kg q4w iv | Complete | Complete | 18 | COL 1.5 mg daily | Yes | |
| 17 | 50 | 8 mg/kg q4w iv | Complete | Complete | 22 | Monotherapy | Yes | |
| 18 | 25 | 8 mg/kg q4w iv | Complete | Partial | 19 | Pred 5 mg daily; ANA 50 mg weekly | Yes | |
| 19 | 59 | 8 mg/kg q4w iv | Complete | Partial | 6 | Pred 15 mg daily | Yes | |
| 20 | 49 | 8 mg/kg q4w iv | Partial | Partial | 4 | COL 1.5 mg daily | Yes | |

Complete response is defined as complete resolution of symptoms or complete normalisation of serological inflammatory markers SAA and CRP (<10 mg/L); Partial response is defined as good but incomplete resolution of symptoms or reduction by >50% but not complete normalisation of serological inflammatory markers SAA and CRP. Pred: prednisolone.

surprise whilst not all patients reported complete symptom resolution, all patients reported feeling at least somewhat better. Furthermore, two patients with MKD showed complete clinical and serological response to TCZ; this has previously been described only in one other patient (48). The response has been sustained to date in all patients who remain on TCZ (17, 85%); none have discontinued treatment due to loss of efficacy, however, longer follow-up is required.

Treatment-related AEs were largely infections. Despite three patients requiring hospitalisation for AEs, all elected to continue treatment feeling that their clinical improvement justified the risks. Six patients temporarily stopped treatment due to AEs, and none yet have permanently discontinued TCZ therapy due to AEs.

At present IL-1 inhibition remains the first-line therapeutic option in patients with confirmed or suspected systemic autoinflammatory disorders as they have a proven safety and efficacy profile (49, 50) and are generally well tolerated. However, this small series with an on-treatment follow-up of 23 months (13–35) demonstrates that TCZ appears both relatively safe and effective even in the situations of renal failure, solid organ transplantation and extensively pre-treated diseases, and has resulted in stabilisation or reduction of amyloid deposits in all patients with AA amyloidosis. A therapeutic trial of TCZ is therefore reasonable in patients who fail to respond to other treatments, even in those in whom a firm diagnosis has not yet been made.

## References


1. LANE T, LOEFFLER JM, ROWCZENIO DM *et al*.: AA amyloidosis complicating the inherited periodic fever syndromes. *Arthritis Rheum* 2013; 65: 1116-21.
2. LACHMANN HJ, GOODMAN HJB, GILBERTSON JA *et al*.: Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; 356: 2361-71.
3. GILLMORE JD, LOVAT LB, PERSEY MR, PEPYS MB, HAWKINS PN: Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 2001; 358: 24-9.
4. TER HAAR N, LACHMANN H, OZEN S *et al*.: Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis* 2013; 72: 678-85.
5. RYAN JG, GOLDBACH-MANSKY R: The spectrum of autoinflammatory diseases: recent bench to bedside observations. *Curr Opin Rheumatol* 2008; 20: 66-75.
6. SCARPIONI R, RIGANTE D, CANTARINI L *et al*.: Renal involvement in secondary amyloidosis of Muckle-Wells syndrome: marked improvement of renal function and reduction of proteinuria after therapy with human anti-interleukin-1beta monoclonal antibody canakinumab. *Clin Rheumatol* 2015; 34: 1311-6.
7. GABAY C, EMERY P, VAN VOLLENHOVEN R *et al*.: Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013; 381: 1541-50.
8. PERS YM, FORTUNET C, CONSTANT E *et al*.: Predictors of response and remission in a large cohort of rheumatoid arthritis patients treated with tocilizumab in clinical practice. *Rheumatology* (Oxford) 2014; 53: 76-84.
9. BURMESTER GR, FEIST E, KELLNER H, BRAUN J, IKING-KONERT C, RUBBERT-ROTH A: Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). *Ann Rheum Dis* 2011; 70: 755-9.
10. HIRABAYASHI Y, ISHII T, HARIGAE H: Clinical efficacy of tocilizumab in patients with active rheumatoid arthritis in real clinical practice. *Rheumatol Int* 2010; 30: 1041-8.
11. NAKASHIMA Y, KONDO M, HARADA H *et al*.: Clinical evaluation of tocilizumab for patients with active rheumatoid arthritis refractory to anti-TNF biologics: tocilizumab in combination with methotrexate. *Mod Rheumatol* 2010; 20: 343-52.
12. TAKEUCHI T, TANAKA Y, AMANO K *et al*.: Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients--REACTION 52-week study. *Rheumatology* (Oxford) 2011; 50: 1908-15.
13. WAKABAYASHI H, OKA H, NISHIOKA Y, HASEGAWA M, SUDO A, NISHIOKA K: Do biologics-naive patients with rheumatoid arthritis respond better to tocilizumab than patients for whom anti-TNF agents have failed? A retrospective study. *Clin Exp Rheumatol* 2011; 29: 314-7.
14. YAMANAKA H, TANAKA Y, INOUE E *et al*.: Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). *Mod Rheumatol* 2011; 21: 122-33.
15. BYKERK VP, OSTOR AJ, ALVARO-GRACIA J *et al*.: Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis* 2012; 71: 1950-4.
16. LEFFERS HC, OSTERGAARD M, GLINTBORG B *et al*.: Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. *Ann Rheum Dis* 2011; 70: 1216-22.
17. EMERY P, KEYSTONE E, TONY HP *et al*.: IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; 67: 1516-23.
18. KREMER JM, BLANCO R, BRZOSKO M *et al*.: Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011; 63: 609-21.
19. SMOLEN JS, BEAULIEU A, RUBBERT-ROTH A *et al*.: Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; 371: 987-97.
20. GENOVESE MC, MCKAY JD, NASONOV EL *et al*.: Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008; 58: 2968-80.
21. YAZICI Y, CURTIS JR, INCE A *et al*.: Early effects of tocilizumab in the treatment of moderate to severe active rheumatoid arthritis: a one-week sub-study of a randomised controlled trial (Rapid Onset and Systemic Efficacy [ROSE] Study). *Clin Exp Rheumatol* 2013; 31: 358-64.
22. ADDIMANDA O, POSSEMATO N, MACCHIONI P, SALVARANI C: Efficacy and safety of tocilizumab in refractory rheumatoid arthritis: a real life cohort from a single centre. *Clin Exp Rheumatol* 2014; 32: 460-4.
23. WOO P, WILKINSON N, PRIEUR AM *et al*.: Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. *Arthritis Res Ther* 2005; 7: R1281-1288.
24. YOKOTA S, IMAGAWA T, MORI M *et al*.: Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; 371: 998-1006.
25. YOKOTA S, IMAGAWA T, MORI M *et al*.: Long-term treatment of systemic juvenile idiopathic arthritis with tocilizumab: results of an open-label extension study in Japan. *Ann Rheum Dis* 2013; 72: 627-8.
26. DE BENEDETTI F, BRUNNER HI, RUPERTO N *et al*.: Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2385-95.
27. NISHIMOTO N, KANAKURA Y, AOZASA K *et al*.: Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 2005; 106: 2627-32.
28. ITO H, TAKAZOE M, FUKUDA Y *et al*.: A pilot

randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; 126: 989-96; discussion 947.
29. RAVELLI A, SCHNEIDER R, WEITZMAN S *et al*.: A56: macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis treated with tocilizumab. *Arthritis Rheumatol* 2014; 66 (Suppl. 11): S83-84.
30. DE BENEDETTI F, RUPERTO N, BAILDAM E *et al*.: A14: neutropenia with tocilizumab treatment is not associated with increased infection risk in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum* (Hoboken, NJ) 2014; 66 (Suppl. 11): S23-24.
31. IWAMOTO M, HONMA S, ASANO Y, MINOTA S: Effective and safe administration of tocilizumab to a patient with rheumatoid arthritis on haemodialysis. *Rheumatol Int* 2011; 31: 559-60.
32. NAGAI K, UEDA A, YAMAGATA K: Successful use of tocilizumab in a case of multicentric Castleman's disease and end-stage renal disease. *Ther Apher Dial* 2014; 18: 210-1.
33. KAWABATA H, KOTANI S, MATSUMURA Y *et al*.: Successful treatment of a patient with multicentric Castleman's disease who presented with thrombocytopenia, ascites, renal failure and myelofibrosis using tocilizumab, an anti-interleukin-6 receptor antibody. *Intern Med* 2013; 52: 1503-7.
34. MORI S, YOSHITAMA T, HIDAKA T, HIRAKATA N, UEKI Y: Effectiveness and safety of tocilizumab therapy for patients with rheumatoid arthritis and renal insufficiency: a real-life registry study in Japan (the ACTRA-RI study). *Ann Rheum Dis* 2015; 74: 627-30.
35. MIYAGAWA I, NAKAYAMADA S, SAITO K *et al*.: Study on the safety and efficacy of tocilizumab, an anti-IL-6 receptor antibody, in patients with rheumatoid arthritis complicated with AA amyloidosis. *Mod Rheumatol* 2014; 24: 405-9.
36. LEDUE TB, WEINER DL, SIPE JD, POULIN SE, COLLINS MF, RIFAI N: Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. *Ann Clin Biochem* 1998; 35: 745-53.
37. TALMUD P, TYBJAERG-HANSEN A, BHATNAGAR D *et al*.: Rapid screening for specific mutations in patients with a clinical diagnosis of familial hypercholesterolaemia. *Atherosclerosis* 1991; 89: 137-41.
38. GERTZ MA, COMENZO R, FALK RH *et al*.: Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. *Am J Hematol* 2005; 79: 319-28.
39. PUCHTLER H, SWEAT F, LEVINE M: On the binding of Congo red by amyloid. *J Histochem Cytochem* 1962; 10: 355-64.
40. TENNENT GA, CAFFERTY KD, PEPYS MB, HAWKINS PN: Congo red overlay immunohistochemistry aids classification of amyloid deposits. *In*: Amyloid and Amyloidosis 1998. KYLE RA, GERTZ MA (Eds.) Pearl River, New York: Parthenon Publishing; 1999: 160-162.
41. HAWKINS PN, LAVENDER JP, PEPYS MB: Evaluation of systemic amyloidosis by scintigraphy with $^{123}$I-labeled serum amyloid P component. *N Engl J Med* 1990; 323: 508-13.
42. HAWKINS PN, PEPYS MB: Imaging amyloidosis with radiolabelled SAP. *Eur J Nucl Med* 1995; 22: 595-9.
43. SRIRANGAN S, CHOY EH: The role of interleukin 6 in the pathophysiology of rheumatoid arthritis. *Ther Adv Musculoskelet Dis* 2010; 2: 247-56.
44. DAYER JM, CHOY E: Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology* (Oxford) 2010; 49: 15-24.
45. WAETZIG GH, ROSE-JOHN S: Hitting a complex target: an update on interleukin-6 trans-signalling. *Expert Opin Ther Targets* 2012; 16: 225-36.
46. MIHARA M, KASUTANI K, OKAZAKI M *et al*.: Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. *Int Immunopharmacol* 2005; 5: 1731-40.
47. VAN HERWAARDEN N, HERFKENS-HOL S, VAN DER MAAS A *et al*.: Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity. *Clin Exp Rheumatol* 2014; 32: 390-4.
48. SHENDI HM, DEVLIN LA, EDGAR JD: Interleukin 6 blockade for hyperimmunoglobulin D and periodic fever syndrome. *J Clin Rheumatol* 2014; 20: 103-5.
49. SELMI C, CERIBELLI A, NAGUWA SM, CANTARINI L, SHOENFELD Y: Safety issues and concerns of new immunomodulators in rheumatology. *Expert Opin Drug Saf* 2015; 14: 389-99.
50. CANTARINI L, LOPALCO G, CASO F *et al*.: Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behçet's disease. *Autoimmun Rev* 2015; 14: 1-9.