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CLINICAL SCIENCE

bDMARD can prevent the progression of AA amyloidosis to end-stage renal disease

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ABSTRACT

Introduction AA amyloidosis (AA) can be the consequence of any chronic inflammatory disease. AA is associated with chronic inflammatory diseases (cid+AA), autoinflammatory syndromes (auto+AA) or AA of unknown origin or idiopathic AA (idio+AA). The major organ manifestation is renal AA that can progress to end-stage renal disease (ESRD) and multiple organ failure.

Materials and methods This study is a monocentric retrospective analysis of the renal outcome and survival of patients with cid+AA (n=34), auto+AA (n=24) and idio+AA (n=25) who were treated with cytokine-inhibiting biological disease-modifying antirheumatic drugs (bDMARDs).

Results 83 patients with renal AA were identified and followed for a mean observational period of 4.82 years. C reactive protein (CRP), serum amyloid alpha and proteinuria were significantly reduced with bDMARD therapy. Progression to ESRD was prevented in 60% (cid+AA), 88% (auto+AA) and 81% (idio+AA) of patients. Tocilizumab was given to 34 patients with cid+AA and idio+AA and was more effective in reducing CRP and progression to ESRD and death compared with other bDMARDs.

Conclusions bDMARDs reduce systemic inflammation in various diseases, leading to a reduction of proteinuria and prevention of ESRD. Importantly, tocilizumab was more effective than other bDMARDs in controlling systemic inflammation in patients with chronic inflammatory diseases and idiopathic AA, leading to better renal and overall survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ AA amyloidosis is caused by various chronic inflammatory conditions with persistently increased levels of interleukin (IL) 6, serum amyloid alpha and/or IL-1 depending on the associated disease.

⇒ Treatment of renal AA amyloidosis as the most common organ manifestation relies on case series having shown the clinical efficacy of various biological disease-modifying antirheumatic drugs (bDMARDs).

WHAT THIS STUDY ADDS

⇒ This is the first comprehensive study to show the efficacy and safety of bDMARD treatment in renal AA amyloidosis, comparing three different aetiological subgroups (chronic inflammatory diseases and AA amyloidosis (cid+AA), autoinflammatory syndrome and AA amyloidosis (auto+AA), and idiopathic AA amyloidosis (idio+AA)) including a high number of patients with a mean observational period of 4.82 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In patients with auto+AA, inhibition of IL-1 has shown excellent clinical efficacy and safety, and in cid+AA and idio+AA tocilizumab has shown superior efficacy compared with other bDMARDs.

⇒ The data suggest preferential use of IL-1 inhibitors and tocilizumab for clinical use in the treatment of AA amyloidosis depending on the respective underlying diseases.

INTRODUCTION

Systemic amyloidoses are rare diseases characterised by deposition of misfolded proteins in various tissues, leading to progressive organ damage including chronic kidney disease (CKD) stage V, malabsorption with cachexia and cardiac failure.[1] They are classified depending on the protein forming the amyloid fibrils in the tissue.[2] Serum amyloid alpha (SAA) amyloidosis (AA) can be the consequence of any chronic inflammatory disease (CID).[3] CIDs are characterised by elevated serum levels of interleukin (IL) 6, IL-1β, tumour necrosis factor (TNF)-α and other proinflammatory cytokines that consecutively lead to an increased production of C reactive protein (CRP) and SAA.[4] SAA is subject to proteolytic cleavage, and the cleavage product can form amyloid fibrils in various tissues.[5] The SAA serum concentration correlates with the progression or regression of the amyloid tissue burden and renal function.[6 7] The characteristic cascade of renal involvement is a subclinical proteinuria at the beginning that progresses to nephrotic syndrome and end-stage renal disease (ESRD).[8] Other organ manifestations rarely precede the renal involvement in AA amyloidosis (AA).[9]

The inflammatory diseases that cause AA can be divided into three major groups.[10] The first group comprises CID, such as rheumatoid arthritis and Crohn's disease (as well as chronic infections), where elevated levels of IL-6 drive persistently increased production of SAA in cid+AA.[11–13] The second group comprises autoinflammatory disorders, such as familial Mediterranean fever (FMF), where dysregulated inflammasomes mediate an

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Table 1 Patients with various primary diseases and AA amyloidosis: demographic parameters at visit 1

	A: cid+AA	B: idio+AA	C: auto+AA	P value (AB vs C)
Patients, n	34	25	24	ns
Female gender, n (%)	26 (76.5)	17 (68.0)	11 (45.8)	0.045
Age at AA (years), mean (SEM)	60.9 (1.9)	63.1 (2.2)	46.6 (2.0)	0.0001
Age at disease onset (years), mean (SEM)	45.2 (3.0)	Unknown	31.7 (3.5)	ns
Treatment V1 to last visit (years), mean (SEM)	5.95 (1.07)	4.54 (1.10)	3.96 (0.81)	ns
Amyloid in renal biopsy, n (%)	34 (100)	25 (100)	24 (100)	ns
Amyloid in FAB, n (%)	22 (64.7)	15 (60.0)	8 (33.4)	0.028
GIT amyloidosis, n (%)	14 (41.2)	10 (40.0)	11 (45.8)	ns
Heart amyloidosis, n (%)	4 (11.8)	1 (4.0)	4 (16.7)	ns
Serum creatinine at V1 (mg/dL), n (%)				
<2.5	20 (58.8)	14 (56.0)	21 (87.5)	0.010
2.5–5	10 (29.4)	8 (32.0)	3 (12.5)	ns
ESRD at V1, n (%)	4 (11.8)	3 (12.0)	0 (0.0)	ns
Protein to creatinine ratio at V1 (g/mol), n (%)				
<300	13 (38.2)	8 (32.0)	11 (45.8)	ns
300–1000	7 (20.6)	8 (32.0)	9 (37.5)	ns
>1000	14 (41.2)	9 (36.0)	4 (16.7)	ns
Primary disease, n	Arthritis: 18 IBD: 8 Others: 8	Idiopathic: 25	FMF: 22 CAPS: 2	
Previous csDMARD, n (%)	30 (96.8)	0	23 (95.8)	0.001
Previous bDMARD, n (%)	14 (45.1)	0	22 (91.7)	0.001
BMI (kg/m^2), mean (SEM)	27.54 (4.59)	32.38 (8.36)	26.84 (5.86)	0.0001
SAA1α/α, n (%)	21 (93.3)	20 (100)	9 (45.0)	0.0000

AA, AA amyloidosis; auto+AA, patients with an autoinflammatory syndrome and AA amyloidosis; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CAPS, cryopyrin-associated periodic syndrome; cid+AA, patients with chronic inflammatory diseases and AA amyloidosis; csDMARD, corticosteroid-sparing disease-modifying antirheumatic drug; ESRD, end-stage renal disease; FAB, fat tissue aspiration biopsy; FMF, familial Mediterranean fever; GIT, gastrointestinal tract; IBD, inflammatory bowel disease; idio+AA, patients with idiopathic AA amyloidosis; SAA, serum amyloid alpha; V1, visit 1.

overproduction of IL-1β, which leads to increased levels of SAA in auto+AA.[14–16] The third group comprises patients without any identifiable underlying disease for their AA, and this subtype is called idiopathic AA (idio+AA).[17–19] Within the group of idio+AA, an important susceptibility factor is obesity in combination with a homozygous *SAA1.1* gene polymorphism.[20]

In this study, we analysed clinical and laboratory parameters at baseline and during follow-up. All patients were treated with biological disease-modifying antirheumatic drugs (bDMARDs).

MATERIALS AND METHODS

Patient cohort

We performed a retrospective analysis of patients with AA who were diagnosed between the years 2010 and 2022. We divided the patients into three groups depending on the underlying disease. The first group comprised 34 patients with seropositive and seronegative rheumatoid arthritis (n=18; classified by the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 rheumatoid arthritis classification criteria[21]); inflammatory bowel diseases (IBD) (n=8; classified according to clinical, endoscopic, radiological and histopathological characteristics), of whom 4 had concomitant axial spondyloarthritis; polymyalgia rheumatica (n=2; classified by the 2012 provisional classification criteria for polymyalgia rheumatica[22]); chronic recurrent multifocal osteomyelitis (n=2; classified by clinical presentation as described by Jansson *et al*[23]); chronic sarcoidosis (n=2; classified according to clinical, laboratory, radiological and histopathological findings as described by Heinle and Chang[24]); systemic lupus erythematosus (n=1; classified by the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus[25]); and Castleman's disease (n=1; diagnosed by consensus diagnostic criteria for idiopathic multicentric Castleman's disease[26]) as the primary disease, designated as cid+AA. The second group comprised 24 patients with FMF (n=22) and cryopyrin-associated periodic syndrome (CAPS; n=2), designated as auto+AA. The third group comprised 25 patients with AA amyloidosis without a detected primary disease, designated as idio+AA. Follow-up investigations with clinical and laboratory measurements were held every 6 months for each subgroup.

Diagnosis of AA

All patients with AA had renal involvement confirmed by kidney biopsy. A positive Congo red staining of the amyloid deposits was confirmed in all cases by an immunofluorescence staining and negative results for other types of amyloid, especially AL, ATTR and AFib. Furthermore, subcutaneous fat tissue aspiration biopsies (FAB) were performed to confirm the systemic nature of AA. The amyloid deposits in the FAB were semiquantified using the amyloid score.[27]

Immunosuppressive treatment

Different bDMARDs were used to treat the various underlying diseases according to guidelines, drug approval (if

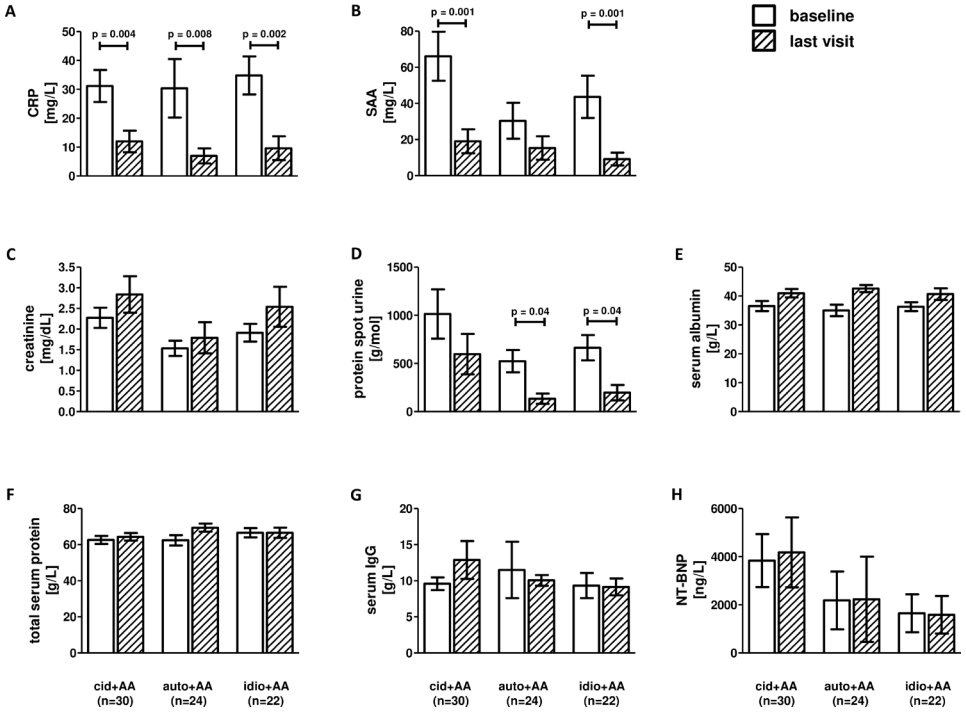

Figure 1 Serum biomarkers and proteinuria were analysed in AA patient subgroups with chronic inflammatory disease (cid+AA), autoinflammatory disease (auto+AA) and idiopathic (idio+AA). bDMARD treatment was initiated at the first visit (baseline) and compared with the last documented visit 4–6 years later. C reactive protein (CRP) (A), serum amyloid alpha (SAA) (B), serum creatinine (C), proteinuria on spot urine (D), serum albumin (E), total serum protein (F), serum IgG (G) and N-terminal brain natriuretic peptide (NT-BNP) (H) were analysed at the first and last visit. AA, AA amyloidosis; bDMARD, biological disease-modifying antirheumatic drug.

present), potential contraindications and patients' tolerance. Patients were categorised by their primary disease and the bDMARD used to control the systemic inflammation. Tocilizumab (TOC) (n=18) as well as other bDMARDs (in total n=16; anakinra n=6; adalimumab n=4; etanercept n=3; infliximab n=1; ustekinumab n=1; secukinumab n=1) were used to treat patients with cid+AA. The IL-1 inhibitors anakinra and canakinumab were prescribed for patients with auto+AA. Patients with idio+AA were treated with either TOC (n=16) or a different bDMARD of various mechanisms (in total n=9; anakinra n=4; adalimumab n=5).

Renal function parameters

Renal function was assessed by serum creatinine levels (mg/dL) and quantification of protein excretion in the spot urine (g protein/mol creatinine). Proteinuria ranged from 500 g/mol to 1000 g/mol (about 5–10 g protein in 24-hour urine). These parameters were determined at each follow-up. Chronic kidney damage was classified according to CKD stages I–V.[28] The definition of CKD was a glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months. A preserved renal function was clinically defined as the absence of CKD stage V, which referred to an estimated GFR >15 mL/min.

Biomarkers

The biomarkers in the serum and urine were quantified in the central lab of our university hospital. The normal range for CRP was <5 mg/L, for SAA <6.3 mg/L, IgG 7–16 g/L, albumin 30–50 g/L, total serum protein 60–80 g/L and N-terminal brain natriuretic peptide (NT-BNP) with age-adjusted ranges. Moreover, proteinuria was quantified using the protein to creatinine ratio normal range of <10 g/mol on spot urine.

Body mass index

Body mass index (BMI) was calculated for each patient dividing body weight (kg) by the square of height in metres.[29] BMI was grouped into underweight (<18.5 kg/m^2), normal weight (18.5–25 kg/m^2), overweight (25–30 kg/m^2) and obesity (>30 kg/m^2).

Genetic analysis

The *SAA1* alleles were determined as *SAA1.1* (*SAA1α*, p.Val52/p.Ala57), *SAA1.2* (*SAA1β*, p.Ala52/p.Val57) or *SAA1.3* (*SAA1γ*, p.Ala52/p.Ala57).

Patients with FMF were diagnosed according to the Tel Hashomer criteria[30] and the revised criteria including molecular genetic results.[31] The *MEFV* gene was analysed by Sanger sequencing of exons 1–10. All patients had at least one pathogenic *MEFV* variant, and majority of the patients have two pathogenic *MEFV* variants. Patients with CAPS were diagnosed according to published criteria.[32] Both patients with CAPS had pathogenic *NLRP3* variants.

Statistical analyses

A Fisher's exact test was used to analyse categorical variables.[33] Numeric variables were determined as mean (SEM) and were compared using a non-parametric Mann-Whitney U test.[34] To compare the long-term efficacy of different treatments, data on patients receiving TOC or other bDMARDs were shown on Kaplan-Meier plots, with every dropout representing a patient

Table 2 Baseline parameters in patients with stable renal function or progressive renal failure at the end of observation

	Stable renal function	Progressive renal failure	P value
Patients, n (%)	57	19	
Female gender, n (%)	38 (66.7)	13 (68.4)	ns
Age at AA (years), mean (SEM)	55.3 (2.0)	59.4 (2.2)	ns
Age at disease onset (years), mean (SEM)	36.1 (3.0)	39.7 (4.9)	ns
Treatment V1 to last visit (years), mean (SEM)	5.0 (0.8)	4.9 (0.9)	ns
Primary disease, n (%)			
Arthritis	10 (17.5)	6 (31.6)	ns
IBD	4 (7.0)	3 (15.8)	
Other	4 (7.0)	3 (15.8)	
Idiopathic	18 (31.6)	4 (21.1)	
Autoinflammatory syndrome	21 (36.8)	3 (15.8)	
Concomitant disease, n (%)			ns
Arterial hypertension	25 (43.9)	6 (31.6)	
Diabetes mellitus type 2	1 (1.8)	2 (10.5)	
Metabolic syndrome	4 (7.0)	1 (5.3)	
None	27 (47.4)	10 (52.6)	
FAB CR stain at V1			ns
3+ (10%–60% area)	3	3	
2+ (1%–10% area)	5	2	
1+ (<1% area)	20	9	
0	10	5	
Not done	12	7	
Serum creatinine at V1, mean (SEM)	1.57 (0.1)	3.06 (0.35)	0.0001
Serum creatinine <2.5 mg/dL at V1, n (%)	42 (73.7)	8 (42.1)	0.024
Protein to creatinine ratio at V1, mean (SEM)	759.2 (226.8)	1428.7 (403.8)	0.021
Protein to creatinine ratio <300 g/mol at V1, n (%)	18 (31.6)	2 (10.5)	ns
CRP at V1, mean (SEM)	37.6 (5.3)	22.2 (3.6)	ns
CRP at last visit (<5 mg/L)	10.8 (2.7)	7.9 (1.6)	ns
P value V1 vs last visit	0.0001	0.0049	
SAA at V1, mean (SEM)	83.4 (20.0)	57.3 (21.2)	ns
SAA at last visit (<8.6 mg/L)	14.2 (4.2)	19.6 (8.2)	ns
P value V1 vs last visit	0.0001	0.0068	
BMI (kg/m^2), mean (SEM)	28.79 (3.59)	27.83 (3.67)	ns
SAA1α/α, n (%)	35 (77.8)	8 (72.7)	ns

AA, AA amyloidosis; BMI, body mass index; CRP, C reactive protein; IBD, inflammatory bowel disease; SAA, serum amyloid alpha; V1, visit 1.

who developed ESRD or progression of amyloidosis on other organs/death, respectively. Statistical analysis was performed using log-rank test. Analysis and graphics were all prepared with GraphPad Prism software. Statistical significance was assumed at $p<0.05$ in every test.

RESULTS

Demographic parameters at baseline

83 patients with AA were included. Patients with auto+AA were significantly younger than those with cid+AA and idio+AA ($p=0.0001$; table 1), as expected. The prevalence of female gender was similar in the cid+AA and idio+AA groups, with a female predominance of 76,5% and 68.0%, compared with the auto+AA group with 45.8% ($p=0.045$; table 1). Patients with cid+AA and auto+AA had significantly higher frequency of former treatment with corticosteroid-sparing disease-modifying antirheumatic drug and bDMARD prior to the diagnosis of AA. In contrast, none of the patients with idio+AA has been treated with disease-modifying antirheumatic drug before the diagnosis of AA. The *SAA1.1+1.1 (SAA1α/α)* genotype can indicate a genetic predisposition to the development of AA. The *SAA1.1+1.1* genotype was present in 93.3% of patients with cid+AA and 100% of those with idio+AA, but only in 45% of those with auto+AA ($p<0.0001$). Our results show that FAB was the organ biopsy with the highest yield of AA deposits (45/83, 54.2%), next to kidney biopsy (table 1). Importantly, patients with auto+AA were less likely to show AA deposits on FAB ($p=0.028$; table 1). Of the 83 patients, AA deposits were detected in the gastrointestinal tract of 35 (42.2%) and in the myocardial biopsies of 9 (10.8%) patients with AA. Obesity was significantly more prevalent in cid+AA and idio+AA than in auto+AA ($p=0.0001$; table 1).

Serum and urine parameters at baseline and at the last visit

The laboratory biomarkers at the first visit (baseline) until the last visit are shown in figure 1. Patients who were in CKD stage V at the first visit were excluded from this analysis (n=7). At baseline, we observed elevated CRP and SAA in all AA subgroups, which were significantly reduced with bDMARD therapy shortly after initiation and remained low until the last visit (figure 1A,B). We observed a modest increase in the mean serum creatinine levels which was not statistically significant in all AA subgroups (figure 1C). A decrease in proteinuria was observed in all AA subgroups with bDMARD therapy (figure 1D). This was significant for patients with auto+AA and idio+AA and a trend was detected for the cid+AA group (figure 1D). In contrast, the serum levels of albumin, total serum protein, IgG and NT-BNP did not change significantly in either group from the first to the last visit (figure 1E–H). These analyses show that bDMARD treatment significantly reduced CRP and SAA, which was associated with reduction of proteinuria and prevention of deterioration of serum creatinine and NT-BNP.

Stabilisation of renal function with bDMARD therapy

Next, we analysed a more detailed time course of the changes of serum creatinine and proteinuria after initiation of bDMARD treatment (table 2). Patients were divided in groups with a preserved renal function and with ESRD at their last visit (figure 2A–H). Serum creatinine and proteinuria were normalised to the baseline parameters and followed until the last documented visit. Analyses of the total cohort (figure 2A,B) and the AA subgroups (figure 2C–H) are shown. During the first 12 months of bDMARD treatment, we observed a stable serum creatinine and a decline of proteinuria. Interestingly, after 18 months and at later time points, we observed a significant rise in serum creatinine and proteinuria in 25% of patients, indicating a significant decline of renal function (figure 2A,B). While 57 of 76 patients (75.0%) remained stable with their kidney function, 19 of 76 patients (25.0%) deteriorated to ESRD (figure 2A,B). We observed a similar time course in patients with all AA subgroups' various treatments with bDMARDs (figure 2C–H). Deterioration of kidney function was observed in 40.0% of cid+AA (figure 2C,D), in 18.2% of idio+AA (figure 2E,F) and in 12.5% of auto+AA (figure 2G,H). These findings indicate that bDMARDs can stabilise the renal function in 75.0% of patients. However, 25.0% of patients still progressed to ESRD despite bDMARD treatment. This effect was more prevalent in

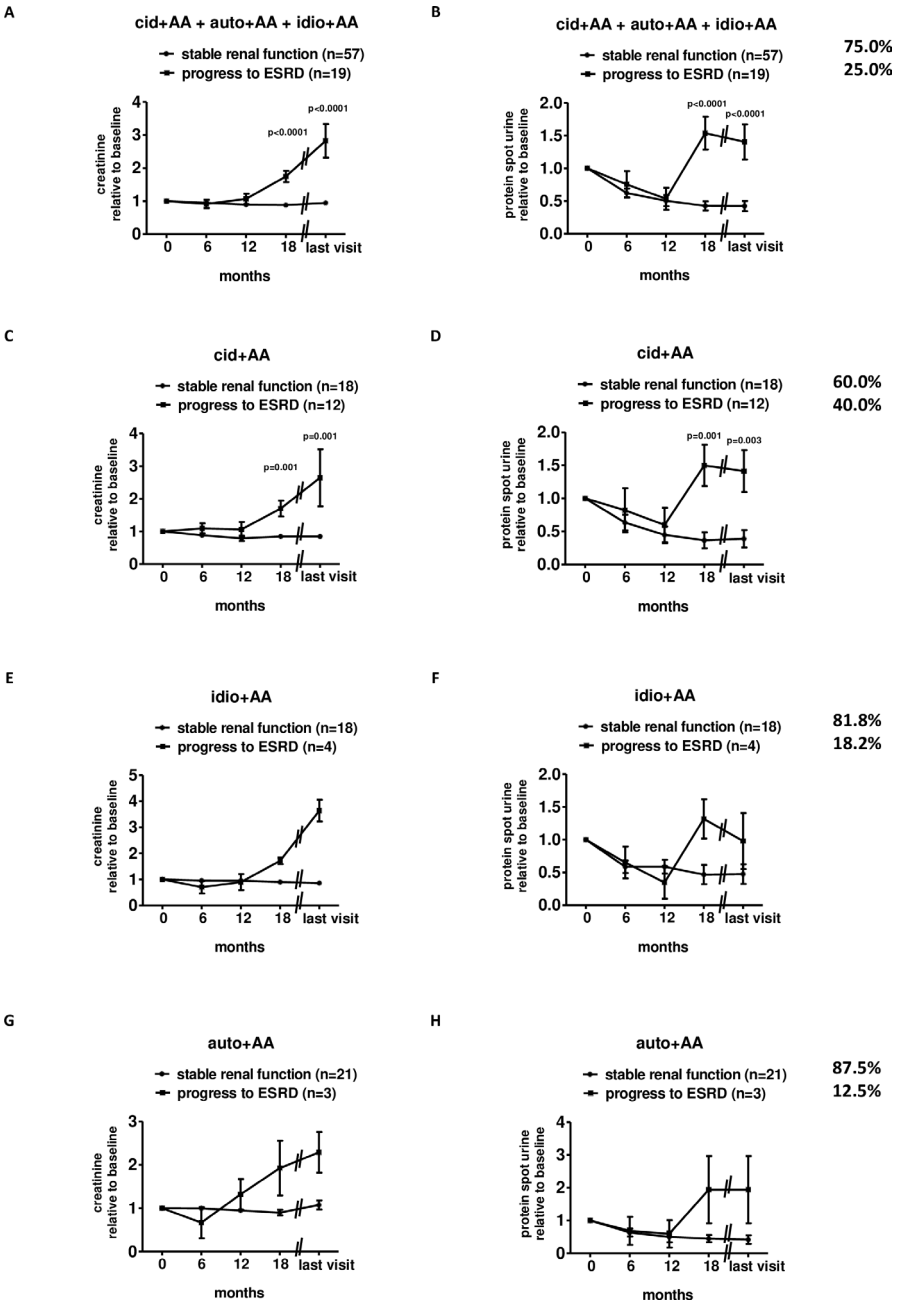

Figure 2 Serum creatinine and spot proteinuria were analysed in the total cohort (A, B) and in the AA subgroups with different aetiologies (C–H). Serum creatinine and proteinuria were normalised with the values at the first visit. Reappointments were scheduled every 6 months. Patients with a preserved renal function (circles) were compared with patients with ESRD at the last visit (squares). AA, AA amyloidosis; auto+AA, patients with an autoinflammatory syndrome and AA amyloidosis; cid+AA, patients with chronic inflammatory diseases and AA amyloidosis; ESRD, end-stage renal disease; idio+AA, patients with idiopathic AA amyloidosis.

patients with cid+AA (12/30, 40%) compared with those with auto+AA (4/22, 18%) and idio+AA (3/24, 13%; p=0.0284).

bDMARD treatment groups

Next, we compared patients who received TOC with patients treated with other bDMARDs. Patients with auto+AA were excluded from this analysis because TOC has not been approved for FMF or CAPS treatment. Among the 59 patients with cid+AA and idio+AA, 34 received TOC (57.6%) and 25 other bDMARDs (42.4%) (table 3). In the TOC group, 33 of 34 patients were female compared with 10 of 25 patients in the non-TOC group (p=0.0001). However, primary and concomitant diseases, CRP levels, and AA deposits in FAB were equally distributed in the TOC and non-TOC subgroups (table 3). The *SAA1.1+1.1* genotype was detected in 41 of 43 patients (95.3%) (table 3). Finally, patients with obesity were also similarly distributed in both subgroups (table 3). CRP and SAA were similarly elevated at the first visit and significantly improved with TOC (p=0.01) and other bDMARD treatment (p=0.045) during the follow-up visits (table 3). However, the suppression of CRP and SAA was more prominent with TOC.

Kaplan-Meier analyses show that TOC therapy better prevented renal progression to ESRD (p=0.0006; figure 3A) compared with other bDMARDs. Importantly, the subgroup analyses showed a similar pattern for cid+AA (p=0.0126; figure 3B) and idio+AA (p=0.0259; figure 3C). Among other bDMARDs, TNF-α

Table 3 Treatment with tocilizumab and other bDMARDs in patients with cid+AA or idio+AA

	TOC	Other bDMARDs	P value
Patients, n (%)	34	25	
Female gender, n (%)	33 (95.6)	10 (40.0)	0.00001
Age at AA (years), mean (SEM)	64.7 (2.3)	62.1 (1.4)	ns
Age at disease onset (years), mean (SEM)	47.0 (4.7)	36.9 (5.2)	ns
Treatment V1 to last visit (years), mean (SEM)	4.9 (0.7)	3.8 (0.6)	ns
Primary disease, n (%)			
Arthritis	9 (26.5)	9 (36.0)	ns
IBD	5 (14.7)	3 (12.0)	
Other	4 (11.8)	4 (16.0)	
Idiopathic	16 (47.1)	9 (36.0)	
Concomitant disease, n (%)			ns
Arterial hypertension	13 (38.2)	9 (36.0)	
Diabetes mellitus type 2	1 (2.9)	1 (4.0)	
Metabolic syndrome	2 (5.9)	2 (8.0)	
None	18 (52.9)	13 (52.0)	
Serum creatinine at V1 (mg/dL), n (%)			
<2.5	20 (58.8)	14 (56.0)	ns
2.5–5	11 (32.4)	7 (28.0)	ns
ESRD at V1, n (%)	3 (8.8)	4 (16.0)	ns
Serum creatinine at last visit (mg/dL), n (%)			
<2.5	24 (70.6)	7 (28.0)	0.002
2.5–5	3 (8.8)	2 (8.0)	ns
ESRD at last visit, n (%)	7 (20.6)	16 (64.0)	0.001
Protein to creatinine ratio at V1 (g/mol), n (%)			
<300	14 (41.2)	7 (28.0)	ns
300–1000	7 (20.6)	8 (32.0)	ns
>1000	13 (38.2)	10 (40.0)	ns
Protein to creatinine ratio at last visit (g/mol), n (%)			
<300	14 (41.2)	3 (12.0)	0.020
300–1000	3 (8.8)	4 (16.0)	ns
>1000	17 (50.0)	18 (72.0)	ns
CRP at V1, mean (SEM)	33.9 (3.7)	36.5 (2.2)	ns
CRP at last visit (<5 mg/L)	5.5 (0.9)	15.9 (1.3)	0.045
P value V1 vs last visit	0.01	0.045	
SAA at V1, mean (SEM)	63.1 (4.6)	30.0 (3.4)	ns
SAA at last visit (<8.6 mg/L)	12.1 (1.8)	7.4 (0.8)	ns
P value V1 vs last visit	0.01	0.045	
BMI (kg/m^2), mean (SEM)	30.74 (1.32)	28.82 (1.48)	ns
SAA1α/α, n (%)	23 (95.8)	18 (93.3)	ns

AA, AA amyloidosis; bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; cid+AA, patients with chronic inflammatory diseases and AA amyloidosis; CRP, C reactive protein; ESRD, end-stage renal disease; IBD, inflammatory bowel disease; idio+AA, patients with idiopathic AA amyloidosis; SAA, serum amyloid alpha; V1, visit 1.

inhibitors had shown a tendency towards a better renal outcome compared with the other immunosuppressants; however, it was not possible to perform quantifiable comparison or statistical analysis due to the small number of cases in the respective subgroups.

Survival of patients with AA

Three patients died at a mean age of 67.7 years in the whole cohort of 83 patients. The three patients died at a median of 10.3 years after the diagnosis of AA. The causes of death comprised a highly inflammatory condition of a rapidly progressive multiorgan failure due to progression of AA. Importantly, no patient under TOC died over the observation period of 4.82 years (figure 3D).

DISCUSSION

83 patients with renal AA and various underlying primary diseases were analysed. The primary diseases were categorised as chronic inflammatory diseases (cid+AA; 40%), autoinflammatory disease (auto+AA; 30%) and idiopathic inflammation (idio+AA; 29%). A comparison with the observations from a British cohort comprising 374 patients with AA (cid+AA 86%), auto+AA (9%) and idio+AA (6%) published in 2006[7] revealed a few interesting differences. The portion of cid+AA was significantly lower in our cohort (Fisher's p<0.00001).[7] This is probably related to the use of bDMARD to control the inflammation in CID between the years 2010 and 2022 in our cohort. The higher rate of autoinflammatory diseases in our cohort (Fisher's p<0.00001) was probably related to country-specific factors and migration pattern. Furthermore, the recognition of autoinflammatory syndromes had improved within the past two decades. Finally, the portion of idio+AA or AA of unknown origin was significantly higher in our cohort (Fisher's p<0.00001). A previous analysis of our group revealed an increasing prevalence of obesity,[35] which probably contributed to the higher frequency of idio+AA in our cohort and others.[36]

The various underlying diseases were treated according to guidelines and the availability of approved bDMARD. Therefore, it was appropriate to categorise our patients according to their primary disease and to the bDMARD used to control the systemic inflammation. bDMARD reduced systemic inflammation in various diseases, leading to a reduction of proteinuria and prevention of ESRD. Patients with rheumatoid arthritis were preferentially treated with anti-IL-6R bDMARD (TOC), patients with axial spondylitis and Crohn's disease were preferentially treated with anti-TNF bDMARD (etanercept, adalimumab and others), and patients with FMF were treated with colchicine or a combination of colchicine and anti-IL-1 bDMARD (anakinra or canakinumab). Patients with idiopathic AA preferentially received TOC if no contraindications were present. The median follow-up with bDMARD treatment was 4.95 years. We observed a preserved renal function and less progression of AA to other organs or death in patients treated with TOC. This is consistent with previous observations of rather low numbers of patients with AA treated with TOC.[37 38] A French cohort described the follow-up of nine patients with renal AA and TOC treatment.[38] In this cohort, the renal function improved in three (33%), stabilised in three (33%) and declined in three (33%) patients during a mean follow-up of 13.1 months.[38] A British group described 20 patients (12 AA, 8 other amyloid type, 4 AA patients with renal transplant, 2 AA patients on dialysis) who were treated with TOC for a median of 23 months. AA deposits were quantified using amyloid scintigraphy and the amyloid deposits were either stable or had improved.[37] Gastroduodenal amyloid deposition had shown a favourable response on treatment with TNF-α inhibitors in patients with AA, whereas renal function did not show a significant improvement.[39]

Together, this highlights the importance of TOC for patients with AA.

Our patients with FMF were treated with colchicine and a combination with anti-IL-1 when necessary according current recommendations.[17] Anakinra[40] and canakinumab,[16] but not

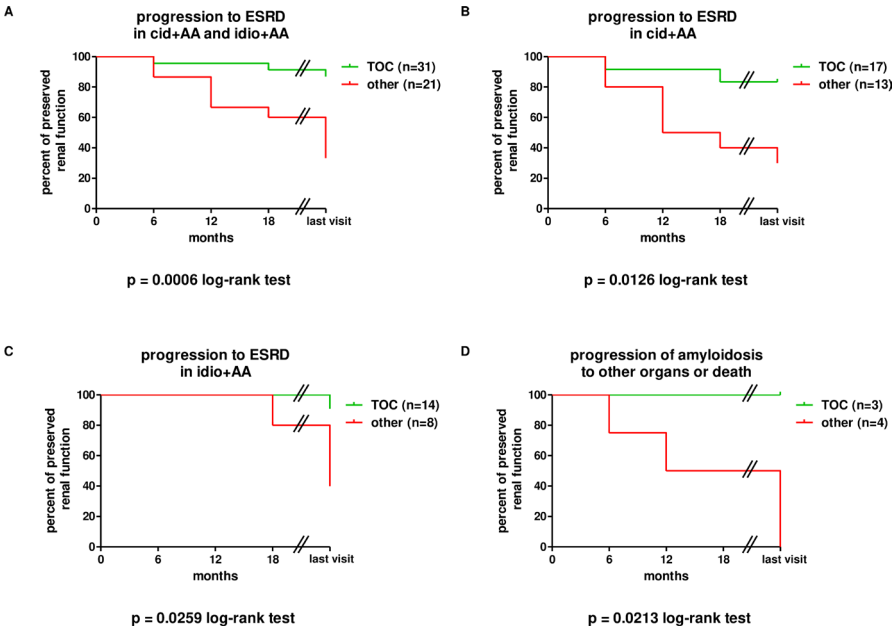

Figure 3 Patients with TOC treatment were compared with other bDMARD treatment. Patients with cid+AA and idio+AA were followed every 6 months until the last visit (A). Subgroup analyses of cid+AA (B) and idio+AA (C) are indicated. In the whole cohort, TOC treatment prevented the progression of AA to other organs and death (D). AA, AA amyloidosis; bDMARD, biological disease-modifying antirheumatic drug; cid+AA, patients with chronic inflammatory diseases and AA amyloidosis; ESRD, end-stage renal disease; TOC, tocilizumab; idio+AA, patients with idiopathic AA amyloidosis.

TOC, were approved for colchicine-resistant FMF treatment. However, other reports showed promising results[41 42] and suggest that TOC might be considered a third-line therapy for FMF and renal AA for patients who cannot tolerate anakinra injections or in countries where canakinumab is not available. All of our patients were in remission with a combination of colchicine and anti-IL-1 and did not require TOC treatment.

Patients with IBD (Crohn's disease or ulcerative colitis) were included in the group of cid+AA. These patients were usually treated with anti-TNF, anti-IL-12/23 or vedolizumab in order to induce disease remission and normalisation of CRP and SAA.[7] A previous report showed that in 24 patients with IBD the proteinuria resolved in 5 patients but progressed in the other 19 patients. Among the progressive disease, 15 patients had ESRD after a median time of 6.3 years, 6 had a kidney transplant and 1 patient had a recurrent AA in the transplant kidney.[14] Another study from Japan showed that AA was a rare complication in patients with IBD, but 40% of these patients with AA died.[43] Our observations are consistent with these reports. We can confirm that control of systemic inflammation remains a challenge in patients with IBD and AA.

Our observation of the renal function and proteinuria over time revealed a stable renal function and a slow decline of proteinuria during the first 12 months of bDMARD therapy. However, 25% of patients had a progressive renal failure after 18 months or later. This is consistent with an earlier report showing that patients with FMF and AA either responded to colchicine treatment or developed ESRD within 20 months.[44] We can only speculate about the underlying pathomechanism of this observation. bDMARD treatment significantly reduced the systemic inflammation and prevented further accumulation of amyloid deposits. We expect a very slow degradation of the prevalent amyloid deposits. The pattern of amyloid deposits in the kidney histology is critical to the amount of proteinuria and renal insufficiency.[45] AA deposits in the glomerulus are associated with a massive proteinuria, while interstitial AA deposits are related with mild proteinuria or absence of proteinuria.[46] Renal biopsies often show interstitial fibrosis and glomerulosclerosis concomitant with the amyloid deposits.[47] All of the kidney biopsy samples also contained fibrosclerotic changes that contribute to the grade of renal insufficiency. We hypothesise that amyloid deposits could trigger secondary fibrosis and renal failure which could still persist after removal of AA deposits.

The strengths of this study are the large number of patients and the comprehensive analysis of various primary diseases as causes of AA and of the consecutive bDMARD therapy. The median follow-up of 4.95 years was sufficient to enable conclusions on the long-term prognosis of these patients. Limitations of our study were the retrospective analysis and missing data during the long-term follow-up of single patients. Another limitation is the heterogeneity of patients with cid+AA regarding the pathophysiology of their underlying primary disease. To minimise heterogeneity, patients with chronic infections were excluded from this cohort. In surplus, all patients from cid+AA subgroup had markedly elevated acute phase reactant with chronically recurring systemic inflammation as common phenotypic characteristic of this subgroup.

Finally, we conclude that bDMARD can control inflammation in most patients with AA, leading to a reduction of proteinuria and prevention of ESRD. However, our data suggest that TOC was superior to other bDMARDs in patients with CID and AA, preserving renal function and preventing AA progression to other organs and death.

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