

A multicenter report of biologic agents for the treatment of secondary amyloidosis in Turkish rheumatoid arthritis and ankylosing spondylitis patients

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Abstract In this multicenter, retrospective study, we evaluated the efficacy and safety of biologic therapies, including anti-TNFs, in secondary (AA) amyloidosis patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA). In addition, the frequency of secondary amyloidosis in RA and AS patients in a single center was estimated. Fifty-one AS (39M, 12F, mean age: 46.7) and 30 RA patients (11M, 19F, mean age: 51.7) with AA amyloidosis from 16 different centers in Turkey were included. Clinical and demographical features of patients were obtained from medical charts. A composite response index (CRI) to biologic therapy—based on creatinine level, proteinuria and disease activity—was used to evaluate the efficacy of treatment. The mean annual incidence of AA amyloidosis in RA and AS patients was 0.23 and 0.42/1000 patients/year,

respectively. The point prevalence in RA and AS groups was 4.59 and 7.58/1000, respectively. In RA group with AA amyloidosis, effective response was obtained in 52.2 % of patients according to CRI. RA patients with RF positivity and more initial disease activity tended to have higher response rates to therapy (*p* values, 0.069 and 0.056). After biologic therapy (median 17 months), two RA patients died and two developed tuberculosis. In AS group, 45.7 % of patients fulfilled the criteria of good response according to CRI. AS patients with higher CRP levels at the time of AA diagnosis and at the beginning of anti-TNF therapy had higher response rates (*p* values, 0.011 and 0.017). During follow-up after anti-TNF therapy (median 38 months), one patient died and tuberculosis developed in two patients. Biologic therapy seems to be effective in at least half of RA

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and AS patients with AA amyloidosis. Tuberculosis was the most important safety concern.

Keywords Secondary amyloidosis · Rheumatoid arthritis · Ankylosing spondylitis · Biologic therapy · Anti-TNF

Introduction

Secondary amyloidosis is a late-stage complication of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) [1, 2]. In general, patients with serious and long disease course are under risk for the development of secondary amyloidosis [3]. It is important to screen, especially patients with long-standing disease. In addition, there are regional, epidemiologic risk factors for the development of amyloidosis [3, 4]. In one previous study conducted at our center, the frequency of clinically apparent amyloidosis in RA was 0.78 %, and it was 1.1 % in AS [5, 6].

The suggested treatment for secondary amyloidosis is treatment of the underlying disease [3, 4]. Although new drugs have been proven to be significantly effective in the treatment of RA- and AS-related secondary amyloidosis, no treatment modality is considered to be ideal [5–10]. Biologic drugs, including anti-TNF agents, have been used in the treatment of secondary amyloidosis; however, there is no controlled study concerning the efficacy of therapy.

Firstly, we evaluated the incidence and prevalence of clinically apparent secondary amyloidosis in RA and AS patients retrospectively in a single center. In the second part of study, we analyzed the clinical features and outcome of RA and AS patients with clinically symptomatic secondary amyloidosis who were treated with any of the biologic agents in various rheumatology centers in Turkey.

Methods

In this retrospective, hospital-based study, the incidence and prevalence of secondary amyloidosis in RA and AS patients were estimated in a single center (center#1)—Trakya University—between 2011 and 2015. During this period, 2177 RA patients (1739 females and 438 males) and 1187 AS patients (812 males and 375 females) were followed in center#1. The incidence rates per 1000 RA or AS population were calculated. Any patient diagnosed with RA or AS in this department in December 2015 was defined as a prevalent case. Point prevalence was calculated by dividing the number of prevalent cases by the RA or AS population in this department in December 2015. In addition, the period prevalence was calculated by dividing the number of all diagnosed cases by the number of RA or AS population within the study period.

In addition, data about response to biologic therapies in clinically apparent amyloidosis patients whose amyloidosis was secondary to RA or AS were collected from different centers. The hospital files in 16 rheumatology centers were examined to determine the treatment response to biologic agents in RA and AS patients with clinically apparent amyloidosis.

RA was diagnosed based on 1987 ACR criteria [11]; modified New York criteria [12] were used to diagnose AS. Biopsy-proven secondary amyloidosis patients who had clinically apparent findings related to secondary amyloidosis were included into the study. Patients with disease onset younger than 16 years of age, subjects with spondyloarthritides not fulfilling the criteria for AS (psoriatic arthritis, reactive arthritis, etc.), and patients with comorbidities like tuberculosis or malignancy that might be associated with secondary amyloidosis were excluded. In addition, it is well known that familial Mediterranean fever (FMF) is a common cause of amyloidosis in our country and that the frequency of sacroiliitis in FMF is high. Therefore, we excluded patients who concomitantly had FMF and AS. Patients whose clinical features were not compatible with FMF were denied this diagnosis. Genetic analysis for FMF was performed in 22 AS patients, and only two were seen to have heterozygous mutations. As none of these patients had clinical features of FMF, they were included into the study.

For RA patients, hospital files were examined to determine the presence of clinically apparent amyloidosis. Data concerning the clinical features, extraarticular involvement and treatment response were obtained. The evaluated extraarticular features included the lung, eye and serous membrane (pericardium, pleura) involvements, vasculitis and subcutaneous nodules. In addition, RF and anti-CCP values of RA patients at the time of initial diagnosis, at the time when amyloidosis developed; renal function tests and proteinuria were recorded. DAS28 score was calculated for all RA patients. Improvement in disease activity was evaluated according to EULAR response criteria [13].

For AS group, chart reviews addressed the presence of uveitis, peripheral arthritis, inflammatory bowel disease, apical fibrosis in chest X-ray, surgical history (prosthesis), BASDAI score, renal functions and proteinuria, ESR and CRP on initial admission, and use of biologic therapies.

During routine follow-up, urinalysis of all RA and AS patients was performed at periodic intervals; if the patient had (++) proteinuria with the dipstick method, protein was quantitated and patients with >500 mg/day proteinuria were further evaluated for the presence of amyloidosis. In addition, RA and AS patients presenting with renal insufficiency were investigated for the presence of AA amyloidosis.

Table 1 Mean annual incidence and point prevalence of clinically apparent secondary amyloidosis in center#1 between 2011 and 2015

	<i>n</i>	<i>n</i> (incident case)	The mean annual incidence (/1000 years)	<i>n</i> (prevalent case)	Point prevalence (/1000)	<i>n</i>	Period prevalence (/1000)
<i>Rheumatoid arthritis</i>							
Females	1739	1	0.14	7	4.02	8	4.6
Males	438	1	0.57	3	6.85	5	11.4
Total	2177	2	0.23	10	4.59	13	5.97
<i>Ankylosing spondylitis</i>							
Females	375	–	–	–	–	–	–
Males	812	2	0.62	9	11.08	10	12.3
Total	1187	2	0.42	9	7.58	10	8.42

Renal insufficiency was defined as a serum creatinine level of >2 mg/dl. For histological confirmation of amyloidosis, rectal, renal, gingival and subcutaneous tissue biopsies were performed. Biopsy samples were stained with Congo red.

We created a composite response index (CRI) in order to evaluate the response of secondary amyloidosis patients to biologic therapy because of the absence of any validated criteria. CRI was based on disease activity, proteinuria and renal functions. RA patients who were responders to biologic therapy according to this CRI were defined as follows: patients with at least 1.2 improvement in DAS28 score at the end of 3 months, patients who had insignificant change in creatinine levels (an increase of maximum 25 %), and patients whose proteinuria regressed at least 25 %. Before and after biologic therapy, tender and swollen joints were counted and DAS28 score was calculated. The same CRI was also used for AS patients. The criterion for response to therapy about disease activity was achievement of ASAS20 response.

For statistical analysis, Chi-square test was used for categorical variables and Fisher's exact test was used as necessary; unpaired *t* test was used for continuous variables.

Results

The incidence and the prevalence of clinically apparent amyloidosis

Within a 4-year period, two RA patients with clinically apparent amyloidosis (one female, one male) were diagnosed. The mean annual incidence of clinically apparent secondary amyloidosis was 0.23 per 1000 patients/year in our RA population. At the end of 2015, a total of ten prevalent secondary amyloidosis patients (seven females, three males) were detected in center#1. The point prevalence of secondary amyloidosis at that time was 4.59/1000 in RA population.

Within the same period, two patients with AS (two males) were diagnosed with secondary amyloidosis. The mean annual incidence of clinically apparent amyloidosis was 0.42 per 1000 patients/year. A total of nine AS-associated secondary amyloidosis patients (nine males) were diagnosed at the end of 2015 in center#1. The point prevalence of clinically apparent amyloidosis in AS population was 7.58/1000. The incidence and point & period prevalences of secondary amyloidosis in RA and AS patients according to gender are shown in Table 1.

Biologic therapy in rheumatoid arthritis patients

We included 30 RA patients with secondary amyloidosis (11 males, 19 females, mean age: 51.7) from different centers. The general clinical characteristics of RA patients are shown in Table 2.

At the time of diagnostic workup for amyloidosis, 29 RA patients had proteinuria. Eight patients presented with only nephrotic-range proteinuria; five patients with nephrotic-range proteinuria and renal insufficiency. Eleven patients presented with only nephritic-range proteinuria; three with nephritic-range proteinuria and renal insufficiency; two presented with nephritic-range proteinuria and massive hematuria. Secondary amyloidosis in one of the RA patients was detected after the development of ESRD while searching for etiology of renal disease. The diagnosis of secondary amyloidosis in 18 RA patients was confirmed by rectal biopsy, in ten by renal biopsy, and in two by ileum biopsy (Fig. 1).

Except for one patient who was undergoing renal replacement therapy at the time of diagnosis for AA amyloidosis, ESRD developed in seven patients during follow-up. In two of these patients, ESRD developed after diagnosis of AA amyloidosis before using biologic agents; in the other five, however, ESRD developed after starting biologics and there was need for renal replacement therapy in five of them. When the features of eight RA-AA amyloidosis patients with ESRD were compared to others,

Table 2 General clinical features of rheumatoid arthritis patients with secondary amyloidosis

<i>n</i> (F/M)	30 (19/11)
Age (years)	51.7 ± 13.4
Disease duration (months)	170.6 ± 114.1
Duration of amyloidosis (months)	51.9 ± 47
Duration of biologics (months)	31.9 ± 34.3
Smoking [<i>n</i> (%)]	8 (26.7)
Juvenile onset [<i>n</i> (%)]	5 (16.7)
Interstitial lung disease [<i>n</i> (%)]	4 (13.3)
RF positivity [<i>n</i> (%)]	23 (76.7)
Anti-CCP positivity [<i>n</i> (%)]	22 (73.3)
ESR (mm/h)	80.4 ± 28.4
CRP (mg/dl)	3.6 ± 2.8
DAS28 score	5.6 ± 0.9
Creatinine (mg/dl)	1.92 ± 1.6
Renal replacement therapy [<i>n</i> (%)]	8 (26.7)
Methotrexate usage [<i>n</i> (%)]	25 (83.3)
Sulphasalazine usage [<i>n</i> (%)]	23 (76.7)
Leflunomide usage [<i>n</i> (%)]	13 (43.3)
Steroid usage [<i>n</i> (%)]	25 (83.3)

it was observed that the mean creatinine level in the first group was significantly higher (3.31 ± 2.5 vs. 1.47 ± 0.9 , $p = 0.026$).

All RA patients with AA amyloidosis included in this study were given TNF-blockers as first-line therapy. The median duration of biologic therapy was 17 months (range 3–100). Therapy results could not be evaluated in four patients (two were lost to follow-up; two were started on therapy recently). At least DAS28 response was obtained in 18 of 26 RA-secondary amyloidosis patients while using biologic agents. Secondary unresponsiveness was present in 12 RA patients, respectively. Ten were administered biologics as second-line therapy, five as third-line therapy, and two as fourth-line therapy. Within the whole study period, 23 patients used anti-TNF agents; ten, rituximab; five, abatacept; four, tocilizumab; one patient used anakinra.

After biologic therapy, the level of proteinuria regressed at least 25 % in 13 of 23 patients, and increased at least 25 % in 5 of 23 patients. The level of proteinuria remained stable in five patients after biologic therapy. Creatinine level decreased at least 25 % in only 2 of 23 patients after biologics; creatinine level increased at least 25 % in 8 of 23 patients. The creatinine level remained stable in 13 patients within the study period. In addition, there were RA-secondary amyloidosis patients with good response according to CRI. In the RA group based on the CRI, there was response in 12 of 23 RA patients (52.2 %) who were not undergoing renal replacement therapy at the beginning of treatment and whose response to biologics could be evaluated. In the

group with good response to biologics, RF positivity (91.7 vs. 54.5 %, $p = 0.069$) and DAS28 score at the time of amyloidosis (6.25 ± 0.4 vs. 5.03 ± 0.97 , $p = 0.056$) tended to be higher.

During follow-up, one patient died of febrile neutropenia which had developed secondary to methotrexate over usage: it was erroneously taken daily after starting anti-TNF therapy. Also, one patient died of miliary tuberculosis. A total of two patients who were using biologics developed tuberculosis. One of these patients was undergoing renal replacement therapy, and two had infections who required hospitalization. Rituximab was discontinued in only one patient because of serious allergic reaction.

Anti-TNF therapy in ankylosing spondylitis patients

We included 51 AS patients with secondary amyloidosis (39 males, 12 females, mean age: 46.7 ± 10.4). General clinical characteristics of AS patients are shown in Table 3. At the time of diagnostic workup for amyloidosis, 43 AS patients had proteinuria. Fifteen patients presented with only nephrotic-range proteinuria; ten with nephrotic-range proteinuria and renal insufficiency; two patients with nephrotic-range proteinuria, renal insufficiency and hematuria. Ten patients presented with only nephritic-range proteinuria; three with nephritic-range proteinuria and renal insufficiency; three presented with nephritic proteinuria, renal insufficiency and massive hematuria. In eight AS patients (seven males and one female), secondary amyloidosis was detected when searching for the etiology of renal disease after ESRD. Secondary amyloidosis in AS patients was confirmed with rectal biopsy in 24; renal biopsy in 19; gingival biopsy in three; ileum and bone marrow biopsies, each in two patients; subcutaneous fat tissue biopsy in just one patient (Fig. 2).

In addition to eight patients undergoing renal replacement therapy, five other patients with AA amyloidosis developed ESRD during follow-up. In two patients, ESRD was diagnosed after diagnosis for AA amyloidosis, before administration of ESRD; in three patients, ESRD developed while using biologics and there was need for renal replacement therapy. When features of 13 patients who had AS-AA amyloidosis and ESRD were compared to others, it was observed that there were more males in the first group (11 males and two females). In addition, the group with ESRD had significantly more patients with renal insufficiency at initial admission (69.2 vs. 26.3 %, $p = 0.009$); on the other hand, sulphasalazine usage (61.5 vs. 92.1 %, $p = 0.019$) and uveitis (0 vs. 26.3 %, $p = 0.048$) were significantly lower in the group with ESRD. Another finding was the significantly higher mean creatinine level in the group with ESRD at the time of diagnosis for AA amyloidosis (3.31 ± 2.5 vs. 1.32 ± 0.9 mg/dl, $p = 0.026$).

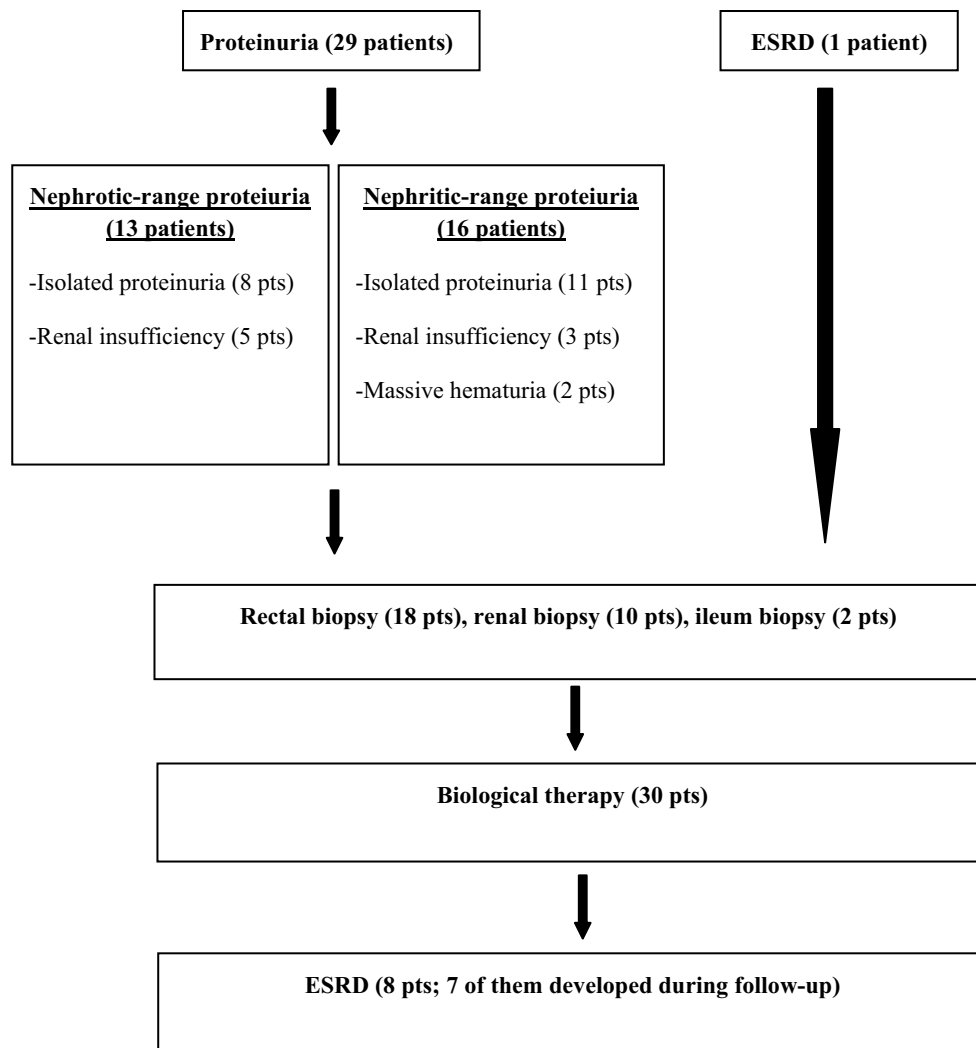


Fig. 1 Finding on clinical presentation and investigation of secondary amyloidosis in RA patients

Ten patients were undergoing any type of renal replacement therapy before starting anti-TNFs. Therapeutic results could not be evaluated in six patients (four were lost to follow-up; two have started therapy recently). Within a median of 38 months of follow-up (range 3–114 months), ASAS20 response was obtained in 40 of 45 AS patients with secondary amyloidosis while using anti-TNF therapy. Secondary unresponsiveness was observed in seven patients. All of them were administered anti-TNF agents as second-line therapy. Anti-TNFs were given as third-line therapy in four patients. After anti-TNF therapy, there was at least 25 % decrease in proteinuria in 21 of 35 patients; proteinuria increased at least 25 % in 6 of 35 patients; it remained stable in eight patients. Creatinine value decreased at least 25 % in only 2 of 35 patients after anti-TNF therapy; creatinine value increased at least 25 % in 7 of 35 patients; creatinine value did not change in 26 patients within the study period.

In addition, we evaluated AS-secondary amyloidosis patients with good response according to CRI. According to CRI, 16 of 35 patients (45.7 %) who were not under any renal replacement therapy and whose anti-TNF response could be evaluated obtained a good response. The group with good response to anti-TNF agents according to CRI had significantly higher CRP levels both at the time of diagnosis for amyloidosis (2.67 ± 2.1 vs. 1.08 ± 0.7 mg/dl), and also before starting anti-TNFs (2.49 ± 1.9 vs. 0.69 ± 0.6 mg/dl) (p values, 0.011 and 0.017) when compared to the group which was not responsive.

During the follow-up period, two patients using anti-TNFs developed tuberculosis: Both of them were undergoing renal replacement therapy. Treatment-requiring pneumonia was diagnosed in two patients. While taking anti-TNF therapy, only one patient died because of pulmonary embolism. In addition, anti-TNF therapy had to be discontinued in three patients because of severe allergic

Table 3 General clinical features of ankylosing spondylitis patients with secondary amyloidosis

<i>n</i> (M/F)	51 (39/12)
Age (years)	46.7 ± 10.4
Disease duration (months)	151.1 ± 105.9
Duration of amyloidosis (months)	61.9 ± 45.1
Duration of biologics (months)	44.3 ± 33.9
Smoking [<i>n</i> (%)]	22 (43.2)
Juvenile onset [<i>n</i> (%)]	5 (9.8)
Hip prosthesis [<i>n</i> (%)]	11 (21.6)
Enthesitis [<i>n</i> (%)]	21 (41.2)
Peripheral arthritis [<i>n</i> (%)]	27 (52.9)
Apical fibrosis [<i>n</i> (%)]	5 (9.8)
Inflammatory bowel disease [<i>n</i> (%)]	2 (3.9)
ESR (mm/h)	73.8 ± 29.2
CRP (mg/dl)	1.84 ± 1.7
BASDAI score	5.7 ± 1.9
Creatinine (mg/dl)	2.24 ± 2.44
Renal replacement therapy [<i>n</i> (%)]	13 (25.5)
Sulphasalazine usage [<i>n</i> (%)]	43 (84.3)
Methotrexate usage [<i>n</i> (%)]	19 (37.3)

reactions: One was using infliximab, one etanercept, and the other was using adalimumab. Anti-TNF therapy was discontinued in one patient who had renal transplantation.

Discussion

In this study, the mean annual incidence and point prevalence of symptomatic amyloidosis in RA patients were, respectively, 0.23/1000 and 4.59/1000 patients/year. In AS group, the mean annual incidence was 0.42/1000 patients/year and the point prevalence was 7.58/1000 patients/year. These prevalence rates are lower than those of our previous RA and AS studies [5, 6]. More effective biologic usage might have contributed to this decrease.

Amyloidosis develops in RA and AS nearly at least 10 years after diagnosis; it generally presents with proteinuria and/or renal dysfunction. In AS patients with high CRP levels at the time of diagnosis of amyloidosis, there will be favorable response to anti-TNF agents. In RA, the favorable response to biologics was relatively in parallel with RF positivity and higher disease activity at the beginning of therapy.

In both our RA and AS patients with AA amyloidosis, the most common initial presentations were proteinuria and/or renal insufficiency. In a significant percentage of patients, like one in six, ESRD had already developed at the time of diagnosis of AA amyloidosis and the diagnosis was reached while in search for the etiology of renal

problems. This result shows that further investigation for amyloidosis is not performed during regular follow-up of patients with inflammatory diseases, like RA and AS; and proves the reality that amyloidosis could only be diagnosed at very late stages of these diseases. Some explanations for this result could be diagnosing patients late during disease course, nonavailability of effective therapies earlier, and follow-up problems associated with poor sociocultural level.

In our study, ESRD developed in about one-fourth of patients in both disease groups. In general, factors associated with the development of ESRD in RA were high creatinine values at initial diagnosis; in AS, they were low level of education and renal insufficiency. Although it was not statistically significant—except one patient—all patients with ESRD in the AS group were males. This might be explained by the more severe clinical course of AS in males. Another noteworthy result in the AS group was the less frequent uveitis and sulphasalazine usage in patients with ESRD. Any protective effect of sulphasalazine against ESRD is unknown; it is difficult to claim any association based on only our data. Despite no serious side effects of sulphasalazine, physicians might have avoided using this drug in patients with renal dysfunction.

In spite of the fact that we do not have any comparative data, we can say that biologic therapies in our RA and AS patient population led to results similar to other RA and AS studies. It appears that the development of AA amyloidosis does not lead to any significant change in the response of disease to biologic agents. DAS28 response in our RA patients was observed in 18 of 26 patients; ASAS20 response was similarly obtained in a very good proportion of patients which was 40 in 45. While evaluating the efficacy of biologic agents on general features of RA and AS, we also formed a CRI to evaluate their effects on proteinuria and renal function. As known, there is no efficacy-proven therapy for AA amyloidosis. Various drugs are being given in new trials; however, no reliable results were obtained [14, 15]. It is generally accepted that treatment of the underlying disease is sufficient; however, it is very difficult to obtain any improvement in renal function. In our study, when CRI was considered, there was good response in 52 % of RA patients and 45 % of AS patients. RA patients who were responsive to therapy tended to have RF positivity and initially more active disease. In the AS group, however, a high CRP value was the most significant parameter associated with response. There are already literature data reporting on the association of high CRP value in AS with responsiveness to anti-TNF therapy [16]. Despite the absence of any controlled studies until now, case reports and small series about RA stated that anti-TNF agents improved clinical findings and prevented the deterioration in renal function in RA-related AA amyloidosis

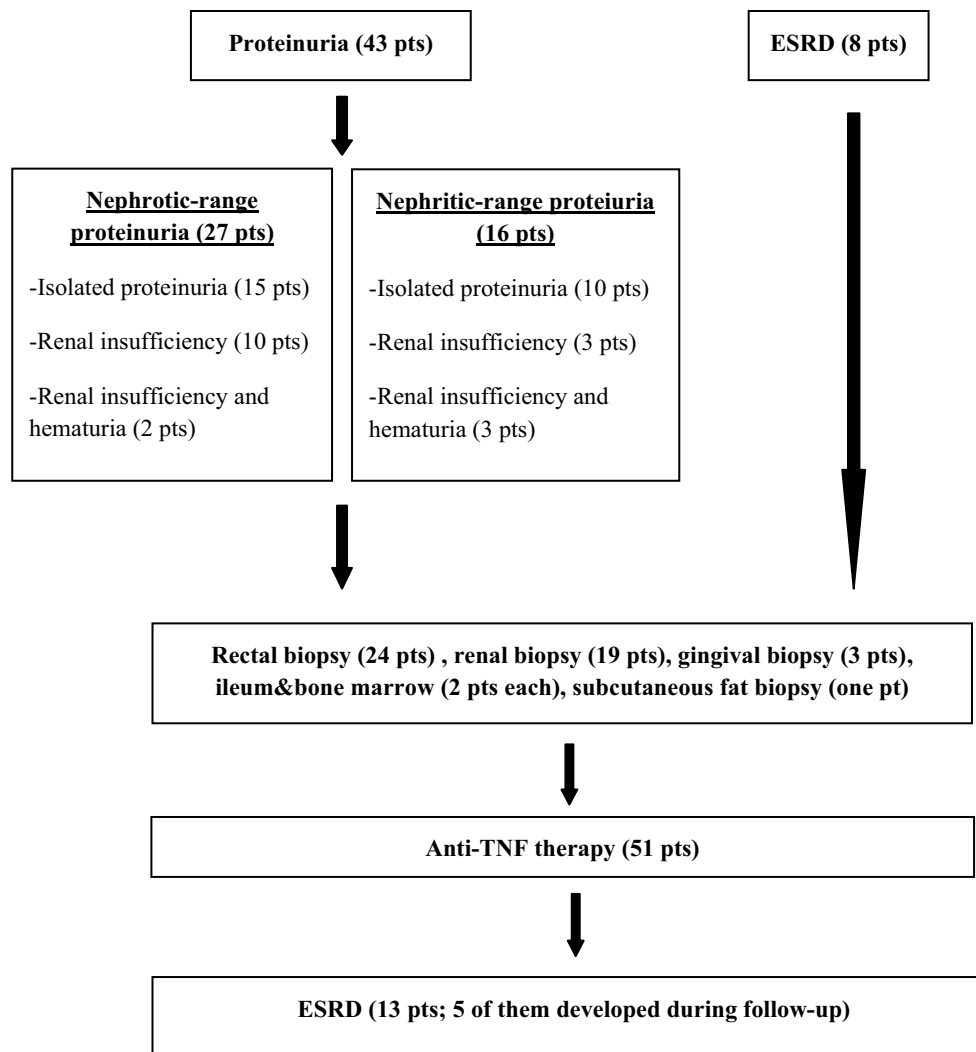


Fig. 2 Presentation findings and investigation of secondary amyloidosis in AS patients

[7–9, 17–19]. In one small RA series, rituximab resulted in effective treatment responses in RA-related AA amyloidosis patients [20]. One another study and case series showed that tocilizumab was effective in secondary amyloidosis [21, 22]. In addition, improvement with abatacept was reported in two RA patients [23]. Small series in AS patients demonstrated that anti-TNF therapy was effective for the treatment of AA amyloidosis [6, 24, 25].

There were two deaths in our RA group and one death in our AS group. The causes of death in the RA group were miliary tuberculosis and sepsis after febrile neutropenia; one AS patient died of pulmonary embolism. As we do not have comparative data about RA and AS populations in general, it seems difficult to comment on mortality. Interestingly, there were two cases of tuberculosis in both AS and RA groups. The incidence of tuberculosis in our country is higher than in Western countries; based on data from the World Health Organization, the frequency

is about 25–49 new cases in every 100,000 people [26]. Although we do not have concurrent comparative data, our multicenter study on anti-TNF agents from almost the same institutions revealed that the frequency of tuberculosis in RA and AS was, respectively, 0.89 and 0.97 % [27]. The data in the current study are limited; however, according to the above-mentioned study, the frequency of tuberculosis in both studies seems to be increased (6.7 and 3.9 %). When it is considered that patients with tuberculosis also have renal failure, it might be said that AA amyloidosis together with renal dysfunction increases the risk of tuberculosis. In one study about the subject, the risk of infection in RA-related AA amyloidosis patients was increased; however, antituberculosis therapy was effective [7]. There are not much data about the risk of tuberculosis in AA amyloidosis.

There are some limitations of our study. The first is that it was not a controlled trial. As it was a multicenter study, data analysis was retrospective; there were some problems,

like loss of follow-up. The effect of biologic therapies on renal survival could have been evaluated better in a cohort with longer follow-up. If there had been historical AA amyloidosis data, more definite results about the effect of biologics on renal survival could have been obtained. Another limitation might be the absence of genetic analysis for FMF which accompanies AS frequently in our country. Nevertheless, none of the AS or RA patients with AA amyloidosis had clinical features or diagnosis of FMF; about half of the patients had no genetic mutations. The last limitation was that we developed a CRI instead of using validated response index. However, we could not find any reliable response criteria for secondary amyloidosis.

As a conclusion, biologic therapies—primarily anti-TNF agents—show similar efficacy in AS and RA patients with AA amyloidosis when compared to patients without AA amyloidosis. Although side effects, in general, do not differ significantly in AA amyloidosis patients, the higher risk of tuberculosis makes it obligatory to be especially cautious about safety issues in this patient population. Studies with longer follow-ups are needed to evaluate the effect of biologics on renal survival.

Compliance with Ethical Standards

Conflict of interest Ömer Nuri Pamuk, Umut Kalyoncu, Kenan Aksu, Ahmet Omma, Yavuz Pehlivan, Yonca Çağatay, Orhan Küçükşahin, Salim Dönmez, Gözde Yıldırım Çetin, Rıdvan Mercan, Özün Bayındır, Ayşe Çefle, Fatih Yıldız, Ayşe Balkarlı, Levent Kılıç, Necati Çakır, Binyamin Kısacık, Mustafa Ferhat Öksüz, Veli Çobankara, Ahmet Mesut Onat, Mehmet Sayarlıoğlu, Mehmet Akif Öztürk, Gülsüm Emel Pamuk and Nurullah Akkoç declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Because of retrospective study design, informed consent was not obtained from all individual participants included in the study.

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