AA Amyloidosis Secondary to Adult Onset Still's Disease: About 19 Cases

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Abstract

Objective: Adult onset Still's disease (AOSD) is an inflammatory disorder characterized by high spiking fever, evanescent rash, polyarthritis, and many other systemic manifestations. Recurrent or persistent disease can lead to AA amyloidosis (AAA). Our objectives were to present 3 French cases and perform a systematic review of the literature, in order to determine the prevalence, characteristics, predisposing factors, and therapeutic response of AOSD-related AAA.

Methods: A systematic literature review was performed by searching MEDLINE from 1971 to 2018. Two independent investigators selected reports of AAA complicating AOSD. New French cases were identified with the help of the Reference Center for rare Auto-Inflammatory Diseases and Amyloidosis (CEREMAIA). Patients with juvenile idiopathic arthritis were excluded.

Results: The prevalence of AAA in AOSD was 0.88% (95%CI [0.49-1.28]) based on 45 articles. In addition to 3 new cases from the CEREMAIA, 16 patients were assessed for clinical presentation, risk factors, and therapeutic response of AOSD-related AAA. Mean age at AOSD onset was 29.6±12.6 years, with a mean delay before AAA diagnosis of 16.75±5.8 years. Renal involvement was the most common manifestation of AAA. The majority of patients presented active AOSD at AAA diagnosis. Various treatments of AOSD-related AAA were attempted including corticosteroids and biotherapies.

Conclusion: AAA is a rare and severe complication that may occur during the course of uncontrolled active AOSD. It could be prevented by early diagnosis and better control of AOSD, with more frequent use of biotherapies.

Introduction

Adult onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology characterized by high spiking fever, evanescent rash, polyarthritis, and many other manifestations including odynophagia, lymphadenopathy, splenomegaly, hepatic and pulmonary involvement, and serositis. It was first described in 1971 by Bywaters [1] in a case series of 14 women presenting with clinical features similar to those of systemic juvenile idiopathic arthritis (sJIA). AOSD is a rare disease with an annual incidence of 0.16 to 0.4 cases per 100 000 persons [2]. In the absence of pathognomonic clinical features or biomarkers, the diagnosis of AOSD relies on the Yamaguchi or Fautrel classification criteria [3,4] after exclusion of a wide differential diagnosis. Patients were classically treated with corticosteroids and synthetic disease-modifying antirheumatic drugs (DMARDS), most commonly methotrexate. Recent studies have revealed a pivotal role of proinflammatory cytokines, namely tumor necrosis factor α (TNF), interleukin (IL)-1, and IL-6, thus paving the way for novel targeted therapies that may potentially allow to control refractory disease [5].

AA amyloidosis (AAA) is a multisystemic disease related to the deposition in tissues of serum amyloid A (SAA) protein secondary to chronic inflammation. Causes are multiple and include chronic rheumatic and inflammatory bowel diseases, monogenic autoinflammatory diseases, chronic infections, and less frequently cancers and immune deficiencies. Recurrent or persistent AOSD due to suboptimal control of the disease is associated with multiple complications, such as chronic destructive arthritis, increased long-term morbidity and mortality, and AAA [6].

Our objectives were to present new French cases and perform a systematic review of the literature in order to determine the prevalence, characteristics, predisposing factors, and therapeutic response of AOSD-related AAA.

Materials and Methods

New French cases were identified with the help of the CEREMAIA (Reference Center for rare Auto-Inflammatory Diseases and Amyloidosis, www.ceremaia.fr). A systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. No previously available protocol was used. We searched MEDLINE from 1971, when the first AOSD case was published, to 2018, in order to identify all studies pertaining to AAA in AOSD. The search was limited to articles published in French or English. Patients with sJIA, defined as onset of symptoms or diagnosis before 16 years old, were excluded.

We searched MEDLINE through PubMed using MESH terms. Separate searches were performed for prevalence and description of AOSD-related AAA. Two independent readers (SGL and MD) first screened titles and abstracts to exclude irrelevant articles and duplicates. Only original cases satisfying the Yamaguchi or Fautrel classification criteria were selected.

Keywords used for the prevalence assessment study were: "Still's Disease, Adult-Onset/complications"[Majr] OR "Still's Disease, Adult-Onset/diagnosis"[Majr] OR "Still's Disease, Adult-Onset/epidemiology"[Majr]. Both prospective and retrospective studies were eligible, with no limit regarding patient number and length of follow-up. We decided to only include articles reporting complications of AOSD (joint destruction, death, amyloidosis…), in order to avoid underestimating the prevalence of AAA by selecting articles that focused on diagnostic features of AOSD. Articles restricted to subgroups of AOSD patients based on age or a specific feature of the disease were excluded, in order to reflect AAA prevalence in the general AOSD population. Trials of second line therapy, which involve patients with more severe disease at higher risk of AAA, were also excluded to avoid selection bias.

Keywords used for the descriptive study were "Still's Disease, Adult-Onset"[Majr] AND "Amyloidosis"[Majr] and “adult onset still disease and amyloidosis”. Clinical features of patients with both AOSD and AAA were assessed through case reports. An investigator (MD) extracted

data from selected articles according to a predefined form. Descriptive statistics were performed using the excel software and R software. Characteristics of AOSD with and without AAA were compared using Fisher's exact test and chi-square test. To represent AOSD without AAA, we selected the case series from the literature that included the largest number of patients while providing detailed information regarding clinical presentation, biotherapy, follow-up, and complications. A 2-sided p-value < 0.05 was considered statistically significant.

Results

French cases identified via the CEREMAIA

Case 1: A 17-year-old man developed the first manifestations of AOSD in 1984. Disease course was characterized by severe joint involvement leading to left hip replacement, as well as recurrent febrile episodes with myalgia, pharyngitis, splenomegaly, and lung involvement. Biological manifestations included leukocytosis with more than 80% neutrophils. Given the suspicion of an autoinflammatory disease, analysis of *TNFRSF1A* and *NLRP3* genes by Sanger sequencing respectively excluded TNF receptor-associated periodic fever syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS). The patient was diagnosed with AOSD at the age of 23 years. He was then sequentially treated with colchicine, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, methotrexate, leflunomide, and etanercept, with suboptimal response to all agents. Anakinra was started at the age of 48 years. At that moment, the patient presented with a nephrotic syndrome. Kidney biopsy confirmed the diagnosis of AAA. A few months later, declining renal function required initiation of hemodialysis.

Case 2 (previously reported by Serratrice et al [8]): In 1996, a woman had been followed since the age of 37 years for recurrent attacks of fever, migratory maculopapular erythema, pharyngitis, and arthritis, with concomitant neutrophilia. She also presented an episode of pericarditis and an episode of idiopathic thrombocytopenic purpura. She was finally diagnosed with AOSD 6 years later and treated with corticosteroids. Disease course was marked by several relapses, partly due to poor compliance. At the age of 51 years, diagnosis of renal AAA was made upon development of a nephrotic syndrome. The introduction of etanercept and colchicine resulted in stabilization of renal function and a marked decrease in proteinuria (0.1 g/L). There was no mutation identified in the *TNFRSF1A* gene.

Case 3: AOSD was diagnosed in a 17-year-old man with arthritis, odynophagia, and fever with polynuclear leukocytosis. He was initially treated with corticosteroids alone, achieving disease control for 5 years. Because of a recrudescence in disease activity, methotrexate, hydroxychloroquine, and immunoglobulins were consecutively administered. Diagnosis of AAA

with renal involvement was made at the age of 29 years, based on a renal biopsy revealing diffuse glomerular and vascular lesions with chronic tubulointerstitial involvement. The patient was unsuccessfully treated with corticosteroids, cyclophosphamide, chlorambucil, and infliximab until he received a renal transplant at the age of 33 years. Persistent active AOSD despite treatment with anakinra lead to a second renal transplant 13 years later for recurrent amyloidosis in the graft. Of note, the patient also suffered from destructive polyarthritis requiring synovectomy and joint replacements.

Literature search

Fifty-seven articles were selected following our 2 searches (figure A). Forty-five were used to assess AAA prevalence [1,9–52]. Sixteen [12,15,22,32,53–64] were used for the descriptive analysis of patients with AOSD and AAA, including 4 articles selected for the prevalence study and 12 individual case reports.

Prevalence study

The analysis included prospective and retrospective studies published between 1971 and 2016, representing a total of 2157 AOSD patients from different countries. AAA was reported in 19 patients, with a prevalence of 0.88 (95%CI [0.49-1.28]). The mean duration of follow-up was 5.4±4.5 years (Table A). Fifty-two deaths were reported during follow-up, including at least 3 patients suffering from AAA. None of the case series published since 2012 reported AAA as a complication of AOSD.

Description of patients with AOSD-related AAA

Overall, 19 patients, including our 3 French cases, were reported with sufficient information to be analyzed. One of the French cases had previously been reported by Serratrice et al [8]. Eight patients were female. The sex ratio was 1.4. The mean age at diagnosis of AOSD was 30.7±11.8 years, with a delay from onset of symptoms of 3.3±2.8 years. There was no familial aggregation. Clinical and laboratory features when available (n=17) are detailed in Table B. Fever and arthralgia/arthritis were present in all patients, and skin rash in 12 of them (64.7%). Neutrophilic leukocytosis and elevation of ESR and/or CRP were reported in 15 patients (82.3%). Thirteen patients had a chronic articular course with joint destruction. Three developed uncomplicated pericarditis. None evolved into a macrophage activation syndrome (MAS). (Table C).

Before the diagnosis of amyloidosis, all patients received corticosteroids. Six were also treated with methotrexate, and three with colchicine. Recent studies reported 2 patients treated with biologic therapies, which consisted in TNF inhibitors. Other treatments administered included NSAIDs (n=6), hydroxychloroquine (n=3), cyclophosphamide (n=2), azathioprine (n=2), gold salts (n=1), penicillamine (n=1) and isoprinosine (n = 1). Only five patients received biologic therapies. When AOSD response was described, Tocilizumab lead to remission (n=1) meanwhile TNF inhibitors and anti-IL1 therapy were ineffective (French case 1 and 3).

The mean delay between the first symptoms of AOSD and the diagnosis of AAA was 16.8±5.8 years. The most common presentation of AAA was renal involvement with nephrotic syndrome (n=8), sub-nephrotic proteinuria (n=5), and isolated renal insufficiency (n=3). Diagnosis of amyloidosis was confirmed on renal (n=14), intestinal (n = 5), bladder (n=1), abdominal fat (n=1) and salivary gland (n=1) biopsies. According to pathology reports, amyloid deposition was predominantly vascular and perivascular. After diagnosis of AAA, patients were treated with corticosteroids (n=10), cyclophosphamide (n=4), colchicine (n=5), chlorambucil (n=3), dimethylsulfoxide (n=2), TNF inhibitors (n=2), anakinra (n=2), tocilizumab (n=2), NSAIDs (n=1), and methotrexate (n=1). Apart from the 3 French cases, there was only scarce information regarding therapeutic outcome. Tocilizumab lead to renal remission with complete disappearance

of proteinuria and a decrease in creatinine [63]. Meanwhile, anti-IL1 therapy proved ineffective (French case 1 and 3), whereas TNF inhibitors lead to mixed outcomes: a partial response with etanercept (French case 2), and no response with disease progression with etanercept (French case 1) and infliximab (French case 3).

Among the 19 patients, 4 deaths were reported. Three were attributed to AAA. The highest number of reported cases of AAA in AOSD was between 1990 and 1999. None were reported after 2012 (figure B) (65–67).

Comparison of AOSD with and without AAA

Ruscitti's cohort study [52] was the study that best met our predefined criteria, namely a large number of patients with detailed information regarding clinical presentation, biologic therapy, complications, and duration of follow-up. None of the patients from this Italian study suffered from AAA. They were compared to the 19 patients with AOSD and AAA. No sex predilection was observed. Patients with AAA tended to be younger at diagnosis of AOSD. They also had more frequent weight loss. On the other hand, odynophagia, myalgia, hepatomegaly, splenomegaly, and lymphadenopathy were less common. No laboratory feature was positively associated with the development of AAA. Joint destruction was not specifically reported in Ruscitti's cohort study. However, 30% of patients presented a chronic disease course, which tends to be complicated by significant articular damage (table D).

Discussion

AAA is an uncommon complication of AOSD. We estimated its overall prevalence at 0.88 % (95%CI [0.49-1.28]). Based on our study, a typical case of AOSD-related AAA would be a patient between 35 and 40 years old with active AOSD despite treatment, who develops a nephrotic syndrome 17 years after disease onset.

This is the first systematic literature review regarding AAA as a complication of AOSD. We intentionally chose to include only patients with adult onset Still disease, because development of AAA in this population has never been specifically assessed. Furthermore, even though AAA in sJIA continuing into adulthood has previously been reported, case series and reports on this topic have insufficient information to allow detailed descriptive analysis as was done in our review.

As a result, AAA prevalence in AOSD has never been evaluated. Estimation of prevalence through case series carries limitations, but rarity of both diseases prevents us from conducting an epidemiological study. In JIA, the prevalence varies between 1.8% and 15% [68–71] based on old studies. More recently, a Finnish study showed an important decline in the occurrence of AAA in JIA, with no new case reported between 1990 and 2005 [72]. Similarly, prevalence of end-stage renal disease due to AAA in rheumatoid arthritis, ankylosing spondylitis, and JIA has been decreasing, concurrent to a decline in the incidence of AAA over the previous decade. This has been attributed to improvement in the therapeutic management of rheumatic diseases [73–75]. AOSD is no exception, especially since the introduction of biotherapies around the year 2000. Approximately a quarter of patients with AOSD are currently treated with biotherapies [5], allowing to control refractory forms of the disease [44,76,77]. Thus, the low prevalence of AOSD-related AAA observed in our review is probably due to a combination of factors, namely better awareness of the disease, shorter diagnostic delay, and improved therapeutic management. In our review, none of the cases reporting AAA as a complication of AOSD was published after 2012 and publication bias might be a possibility. Indeed, without novelty, submission of new AAA cases usually be rejected by journals. However, there is no new case of such association in the prospective and retrospective studies used to assess prevalence either, and for these articles

editor's selection did not depend on the novelty of AAA as a complication of AOSD. The absence of new case since 2012 could also be justified by the very low incidence of AAA secondary to AOSD but in the past forty years there has never been such a long period without any published case of AAA secondary to AOSD.

The average delay between the first symptoms of AOSD and diagnosis of AAA was 16.8 years, similar to that observed by Lachman et al. [78] for inflammatory diseases associated with AAA. In our review, patients experienced significant diagnostic delay and/or multiple therapeutic failures, leading to chronic inflammation. As in rheumatoid arthritis and autoinflammatory diseases, longer disease activity is probably a key element for AAA development [79]. Renal involvement, particularly nephrotic syndrome, was the most common presentation of AAA in AOSD. In a previous case series describing natural history and outcome in AAA, renal dysfunction was also the main manifestation of the disease, affecting 97% of patients [78].

The first step in the management of AAA is to identify and treat its underlying etiology, in order to control the chronic inflammation causing AAA [80]. SAA has been evaluated as a prognostic marker for AAA, with favorable outcome associated with serum concentration inferior to 10 mg/L [81]. However, SAA measurement is not widely available in current practice. Nevertheless, except for the minority of patients in whom SAA and CRP are not correlated, CRP monitoring is usually sufficient to follow and guide treatment of AOSD-related AAA.

Therapeutic management of AAA remains controversial. In AAA from any cause, early studies suggested some efficacy of azathioprine [82], methotrexate associated with corticosteroids [83], chlorambucil [84], colchicine [85], and cyclophosphamide [86]. However, others showed only a partial regression of renal disease with chlorambucil, corticosteroids, cyclophosphamide, and colchicine [53,55,57,60,61]. Therefore, despite these initial glimmers of hope, AAA remained until recently a difficult-to-treat complication with a dismal prognosis. This was well illustrated in a study of 374 patients with AAA, of whom 44% died within a median of 86 months [78].

Fortunately, biologic therapy may reverse this trend. In our review, tocilizumab lead to a renal remission, meanwhile anti-IL1 therapy was ineffective and TNF inhibitors lead to mixed outcomes: partial response but also 2 cases with disease progression.. However, those patients whose AAA responded poorly to biotherapies also presented active AOSD despite treatment. In 7 cases of sJIA with renal amyloidosis from the literature [73,87–92], complete biological remission was described in 2 patients using tocilizumab, while partial remission was achieved in 5 patients using anakinra, tocilizumab, or etanercept. These results concur with studies pertaining to AAA in general. TNF inhibitors have demonstrated some efficacy in AAA secondary to rheumatic diseases [92,93], and in AAA irrespective of its cause [94]. IL6-antagonists have also shown promising results [95]. Similarly, efficacy of IL-1 antagonists has been reported in both AAA of undetermined etiology [96] and in association with familial Mediterranean fever (FMF) [97]. Thus, despite the scarcity of published cases, the current data pertaining to biologic therapy is promising. Several questions remain, namely regarding the effectiveness and long-term safety of biotherapies, as well as the role of the underlying inflammatory disease in selecting the optimal treatment for AAA.

AAA may lead to end-stage renal failure and require a renal transplant [98]. Thanks to the CEREMAIA, we reported the first case of renal transplantation for AAA secondary to AOSD. Recurrence of AAA in the renal graft has previously been reported [99,100]. Canaud et al. [101] noted a 14% recurrence rate, which was associated with a significantly increased risk of mortality. Unfortunately, AAA developed in the graft of our patient, thus highlighting the importance of sustained AOSD control and regular screening for its complications.

Our review highlights the poor outcome of AOSD complicated by AAA. Four out of 19 patients died. These results concur with those of Smith and al., who followed 389 AOSD and JIA patients for a mean of 11 years. Sixteen of them developed AAA. Among those, 7 (43%) died, compared to 14 (3.7%) patients without AAA [102]. AOSD is heterogeneous in terms of clinical presentation, evolution, and severity, such that AAA is not its only prognostic factor. Other severe complications of AOSD can lead to death, including severe organ failure, MAS, and adverse treatment effects [103]. Other than AAA, life-threatening complications were rare in our

patients. None of them presented MAS, which is one of the most common and serious complications of AOSD with an incidence of 12-15% [76,103]. Given that MAS tends to be an early complication of AOSD [104–106] with severe symptoms that rarely go unnoticed, its presence may expedite the diagnosis and treatment of AOSD, thus avoiding prolonged inflammation.

Finally, comparison of characteristics of AOSD with and without AAA has several limitations, including the small number of patients with AAA and the questionable comparability of the 2 groups. Indeed, the AOSD with AAA group is not a true cohort, but rather a compilation of case reports. Nevertheless, our work revealed some trends, namely increased risk of AAA in patients developing AOSD at a young age; this will need to be confirmed in future studies. We also observed a high prevalence of joint destruction in AOSD patients suffering from AAA (76%), which represents a more chronic form of the disease. Prevalence of joint destruction was twice as high as its previously reported prevalence in the chronic form of AOSD [107], thus suggesting an association between joint destruction and AAA. In FMF, joint involvement has also been identified as a risk factor for AAA [108,109]. This association may be explained by the production of an amyloid precursor by the synovial membrane, as was shown by O'Hara et al. in patients with active rheumatoid arthritis [110].

Conclusion

AA amyloidosis is a rare complication of AOSD, caused by persistent or recurrent inflammation due to suboptimal disease control. Early diagnosis and treatment of AOSD could prevent this complication. The growing use of biologic therapy is now allowing to control previously refractory disease. It may therefore contribute to a decline in AAA development. Finally, renal involvement is a frequent and serious early manifestation of AAA. As a result, closer surveillance of renal function and proteinuria should be considered in uncontrolled AOSD.

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Figure A. Flow-chart diagram depicting selection process

57 articles selected : 45 were used to assess AAA prevalence and sixteen for the descriptive analysis of patients with AOSD and AAA.

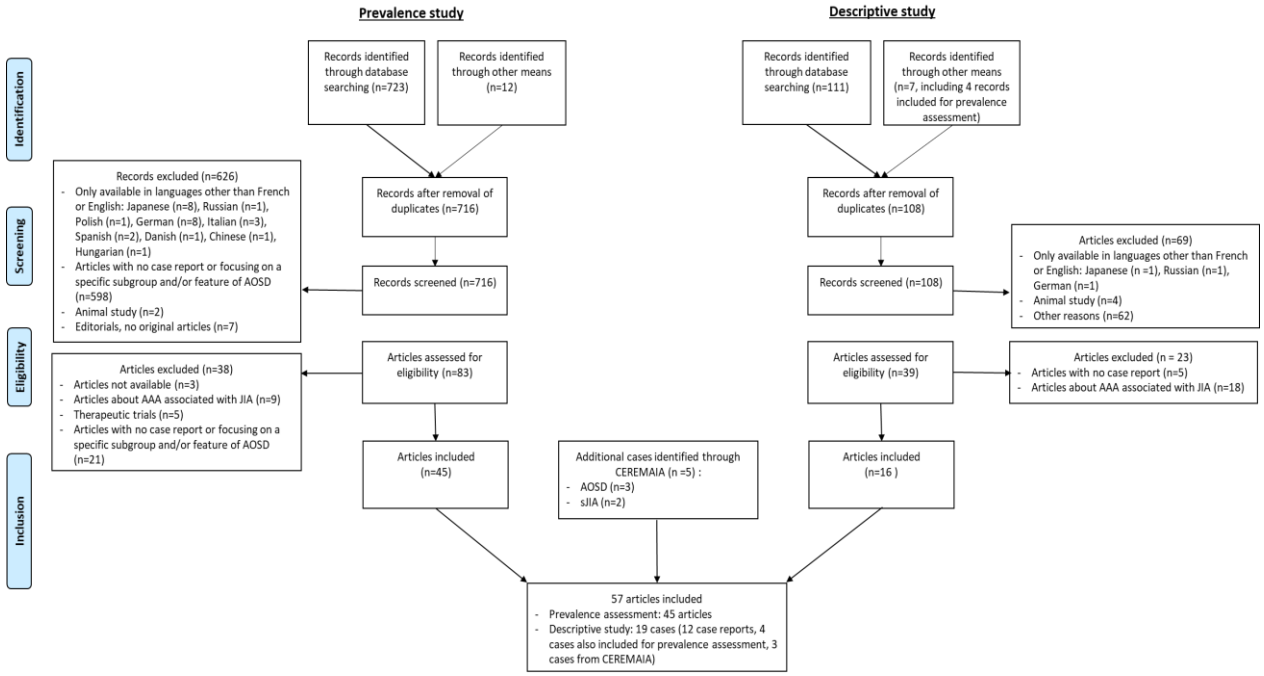

Figure B. Number of new cases of AOSD-related AAA published per decade (colors should be used)

Decline in the incidence of AAA and mortality due to AAA in AOSD over decades

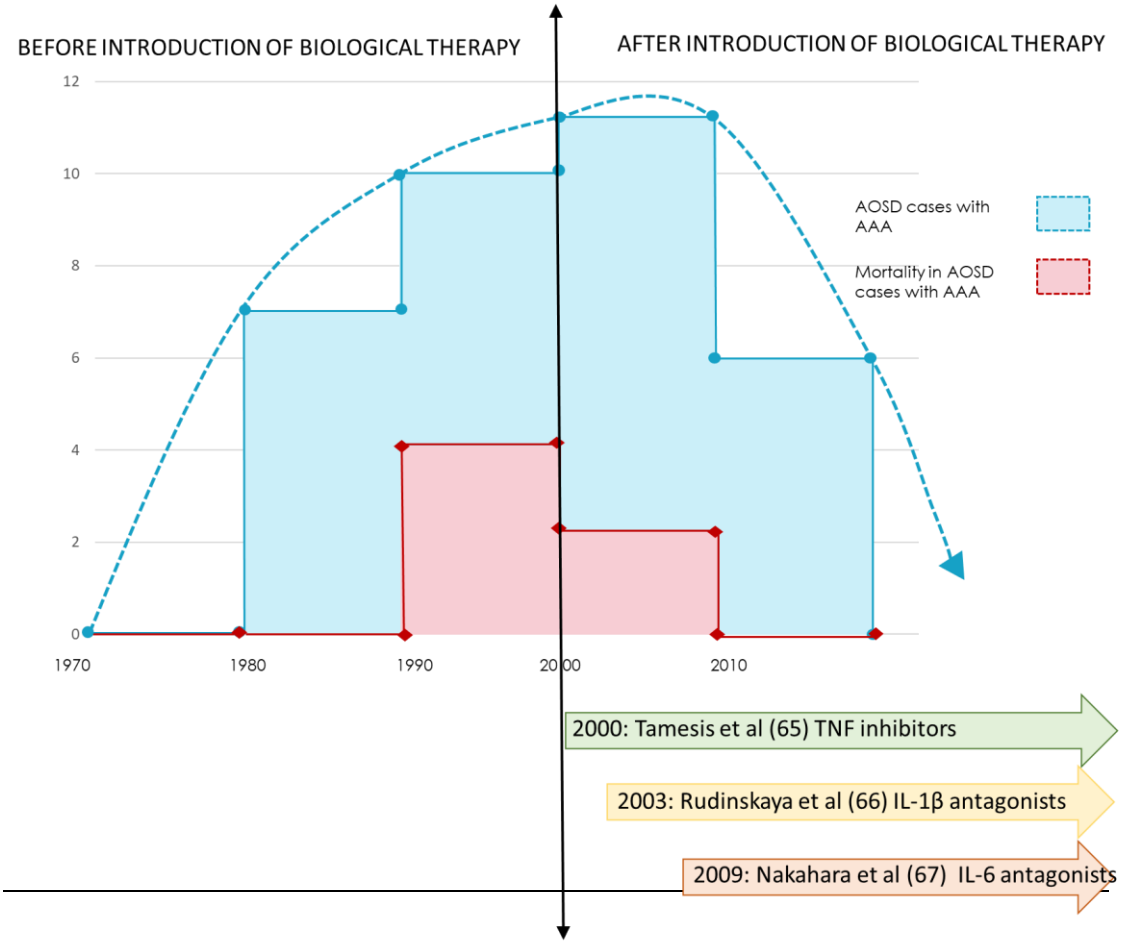

Table A . Case series used for assessment of AAA prevalence in AOSD

	Country of study	Number of patients	Women	Men	Follow-up (years)	Number of amyloidosis cases	Death (with amyloidosis /without amyloidosis)
BYWATERS et al. 1971 [1]	ENGLAND	14	14	0	NS	0	0
ESDAILE et al 1980 [8]	CANADA	6	NS	NS	NS	0	0/0
ELKON et al 1982 [9]	ENGLAND	11	11	0	20.2	1	0/1
LARSON et al 1984 [10]	USA	14	6	8	NS	0	0
VIGNERON et al 1986 [11]	FRANCE	42	NS	NS	NS	2	NS
REGINATO et al 1987 [12]	USA	23	11	12	NS	0	0/1
WOUTERS et al [13]	NETHERLANDS	25	7	18	NS	0	0
CUSH et al 1987 [14]	USA	21	13	8	NS	1	0/2
FLIPO et al 1989 [15]	FRANCE	11	6	5	3	0	0
CABANE et al 1990 [16]	FRANCE	8	NS	NS	14.5	3	2/0
OHTA et al 1990 [17]	JAPAN	90	NS	NS	NS	1	1
POUCHOT et al 1991 [18]	CANADA	60	NS	NS	6	0	NS
SANCHEZ LORIA et al 1992 [19]	ARGENTINA	15	10	5	3.7	0	0
SINGH YN. et al 1992 [20]	INDIA	27	7	20	2.2	1	0/1
BAMBERY et al 1992 [21]	INDIA	18	10	8	15	1	1/1
MASSON et al 1996 [22]	FRANCE	65	NS	NS	NS	0	1
MOK et al 1998 [23]	CHINA	16	NS	NS	8	0	0
LOUTHRENOO et al 2001 [24]	THAILAND	16	13	3	NS	0	0
AL-ARFAJ et al 2001 [25]	SAUDI ARABIA	14	6	14	2.43	0	0
APPENZELLER et al 2005 [26]	BRAZIL	17	9	7	4.8	0	0
PAY et al 2006 [27]	TURKEY	95	50	45	1.1	0	0
AKRITIDIS et al 2006 [28]	GREECE	11	6	5	8.2	0	0
EVENSEN et al 2006 [29]	NORWAY	13	3	10	6.3	0	0/1
MARZOUK et al 2006 [30]	TUNISIA	19	14	5	NS	3	0
CHEIKHROUHOU et al 2007 [31]	TUNISIA	11	7	4	NS	1	0
UPPAL et al 2007 [32]	KUWAIT	28	22	6	3.7	0	0
SINGH S. et al 2008 [33]	INDIA	14	5	9	1.6	0	0
MEHRPOOR et al 2008 [34]	IRAN	28	21	7	NS	0	0
CAGATAY et al 2009 [35]	TURKEY	84	59	27	3.7	3	0
ZHU et al 2009 [36]	CHINA	77	54	23	NS	0	0/1
ZENG et al 2009 [37]	CHINA	61	45	16	3.6	0	0/6
LEE et al 2009 [38]	SOUTH KOREA	71	63	8	3.2	0	0/9
PRIORI et al 2010 [39]	ITALY	41	23	18	NS	0	0/1
KONG et al 2010 [40]	CHINA	104	NS	NS	3.5	0	0
RIERA et al 2011 [41]	SPAIN	41	25	16	9.4	1	0
JIANG et al 2012 [42]	CHINA	70	44	26	2.5	0	0/3
FRANCHINI et al 2012 [43]	ITALY	66	38	28	2.2	1	0/1
KIM HA et al 2012 [44]	SOUTH KOREA	54	39	15	2.2	0	0
ILIOU et al 2013 [45]	GREECE	44	23	21	7	0	0
GERFAUD–VALENTIN et al 2014 [46]	FRANCE	57	30	27	8.4	0	0/3
KIM YJ. et al 2014 [47]	SOUTH KOREA	82	60	22	3	0	0/2
LIU et al 2015 [48]	CHINA	75	44	31	1	0	0
KALYONCU et al 2016 [49]	TURKEY	356	210	146	1.83	0	0
BALCI et al 2016 [40]	TURKEY	42	32	10	6.25	0	0/1
RUSCITTI et al 2016 [51]	ITALY	100	34	66	3.5	0	0/16
		2157	1074	699	mean: 5.4±4.5	19	55

Table B. Summary of clinical and biological features of 17 patients with AOSD and AAA

	Patients with AOSD and AAA n=17 (%)
Clinical signs	
Fever	17 (100)
Arthritis / Arthralgia	17 (100)
Maculopapular erythema / Rash	11 (64.7)
Pericarditis	3 (17.6)
Splenomegaly	7 (41.2)
Hepatomegaly	5 (29.4)
Lymphadenopathy	5 (29.4)
Myalgia	5 (29.4)
Pharyngitis / Odynophagia	4 (23.5)
Deterioration of general state	5 (29.4)
Biological signs	
Leukocytosis	14 (82.3)
with neutrophilia	14 (82.3)
Elevation of ESR and/or CRP	14 (82.3)
Negative ANA and RF	10 (58.9)
Abnormal liver function tests	2 (11.7)

Table C. Epidemiological description of AOSD cases complicated by AAA (*: used for AAA prevalence assessment)

	Sex	Familial cases of AOSD	Age at onset of symptoms (years)	Age at diagnosis of AOSD (years)	Age at diagnosis of amyloidosis (years)	Treatments received before amyloidosis diagnosis	Poor compliance	Other complications of AOSD	First symptoms of amyloidosis	Sites of biopsy	Location of amyloid deposits	Treatments received after amyloidosis diagnosis	Response to biological therapy
HARRINGTON et al 1981 [53]	F	-	26	NS	56	NSAIDS/CT	-	Joint destruction	Nephrotic syndrome	Kidney	Glomerular mesangium	Colchicine/ NSAIDS/CT	-
TAKAHASHI et al 1985 [54]	M	-	NS	31	37	CT	-	Joint destruction, Pericarditis	Diarrhea, Proteinuria	Stomach	NS	CT/DMSO	-
VIGNERON et al 1986 [11]*	M	-	27	28	33	CT/Hydroxychlorooquine /Isoprinosine	-	Joint destruction	Proteinuria and Hepatomegaly	Kidney	Glomerular	NS	-
HORLAIT et al 1988 [55]	M	-	17	NS	26	NS	-	Joint destruction	Proteinuria	Kidney and abdominal fat	NS	Chlorambucil/ Colchicine	-
CUSH et al 1987 [15]*	F	-	16	NS	56	CT	-	Joint destruction	NS	NS	NS	NS	-
WENDLING et al 1990 [56]	F	-	56	57	62	CT/Colchicine	-	-	Nephrotic syndrome	Rectum, Kidney	NS	NS	-
BAMBERY et al 1992 [22]*	F	-	NS	NS	8 years after AOSD diagnosis	NSAIDS/CT	-	Death	Renal Failure	Kidney	NS	NS	-
ISHII et al 1993 [57]	F	-	32	33	39	CT/GT/MTX/ Cyclophosphamide	-	Joint destruction Death	Renal Failure	Duodenum, Rectum, Kidney	Rectal and renal biopsy : Perivascular	CT/ Cyclophosphamide	-
RIVERA et al 1997 [58]	M	-	NS	26	42	NSAIDS/CT/AZT	-	Joint destruction	Renal Failure	Kidney	Arteriolar	NS	-
FAUTREL et al 1999 [59]	M	-	NS	32	NS	-	-	Joint destruction and death	Nephrotic syndrome	NS	NS	CT/MTX	-
OH et al 2000 [60]	M	-	NS	21	25	CT/NSAIDS/Colchicine MTX	-	Joint destruction	Nephrotic syndrome	Kidney	Mesangium and glomerular capillary walls	CT/Colchicine/ Cyclophosphamide	-
BEN GORBEL et al 2004 [61]	F	-	28	34	34	CT/D- Penicillamine MTX	-	-	Nephrotic syndrome	Kidney	Mesangium and glomerular capillary walls	Colchicine/ Chlorambucil	-
AMEMORI et al 2006 [62]	F	-	45	NS	63	CT	-	Death	Proteinuria	Kidney	NS	CT/DMSO	-
CHEIKHROUHOU et al 2007 [32]*	M	-	NS	7 months after first symptoms	NS	CT	-	Joint destruction	NS	Kidney	NS	CT/ Cyclophosphamide	-
KISHIDA et al 2011 [63]	M	-	18	18	39	CT/MTX/AZT Cyclophosphamide	-	Joint destruction, Pericarditis	Proteinuria	Stomach	NS	Tocilizumab	Tocilizumab : AOSD remission Renal remission with complete disappearance of proteinuria and a decrease in creatinine
BENITO et al 2012 [64]	M	-	31	NS	49	CT/ETN	-	-	Acute urinary retention/ Hematuria	Bladder/ Rectum	Stromal and vascular	NS	NS
Case report 1	M	-	17	23	48	Colchicine/CT/NSAIDS Hydrohychloroquine MTX/ETN	-	Joint destruction	Nephrotic syndrome	Kidney/ Salivary glands	Salivary glands: peri-canillar and intravascular KB: intravascular	Anakinra/ CT	ETN : suboptimal response on AOSD, AAA development Anakinra : No efficiency on renal AAA, NS for AOSD
Case report 2 [8]	F	-	42	48	51	NSAIDS/CT	Yes	Pericarditis	Nephrotic Syndrome	NS	NS	ETN/Colchicine/CT	ETN : Stabilization renal function and decrease proteinuria
Case report 3	M	-	NS	17	29	CT/MTX Hydroxychloroquine	-	Joint destruction	Nephrotic syndrome	Kidney	KB : Glomerular and vascular	IFX/Anakinra/CT/ Chlorambucil / Cyclophosphamide	INX and anakinra : No efficiency on AOSD and AAA

Table D. Comparison of AOSD with AAA and AOSD without AAA

	AOSD without amyloidosis n=100 (%)[52]	**AOSD with amyloidosis n=17 (%)**	**p**
Sex ratio M/F	1.94	1.42	0.57
Male	66 (66)	10 (58.9)	
Female	34 (34)	7 (41.1)	
Age at diagnosis (years)	45.35	30.90	
	±16.23	±12.38	
Clinical features			
Fever	100 (100)	17 (100)	1
Weight loss	5 (5)	5 (29.4)	0.006
Rash	78 (78)	11 (64.7)	0.24
Arthritis / Arthralgia	86 (86)	17 (100)	0.22
Sore throat	64 (64)	4 (23.5)	0.002
Myalgia	57 (57)	5 (29.4)	0.04
Lymphadenopathy	57 (57)	5 (29.4)	0.04
Splenomegaly	79 (79)	7 (41.2)	0.003
Liver involvement	62 (62)	6 (35.3)	0.04
Complications			
MAS	13 (13)	0 (0)	0.22
Pericarditis	15 (15)	3 (17.6)	0.73
Joint destruction	NS	13(76.4)	-

ABBREVIATION

F: Female

M: Male

NS: Not specified

CT: Corticosteroids

NSAIDS: Non-steroidal anti-inflammatory drugs

AZT: Azathioprine

ETN: Etanercept

GT: Gold therapy

DMSO: Dimethylsulfoxide

ETN: Etanercept

IFX: Infliximab

KB: Kidney biopsy

MTX: Methotrexate

ESR: Erythrocyte sedimentation rate

CRP: C-reactive protein

ANA: Antinuclear antibody

RF: Rheumatoid factor

MAS: Macrophage activation syndrome