



HAL
open science

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

M. Delplanque, J. Pouchot, S. Ducharme-Bénard, B.J Fautrel, A. Benyamine, L. Daniel, T. Gendre, G. Grateau, S. Georgin-Lavialle

► **To cite this version:**

M. Delplanque, J. Pouchot, S. Ducharme-Bénard, B.J Fautrel, A. Benyamine, et al.. AA Amyloidosis Secondary to Adult Onset Still's Disease: About 19 Cases. *Seminars in Arthritis and Rheumatism*, 2020, 50 (1), pp.156–165. <10.1016/j.semarthrit.2019.08.005>. <hal-03894255>

HAL Id: hal-03894255

<https://hal.sorbonne-universite.fr/hal-03894255v1>

Submitted on 30 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

AA amyloidosis secondary to adult onset Still's disease: about 19 cases

Authors

M. Delplanque^{1*}, J. Pouchot², S. Ducharme-Bénard^{3**}, B.J Fautrel^{4*}, A. Benyamine⁵, L. Daniel⁶, T. Gendre⁷, G. Grateau^{1*}, S. Georgin-Lavialle^{1*}.

Affiliations:

1 Sorbonne Université, AP-HP, Hôpital Tenon, Service de médecine interne, Centre de référence des maladies auto-inflammatoires et des amyloses d'origine inflammatoire (CEREMAIA), F-75020, Paris

2 Service Médecine Interne, AP-HP Hôpital Européen George Pompidou, Paris, France

3 Service de Médecine Interne, Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada

4 Sorbonne Université, AP-AP, Hôpital Pitié Salpêtrière, Service de Rhumatologie, Paris, France; INSERM, Institut Pierre Louis d'Epidémiologie et Santé publique, Paris, France.4 Service Médecine Interne, APHM Hôpital Nord, Marseille, France

5 Service Médecine Interne, APHM Hôpital Nord, Marseille, France

6 Service de Pathologie, APHM Hôpital La Timone, Marseille, France

7 Service de Neurologie, Hôpital Henri Mondor, Paris, France

*Paris 6 University, DHU I2B **Montreal University

Corresponding author:

Sophie Georgin-Lavialle, MD, PhD

Sorbonne Université, AP-HP, Hôpital Tenon, Service de médecine interne, Centre de référence des maladies auto-inflammatoires et des amyloses d'origine inflammatoire (CEREMAIA), 75020, Paris. Tel: 00 331 56 01 60 77 Fax: 00 33 1 56 01 71 46 E-Mail: sophie.georgin-lavialle@aphp.fr

Key words: Adult onset Still's disease, AA amyloidosis, kidney disease, systematic literature review

Conflict of interest: None

Funding statement: No financial support was received

Word count: Manuscript = 3165 words Abstract = 236 words

[Tapez ici]

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

[Tapez ici]

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

[Tapez ici]

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

[Tapez ici]

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

[Tapez ici]

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].

[Tapez ici]

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

[Tapez ici]

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.

References

1. Bywaters EG. Still's disease in the adult. *Ann Rheum Dis.* mars 1971;30(2):121-33.
2. Kadavath S, Efthimiou P. Adult-onset Still's disease-pathogenesis, clinical manifestations, and new treatment options. *Ann Med.* févr 2015;47(1):6-14.
3. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol.* mars 1992;19(3):424-30.
4. Fautrel B, Zing E, Golmard J-L, Le Moel G, Bissery A, Rioux C, et al. Proposal for a new set of classification criteria for adult-onset still disease. *Medicine (Baltimore).* mai 2002;81(3):194-200.
5. Castañeda S, Blanco R, González-Gay MA. Adult-onset Still's disease: Advances in the treatment. *Best Pract Res Clin Rheumatol.* avr 2016;30(2):222-38.
6. Stojanovic KS, Georjgin-Lavialle S, Grateau G. [AA amyloidosis]. *Nephrol Ther.* juin 2017;13(4):258-64.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 21 juill 2009;6(7):e1000097.
8. Serratrice J, Granel B, Disdier P, Weiller P-J, Dussol B. Resolution with etanercept of nephrotic syndrome due to renal AA amyloidosis in adult Still's disease. *Am J Med.* nov 2003;115(7):589-90.
9. Esdaile JM, Tannenbaum H, Hawkins D. Adult Still's disease. *Am J Med.* juin 1980;68(6):825-30.
10. Elkon KB, Hughes GR, Bywaters EG, Ryan PF, Inman RD, Bowley NB, et al. Adult-onset Still's disease. Twenty-year followup and further studies of patients with active disease. *Arthritis Rheum.* juin 1982;25(6):647-54.
11. Larson EB. Adult Still's disease. Evolution of a clinical syndrome and diagnosis, treatment, and follow-up of 17 patients. *Medicine (Baltimore).* mars 1984;63(2):82-91.
12. Vigneron AM, Kaplan G, Labrousse C, Leroux-Robert C, Rene E, Kahn MF. [Amyloidosis in adult Still's disease. Apropos of 2 cases]. *Ann Med Interne (Paris).* 1986;137(5):406-8.
13. Reginato AJ, Schumacher HR, Baker DG, O'Connor CR, Ferreiros J. Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. *Semin Arthritis Rheum.* août 1987;17(1):39-57.
14. Wouters JM, van de Putte LB. Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. *Q J Med.* nov 1986;61(235):1055-65.
15. Cush JJ, Medsger TA, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. *Arthritis Rheum.* févr 1987;30(2):186-94.
16. Flipo RM, Gosset D, Savinel P, Hachulla E, Hatron PY, Devulder B. [Adult Still's disease. A too often unrecognized illness. A study of a series of 11 cases]. *Rev Med Interne.* juin 1989;10(3):217-22.
17. Cabane J, Michon A, Ziza JM, Bourgeois P, Blétry O, Godeau P, et al. Comparison of long term evolution of adult onset and juvenile onset Still's disease, both followed up for more than 10 years. *Ann Rheum Dis.* mai 1990;49(5):283-5.
18. Ohta A, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H, et al. Adult Still's disease: a multicenter survey of Japanese patients. *J Rheumatol.* août 1990;17(8):1058-63.

[Tapez ici]

19. Pouchot J, Sampalis JS, Beaudet F, Carette S, Décary F, Salusinsky-Sternbach M, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)*. mars 1991;70(2):118-36.
20. Sánchez Loria DM, Moreno Alvarez MJ, Maldonado Cocco JA, Scheines EJ, Messina OD. Adult onset Still's disease: clinical features and course. *Clin Rheumatol*. déc 1992;11(4):516-20.
21. Singh YN, Adya CM, Kumar A, Malaviya AN. Adult-onset Still's disease in India. *Br J Rheumatol*. juin 1992;31(6):417-9.
22. Bamberg P, Thomas RJ, Malhotra HS, Kaur U, Bhusnurmath SR, Deodhar SD. Adult onset Still's disease: clinical experience with 18 patients over 15 years in northern India. *Ann Rheum Dis*. avr 1992;51(4):529-32.
23. Masson C, Le Loet X, Liote F, Dubost JJ, Boissier MC, Perroux-Goumy L, et al. Comparative study of 6 types of criteria in adult Still's disease. *J Rheumatol*. mars 1996;23(3):495-7.
24. Mok CC, Lau CS, Wong RW. Clinical characteristics, treatment, and outcome of adult onset Still's disease in southern Chinese. *J Rheumatol*. déc 1998;25(12):2345-51.
25. Louthrenoo W, Aramsareewong T, Sukitawut W. Adult onset Still's disease: clinical features and outcome in 16 Thai patients. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis*. oct 2001;7(5):301-7.
26. Al-Arfaj AS, Al-Saleh S. Adult-Onset Still's disease in Saudi Arabia. *Clin Rheumatol*. 2001;20(3):197-200.
27. Appenzeller S, Castro GRW, Costallat LTL, Samara AM, Bértolo MB. Adult-onset Still disease in southeast Brazil. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis*. avr 2005;11(2):76-80.
28. Pay S, Türkçapar N, Kalyoncu M, Simşek I, Beyan E, Ertenli I, et al. A multicenter study of patients with adult-onset Still's disease compared with systemic juvenile idiopathic arthritis. *Clin Rheumatol*. sept 2006;25(5):639-44.
29. Akritidis N, Papadopoulos A, Pappas G. Long-term follow-up of patients with adult-onset Still's disease. *Scand J Rheumatol*. oct 2006;35(5):395-7.
30. Evensen KJ, Nossent HC. Epidemiology and outcome of adult-onset Still's disease in Northern Norway. *Scand J Rheumatol*. févr 2006;35(1):48-51.
31. Marzouk S, Kaddour N., Frigui M., Jallouli F., Frikha F. La maladie de Still à propos de 19 cas. 2006.
32. Cheikhrouhou Abdelmoula L, Tekaya R, Ben Hadj Yahia C, Chaabouni L, Zouari R. [Adult onset Still's disease: about 11 cases]. *Tunis Med*. juin 2007;85(6):461-4.
33. Uppal SS, Al-Mutairi M, Hayat S, Abraham M, Malaviya A. Ten years of clinical experience with adult onset Still's disease: is the outcome improving? *Clin Rheumatol*. juill 2007;26(7):1055-60.
34. Singh S, Samant R, Joshi VR. Adult onset Still's disease: a study of 14 cases. *Clin Rheumatol*. janv 2008;27(1):35-9.
35. Mehrpoor G, Owlia MB, Soleimani H, Ayatollahi J. Adult-onset Still's disease: a report of 28 cases and review of the literature. *Mod Rheumatol*. 2008;18(5):480-5.

[Tapez ici]

36. Cagatay Y, Gul A, Cagatay A, Kamali S, Karadeniz A, Inanc M, et al. Adult-onset Still's disease. *Int J Clin Pract.* juill 2009;63(7):1050-5.
37. Zhu G, Liu G, Liu Y, Xie Q, Shi G. Liver abnormalities in adult onset Still's disease: a retrospective study of 77 Chinese patients. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis.* sept 2009;15(6):284-8.
38. Zeng T, Zou Y-Q, Wu M-F, Yang C-D. Clinical features and prognosis of adult-onset still's disease: 61 cases from China. *J Rheumatol.* mai 2009;36(5):1026-31.
39. Lee S-W, Park Y-B, Song J-S, Lee S-K. The mid-range of the adjusted level of ferritin can predict the chronic course in patients with adult onset Still's disease. *J Rheumatol.* janv 2009;36(1):156-62.
40. Priori R, Colafrancesco S, Gattamelata A, Di Franco M, Di Tondo U, Valesini G. Adult-onset Still disease: a rare disorder with a potentially fatal outcome. *Auto-Immun Highlights.* mai 2010;1(1):53-9.
41. Kong X-D, Xu D, Zhang W, Zhao Y, Zeng X, Zhang F. Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. *Clin Rheumatol.* sept 2010;29(9):1015-9.
42. Riera E, Olivé A, Narváez J, Holgado S, Santo P, Mateo L, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol.* avr 2011;29(2):331-6.
43. Jiang L, Wang Z, Dai X, Jin X. Evaluation of clinical measures and different criteria for diagnosis of adult-onset Still's disease in a Chinese population. *J Rheumatol.* avr 2011;38(4):741-6.
44. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. *Arthritis Rheum.* août 2010;62(8):2530-5.
45. Kim H-A, Sung J-M, Suh C-H. Therapeutic responses and prognosis in adult-onset Still's disease. *Rheumatol Int.* mai 2012;32(5):1291-8.
46. Iliou C, Papagoras C, Tsifetaki N, Voulgari PV, Drosos AA. Adult-onset Still's disease: clinical, serological and therapeutic considerations. *Clin Exp Rheumatol.* févr 2013;31(1):47-52.
47. Gerfaud-Valentin M, Maucourt-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I, et al. Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. *Medicine (Baltimore).* mars 2014;93(2):91-9.
48. Kim YJ, Koo BS, Kim Y-G, Lee C-K, Yoo B. Clinical features and prognosis in 82 patients with adult-onset Still's disease. *Clin Exp Rheumatol.* févr 2014;32(1):28-33.
49. Liu Z, Lv X, Tang G. Clinical features and prognosis of adult-onset Still's disease: 75 cases from China. *Int J Clin Exp Med.* 15 sept 2015;8(9):16634-9.
50. Kalyoncu U, Solmaz D, Emmungil H, Yazici A, Kasifoglu T, Kimyon G, et al. Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still's disease: Data from a large multicenter cohort. *J Autoimmun.* mai 2016;69:59-63.
51. Balci MA, Pamuk ÖN, Pamuk GE, Uzundere FK, Donmez S. Epidemiology and outcome of adult-onset Still's disease in Northwestern Thrace region in Turkey. *Clin Exp Rheumatol.* déc 2015;33(6):818-23.

[Tapez ici]

52. Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, et al. Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. *BMC Med.* 1 déc 2016;14(1):194.
53. Harrington TM, Moran JJ, Davis DE. Amyloidosis in adult onset Still's disease. *J Rheumatol.* oct 1981;8(5):833-6.
54. Takahashi A, Matsumoto J, Nishimura S, Tanida N, Imura S, Isobe T, et al. Improvement of endoscopic and histologic findings of AA-type gastrointestinal amyloidosis by treatment with dimethyl sulfoxide and prednisolone. *Gastroenterol Jpn.* avr 1985;20(2):143-7.
55. Horlait S, Bernard JF, Lioté F, Bardin T, Cywiner-Golenzer C, Meyer O, et al. [Secondary amylosis in Still's disease in an adult. Value of biopsy of the subcutaneous abdominal fatty tissue]. *Rev Rhum Mal Osteoartic.* juin 1988;55(8):630-1.
56. Wendling D, Humbert PG, Billerey C, Fest T, Dupond JL. Adult onset Still's disease and related renal amyloidosis. *Ann Rheum Dis.* avr 1991;50(4):257-9.
57. Ishii T, Sasaki T, Muryoi T, Murai C, Hatakeyama A, Oosaki H, et al. Systemic amyloidosis in a patient with adult onset Still's disease. *Intern Med Tokyo Jpn.* janv 1993;32(1):50-2.
58. Rivera F, Gil CM, Gil MT, Batlle-Gualda E, Trigueros M, Olivares J. Vascular renal AA amyloidosis in adult Still's disease. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc.* août 1997;12(8):1714-6.
59. Fautrel B, Borget C, Rozenberg S, Meyer O, Le Loët X, Masson C, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. *J Rheumatol.* févr 1999;26(2):373-8.
60. Oh YB, Bae SC, Jung JH, Kim TH, Jun JB, Jung SS, et al. Secondary renal amyloidosis in adult onset Still's disease: case report and review of the literature. *Korean J Intern Med.* juill 2000;15(2):131-4.
61. Ben Ghorbel I, Khanfir M, Houman MH. [Amyloidosis in adult onset Still's disease]. *Rev Med Interne.* sept 2004;25(9):675-7.
62. Amemori S, Iwakiri R, Endo H, Ootani A, Ogata S, Noda T, et al. Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. *J Gastroenterol.* mai 2006;41(5):444-9.
63. Kishida D, Okuda Y, Onishi M, Takebayashi M, Matoba K, Jouyama K, et al. Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by chronic active hepatitis B and amyloid A amyloidosis. *Mod Rheumatol.* avr 2011;21(2):215-8.
64. Benito P, Fernández I, Pérez-Carral JR, Fernández S, Cruceyra G, Menéndez CL. Secondary bladder amyloidosis: a new case report. *Arch Esp Urol.* sept 2012;65(7):699-702.
65. Tamesis ER., Reginato AM., Hubscher O., Reginato AJ. Etanercept in recalcitrant Adult Onset Still's Disease. 2000;
66. Rudinskaya A, Trock DH. Successful treatment of a patient with refractory adult-onset still disease with anakinra. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis.* oct 2003;9(5):330-2.
67. Nakahara H, Mima T, Yoshio-Hoshino N, Matsushita M, Hashimoto J, Nishimoto N. A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. *Mod Rheumatol.* 2009;19(1):69-72.

[Tapez ici]

68. Dhillon V, Woo P, Isenberg D. Amyloidosis in the rheumatic diseases. *Ann Rheum Dis.* août 1989;48(8):696-701.
69. Filipowicz-Sosnowska AM, Roztropowicz-Denisiewicz K, Rosenthal CJ, Baum J. The amyloidosis of juvenile rheumatoid arthritis--comparative studies in Polish and American children. I. Levels of serum SAA protein. *Arthritis Rheum.* août 1978;21(6):699-703.
70. David J, Vouyiouka O, Ansell BM, Hall A, Woo P. Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. *Clin Exp Rheumatol.* févr 1993;11(1):85-90.
71. Ozdogan H, Kasapçopur O, Dede H, Arisoy N, Beceren T, Yurdakul S, et al. Juvenile chronic arthritis in a Turkish population. *Clin Exp Rheumatol.* août 1991;9(4):431-5.
72. Immonen K, Savolainen HA, Hakala M. Why can we no longer find juvenile idiopathic arthritis-associated amyloidosis in childhood or in adolescence in Finland? *Scand J Rheumatol.* oct 2007;36(5):402-3.
73. Immonen K, Savolainen A, Kautiainen H, Hakala M. Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis. *J Rheumatol.* mai 2008;35(5):907-12.
74. Immonen K, Finne P, Grönhagen-Riska C, Pettersson T, Klaukka T, Kautiainen H, et al. A marked decline in the incidence of renal replacement therapy for amyloidosis associated with inflammatory rheumatic diseases - data from nationwide registries in Finland. *Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis.* mars 2011;18(1):25-8.
75. Vasala M, Immonen K, Kautiainen H, Hakala M. More evidence of declining incidence of amyloidosis associated with inflammatory rheumatic diseases. *Scand J Rheumatol.* nov 2010;39(6):461-5.
76. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. *Autoimmun Rev.* juill 2014;13(7):708-22.
77. Al-Homood IA. Biologic treatments for adult-onset Still's disease. *Rheumatol Oxf Engl.* janv 2014;53(1):32-8.
78. Lachmann HJ, Goodman HJB, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med.* 7 juin 2007;356(23):2361-71.
79. Koivuniemi R, Paimela L, Suomalainen R, Tornroth T, Leirisalo-Repo M. Amyloidosis is frequently undetected in patients with rheumatoid arthritis. *Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis.* déc 2008;15(4):262-8.
80. Lebrazi H, Hachulla E, Saïle R. Mécanismes de l'amylose et protéines impliquées. *Rev Med Int.* 21(1):35-49.
81. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet Lond Engl.* 7 juill 2001;358(9275):24-9.
82. Shapiro DL, Spiera H. Regression of the nephrotic syndrome in rheumatoid arthritis and amyloidosis treated with azathioprine. A case report. *Arthritis Rheum.* déc 1995;38(12):1851-4.
83. Komatsuda A, Morita K, Ohtani H, Yamaguchi A, Miura AB. Remission of the nephrotic syndrome in a patient with renal amyloidosis due to rheumatoid arthritis treated with prednisolone and methotrexate. *Am J Kidney Dis Off J Natl Kidney Found.* nov 1998;32(5):E7.

[Tapez ici]

84. Ortiz-Santamaría V, Olivé A, Valls-Roc M, Tena X. Treatment of AA amyloid with chlorambucil. *Rheumatol Oxf Engl.* juill 2002;41(7):833.
85. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med.* 17 avr 1986;314(16):1001-5.
86. Chevrel G, Jenvrin C, McGregor B, Miossec P. Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. *Rheumatol Oxf Engl.* juill 2001;40(7):821-5.
87. Duarte C, Gomes C, Correia AJ, Salgado M. Renal amyloidosis: an uncommon complication of juvenile idiopathic arthritis. *Clin Rheumatol.* juill 2006;25(4):548-9.
88. De La Torre M, Arboleya L, Pozo S, Pinto J, Velasco J. Rapid and sustained response to tocilizumab, anti-interleukin-6 receptor antibody, in a patient with nephrotic syndrome secondary to systemic juvenile idiopathic arthritis-related amyloidosis. *NDT Plus.* juin 2011;4(3):178-80.
89. Sharma A, Gupta A, Mitra S, Nada R, Bhattad S, Singh S. Systemic Juvenile Idiopathic Arthritis with Amyloidosis: An Uncommon Complication with a Favourable Outcome. *Indian J Pediatr.* mai 2016;83(5):477-8.
90. Topaloglu R, Batu ED, Orhan D, Ozen S, Besbas N. Anti-interleukin 1 treatment in secondary amyloidosis associated with autoinflammatory diseases. *Pediatr Nephrol Berl Ger.* avr 2016;31(4):633-40.
91. Chantarogh S, Vilaiyuk S, Tim-Aroon T, Worawichawong S. Clinical improvement of renal amyloidosis in a patient with systemic-onset juvenile idiopathic arthritis who received tocilizumab treatment: a case report and literature review. *BMC Nephrol.* 12 mai 2017;18(1):159.
92. Gottenberg J-E, Merle-Vincent F, Bentaberry F, Allanore Y, Berenbaum F, Fautrel B, et al. Anti-tumor necrosis factor alpha therapy in fifteen patients with AA amyloidosis secondary to inflammatory arthritides: a followup report of tolerability and efficacy. *Arthritis Rheum.* juill 2003;48(7):2019-24.
93. Fernández-Nebro A, Olivé A, Castro MC, Varela AH, Riera E, Irigoyen MV, et al. Long-term TNF-alpha blockade in patients with amyloid A amyloidosis complicating rheumatic diseases. *Am J Med.* mai 2010;123(5):454-61.
94. Esatoglu SN, Hatemi G, Ugurlu S, Gokturk A, Tascilar K, Ozdogan H. Long-term follow-up of secondary amyloidosis patients treated with tumor necrosis factor inhibitor therapy: A STROBE-compliant observational study. *Medicine (Baltimore).* août 2017;96(34):e7859.
95. Courties A, Grateau G, Philippe P, Flipo R-M, Astudillo L, Aubry-Rozier B, et al. AA amyloidosis treated with tocilizumab: case series and updated literature review. *Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis.* 2015;22(2):84-92.
96. Lane T, Wechalekar AD, Gillmore JD, Hawkins PN, Lachmann HJ. Safety and efficacy of empirical interleukin-1 inhibition using anakinra in AA amyloidosis of uncertain aetiology. *Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis.* sept 2017;24(3):189-93.
97. Varan Ö, Kucuk H, Babaoglu H, Guven SC, Ozturk MA, Haznedaroglu S, et al. Efficacy and safety of interleukin-1 inhibitors in familial Mediterranean fever patients complicated with amyloidosis. *Mod Rheumatol.* 27 avr 2018;1-4.

[Tapez ici]

98. Sherif AM, Refaie AF, Sobh MA-K, Mohamed NA-H, Sheashaa HA, Ghoneim MA. Long-term outcome of live donor kidney transplantation for renal amyloidosis. *Am J Kidney Dis Off J Natl Kidney Found.* août 2003;42(2):370-5.
99. Hartmann A, Holdaas H, Fauchald P, Nordal KP, Berg KJ, Talseth T, et al. Fifteen years' experience with renal transplantation in systemic amyloidosis. *Transpl Int Off J Eur Soc Organ Transplant.* mars 1992;5(1):15-8.
100. Rojas R, Josephson MA, Chang A, Meehan SM. AA amyloidosis in the renal allograft: a report of two cases and review of the literature. *Clin Kidney J.* avr 2012;5(2):146-9.
101. Canaud G, Audard V, Kofman T, Lang P, Legendre C, Grimbert P. Recurrence from primary and secondary glomerulopathy after renal transplant. *Transpl Int Off J Eur Soc Organ Transplant.* août 2012;25(8):812-24.
102. Smith ME, Ansell BM, Bywaters EG. Mortality and prognosis related to the amyloidosis of Still's disease. *Ann Rheum Dis.* mars 1968;27(2):137-45.
103. Mitrovic S, Fautrel B. Complications of adult-onset Still's disease and their management. *Expert Rev Clin Immunol.* mai 2018;14(5):351-65.
104. Hot A, Toh M-L, Coppéré B, Perard L, Madoux MHG, Mausservey C, et al. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. *Medicine (Baltimore).* janv 2010;89(1):37-46.
105. Bae C-B, Jung J-Y, Kim H-A, Suh C-H. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features, predictive factors, and prognosis in 21 patients. *Medicine (Baltimore).* janv 2015;94(4):e451.
106. Arlet J-B, Le THD, Marinho A, Amoura Z, Wechsler B, Papo T, et al. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. *Ann Rheum Dis.* déc 2006;65(12):1596-601.
107. Fautrel B. Adult-onset Still disease. *Best Pract Res Clin Rheumatol.* oct 2008;22(5):773-92.
108. Gershoni-Baruch R, Brik R, Lidar M, Shinawi M, Livneh A. Male sex coupled with articular manifestations cause a 4-fold increase in susceptibility to amyloidosis in patients with familial Mediterranean fever homozygous for the M694V-MEFV mutation. *J Rheumatol.* févr 2003;30(2):308-12.
109. Mukhin NA, Kozlovskaya LV, Bogdanova MV, Rameev VV, Moiseev SV, Simonyan AK. Predictors of AA amyloidosis in familial Mediterranean fever. *Rheumatol Int.* juill 2015;35(7):1257-61.
110. O'Hara R, Murphy EP, Whitehead AS, FitzGerald O, Bresnihan B. Acute-phase serum amyloid A production by rheumatoid arthritis synovial tissue. *Arthritis Res.* 2000;2(2):142-4.

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.

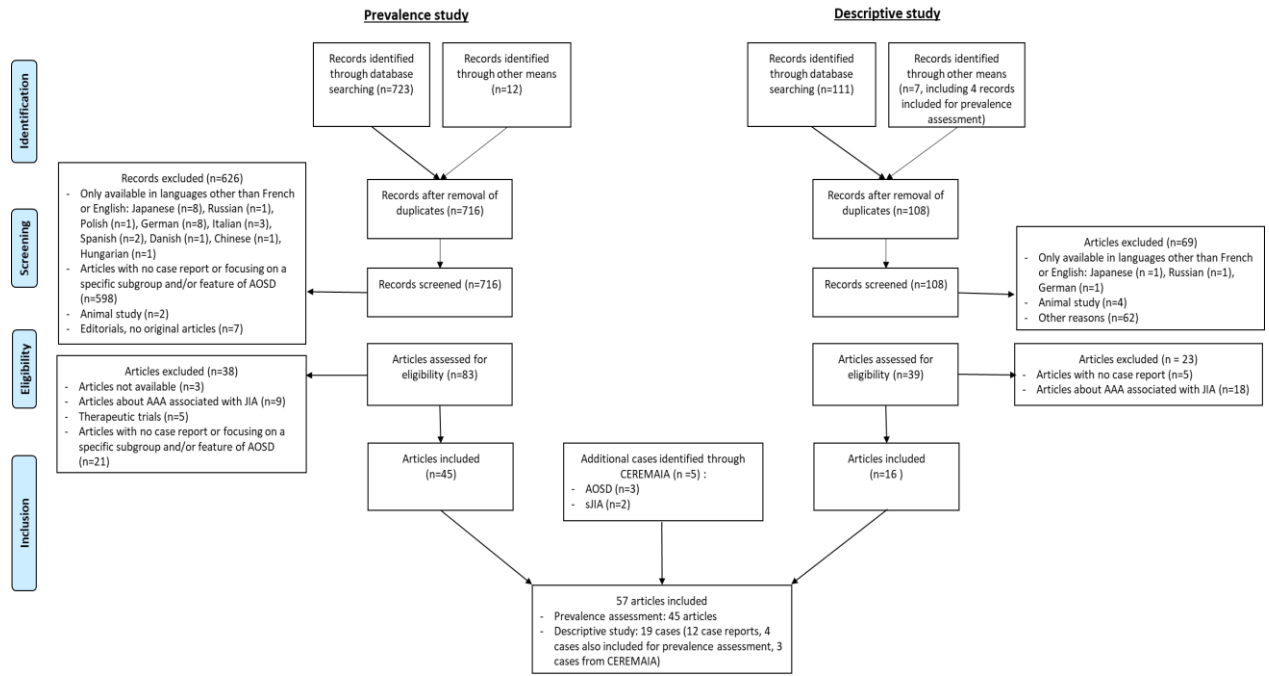
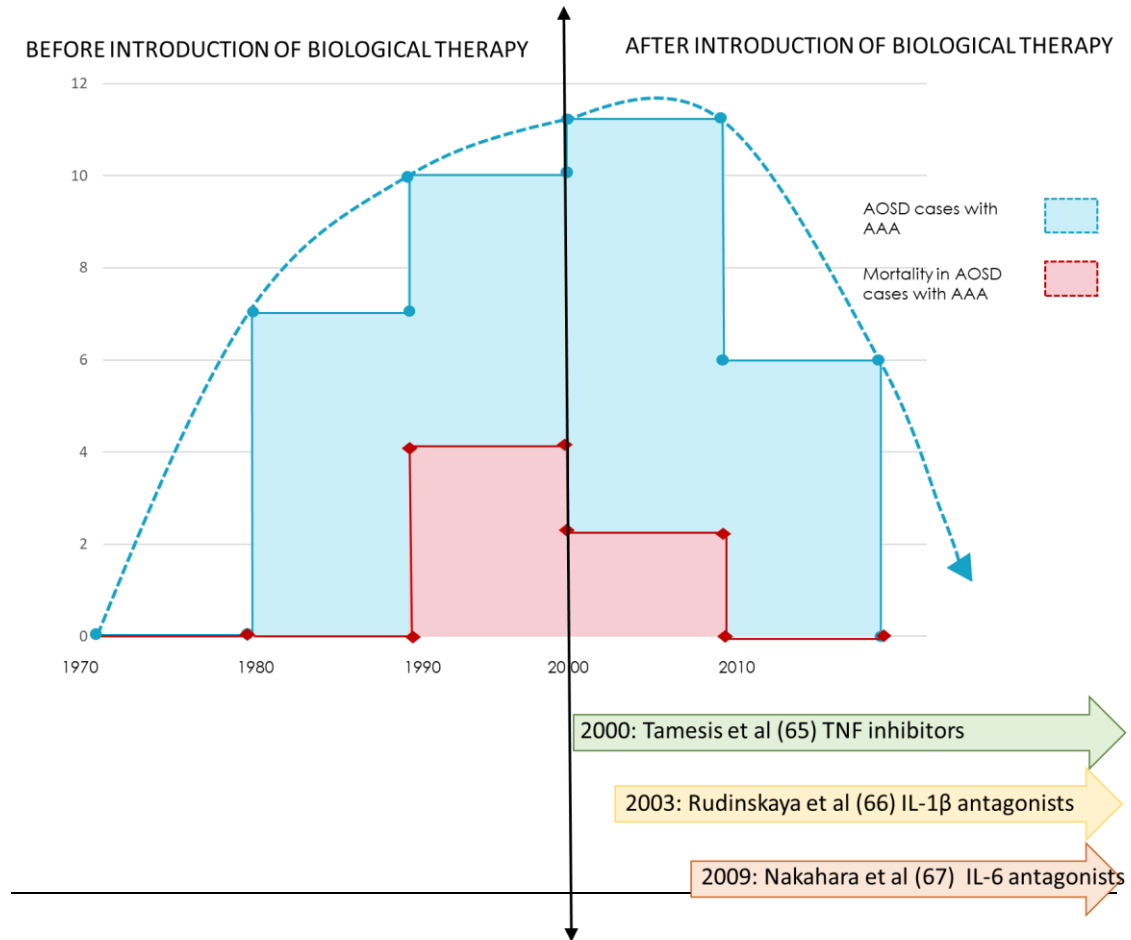


Figure B. Number of new cases of AOSD-related AAA published per decade (colors should be used)

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



[Tapez ici]

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

[Tapez ici]

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)

[Tapez ici]

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/Hydroxychloroquine /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	-
CHEIKHROUHOUI 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 Hydroxychloroquine MTX/ETN	-	Joint destruction	Nephrotic syndrome	Kidney/ Salivary glands	Salivary glands: pericardial 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

[Tapez ici]

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)	-

[Tapez ici]

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