Autoimmunity Reviews 13 (2014) 708–722

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Adult-onset Still's disease

Mathieu Gerfaud-Valentin [a,b,c], Yvan Jamilloux [a,d,g], Jean Iwaz [b,c,e,f], Pascal Sève [a,b,c,*]

[a] Hospices Civils de Lyon, Hôpital Universitaire de la Croix-Rousse, Service de médecine interne, F-69004 Lyon, France
[b] Université Lyon I, F-69100 Villeurbanne, France
[c] Université de Lyon, F-69000 Lyon, France
[d] Inserm U1111, Centre International de Recherche en Infectiologie, F-69365 Lyon, France
[e] Hospices Civils de Lyon, Service de Biostatistique, F-69000 Lyon, France
[f] CNRS UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique Santé, F-69310 Pierre-Bénite, France
[g] Département de Biochimie, Université de Lausanne, 1006 Epalinges, Switzerland

ARTICLE INFO

Article history:
Received 1 January 2014
Accepted 2 January 2014
Available online 19 March 2014

Keywords:
Adult-onset Still's disease
Macrophage activation syndrome
Hemophagocytic lymphohistiocytosis
Hyperferritinemia
Autoinflammatory disorder
Anakinra

ABSTRACT

First described in 1971, adult-onset Still's disease (AOSD) is a rare multisystemic disorder considered as a complex (multigenic) autoinflammatory syndrome.
A genetic background would confer susceptibility to the development of autoinflammatory reactions to environmental triggers. Macrophage and neutrophil activation is a hallmark of AOSD which can lead to a reactive hemophagocytic lymphohistiocytosis. As in the latter disease, the cytotoxic function of natural killer cells is decreased in patients with active AOSD. IL-18 and IL-1β, two proinflammatory cytokines processed through the inflammasome machinery, are key factors in the pathogenesis of AOSD; they cause IL-6 and Th1 cytokine secretion as well as NK cell dysregulation leading to macrophage activation.
The clinico-biological picture of AOSD usually includes high spiking fever with joint symptoms, evanescent skin rash, sore throat, striking neutrophilic leukocytosis, hyperferritinemia with collapsed glycosylated ferritin (<20%), and abnormal liver function tests.
According to the clinical presentation of the disease at diagnosis, two AOSD phenotypes may be distinguished: i) a highly symptomatic, systemic and feverish one, which would evolve into a systemic (mono- or polycyclic) pattern; ii) a more indolent one with arthritis in the foreground and poor systemic symptomatology, which would evolve into a chronic articular pattern.
Steroid- and methotrexate-refractory AOSD cases benefit now from recent insights into autoinflammatory disorders: anakinra seems to be an efficient, well tolerated, steroid-sparing treatment in systemic patterns; tocilizumab seems efficient in AOSD with active arthritis and systemic symptoms while TNFα-blockers could be interesting in chronic polyarticular refractory AOSD.

Contents

* Corresponding author at: Service de médecine interne, Hôpital de la Croix-Rousse, 103 Grande Rue de la Croix-Rousse, F-69317 Lyon Cedex 04, France. Tel.: +33 426 732 640; fax: +33 426 732 637.
E-mail address: pascal.seve@chu-lyon.fr (P. Sève).

http://dx.doi.org/10.1016/j.autrev.2014.01.058
1568-9972/

1. Introduction

In 1897, Sir George Frederick Still described 22 children with symptoms consistent with the current systemic onset of juvenile idiopathic arthritis (SOJIA) [1]. One year before, the first case of an adult patient exhibiting the same symptoms had been reported in *The Lancet*. Then, numerous cases of patients suffering from high spiking fever, polyarthritis, lymphadenopathy, evanescent rash, sore throat and a striking leukocytosis of unknown origin were described and grouped in Europe under 'Wissler–Fanconi syndrome' [2]. In 1971, EG Bywaters described the first series of 14 adults with the same symptoms as those seen in the pediatric Still's disease, defining thus the adult-onset Still's disease (AOSD) [3]. Today, AOSD remains a rare multisystemic autoinflammatory disorder of unknown etiology and difficult diagnosis because of the wide range of differential diagnoses. Nonetheless, an early diagnosis may improve the prognosis [4]; this calls for a better knowledge of this complex disease.

The evolutive and prognostic patterns of AOSD have been better defined recently and the therapeutic strategies have benefited from progresses in the understanding of monogenic autoinflammatory diseases. This review will focus on these two topics.

2. Epidemiology and pathophysiology

2.1. Epidemiology

Robust epidemiologic data on AOSD are lacking. The disease occurs worldwide and affects usually young adults (the median age at diagnosis is circa 36 years [4,5]) though onsets were described up to 83 years [6,7]. Its incidence has been estimated at 0.16 (per 100,000 persons) in France [8], 0.22 in Japan [9], and 0.4 in Norway [10]. In the Japanese and the European populations, the reported prevalence rates range from 1 to 34 cases per 1 million persons. In rheumatologic case series, women seem to be more often affected than men; they represent up to 70% of the patients [5,11,12]; however, in internal medicine case series, women represent only 45 to 53% of the patients [4,13]. The hormonal influences are poorly understood; nevertheless, the second trimester of pregnancy and the postpartum period would increase the risk of disease recurrence [14].

2.2. Genetics

Although no familial trend has been reported in AOSD, some studies have reported associations with HLA antigens. HLA-Bw35 was the first identified as a susceptibility antigen and associated with a mild self-limiting pattern of the disease [15]. HLA-DR4 was found more prevalent in 29 AOSD cases vs. healthy controls and HLA-DRw6 was associated with the occurrence of proximal arthralgia [16]. In a survey on 55 patients from Canada, Pouchot et al. described a strong association between AOSD and HLA-B17, -B18, -B35, and -DR2 [13]. In Japan, HLA-DRB1*1501 (DR2) and HLA-DRB1*1201 (DR5) have been found associated with chronic AOSD whereas HLA-DQB1*0602 (DQ1) has been found associated with both chronic and systemic AOSD [17]. Finally, a Korean study compared 47 AOSD cases with 144 healthy controls focusing on the HLA-DRB1 genotype; AOSD patients had more frequentlyHLA-DRB1*12 and -DRB1*15, and less frequently HLA-DRB1*04. Patients with the monocyclic systemic pattern had more frequent HLA-DRB1*14 [18]. In summary, no consistent results have been obtained from association studies between AOSD and HLA loci. This may result either from a real absence of association or from a wide heterogeneity of such an association between different ethnic groups.

More recently, a Japanese study evaluating polymorphisms in the interleukin (IL)-18 gene discovered that the frequency of diplotype configuration S01/S01 was significantly higher in AOSD patients than in healthy controls [19]. Also, a functional promoter polymorphism in the macrophage migration inhibitory factor (MIF) gene seemed to influence plasma MIF levels in AOSD and may contribute to disease susceptibility [20]. Furthermore, SOJIA has been associated with a functional polymorphism in the IL-6 gene promoter that affects gene transcription and, therefore, IL-6 levels [21]. Conversely, in 96 Korean patients, no mutation in the MEFV gene (responsible for familial Mediterranean fever) was associated with the development of AOSD [22].

2.3. Triggering factors

So far, the etiology of AOSD remains unknown. An infectious etiology has been suspected because of similar clinical presentations between AOSD and established infectious syndromes; e.g., abrupt onset, high fever, generalized adenopathy, splenomegaly, and leukocytosis. Many microorganisms were thus searched for. A number of viruses (rubella, measles, Echovirus 7, Coxsackievirus B4, Cytomegalovirus, Epstein–Barr virus, Human herpesvirus 6, Parainfluenza, Influenza A, Adenovirus, hepatitis B and C, and Parvovirus B19) [23–26] and bacteria (*Mycoplasma pneumonia*, *Chlamydia pneumonia*, *Yersinia enterocolitica*, *Brucella abortus*, and *Borrelia burgdorferi*) [27,28] were isolated in patients with AOSD but their responsibility has never been clearly established. It is proposed that infection can trigger an interplay between host genetic factors, autoimmunity mechanisms, and pathogenic antigens, leading ultimately to the disease pathogenesis.

Besides, a recent literature review presented 28 cases of AOSD-like disease associated with malignancies including solid cancer (60% of the cases, mainly breast and lung) and hematological malignancies (40%, mainly malignant lymphoma) [29]. Thus, it is probable that malignancies can also trigger the onset of AOSD as already described in hemophagocytic lymphohistiocytosis [30].

2.4. Immunopathogenesis

The recent improvements in the understanding of monogenic autoinflammatory diseases provided valuable evidence about the immunopathogenetic mechanisms of AOSD (Fig. 1).

2.4.1. Innate immunity

2.4.1.1. Activation of innate immune cells. Neutrophil and macrophage activation is a hallmark of AOSD. CXCL 8 (ex-IL-8) levels were found increased in AOSD patients (vs. healthy controls) but did not correlate with the disease activity [29]. This chemokine mobilizes and activates neutrophils at the site of inflammation and is associated with the persistence of chronic articular AOSD [32]. Furthermore, the neutrophil activation marker CD64 (FcγR1) was found upregulated and correlated with active AOSD [33].

Many markers reflecting macrophage activation correlated with the activity of the disease. Macrophage-colony stimulating factor (M-CSF) and interferon (IFN) γ are both increased in the serum of AOSD patients [31,34,35]. Also, calprotectin, MIF, and intracellular adhesion molecule-1 (ICAM-1) may serve as useful markers for AOSD activity and severity [36–38]. The disease is also strongly associated with the reactive hemophagocytic lymphohistiocytosis (RHL, previously termed macrophage-activation syndrome), which is a life-threatening complication [39–42]. In AOSD as in RHL, recent findings argue for a potent immunomodulatory role of high ferritin levels in both steady AOSD and RHL [43–45].

2.4.1.2. Natural killer (NK) cells. The levels and cytotoxic functions of NK cells and NKT cells were decreased in AOSD (vs. no disease or inactive AOSD) [46,47]. These parameters correlate with the disease control; they improve during efficient treatment of AOSD. Pro-inflammatory cytokines, mostly IL-18, were suspected to cause NK cell priming to secrete IFNγ and to be associated with familial hemophagocytic lymphohistiocytosis susceptibility [48–50]. Furthermore, the impairment of NK cell cytotoxicity was associated with familial hemophagocytic lymphohistiocytosis, the most frequent form being secondary to perforin deficiency [30,51]. Perforin is a pivotal effector molecule for cytotoxicity and is present in the granules of cytotoxic T cells and NK cells. A decreased perforin expression was reported in SOJIA [52]. Given the high association between RHL and AOSD, these disorders might share a common final pathway of abnormal IL-18 secretion and abnormal NK cell cytotoxicity; they may constitute two syndromes of the same spectrum.

2.4.1.3. Cytokines and chemokines. The levels of most of the major proinflammatory cytokines have been found elevated during AOSD but the cytokine profile is not specific and cannot differentiate AOSD patients from subjects with sepsis. The cytokine profile has thus a limited use in clinical practice [53].

The proinflammatory IL-1β, whose activation results mainly from caspase-1 cleavage through the inflammasome activation, has been implicated in the pathogenesis of AOSD [54]. Its serum concentration was significantly higher in patients than in controls. The most striking argument for its involvement was given by Pascual et al. in the context of the juvenile form of the disease [55]. This team has shown that peripheral blood mononuclear cells of healthy subjects incubated with serum from patients with Still's disease secrete large amounts of IL-1β and

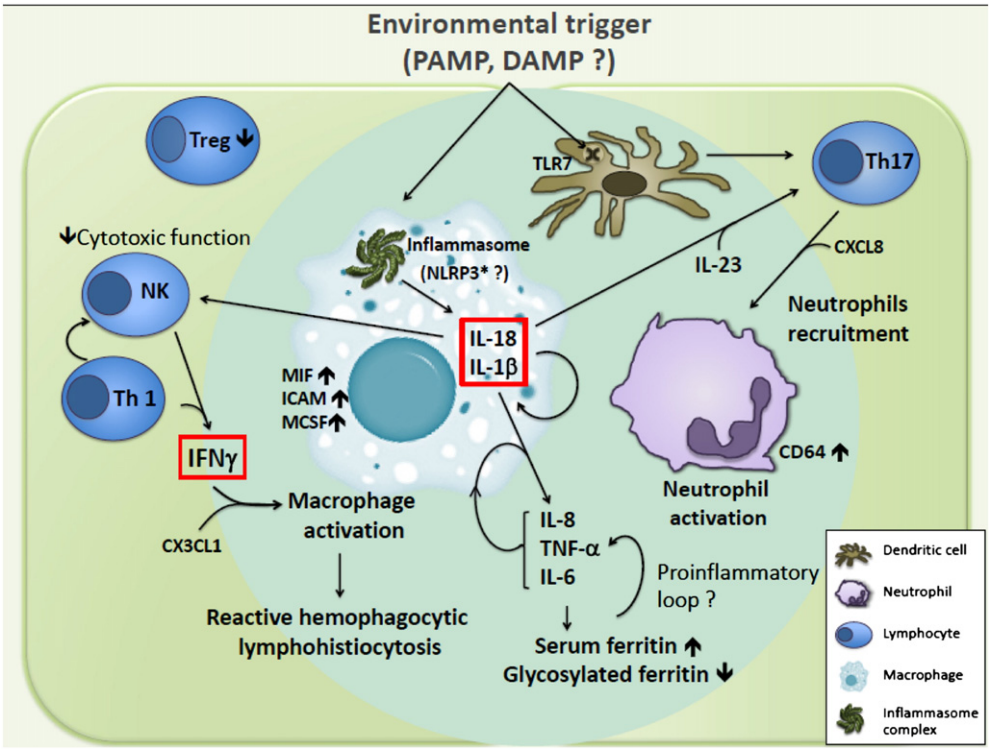

Fig. 1. Proposed pathophysiological model for adult-onset Still's disease. Danger signals (pathogen-associated or damage-associated molecular patterns) set fire to a dysregulated NLRP3 inflammasome (NLRP3*), which triggers the activation and secretion of proinflammatory cytokines (i.e., interleukin (IL)-1β and IL-18) and then Th1-polarization of CD4-lymphocytes. At the same time, upon Toll-like receptor (TLR)-7 activation, dendritic cells induce Th17 response and neutrophil recruitment. IL-1β – upstream of TNFα, IL-8, and IL-6 – induces its own production, through IL-1 receptor, in an autocrine way. IL-6 is responsible for the liver synthesis and fast release of ferritin. IL-18 triggers a natural killer (NK) cell-mediated IFNγ production, which in turn increases macrophage activation. In AOSD, NK cells are abnormal, their cytotoxic function is decreased. In some cases, macrophage activation can lead to reactive hemophagocytic lymphohistiocytosis, a life-threatening complication of AOSD.

express strongly genes of innate immunity. The pivotal role of IL-1β emerged from reports that showed the dramatic efficacy of anti-IL-1 treatments in AOSD (see Section 5 below). The absence of association between polymorphisms in the genes of IL-1β or those of its receptor antagonist and AOSD susceptibility [56], suggests an interplay between pathogens and a genetically determined dysregulation of IL-1β processing.

Interleukin-18, another proinflammatory cytokine processed through the inflammasome machinery, induces the production of Th1 cytokines [57,58]. Compared with healthy controls, its level was higher in AOSD patients' sera [17,31], synovial biopsies [59], lymph nodes [60] and the liver where locally activated macrophages produce a high amount of IL-18 and may contribute to AOSD-related hepatitis [61]. IL-18 levels were also significantly higher in patients with AOSD-related RHL [62]. These mechanisms may reinforce the pathological secretion of IFNγ by NK cells under the effect of IL-18. Finally, IL-18 should be useful to monitor the response to treatment [59,63–65] but it remains unclear whether IL-18 could serve or not as a therapeutic target [66].

In untreated AOSD, the levels of IL-6 were found increased both in salmon-colored skin rash specimens and in serum and correlated with disease activity [31,32,67]. This cytokine may also be responsible for some clinical features of AOSD (fever, skin rash) and for the production of acute-phase proteins by the liver. Strong evidence for the IL-6 pivotal role in the development of SOJIA has been previously reviewed [68]. However, IL-6 and its receptor (IL-6R) are downstream of IL-1β, and IL-6 increased levels may be consecutive to overproduction of IL-1β.

Tumor necrosis factor (TNF)-α levels were also found increased in sera and tissues from AOSD patients but not correlated with disease activity [17,35]. Conversely, its type 2 soluble receptor level correlated with serum C reactive protein (CRP) and has been proposed as an activity marker [17].

Moreover, many chemokines are involved in the inflammatory reaction. In AOSD, two of them are of particular interest. The above-mentioned CXCL8 is a major neutrophil inducer. The fractalkine (CX_3CL1) was correlated with the disease activity and with the levels of serum CRP, ferritin, IL-18, and soluble IL-2 receptor (CD25). It was also correlated with the onset of RHL [69].

2.4.1.4. Innate immune system receptors. Toll-like receptor (TLR) 7 ligation promotes the recruitment of neutrophils and the amplification of Th17-driven inflammatory responses. A recent study demonstrated that theTLR7-MyD88 pathway was overexpressed in the dendritic cells of AOSD patients vs. healthy controls. The expression levels of TLR7 were positively correlated with AOSD activity and with the serum levels of cytokines IL- 1β, IL-6, IL-18, and IFN-γ. After treatment, remission was associated with decreased TLR7 levels. Nevertheless, the receptor expression profile was similar to that of patients with systemic lupus erythematosus and may reflect only the involvement of the TLR7 pathway during inflammatory diseases [70].

Inflammasomes are multiprotein complexes whose activation depends on the recognition of various stimuli such as PAMPs (pathogen-associated molecular patterns) or DAMPs (damage-associated molecular patterns) [71]. These complexes are responsible for pro-IL-1β and pro-IL-18 activation. Recent publications have suggested that an abnormality of the NLRP3 (Nod-like receptor 3 or cryopyrin) inflammasome could be an important mechanism in AOSD pathophysiology [72,73]. So far, no polymorphism in the NLRP3 gene has been identified in AOSD patients. Thus, the inflammatory status of AOSD could result either from a reduced threshold of activation or from a deregulation of the inflammasome. Antoniou et al. have recently provided evidence for an increased NLRP3-mediated IL-1β production in one case of atypical AOSD [72]. This response was markedly decreased after remission, which is similar to the pattern of response to treatment seen in patients with autoinflammatory diseases due to NLRP3 mutations: the cryopyrin-associated periodic syndromes (CAPS) [74].

2.4.2. Adaptative immunity

2.4.2.1. Th1 cellular immune response. The increased concentrations of the α-soluble receptor of IL-2 (CD25) seen in AOSD patients argue for T cell activation and proliferation [17,31]. Compared with healthy controls, IL-4-producing T cells in serum, skin, and synovium in AOSD patients predominate over IFN-γ-producing T cells. This reflects a Th1 polarization of CD4+ T cells, which then activate macrophages, NK cells, and promote cell-mediated immunity [75].

2.4.2.2. Th17 and Treg involvement. The differentiation of naïve T cells into Th17 cells is supported by several cytokines including IL-1β, IL-6, and IL-23. Furthermore, IL-18 synergizes with IL-23 to promote IL-17 production by IL-23-primed CD4+ T cells. Interleukin-17 is a proinflammatory cytokine that amplifies inflammation, stimulates the production of neutrophil-recruiting chemokines (including CXCL-8), and enhances granulopoiesis [76]. Recently, Chen et al. have shown that circulating Th17 cells are significantly higher in patients with active untreated AOSD than in healthy controls [77]. The levels of Th17 correlated with the disease activity, with ferritin levels, and with remission after treatment. However, it is still unknown whether Th17 cells are part of the pathogenic mechanism or only markers of AOSD progression. Indeed, Th17 polarization could occur downstream of other more complex mechanisms. For example, some missense mutations of the NLRP3 gene may cause inflammasome hyperactivation, overproduction ofIL-1β, and a subsequent increase in Th17 differentiation [78]. Nevertheless, some data propose Th17 cells as possible targets for therapy [78,79].

Finally but not surprisingly, it has been shown that circulating CD4+ $CD25^{high}$ regulatory T cells (Treg) and transforming growth factor (TGF)-β are inversely correlated with AOSD activity scores. Higher levels of Treg would correlate with a better prognosis of the disease [80].

2.4.3. Is AOSD an autoinflammatory disease?

Autoinflammatory diseases affect primarily the innate immune system and are characterized by an inappropriate activation of the phagocytes. Historically, this group comprised rare disorders of Mendelian inheritance like CAPS, TNF receptor-associated periodic syndromes (TRAPS), and familial Mediterranean fever. These share with AOSD the absence of evidence for a link with microorganisms and the absence of autoantibodies or autoantigen-specific T cells. Their typical clinical manifestations resemble closely those of AOSD and include recurrent inflammatory attacks of fever with skin involvement, serositis, and arthritis. As in AOSD, a dramatic response to IL-1β blockade is characteristic of these autoinflammatory disorders. Nevertheless, some features seem to differentiate AOSD: the characteristic profile of the fever, the longer duration of the exacerbations, and the possible occurrence of bone and cartilage destruction. Although RHL has been recently categorized as an autoinflammatory disease, it is less likely to occur in the context of autoinflammatory diseases than in AOSD. Furthermore, most of the autoinflammatory diseases are hereditary and due to mutations in a single gene whereas AOSD does not cluster in families, ethnic groups, or geographic areas. Thus, AOSD has been categorized as a multigenic (or complex) autoinflammatory disorder and put it at the crossroads of autoinflammatory and autoimmune diseases [54,81–83].

3. Clinical features, diagnostic tests, and diagnostic criteria

Most of the herein discussed features come from the analysis of the main case series published in the medical literature and summarized in Table 1 [5,11–13,84–89].

Table 1
Comparison between the main literature series dedicated to adult-onset Still's disease.

	Pouchot [13]	Fautrel [84]	Pay [85]	Cagatay [11]	Zhu [86]	Kong [87]	Colina [89]	Chen [12]	Gerfaud-Valentin [4]
Findings	1991	2002	2005	2007	2009	2010	2011	2012	2013
Number of patients	62	72	95	84	77	104	76	61	57
Males	34 (55)		45 (47)	25 (30)	23 (30)		32 (42)	29 (48)	27 (47)
Females	28 (45)		50 (53)	59 (70)	54 (70)		44 (68)	32 (52)	30 (53)
Diagnosis at ages 16 to 35	50 (81)			45 (54)	51 (66)			43 (70)	27 (47)
Age at diagnosis (years)									
Mean		35.2				32.5 [16–64]	36 [11–70]		
Median [range]			27 [16–82]						36 [16–75]
Delay to final diagnosis (months)									
Mean							21 months		
Median [range]			3 [0.5–84]						4 [0–312]
Fever	62 (100)	61 (85)	94 (99)	80 (95)	77 (100)	104 (100)	76 (100)	61 (100)	54 (95)
Weight loss			17 (18)	16 (19)					25 (44)
Rash	54 (87)	51 (71)	78 (82)	50 (60)	66 (86)	98 (94)	44 (58)	48 (79)	44 (77)
Arthralgia/arthritis	62 (100)	64 (89)	95/95 (100)	81 (96)	67 (87)	93 (90)	55 (72)	49 (80)	54 (95)
Sore throat/pharyngitis	57 (92)	38 (53)	63 (66)	55 (66)	60 (78)	81 (78)	28 (37)	51 (84)	30 (53)
Myalgia	52 (84)		66 (70)	11 (13)	43 (56)		8 (13)	22 (36)	25 (44)
Lymphadenopathy	46 (74)	32 (45)	35 (37)	28 (33)	35 (45)	69 (66)	29 (38)	32 (52)	34 (60)
Splenomegaly	34 (55)		40 (42)	24 (29)	22 (29)	HSMG 46 (44)	22 (29)	39 (64)	17 (30)
Hepatomegaly	27 (44)		43 (45)	32 (38)	9 (12)			13 (21)	12 (21)
Pleurisy	33 (53)		21 (22)	8 (10)	9 (12)	Both 31 (30)	18 (24)	7 (11)	10 (18)
Pericarditis	23 (37)	15 (21)	8 (8)	10 (12)	2 (3)		15 (20)	6 (10)	11 (19)
Abdominal pain	30 (48)			1 (1)	16 (21)			2 (3)	10 (18)
Evolutive onset									
Monocyclic			20 (21)	28 (33)			20 (26)		17 (30)
Polycyclic			16 (17)	28 (33)			23 (30)		25 (44)
Chronic			39 (41)	23 (27)			33 (43)		15 (26)
White blood cells $\geq 10^4/mm^3$	58 (94)	64 (89)		69 (82)	63 (82)	102 (98)	69 (91)	49 (80)	39/54 (72)
PMN $\geq 80\%$	55 (89)	50 (69)	60 (79)	35 (56)				36 (59)	39/50 (78)
Anemia	42 (68)			30 (36)	29 (38)	72 (69)	40 (53)	11 (18)	32/49 (65)
Heightened C-reactive protein			87 (97)		52 (66)	86 (92)	74 (97)	52/52 (100)	49/51 (96)
Elevated eythrocyte sedimentation rate	62 (100)		89 (94)	79 (94)	44 (90)	100 (96)	73 (96)	60 (98)	24/25 (96)
High serum ferritin (>500 μg/L)		50 (69)	81 (89)	80 (95)	30 (97)	75 (72)	68 (89)	17/18 (94)	39/51 (76)
Glycosylated ferritin ≤20%		52 (72)							28/37 (76)
Elevated liver enzymes	47 (76)	53 (74)	59 (64)	30 (36)	48 (62)	65 (62)	57 (75)	43 (70)	27/50 (54)
Negative for rheumatoid factor	58 (94)	71 (99)			63 (94)	99 (95)	72 (95)	57 (93)	49/49 (100)
Negative for antinuclear antibodies	55 (89)	66 (92)			69 (93)	104(100)	69 (91)	55 (90)	4/52 (8)

Values expressed as number (percentage), median [range], or positive/tested (percentage of tested) — HSMG: hepatosplenomegaly.

3.1. Clinical features

The following constellation of non-specific symptoms could be evocative of AOSD.

Fever occurs in 60 to 100% of the patients. It typically spikes daily or twice daily, the highest temperatures (>39 °C) occurring in the evening. Fever precedes usually the onset of other manifestations. Nowadays, in Europe, AOSD accounts for 3 to 20% of fevers of unknown origin [90,91].

Joint pain is the most common symptom (70 to 100%). Arthralgia and arthritis involve predominantly the wrists, the knees, and the ankles. Even though arthritis is initially mild and transient, it may evolve into a chronic destructive symmetrical polyarthritis with a classical carpal ankylosis [3,92]. Joint fluid aspiration often reveals an inflammatory fluid with neutrophil predominance [13].

In 60 to 80% of AOSD cases, a macular or maculopapular evanescent salmon-pink skin rash appears together with the fever spikes. It is predominantly found on the proximal limbs and trunk [90,93].

Sore throat can be an early symptom of AOSD. It occurs in about 70% of the patients before or during the first month of each disease flare. It has been linked to a viral infection, an inflammation of the crico-arytenoid joints, or an aseptic non-exudative pharyngitis [94].

Other symptoms were reported during AOSD: myalgia (45%), enlargement of the lymph nodes (50%), splenomegaly (40%), hepatomegaly (30%), pleurisy (21%), pericarditis (16%), weight loss (27%), and abdominal pain (18%). Interstitial lung infiltrates have been reported but improved rapidly after treatment [95–98]. Pulmonary hypertension is rare [99,100].

Much less frequent manifestations may be found in the literature, mainly in single-case reports. These include ischemic stroke, reversible posterior leukoencephalopathy syndrome [101], bilateral perception of deafness [102], aseptic meningitis or encephalitis [103–107], collapsing glomerulopathy [108,109], membranous glomerulonephritis [110], even necrotizing crescentic glomerulonephritis [111,112] or tubulo-interstitial nephritis [113], conjunctivitis (local case), uveitis [114], retinopathy [115], inflammatory orbital pseudotumor [116], pseudo-angiocholitis [117]; portal vein thrombosis [118], necrotizing granulomatous lymphadenopathy [119], and angioedema [120].

3.2. Laboratory findings

Laboratory tests reflect the non-specific systemic inflammatory nature of the disease.

Increases in the erythrocyte sedimentation rate and CRP level are common in AOSD (90 to 100%). A neutrophilic leukocytosis (>80% polymorphonuclear cells) is found in about 80% of cases and allowed differentiating AOSD from other fevers of 'unknown origin' [88]. As in other inflammatory diseases, anemia (50%) and thrombocytosis (26%) are common findings.

Recently, some authors suggested that uncommon conditions such as AOSD, RHL, catastrophic anti-phospholipid syndrome and septic shock should be included under a common syndrome entity termed 'hyperferritinemic syndrome' to underline the pro-inflammatory role of ferritin. They have suggested that exceptionally high serum ferritin levels observed in these four clinical conditions may contribute to the development of a cytokine storm [44]. During AOSD, serum ferritin

levels are higher than in several other autoimmune, inflammatory, infectious, or neoplastic diseases. A threshold of five times the normal value (i.e., 1000 μg/L) is suggestive of AOSD [121,122]. However, the specificity for AOSD remains poor (41 to 46%) since similar levels may be found during infection, neoplastic conditions, or storage diseases such as Gaucher's disease [39,122,123]. So, serum ferritin is of limited value in diagnosing AOSD but may be useful as a marker of disease activity [124,125].

In the early 2000s, Fautrel et al. underlined the usefulness of low glycosylated ferritin (GF) as a diagnostic marker for AOSD. In a retrospective study of 49 AOSD cases and 120 controls, GF was significantly lower in cases (15.9 ± 11.9%) than in controls (31.5 ± 18.7%). Furthermore, combining a GF level <20% with a fivefold elevation of serum ferritin led to a 92.9% specificity for AOSD (43.2% sensitivity) [39]. However, this condition may be also encountered in RHL of other cause than AOSD [126]. From a study on 14 patients, Vignes et al. concluded that a persistent low GF level could be a useful diagnostic marker for AOSD several months after disease remission [127]. This could not be confirmed by another study because only one out of the five GF levels assayed during remission within the first 3 years of follow-up was <20% [4].

Liver abnormalities are common (65%); mainly a mild to moderate increase in aminotransferase activity.

Pathology examinations can help in differentiating AOSD from lymphoma or other inflammatory diseases in the initial diagnostic approach. A non-specific interstitial inflammation is the most common finding in the myocardium, lung, liver, and gastrointestinal tract tissues [128]. Hepatic necrosis has been described in fulminant-hepatitis-complicated AOSD [129,130]. Bone marrow examination rules out lymphoma or confirms hemophagocytosis [4,40]. However, a non-specific 'reactive inflammatory bone marrow' including granulocytic hyperplasia and hypercellularity seems to be the most prevalent abnormality on bone marrow examination [85]. Studying lymph node biopsies in 12 AOSD patients, Jeon et al. proposed a four-pattern classification of histological abnormalities in which the main subset included paracortical hyperplasia, vascular proliferation, scattered large B/T immunoblasts, and a reactive lymphocyte infiltrate [131]. Data on unselected patients are lacking to confirm this classification.

Radiographs are not usually very helpful in establishing the diagnosis; they are either normal or show soft-tissue swelling, joint effusion, or mild periarticular demineralization. In one study, 41% of the patients developed a distinctive pattern of intercarpal and carpometacarpal joint space narrowing (bilateral in 69%) that led to pericapitate ankylosis in 25% of the cases [13]. Patients who have the chronic articular disease pattern present more often with joint erosions [4]. Computed tomography can complete the clinical picture showing deep lymph nodes, splenomegaly, hepatomegaly, or serous effusions but it is often performed to rule out an underlying neoplastic disease [132,133].

Literature data on ^{18}FDG-PET–CT in AOSD are limited to a few clinical cases [134]. A previous report on nine ^{18}FDG-PET–CTs has shown that the lymph nodes and the glands are the main sites of hypermetabolism [4]. In the case of fever of unknown origin, ^{18}FDG-PET–CT may support the diagnosis of AOSD by rejecting the hypotheses of infection, solid tumor, or large vessel vasculitis [135,136]. The technique may be interesting in monitoring disease progression and the response to treatment; this has to be confirmed in other prospective cohorts [134,137].

So, as no clinical or laboratory test is specific, the diagnostic of AOSD remains one of exclusion. Infectious, neoplastic and autoimmune diseases can mimic the clinical manifestation of AOSD and should be ruled out before considering this diagnosis (Table 2).

Table 2
Differential diagnosis of adult-onset Still's disease.

Diseases	Diagnostic tests
Infections	
Viral infections	Serology, PCR
HIV	
Herpesviridae	
Measles, rubella…	
Viral hepatitis	
Parvovirus B19	
Infective endocarditis	Blood cultures, ultrasonography
Borreliosis, Brucellosis, Yersiniosis	Serology, PCR
Mycoplasma pneumoniae, syphilis …	Serology, PCR
Toxoplasmosis	Serology, PCR
Neoplasia	
Malignant lymphoma	CT, PET/CT, Bone marrow examination, lymph node biopsy
Multicentric Castleman disease	Lymph node biopsy
Angioimmunoblastic T cell lymphoma	Lymph node biopsy
Drug reactions	
Drug reaction with eosinophilia and systemic symptoms	Eosinophil count, skin biopsy
Autoimmune diseases	
Systemic lupus erythematosus	Antinuclear autoantibodies
Idiopathic inflammatory myositis	Idem, muscle biopsy
Rheumatoid arthritis	Anti-citrullinated peptids autoantibodies, rheumatoid factor
Systemic vasculitides	ANCA, tissue biopsy, arteriography
Autoinflammatory diseases	
Familial Mediterranean fever	Familial history, MEFV gene analysis
Mevalonate kinase deficiency	Urinary mevalonic acid, mevalonate kinase analysis
TNF receptor-associated periodic syndrome	TNFRSF1A gene analysis
Reactive arthritis	HLA B27, magnetic resonance imaging
Other	
Sarcoïdosis	
Neutrophilic dermatosis	
Kikuchi–Fujimoto disease	

PCR: polymerase chain reaction — CT: computed tomography — ANCA: anti-neutrophil cytoplasmic antibodies.

3.3. Diagnostic criteria

Several sets of classification criteria have been proposed for research and diagnosis; all stemmed from retrospective studies [84,123,138–140]. In a recent study comparing four sets of diagnostic criteria in a Chinese population, the Yamaguchi set had the highest sensitivity (78.57%) and a 87.14% better accuracy [141]. This study did not include Fautrel's criteria described in 2002 that included GF ≤20% and allowed avoiding the exclusion criteria required in the Yamaguchi set. Fautrel's classification was 80.6% sensitive and 98.5% specific [84]. Now, most studies on AOSD include patients who meet Yamaguchi's (Table 3) and/or Fautrel's (Table 4) criteria.

4. Outcome, prognosis, and complications of AOSD

4.1. Natural history of AOSD

Conventionally, three patterns of natural history of AOSD have been described on the basis of the course of the disease [13,138,142]. Monocyclic AOSD is characterized by a systemic self-limited single episode that fades within months (median: 9 months); most patients become asymptomatic within a year [142]. The polycyclic (or intermittent) pattern of AOSD associates multiple flares with systemic or joint symptoms separated by remissions lasting a couple of weeks to a couple of years; flares would become less severe over time. Finally, chronic AOSD is a persistently active disease usually associated with polyarthritis. In the latter pattern, disability can be important. The distribution of the patterns in the patients varies widely. For example, the chronic onset represented 43% of AOSD cases in some rheumatologic series [5] whereas it represented only 26% in a recent internal medicine series [4]. On

Table 3
Yamaguchi classification criteria for adult-onset Still's disease [123].

Major criteria	Minor criteria	Exclusion criteria
Fever ≥39 °C lasting 1 week or longer	Sore throat	Infections
Arthralgia or arthritis lasting 2 weeks or longer	Recent development of significant lymphadenopathy	Malignancies (mainly malignant lymphoma)
Typical rash	Hepatomegaly or splenomegaly	Other rheumatic disease (mainly systemic vasculitides)
Leucocytosis ≥10,000/mm^3 with ≥80% polymorphonuclear cells	Abnormal liver function tests Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)	

Five or more criteria required, of whom 2 or more must be major.

average, 30% of patients would develop a monocyclic AOSD, 30% a polycyclic AOSD, and 40% a chronic AOSD (Table 1).

Recent data have suggested that these three patterns may be grouped into only two: a systemic form that includes the monocyclic and the polycyclic patterns and another chronic articular form. In fact, it is probable that the immunological imbalance would be different between the two forms, which would explain the difference in effectiveness of specific biologic agents (see Section 5.)[143,144].

4.2. Prognosis

Few studies have focused on the prognostic factors in AOSD. It seems that polyarthritis and joint erosion at disease onset are predictive of a chronic progression and a poor functional prognosis [4,5,138]. Conversely, high fever (>39.5 °C) at disease onset correlated with a systemic form, mainly monocyclic AOSD [4]. Lymphadenopathy and splenomegaly were more frequent in RHL-complicated AOSD [40]. Splenomegaly has been also associated with steroid dependence [145].

Kong et al. have found that leukocytosis ≥30,000/mm^3 was associated with AOSD relapses [87]. An elevated erythrocyte sedimentation rate or CRP has been found significantly associated with poor prognoses or higher relapse rates [87,145]. Thrombocytopenia at disease onset could predict the occurrence of complications [4] and has been associated with high mortality rates during RHL-complicated adult systemic diseases including AOSD [146]. As mentioned above, high serum ferritin levels correlated with disease activity and have been linked to a chronic pattern, recurrent flares, and poor prognoses [5,87,124,125]. GF assessment seems to reduce the time to diagnosis and thereby favor a good-prognosis monocyclic course of AOSD [4]. Of note, the highest serum ferritin levels as the lowest GF levels would correlate with the occurrence of RHL in AOSD patients [4,40,44].

In summary, in AOSD, it is difficult to define strong prognostic factors on the basis of retrospective studies that identified heterogeneous prognostic criteria. According to our experience and knowledge, we suggest distinguishing two AOSD phenotypes according to the clinical presentation of the disease at diagnosis. On the one hand, a highly symptomatic onset with high fever, serositis, elevated liver enzymes, arthralgia but rare arthritis, which would evolve into a systemic (monocyclic or polycyclic) AOSD; and, on the other hand, a more indolent onset with arthritis, sometimes radiological joint erosions, and poor systemic symptomatology, which would have a chronic course. Further studies, ideally prospective, in independent populations are needed to support this suggestion.

Table 4
Fautrel classification criteria for adult-onset Still's disease [84].

Major criteria	Minor criteria
Spiking fever ≥39 °C	Maculopapular rash
Arthralgia	Leukocytosis ≥10,000/mm^3
Transient erythema	
Pharyngitis	
Polymorphonuclear cells ≥80%	
Glycosylated ferritin ≤20%	

Four or more major criteria required or 3 major + 2 minor criteria.

4.3. Complications

The disease may present several rare manifestations which can limit life expectancy. RHL, which occurs in about 12 to 15% of AOSD cases (probably less in rheumatologic cohorts), is the most frequent [4,40,147]. The prognosis of RHL-complicated AOSD seems better than that RHL in other settings; only one patient died among the total of 14 cases reported on by Hot et al. and Arlet et al. [38,146]. Other complications are even rarer; these include: myocarditis [148–163], tamponnade and constrictive pericarditis [164,165], endocarditis [166]; shock, multiple organ failure, acute respiratory distress syndrome, intra-alveolar hemorrhage, disseminated intravascular coagulation [167–181]; thrombotic microangiopathy [182–184]; and fulminant hepatitis [129,130]. As in other autoinflammatory syndromes, AA amyloidosis has been reported in a few cases of chronic uncontrolled inflammation [185–189]. Put together, these complications of systemic AOSD concerned about one third of AOSD patients seen in a tertiary center of internal medicine [4].

The current treatments of AOSD are also source of many complications. In a cohort of 57 subjects, 21% of NSAIDs-treated patients experienced gastrointestinal side effects despite proton pump inhibitor administration, 75% of corticosteroid-treated patients suffered from adverse events (Cushing syndrome, osteoporosis, aseptic osteonecrosis, diabetes, hypertension, cataract, psychiatric disorders) whereas one third of methotrexate-treated patients experienced complications (elevated liver enzymes (15%), low blood cell counts (10%), and cough (6%)) [4]. Furthermore, the treatments used in AOSD would increase the risk of infectious complications [124,145].

Nevertheless, in Western countries, AOSD remains a benign and non-fatal disease with a low mortality rate [189]; only two deaths (3%) could be attributed to the disease in a report by Pouchot et al. [13] and none of the three deaths in a report by Gerfaud-Valentin et al. [4]. In contrast, two recent studies in Asiatic patients [124,145] have reported high mortality rates (9.26% and 10%, respectively) due to infections and disease progression but only a small proportion of the patients had received biologic agents. Despite differences in access to health care between countries, multicentric studies are needed to investigate whether AOSD prognosis is significantly influenced by ethnicity. In the literature, deaths during AOSD were due to infections [23,124,138,190], acute respiratory distress syndrome [124,191], multiple organ failure during RHL [148,192], thrombotic microangiopathy [193,194], or involvement of the central nervous system [192,193,195].

Overall, current studies suggest that AOSD is a relatively benign disease and that most deaths are related to side effects of long-term treatments.

5. Treatment

As the current information on treatment efficacy is obtained from small retrospective case series and not from prospective double-blinded randomized trials, the treatment of AOSD remains empirical. Recently, the management of AOSD benefited from proofs of the efficacy of targeted biotherapies.

5.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

In two retrospective studies, NSAIDs failed to control the symptoms of AOSD in 82% to 84% of patients whereas 20% experienced adverse events [4,196]. The risk/benefit ratio being unfavorable, NSAIDs should no longer be considered as a first line treatment in AOSD but rather a supportive treatment during the diagnostic process and be reserved for the early reminiscences of the disease whenever corticosteroids and disease-modifying antirheumatic drugs (DMARDs) prove insufficient [196]. Here, high-dose indomethacin (150–250 mg/day) should be used first [13,138,142].

5.2. Corticosteroids

Corticosteroids are effective in controlling the disease in about 65% of patients [66,85]. Their efficacy is greater in the systemic pattern of AOSD [196]. Based on retrospective case series, the initial dosage ranged from 0.5 to 1 mg/kg/day. Patients with serious visceral involvement could achieve a quick response with intravenous infusion of high-dose methylprednisolone. The response to corticosteroids is often quick: it occurs within a couple of hours or a few days [40,154,156,158,163]. The tapering begins usually after 4 to 6 weeks. Kong et al. have reported that patients treated with high prednisone dosage (≥40 mg, 0.8 mg/kg) achieved quicker remissions and had less relapses than those who received a lower dosage [88], which is consistent with the recent findings of Kim et al. [89]. Furthermore, incomplete-responder patients to a daily single dose of prednisone could achieve remission with multiple daily doses of prednisone or dexamethasone [13,197]. Unfortunately, steroid dependence occurs in 42% to 45% of the cases. This exposes the patients to serious mid- and long-term side effects (see Section 4.3.) [4,145]. Steroid-dependence has been associated with splenomegaly, low rate of GF, elevated erythrocyte sedimentation rate, or young age at AOSD onset [4,146]. These findings argue for an early addition of a steroid-sparing treatment in such patients.

5.3. Methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs)

While few data argue for a beneficial use of hydroxychloroquine in AOSD [13,85], methotrexate remains the most used DMARD in this disease [4], especially for its steroid-sparing effect. In 1999, Fautrel et al. reported on low-dose methotrexate (7.5–17.5 mg/week) in 26 steroid-dependent patients. Twenty-three (88%) patients achieved a partial remission and 18 (69%) a complete remission. Eleven patients (39%) stopped corticosteroids whereas the mean daily prednisone intake was decreased by 21.5 mg (i.e., 69%) [198]. The effect of methotrexate is the same in systemic and in chronic articular AOSD [196,198]; it allows controlling the disease in 40% to 70% of steroid-dependent AOSD patients [4,196]. Thus, methotrexate should be added to prednisone when the latter fails to control the disease or in case of steroid-dependence. The presence of liver enzyme abnormalities does not contraindicate methotrexate prescription, but a close biological monitoring is necessary.

A few retrospective data on cyclosporine A suggest that it could be as effective as methotrexate in systemic AOSD [196,199]. Nonetheless, its lower tolerance argues for its use in the case of severe complications with failure of intravenous corticosteroids [199].

5.4. Intravenous immunoglobulins (IVIG)

According to a few retrospective case series, 4% to 43% of AOSD patients receive IVIG during the disease course [145,196]. In a previous study [4], IVIG were significantly more prescribed in non-monocyclic, complicated and steroid-dependent AOSD although no data are available to support this choice. Indeed, robust data on IVIG in AOSD are still poor. In two open-label studies, they were shown effective in 8/14 patients, early in the disease course [200,201]. For Kim et al., IVIG have no consequence on the course and prognosis of AOSD [145]. Their corticosteroid-sparing ability remains to be determined. However, it may be worth to use IVIG in life-threatening manifestations as reported in RHL [202]. Importantly, IVIG are well tolerated; only one patient among 23 IVIG-treated patients presented a severe adverse event (an acute renal failure) [4]. Finally, it should be noted that monthly infusions of IVIG are useful to control AOSD during pregnancy [14,203].

5.5. Biologic agents

A growing body of evidence supports the efficacy of several biologic agents in the treatment of corticosteroid- and DMARD-refractory AOSD. In recent case series, about one quarter of the cohorts were administered these biotherapies [4,196]. Details on the major studies discussed in this section are shown in Table 5.

5.5.1. TNFα-blockers

The first open-label prospective trial of etanercept, a recombinant form of the human 75-kd TNF receptor fusion protein, in 12 refractory chronic polyarthritis was published in 2002 [204]. At 6 months, seven patients achieved at least ACR-20 response criteria [205]. Among the three patients with concomitant systemic symptoms of AOSD, only one improved. Between 2001 and 2004, three small studies on a total of 13 patients with severe chronic AOSD reported impressive results with infliximab (3–5 mg/kg at weeks 0, 2, 6 and then once every 6–8 weeks), a chimeric monoclonal antibody that binds to soluble TNFα and inhibits the interaction with its cellular receptors. Infliximab had a marked and rapid efficacy on both systemic and articular symptoms and also a steroid-sparing effect [206–208]. However, these enthusiastic results should be tempered by the results of the French 'Club Rhumatisme et Inflammation' study on infliximab and etanercept in 20 chronic AOSD cases [209]. After a mean follow-up of 13 months, five patients had complete remissions (one with etanercept and four with infliximab), 11 achieved partial remissions, and TNFα-blockers failed to control the disease in the remaining four patients. At the last visit, 11 patients had discontinued anti-TNFα therapy because of insufficient efficacy and four because of side effects. Data on adalimumab are limited to a few cases [210]. It should be noted that RHL has been associated with etanercept [211] and adalimumab [212] in two patients.

In summary, TNFα-blockers may be interesting in chronic polyarticular refractory AOSD probably more than in the systemic patterns of the disease [4,85,145,196]. Although a head-to-head comparison is not available, infliximab may be more effective than etanercept; it induced more remissions. Unfortunately, the efficacy of TNFα-blockers seems to be limited in time and switching from one to another is useful in about 50% of cases [4,213].

5.5.2. IL-1β antagonists

Anakinra is a recombinant receptor antagonist of IL-1 used in cryopyrin-associated periodic syndromes and other autoinflammatory diseases [214,215]. Its efficacy in AOSD (100 mg daily subcutaneous injection) supported the pivotal role of IL-1β in the pathogenesis of the disease [55].

Rudinskaya and Trock in 2003, then Vasques Gondhino et al. and Fitzgerald et al. in 2005 [216–218] reported on the first six refractory AOSD cases efficiently treated with anakinra. In 2007, two other series totalizing eight patients described a good efficacy of anakinra in

Table 5
Main case series on biologic agents in refractory adult-onset Still's disease.

Targeted biotherapy and 1st author, year [Ref.]	Patients	AOSD pattern	Design	Mean follow-up (months)	Complete remissions (n; %)	Partial remissions	Steroid-spared (n; MSDD (mg))	Steroid stopped	Infections (severe ones)	Severe skin rashes
Etanercept										
Husni, 2002 [204]	12	CPA	Prospective open-label	6	0	7	NA	0	1 (0)	0
Infliximab										
Cavagna, 2001[206]	3	CPA	Case series	2	0	2	NA	NA	0 (0)	1
Kraetsh, 2001 [207]	6	S; CPA	Case series	NA	4; 67	2	3	NA	0 (0)	0
Kokkinos, 2004 [208]	4	S; CPA	Case series	11	4; 100	0	2	1	0 (0)	0
Etanercept, infliximab										
Fautrel, 2005 [209]	20	CPA	Case series	13	5; 25	11	NA	NA	2 (0)	0
Anakinra										
Fitzgerald, 2005 [218]	4	S	Case series	11.5	3; 75	1	4	3	1 (0)	0
Kalliolias, 2007 [219]	4	S	Case series	11	1; 25	3	4	3	0 (0)	0
Kötter, 2007 [220]	4	S; CPA	Case series	21	4; 100	0	≥2	NA	0 (0)	0
Lequerré, 2008 [221]	15	S; CPA	Case series	14	9; 64	2	8; MSDD: 18.2	2	2 (0)	1
Laskari, 2011 [222]	25	S; CPA	Case series	15	21; 84	3	NA	12	7 (0)	3
Nordström, 2012 [226]	12	S; CPA	Prospective randomized open-label	6	6; 50	NA	NA; MSDD: 10.8	3	0 (0)	0
Giampietro, 2013 [223]	28	S (54%); CPA (46%)	Case series	23	12; 43	4	15; MSDD: 24.7	NA	NA (0)	2
Tocilizumab										
Puéchal, 2011 [240]	14	CPA	Case series	6	8; 57	1	NA; MSDD: 13	NA	0 (0)	1
Cipriani, 2013 [241]	11	S; CPA	Case series	12	9; 82	2	3	8	1 (0)	0
Elkayam, 2014 [242]	15	CPA	Case series	16	12; 80	2	5; MSDD: 23.8	9	0 (0)	0

CPA: chronic polyarthritis — S: systemic pattern — MSDD: mean steroid dose decreasing — NA: not available.

steroid-, DMARD-, and some TNFα-blocker-refractory AOSD cases with systemic symptoms [219,220]. The symptoms disappeared within a few days after the first injection and the inflammatory markers reverted to normal within 2–4 weeks. Moreover, anakinra allowed a fast steroid tapering. A self-limited injection-site erythema was the only adverse event reported. However, relapses occurred within a few days of treatment discontinuation.

The French 'Club Rhumatisme et inflammation' group provided the two largest studies on anakinra in AOSD. In the first, Lequerré et al. reported on 15 anakinra-treated refractory AOSD patients of whom 13 had systemic symptoms [221]. In the second, Giampetro et al. reported on a long-term follow-up of 28 patients. Initially, all responded positively to anakinra. After a 23-month mean follow-up, 16 patients were still treated with anakinra of whom 12 achieved a complete remission. Four patients among the six receiving anakinra without methotrexate achieved a complete remission. In only three patients, anakinra discontinuation was possible without relapse. Six additional patients experienced tapering of anakinra: two achieved a sustained remission whereas four relapsed. Less flares occurred during a progressive dose reduction from 7 to 3 injections/week than after the dose was immediately reduced to one injection every 2 days [222]. In these two studies, the steroid-sparing effect of anakinra was important (see Table 5).

Several studies in SOJIA suggest a better efficacy of anakinra when administered early in the course of the disease [221,223,224]. Therefore, the 2012 consensus treatment plans for new-onset SOJIA made anakinra a second-line treatment to consider (just as methotrexate or tocilizumab) when steroids alone fail to control the disease [224]. Moulis et al. have reported on two adult patients with dramatic side effects secondary to conventional treatment that had a remarkable response after administration of anakinra [225]. Laskari et al. reported on 25 AOSD patients treated early (mean disease duration: 7 months) with anakinra of whom 84% achieved a rapid (median: 0.2 months) and sustained clinical remission after a 15-month median follow-up period [222]. Moreover, comparing in a randomized manner the outcomes of 12 AOSD patients treated with anakinra vs. 10 patients treated with a DMARD in steroid-dependent AOSD, Nordström et al. reported greater improvements in the anakinra group [226]. Accordingly, whether a better efficacy could be reached with an early treatment with anakinra (avoiding the adverse effects of a prolonged corticotherapy, and limiting the social impact of a poorly controlled disease) remains to be demonstrated [227].

Overall, anakinra seems to be rapidly and frequently efficient, well tolerated, and steroid-sparing in refractory AOSD. A persistent complete remission could be achieved in 50 to 80% of cases versus 25% with TNFα-blockers. However, the treatment is purely suspensive; relapses could occur soon after discontinuation. As seen in SOJIA, the most impressive results were obtained in the systemic forms of AOSD [221,228,223]. Anakinra requires daily injections and is associated with common painful local adverse reactions. Thereby, and in the case of insufficient response to anakinra due to its short half-live, IL-1 antagonists that have longer half-lives are promising. Canakinumab, a human monoclonal antibody targeted against IL-1β, can be administered every 8 weeks and rilonacept, a soluble dimeric trap fusion protein, can be administered once a week. Both have been reported efficient in AOSD and SOJIA [229–232].

5.5.3. IL-6 antagonists

As discussed above, IL-6 is markedly elevated in active AOSD and was considered as a suitable target in the treatment of refractory AOSD [32,35]. A few isolated reports have shown promising results with tocilizumab, a humanized anti-IL-6 receptor antibody that blocks membrane-bound and soluble IL-6 receptors in steroid-, DMARD-, TNFα blocker- and even cyclosporine-refractory AOSD [103,233–239].

In 2011, Puéchal et al. reported on the first series of 14 patients with refractory AOSD treated with 5–8 mg/kg tocilizumab every 2 or 4 weeks. Eleven patients completed successfully the 6-month study. One patient withdrew because of necrotizing angiodermatitis, another because of chest pain and chills at each infusion, and a third because of systemic flare. The mean Disease Activity Score (DAS) 28 dropped from 5.61 to 2.91 at the 6-month follow-up visit. The systemic

symptoms resolved in six out of seven patients and corticosteroid dose was reduced by 56% [240].

In 2013, Cipriani et al. reported on 11 patients with refractory AOSD treated with 8 mg/kg tocilizumab monthly during 12 months [241]. The patients responded rapidly and experienced a sustained clinical remission over time during the treatment. The median DAS 28 decreased from 5.62 at baseline to 1.61. Remissions of fever and improvements of systemic symptoms were observed in the eight patients with such symptoms. The beneficial effect of tocilizumab seemed preserved after 6 months of treatment cessation. Very recent results on 15 Israeli tocilizumab-treated refractory AOSD patients seem to confirm these data [242]; at the end of a 16-month mean follow-up, only two patients suffered from persistent arthralgia whereas a single patient had to be switched to canakinumab to control a RHL. Interestingly, one patient suffering from secondary amyloidosis with proteinuria up to 2 g/24 h showed a complete resolution of proteinuria after 6 months of tocilizumab.

Moreover, a randomized placebo-controlled trial demonstrated the efficacy of tocilizumab in the pediatric onset of the disease in which 85% of the children with severe persistent SOJIA met the composite primary end point (ACR Pedi 30 improvement in three out of six variables) vs. 24% in the placebo group [243].

Overall, the literature reported on 40 patients with refractory AOSD treated with tocilizumab. Beneficial effects were better documented with the chronic arthritis pattern of the disease but tocilizumab seems effective on the accompanying systemic symptoms too. As anakinra, tocilizumab showed a marked corticosteroid-sparing effect and a good safety profile. A French nationwide registry is currently built to collect additional information on the long-term efficacy and tolerance of tocilizumab in AOSD in clinical practice.

5.5.4. Proposal for a therapeutic strategy in AOSD

According to the above data, we propose a therapeutic strategy for AOSD (summarized in Fig. 2). Corticosteroids are the first-line treatment for inducing remission. Then, introduction of methotrexate should

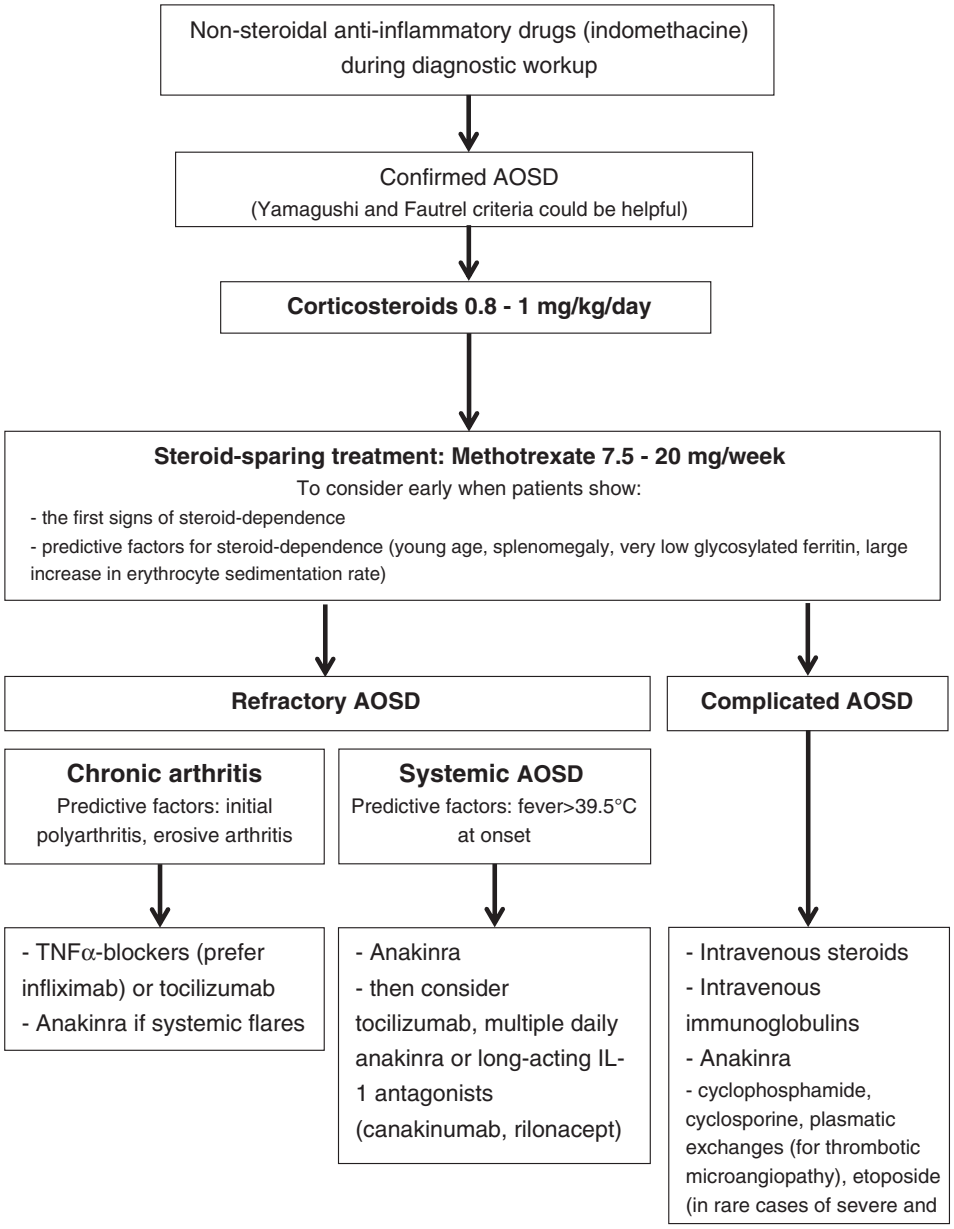

Fig. 2. Proposal for a therapeutic strategy in adult-onset Still's disease.

not be delayed when the patient exhibits the first signs or predictive factors of steroid-dependence. In the case of refractory AOSD, the chronic arthritis should be first treated with tocilizumab or infliximab whereas a systemic pattern should be treated with anakinra. Further studies are required to see whether an earlier administration of anakinra or tocilizumab is more beneficial.

Take-home messages

- Recent insights into the pathophysiology of AOSD categorized it as a 'complex' autoinflammatory disorder and put it at the crossroads of autoinflammatory and autoimmune diseases.
- According to the clinical presentation of the disease at diagnosis, two phenotypes may be distinguished: i) a highly symptomatic, systemic and feverish one which would evolve into a systemic pattern; ii) a more indolent one with arthritis in the foreground and poor systemic symptomatology which would evolve into a chronic articular pattern.
- Despite life-threatening complications such as RHL, the prognosis of AOSD remains good and the mortality rate remains very low.
- Corticosteroids (0.8–1 mg/kg/d) and low-dose methotrexate is the mainstay of AOSD treatment.
- TNFα-blockers (mainly infliximab) could be interesting in chronic polyarticular refractory AOSD.
- Anakinra seems to be an effective, well tolerated, and steroid-sparing, but only a suspensive treatment in refractory systemic AOSD.
- Inhibiting the IL-6 pathway with tocilizumab seems efficient in refractory AOSD with active arthritis.

Acknowledgements

Dr. Yvan Jamilloux acknowledges the Foundation for the Development of Internal Medicine in Europe (FDIME), the *Société Nationale Française de Médecine Interne* (SNFMI), and Genzyme for their help in funding his PhD research project.

References

[1] Still GF. On a form of chronic joint disease in children. Med Chir Trans 1897;80:47–60.
[2] Riolet J. Wissler–Fanconi syndrome. Rev Rhum Mal Osteoartic 1964;31:388–97.
[3] Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30:121–33.
[4] Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I, et al. Adult-onset Still disease: manifestations, treatments, outcome, and prognostic factors in 57 patients. Medicine (Baltimore) 2014;93:91–9.
[5] Sampalis JS, Esdaile JM, Medsger TA, Patridge AJ, et al. A controlled study of the long-term prognosis of adult Still's disease. Am J Med 1995;98:384–8.
[6] Ichiki H, Shishido M, Nishiyama S. Two cases of adult onset of Still's disease in the elderly. Jpn J Geriatr 1992;29:960–4.
[7] Wouters JM, van Rijswijk MH, van de Putte LB. Adult onset Still's disease in the elderly: a report of two cases. J Rheumatol 1985;12:791–3.
[8] Magadur-Joly G, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 1995;54:587–90.
[9] Wakai K, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R, et al. Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. J Epidemiol 1997;7:221–5.
[10] Evensen KJ, Nossent HC. Epidemiology and outcome of adult-onset Still's disease in Northern Norway. Scand J Rheumatol 2006;35:48–51.
[11] Cagatay Y, Gul A, Cagatay A, Kamali S, Karadeniz A, Inanc M, et al. Adult-onset Still's disease. Int J Clin Pract 2009;63:1050–5.
[12] Chen P-D, Yu S-L, Chen S, Weng X-H. Retrospective study of 61 patients with adult-onset Still's disease admitted with fever of unknown origin in China. Clin Rheumatol 2012;31:175–81.
[13] 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) 1991;70:118–36.
[14] Gerfaud-Valentin M, Hot A, Huissoud C, Durieu I, Broussolle C, Sève P. Adult-onset Still's disease and pregnancy: about ten cases and review of the literature. Rheumatol Int 2013. http://dx.doi.org/10.1007/s00296-013-2765-5 [Epub ahead of print].
[15] Terkeltaub R, Esdaile J, Décary F, Harth M, Lister J, Lapointe N. HLA-Bw35 and prognosis in adult Still's disease. Arthritis Rheum 1981;12:1469–72.
[16] Wouters JM, Reekers P, van de Putte LB. Adult-onset Still's disease. Disease course and HLA associations. Arthritis Rheum 1986;29:415–8.
[17] Fujii T, Nojima T, Yasuoka H, Satoh S, Nakamura K, Kuwana M, et al. Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Association with chronic articular disease. Rheumatology (Oxford) 2001;40:1398–404.
[18] Joung CI, Lee HS, Lee SW, Kim CG, Song YH, Jun JB, et al. Association between HLA-DR B1 and clinical features of adult onset Still's disease in Korea. Clin Exp Rheumatol 2003;21:489–92.
[19] Sugiura T, Maeno N, Kawaguchi Y, Takei S, Imanaka H, Kawano Y, et al. A promoter haplotype of the interleukin-18 gene is associated with juvenile idiopathic arthritis in the Japanese population. Arthritis Res Ther 2006;8:R60.
[20] Wang F-F, Huang X-F, Shen N, Leng L, Bucala R, Chen S-L, et al. A genetic role for macrophage migration inhibitory factor (MIF) in adult-onset Still's disease. Arthritis Res Ther 2013;15:R65.
[21] Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369–76.
[22] Kim JJ, Kim J-K, Shim S-C, Choe J-Y, Kim T-H, Jun J-B, et al. MEFV gene mutations and their clinical significance in Korean patients with adult-onset Still's disease. Clin Exp Rheumatol 2013;31(Suppl. 77):60–3.
[23] 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 1990;17:1058–63.
[24] Wouters JM, van der Veen J, van de Putte LB, de Rooij DJ. Adult onset Still's disease and viral infections. Ann Rheum Dis 1988;47:764–7.
[25] Escudero FJ, Len O, Falcó V, de Sevilla TF, Sellas A. Rubella infection in adult onset Still's disease. Ann Rheum Dis 2000;59:493.
[26] van de Putte LB, Wouters JM. Adult-onset Still's disease. Baillieres Clin Rheumatol 1991;5:263–75.
[27] Perez C, Artola V. Adult Still's disease associated with *Mycoplasma pneumoniae* infection. Clin Infect Dis 2011;32:E105–6.
[28] Kádár J, Petrovicz E. Adult-onset Still's disease. Best Pract Res Clin Rheumatol 2003;18:663–76.
[29] Liozon E, Ly KH, Vidal-Cathala E, Fauchais AL. Adult-onset Still's disease as a manifestation of malignancy: report of a patient with melanoma and literature review. Rev Med Interne 2014;35:60–4.
[30] Larroche C, Mouthon L. Pathogenesis of hemophagocytic syndrome (HPS). Autoimmun Rev 2004;3:69–75.
[31] Choi J-H, Suh C-H, Lee Y-M, Suh Y-J, Lee S-K, Kim S-S, et al. Serum cytokine profiles in patients with adult onset Still's disease. J Rheumatol 2003;30:2422–7.
[32] Chen D-Y, Lan J-L, Lin F-J, Hsieh T-Y. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. J Rheumatol 2004;31:2189–98.
[33] Komiya A, Matsui T, Nogi S, Iwata K, Futami H, Takaoka H, et al. Neutrophil CD64 is upregulated in patients with active adult-onset Still's disease. Scand J Rheumatol 2012;41:156–8.
[34] Matsui K, Tsuchida T, Hiroishi K, Tominaga K, Hayashi N, Hada T, et al. High serum level of macrophage-colony stimulating factor (M-CSF) in adult-onset Still's disease. Rheumatology (Oxford) 1999;38:477–8.
[35] Hoshino T, Ohta A, Yang D, Kawamoto M, Kikuchi M, Inoue Y, et al. Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease. J Rheumatol 1998;25:396–8.
[36] Jung S-Y, Park Y-B, Ha Y-J, Lee K-H, Lee S-K. Serum calprotectin as a marker for disease activity and severity in adult-onset Still's disease. J Rheumatol 2010;37:1029–34.
[37] Zou Y-Q, Lu L-J, Li S-J, Zeng T, Wang X-D, Bao C-D, et al. The levels of macrophage migration inhibitory factor as an indicator of disease activity and severity in adult-onset Still's disease. Clin Biochem 2008;41:519–24.
[38] Chen D-Y, Lan J-L, Lin F-J, Hsieh T-Y. Association of intercellular adhesion molecule-1 with clinical manifestations and interleukin-18 in patients with active, untreated adult-onset Still's disease. Arthritis Rheum 2005;53:320–7.
[39] Fautrel B, Le Moël G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol 2001;28:322–9.
[40] 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) 2010;89:37–46.
[41] Min J-K, Cho C-S, Kim H-Y, Oh E-J. Bone marrow findings in patients with adult Still's disease. Scand J Rheumatol 2003;32:119–21.
[42] Behrens EM. Macrophage activation syndrome in rheumatic disease: what is the role of the antigen presenting cell? Autoimmun Rev 2008;7:305–8.
[43] Mehta B, Efthimiou P. Ferritin in adult-onset still's disease: just a useful innocent bystander? Int J Inflamm 2012;2012. http://dx.doi.org/10.1155/2012/298405.
[44] Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013;11:185.
[45] Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. Autoimmun Rev 2007;6:457–63.
[46] Lee S-J, Cho Y-N, Kim T-J, Park S-C, Park D-J, Jin H-M, et al. Natural killer T cell deficiency in active adult-onset Still's disease: correlation of deficiency of natural killer T cells with dysfunction of natural killer cells. Arthritis Rheum 2012;64:2868–77.
[47] Park JH, Kim H-S, Lee JS, Kim JJ, Jung K-H, Park Y-W, et al. Natural killer cell cytolytic function in Korean patients with adult-onset Still's disease. J Rheumatol 2012;39:2000–7.

[48] Chaix J, Tessmer MS, Hoebe K, Fuséri N, Ryffel B, Dalod M, et al. Cutting edge: priming of NK cells by IL-18. J Immunol 2008;181:1627–31.
[49] Wada T, Kanegane H, Ohta K, Katoh F, Imamura T, Nakazawa Y, et al. Sustained elevation of serum interleukin-18 and its association with hemophagocytic lymphohistiocytosis in XIAP deficiency. Cytokine 2014;65:74–8.
[50] Novick D, Kim S, Kaplanski G, Dinarello CA. Interleukin-18, more than a Th1 cytokine. Semin Immunol 2013. http://dx.doi.org/10.1016/j.smim.2013.10.014.
[51] Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med 2012;63:233–46.
[52] Wulffraat NM, Rijkers GT, Elst E, Brooimans R, Kuis W. Reduced perforin expression in systemic juvenile idiopathic arthritis is restored by autologous stem-cell transplantation. Rheumatology (Oxford) 2003;42:375–9.
[53] Rau M, Schiller M, Krienke S, Heyder P, Lorenz H, Blank N. Clinical manifestations but not cytokine profiles differentiate adult-onset Still's disease and sepsis. J Rheumatol 2010;37:2369–76.
[54] Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. Cell 2010;140:784–90.
[55] Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 2005;201:1479–86.
[56] Youm J-Y, Woo J-H, Kim T-H, Bae S-C, Yoo D-H. Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms in Korean patients with adult-onset Still's disease. Scand J Rheumatol 2007;36:390–3.
[57] Carroll HP, Paunovic V, Gadina M. Signalling, inflammation and arthritis: crossed signals: the role of interleukin-15 and -18 in autoimmunity. Rheumatology (Oxford) 2008;47:1269–77.
[58] Lotito APN, Silva CAA, Mello SBV. Interleukin-18 in chronic joint diseases. Autoimmun Rev 2007;6:253–6.
[59] Rooney T, Murphy E, Benito M, Roux-Lombard P, FitzGerald O, Dayer J-M, et al. Synovial tissue interleukin-18 expression and the response to treatment in patients with inflammatory arthritis. Ann Rheum Dis 2004;63:1393–8.
[60] Conigliaro P, Priori R, Bombardieri M, Alessandri C, Barone F, Pitzalis C, et al. Lymph node IL-18 expression in adult-onset Still's disease. Ann Rheum Dis 2009;68:442–3.
[61] Priori R, Barone F, Alessandri C, Colafrancesco S, McInnes IB, Pitzalis C, et al. Markedly increased IL-18 liver expression in adult-onset Still's disease-related hepatitis. Rheumatology (Oxford) 2011;50:776–80.
[62] Maruyama J, Inokuma S. Cytokine profiles of macrophage activation syndrome associated with rheumatic diseases. J Rheumatol 2010;37:967–73.
[63] Kawaguchi Y, Terajima H, Harigai M, Hara M, Kamatani N. Interleukin-18 as a novel diagnostic marker and indicator of disease severity in adult-onset Still's disease. Arthritis Rheum 2001;44:1716–7.
[64] Kawashima M, Yamamura M, Taniai M, Yamauchi H, Tanimoto T, Kurimoto M, et al. Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease. Arthritis Rheum 2001;44:550–60.
[65] Colafrancesco S, Priori R, Alessandri C, Perricone C, Pendolino M, Picarelli G, et al. IL-18 serum level in adult onset Still's disease: a marker of disease activity. Int J Inflamm 2012;2012:156890.
[66] Nagashima T, Iwamoto M, Matsumoto K, Minota S. Interleukin-18 in adult-onset Still's disease: treatment target or disease activity indicator? Intern Med 2012;51:449.
[67] Scheinberg MA, Chapira E, Fernandes ML, Hubscher O. Interleukin 6: a possible marker of disease activity in adult onset Still's disease. Clin Exp Rheumatol 1996;14:653–5.
[68] Martini A. Systemic juvenile idiopathic arthritis. Autoimmun Rev 2012;12:56–9.
[69] Kasama T, Furuya H, Yanai R, Ohtsuka K, Takahashi R, Yajima N, et al. Correlation of serum CX3CL1 level with disease activity in adult-onset Still's disease and significant involvement in hemophagocytic syndrome. Clin Rheumatol 2012;31:853–60.
[70] Chen D-Y, Lin C-C, Chen Y-M, Lan J-L, Hung W-T, Chen H-H, et al. Involvement of TLR7 MyD88-dependent signaling pathway in the pathogenesis of adult-onset Still's disease. Arthritis Res Ther 2013;15:R39.
[71] Jamilloux Y, Henry T. The inflammasomes: platforms of innate immunity. Med Sci 2013;29:975–84.
[72] Antoniou KM, Margaritopoulos GA, Giannarakis I, Choulaki C, Fountoulakis N, Siafakas NM, et al. Adult onset Still's disease: a case report with a rare clinical manifestation and pathophysiological correlations. Case Rep Med 2013;2013:981232.
[73] Hayem F, Hayem G. Still's disease and the mitochondrion: the other face of an old friend? Med Hypotheses 2012;79:136–7.
[74] Gattorno M, Tassi S, Carta S, Delfino L, Ferlito F, Pelagatti MA, et al. Pattern of interleukin-1beta secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations. Arthritis Rheum 2007;56:3138–48.
[75] Chen DY, Lan JL, Lin FJ, Hsieh TY, Wen MC. Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease. Ann Rheum Dis 2004;63:1300–6.
[76] Bettelli E, Korn T, Oukka M, Kuchroo VK. Induction and effector functions of T(H)17 cells. Nature 2008;453:1051–7.
[77] Waite JC, Skokos D. Th17 response and inflammatory autoimmune diseases. Int J Inflamm 2012;2012:819467.
[78] Meng G, Zhang F, Fuss I, Kitani A, Strober W. A mutation in the Nlrp3 gene causing inflammasome hyperactivation potentiates Th17 cell-dominant immune responses. Immunity 2009;30:860–74.
[79] Chen D-Y, Chen Y-M, Lan J-L, Lin C-C, Chen H-H, Hsieh C-W. Potential role of Th17 cells in the pathogenesis of adult-onset Still's disease. Rheumatology (Oxford) 2010;49:2305–12.
[80] Chen D-Y, Chen Y-M, Chen H-H, Hsieh C-W, Lin C-C, Lan J-L. The associations of circulating CD4 + CD25high regulatory T cells and TGF-β with disease activity and clinical course in patients with adult-onset Still's disease. Connect Tissue Res 2010;51:370–7.
[81] Doria A, Zen M, Bettio S, Gatto M, Bassi N, Nalotto L, et al. Autoinflammation and autoimmunity: bridging the divide. Autoimmun Rev 2012;12:22–30.
[82] Hayem F. Is Still's disease an autoinflammatory syndrome. Joint Bone Spine 2009;76:7–9.
[83] Rossi-Semerano L, Koné-Paut I. Is Still's disease an autoinflammatory syndrome? Int J Inflamm 2012;2012:480373.
[84] 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) 2002;81:194–200.
[85] 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 2006;25:639–44.
[86] 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 2009;15:284–8.
[87] 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 2010;29:1015–9.
[88] 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 2013;32:28–33.
[89] Colina M, Zucchini W, Ciancio G, Orzincolo C, Trotta F, Govoni M. The evolution of adult-onset Still disease: an observational and comparative study in a cohort of 76 Italian patients. Semin Arthritis Rheum 2011;41:279–85.
[90] Crispín JC, Martínez-Baños D, Alcocer-Varela J. Adult-onset Still disease as the cause of fever of unknown origin. Medicine (Baltimore) 2005;84:331–7.
[91] Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. Scand J Infect Dis 2006;38:632–8.
[92] 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 1982;25:647–54.
[93] Bagnari V, Colina M, Ciancio G, Govoni M, Trotta F. Adult-onset Still's disease. Rheumatol Int 2010;30:855–62.
[94] Nguyen KH, Weisman MH. Severe sore throat as a presenting symptom of adult onset Still's disease: a case series and review of the literature. J Rheumatol 1997;24:592–7.
[95] Cheema GS, Quismorio Jr FP. Pulmonary involvement in adult-onset Still's disease. Curr Opin Pulm Med 1999;5:305–9.
[96] Sato H, Yokoe I, Nishio S, Onishi T, Takao T, Kobayashi Y, et al. A case of adult onset Still's disease complicated with cryptogenic organizing pneumonia. Intern Med 2011;50:247–51.
[97] Ghosal A, Pal RB, Das SK, Das T. An unusual presentation of adult onset Still's disease. Med J Malaysia 2012;67:532–3.
[98] Corbett AJ, Zizic TM, Stevens MB. Adult-onset Still's disease with an associated severe restrictive pulmonary defect: a case report. Ann Rheum Dis 1983;42:452–4.
[99] Campos M, Schiopu E. Pulmonary arterial hypertension in adult-onset Still's disease: rapid response to anakinra. Case Rep Rheumatol 2012;2012:537613.
[100] Mubashir E, Ahmed MM, Hayat S, Heldmann M, Berney SM. Pulmonary hypertension in a patient with adult-onset Stills disease. Clin Rheumatol 2007;26:1359–61.
[101] Khobragade AK, Chogle AR, Ram RP, Mascarenhas J, Kothari S, Kawadkar S, et al. Reversible posterior leukoencephalopathy syndrome in a case of adult onset Still's disease with concurrent thrombotic thrombocytopenic purpura: response to high dose immunoglobulin infusions. J Assoc Physicians India 2012;60:59–62.
[102] Zenone T, Boibieux A, Chaumentin G, Margotton A, Ninet J, Peyramond D, et al. Bilateral perception deafness in adult onset Still disease. Presse Med 1996;25:1213.
[103] Akkara Veetil BM, Yee AH, Warrington KJ, Aksamit Jr AJ, Mason TG. Aseptic meningitis in adult onset Still's disease. Rheumatol Int 2012;32:4031–4.
[104] Sabnis GR, Gokhale YA, Kulkarni UP. Tocilizumab in refractory adult-onset Still's disease with aseptic meningitis—efficacy of interleukin-6 blockade and review of the literature. Semin Arthritis Rheum 2011;40:365–8.
[105] Tabak F, Tanverdi M, Ozaras R, Mert A, Tartan Z, Ozturk R, et al. Neutrophilic pleocytosis in cerebrospinal fluid: adult-onset Still's disease. Intern Med 2003;42:1039–41.
[106] Zhao H, Yuan Y, Li Y, Si C-W, Tian G-S, Wang G-Q, et al. Encephalic large arteries narrowness and peripheral neuropathy in a patient with adult-onset Still's disease. Rheumatol Int 2008;28:1261–4.
[107] Shaikh AG, Hain TC, Zee DS. Oculomotor disorders in adult-onset Still's disease. J Neurol 2010;257:136–8.
[108] Kumar S, Sheaff M, Yaqoob M. Collapsing glomerulopathy in adult still's disease. Am J Kidney Dis 2004;43:e4-10.
[109] Bennett AN, Peterson P, Sangle S, Hangartner R, Abbs IC, Hughes GRV, et al. Adult onset Still's disease and collapsing glomerulopathy: successful treatment with intravenous immunoglobulins and mycophenolate mofetil. Rheumatology (Oxford) 2004;43:795–9.
[110] Babacan T, Onat AM, Pehlivan Y, Comez G, Karakök M. Successful treatment of refractory adult Still's disease and membranous glomerulonephritis with infliximab. Clin Rheumatol 2010;29:423–6.
[111] Sayegh J, Besson V, Lavigne C, Croue A, Augusto J-F. Necrotizing crescentic immunoglobulin A glomerulonephritis in adult-onset Still's disease. Clin Exp Nephrol 2011;15:978–9.
[112] Thonhofer R, Soleiman A, Kriessmayr M, Thonhofer U, Wipfler E, Gaugg M, et al. Decrease of proteinuria in a patient with adult-onset Still's disease and glomerulonephritis after anti-TNFalpha therapy. Scand J Rheumatol 2006;35:485–8.
[113] Sugimoto T, Yasuda M, Sakaguchi M, Osawa N, Tanaka Y, Uzu T, et al. Hyponatraemia due to renal proximal tubule dysfunction in a patient with adult-onset Still's disease. QJM 2008;101:163–4.

[114] Cush JJ, Leibowitz IH, Friedman SA. Adult-onset Still's disease and inflammatory orbital pseudotumor. N Y State J Med 1985;85:110–1.
[115] Liu F-C, Chiang S-Y, Chang D-M, Lai J-H, Hou T-Y, Chen C-H. Purtscher's-like retinopathy as an initial presentation of adult-onset Still's disease: a case report and review of the literature. Clin Rheumatol 2007;26:1204–6.
[116] Jiang W, Tang L, Duan X, Jiang B. A case of uveitis in adult-onset Still's disease with ophthalmologic symptoms. Rheumatol Int 2013;33:1867–72.
[117] Marie I, Ducrotté P, Riachi G, François A, Levesque H, Courtois H. Pseudo-angiocholitis revealing adult-onset Still's disease. Dig Dis Sci 2004;49:627–8.
[118] Morita H, Nishiwaki H, Nagayama Y, Yoshimura A. Portal vein thrombosis in adult-onset Still's disease: a case report and literature review. Rheumatol Int 2009;29:1515–8.
[119] Assimakopoulos SF, Karamouzos V, Papakonstantinou C, Zolota V, Labropoulou-Karatza C, Gogos C. Suppurative necrotizing granulomatous lymphadenitis in adult-onset Still's disease: a case report. J Med Case Reports 2012;6:354.
[120] Soy M. A case of adult-onset Still's disease presenting with angioedema. Clin Rheumatol 2004;23:92.
[121] Ota T, Higashi S, Suzuki H, Eto S. Increased serum ferritin levels in adult Still's disease. Lancet 1987;1:562–3.
[122] Fautrel B. Ferritin levels in adult Still's disease: any sugar? Joint Bone Spine 2002;69:355–7.
[123] 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 1992; 19:424–30.
[124] 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 2009;36:1026–31.
[125] 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 2009;36:156–62.
[126] Fardet L, Coppo P, Kettaneh A, Dehoux M, Cabane J, Lambotte O. Low glycosylated ferritin, a good marker for the diagnosis of hemophagocytic syndrome. Arthritis Rheum 2008;58:1521–7.
[127] Vignes S, Le Moël G, Fautrel B, Wechsler B, Godeau P, Piette JC. Percentage of glycosylated serum ferritin remains low throughout the course of adult onset Still's disease. Ann Rheum Dis 2000;59:347–50.
[128] Zhao D-B, Dai S-M, Liu X-P, Xu H. Interstitial inflammation in visceral organs is a pathologic feature of adult-onset Still's disease. Rheumatol Int 2011;31:923–7.
[129] Dino O, Provenzano G, Giannuoli G, Sciarrino E, Pouyet M, Pagliaro L. Fulminant hepatic failure in adult onset Still's disease. J Rheumatol 1996;23:784–5.
[130] Taccone FS, Lucidi V, Donckier V, Bourgeois N, Decaux G, Vandergheynst F. Fulminant hepatitis requiring MARS and liver transplantation in a patient with Still's disease. Eur J Intern Med 2008;19:e26–8.
[131] Jeon YK, Paik JH, Park S-S, Park SO, Kim YA, Kim JE, et al. Spectrum of lymph node pathology in adult onset Still's disease; analysis of 12 patients with one follow up biopsy. J Clin Pathol 2004;57:1052–6.
[132] Wu N, Li Q, Gu C-X, Ahmed T, Yao X-P. Paraneoplastic syndrome mimicking adult-onset Still's disease caused by advanced lung cancer: a case report. BMC Cancer 2011;11:487.
[133] Kato T, Tanabe J, Kanemoto M, Kobayashi C, Morita S, Karahashi T. A case of extranodal NK/T-cell lymphoma, nasal type mimicking typical manifestations of adult-onset Still's disease (AOSD) with hemophagocytic syndrome: diagnostic consideration between malignant lymphoma without lymphadenopathy and AOSD. Mod Rheumatol 2009;19:675–80.
[134] Choe J-Y, Chung DS, Park S-H, Kwon H-H, Kim S-K. Clinical significance of 18F-fluoro-dexoxyglucose positron emission tomography in patients with adult-onset Still's disease: report of two cases and review of literatures. Rheumatol Int 2010;30:1673–6.
[135] Kim YJ, Kim SI, Hong K-W, Kang MW. Diagnostic value of 18F-FDG PET/CT in patients with fever of unknown origin. Intern Med J 2012;42:834–7.
[136] Crouzet J, Boudousq V, Lechiche C, Pouget JP, Kotzki PO, Collombier L, et al. Place of (18F-FDG-PET with computed tomography in the diagnostic algorithm of patients with fever of unknown origin. Eur J Clin Microbiol Infect Dis 2012;31:1727–33.
[137] Yamashita H, Kubota K, Takahashi Y, Minamimoto R, Morooka M, Kaneko H, et al. Clinical value of (18)F-fluoro-dexoxyglucose positron emission tomography/computed tomography in patients with adult-onset Still's disease: a seven-case series and review of the literature. Mod Rheumatol 2013 [Epub ahead of print].
[138] Cush JJ, Medsger Jr TA, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum 1987;30:186–94.
[139] Calabro JJ, Londino Jr AV. Adult onset Still's disease. J Rheumatol 1986;13:827–8.
[140] Reginato AJ, Schumacher Jr 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 1987;17:39–57.
[141] 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 2011;38:741–6.
[142] Wouters JM, van de Putte LB. Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. QJM 1986;61:1055–65.
[143] Mavragani CP, Spyridakis EG, Koutsilieris M. Adult-onset Still's disease: from pathophysiology to targeted therapies. Int J Inflamm 2012;2012:879020.
[144] Lin Y-T, Wang C-T, Gershwin ME, Chiang B-L. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. Autoimmun Rev 2011;10:482–9.
[145] Kim H-A, Sung J-M, Suh C-H. Therapeutic responses and prognosis in adult-onset Still's disease. Rheumatol Int 2012;32:1291–8.
[146] Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre M-H, et al. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum 2003;49:633–9.
[147] 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 2006;65:1596–601.
[148] Colina M, Govoni M, Trotta F. Fatal myocarditis in adult-onset Still disease with diffuse intravascular coagulation. Rheumatol Int 2009;29:1355–7.
[149] Bank I, Marboe CC, Redberg RF, Jacobs J. Myocarditis in adult Still's disease. Arthritis Rheum 1985;28:452–4.
[150] Bergemer AM, Fouquet B, Goupille P, Charbonnier B, Valat JP. Myocarditis in Still's disease in adults. Rev Rhum Mal Osteoartic 1988;55:945–8.
[151] Sachs RN, Talvard O, Lanfranchi J. Myocarditis in adult Still's disease. Int J Cardiol 1990;27:377–80.
[152] Roblot P, Boiffard O, Allal J, Breux J, Fieuzal S, Becq-Giraudon B. Myocarditis in adult-onset Still's disease: one case. Rev Med Interne 1990;11:S368.
[153] Hosaka S, Takashina N, Ishikawa A, Kondo H, Kashiwazaki S. Adult Still's disease with myocarditis and peritonitis. Intern Med 1992;31:812–5.
[154] Ueda T, Mizushige K, Sakamoto S, Senda S, Morita H, Tokuda M, et al. Adult Still's disease with myocardial dysfunction induced by microangiopathy. Jpn Circ J 1997;61:74–7.
[155] Nishimagi E, Hirata S, Kawaguchi Y, Okamoto H, Hara M, Kamatani N. Myocardial dysfunction in a patient with adult-onset Still's disease (AOSD). Clin Exp Rheumatol 2004;22:506–7.
[156] Krzossok S, Benck U, van der Woude FJ, Braun C. Disseminated intravascular coagulation, perimyocarditis and bilateral pleural empyema in adult Still's disease. Dtsch Med Wochenschr 2004;129:2535–7.
[157] Kristensen LE, Bartosik I. Myocarditis in adult-onset Still's disease despite significant immunosuppressive therapy. Scand J Rheumatol 2006;35:330–1.
[158] Ballard M, Chazerain P, Charpentier J, Manet M, Aerts J, Ziza J. Severe myocarditis in an adult-onset Still's disease. Rev Med Interne 2002;23:S653.
[159] Jadhav P, Nanayakkara N. Myocarditis in adult onset Stills disease. Int J Rheum Dis 2009;12:272–4.
[160] Kuek A, Weerakoon A, Ahmed K, Ostör AJK. Adult-onset Still's disease and myocarditis: successful treatment with intravenous immunoglobulin and maintenance of remission with etanercept. Rheumatology (Oxford) 2007;46:1043–4.
[161] Cavallasca JA, Vigliano CA, Perandones CE, Tate GA. Myocarditis as a form of relapse in two patients with adult Still's disease. Rheumatol Int 2010;30:1095–7.
[162] Raffeiner B, Botsios C, Dinarello C, Ometto F, Punzi L, Ramonda R. Adult-onset Still's disease with myocarditis successfully treated with the interleukin-1 receptor antagonist anakinra. Joint Bone Spine 2011;78:100–1.
[163] Fontaine C, Millot O, Reny J, Berdagué P, Rey J, Oziol E. Dilated cardiomyopathy with normal creatin kinase in an adult-onset Still's disease. Rev Med Interne 2003;24:S116.
[164] Parvez N, Carpenter JL. Cardiac tamponade in Still disease: a review of the literature. South Med J 2009;102:832–7.
[165] Buss SJ, Wolf D, Mereles D, Blank N, Katus HA, Hardt SE. A rare case of reversible constrictive pericarditis with severe pericardial thickening in a patient with adult onset Still's disease. Int J Cardiol 2010;144:e23–5.
[166] García-Porrúa C, González-Juanatey C, González-Gay MA. Endocarditis in adult onset Still's disease: a 12 month followup. J Rheumatol 2001;28:2141–2.
[167] Mejjad O, Vittecoq O, Tamion F, Girault C, Lecot S, Cailleux N, et al. A shock associated with adult-onset Still's disease. Joint Bone Spine 2001;68:76–8.
[168] Iglesias J, Sathiraju S, Marik PE. Severe systemic inflammatory response syndrome with shock and ARDS resulting from Still's disease: clinical response with high-dose pulse methylprednisolone, therapy. Chest 1999;115:1738–40.
[169] Mito K, Yamakami Y, Mizunoe S, Tokimatsu I, Hiramatsu K, Nagai H, et al. A case of adult-onset Still's disease complicated with acute respiratory distress syndrome. J Jpn Respir Soc 2002;40:894–9.
[170] Suleiman M, Wolfovitz E, Boulman N, Levy Y. Adult onset Still's disease as a cause of ARDS and acute respiratory failure. Scand J Rheumatol 2002;31:181–3.
[171] Ota A. Adult Still disease and ARDS. J Jpn Soc Intern Med 2001;90:1403–8.
[172] Yokoyama M, Suwa A, Shinozawa T, Fujii T, Mimori T, Akizuki M, et al. A case of adult onset Still's disease complicated with adult respiratory distress syndrome and disseminated intravascular coagulation. Jpn J Clin Immunol 1995;18:207–14.
[173] Pedersen JE. ARDS-associated with adult Still's disease. Intensive Care Med 1991;17:372.
[174] Hirohata S, Kamoshita H, Taketani T, Maeda S. Adult Still's disease complicated with adult respiratory distress. Arch Intern Med 1986;146:2409–10.
[175] Sari I, Birlik M, Binicier O, Akar S, Yilmaz E, Onen F, et al. A case of adult-onset Still's disease complicated with diffuse alveolar hemorrhage. J Korean Med Sci 2009;24:155–7.
[176] Arai Y, Handa T, Mitani K. Adult-onset Still disease presenting with disseminated intravascular coagulation. Jpn J Clin Hematol 2004;45:316–8.
[177] Park J-H, Bae JH, Choi Y-S, Lee H-S, Jun J-B, Jung S, et al. Adult-onset Still's disease with disseminated intravascular coagulation and multiple organ dysfunctions dramatically treated with cyclosporine A. J Korean Med Sci 2004;19:137–41.
[178] Sanada I, Kawano F, Tsukamoto A, Kiyokawa T, Shido T, Koga S. Disseminated intravascular coagulation in a case of adult onset Still's disease. Jpn J Clin Hematol 1997;38:1194–8.
[179] Bray VJ, Singleton JD. Disseminated intravascular coagulation in Still's disease. Semin Arthritis Rheum 1994;24:222–9.
[180] Mori T, Tanigawa M, Iwasaki E, Tamaki S, Ono T, Wada H, et al. Cyclosporine therapy of adult onset Still's disease with disseminated intravascular coagulation. Jpn J Clin Hematol 1993;34:147–52.

[181] Aellen P, Raccaud O, Waldburger M, Chamot AM, Gerster JC. Still's disease in adults with disseminated intravascular coagulation. Schweiz Rundsch Med Prax 1991;80:376–8.
[182] Salamon L, Salamon T, Morovic-Vergles J. Thrombotic microangiopathy in adult-onset Still's disease: case report and review of the literature. Wien Klin Wochenschr 2009;121:583–8.
[183] Portolés J, de Tomás E, Espinosa A, Gallego E, Nieva GS, Blanco J. Thrombotic thrombocytopenic purpura and acute renal failure in adult Still's disease. Nephrol Dial Transplant 1997;12:1471–3.
[184] Quéméneur T, Noel L-H, Kyndt X, Droz D, Fleury D, Binaut R, et al. Thrombotic microangiopathy in adult Still's disease. Scand J Rheumatol 2005;34:399–403.
[185] Ben Ghorbel I, Khanfir M, Houman MH. Amyloidosis in adult onset Still's disease. Rev Med Interne 2004;25:675–7.
[186] 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 jan. 1993;32(1):50–2.
[187] 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 2000;15:131–4.
[188] 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 1997;12:1714–6.
[189] 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 2007;26:1055–60.
[190] Michel M, Hayem G, Rat AC, Meyer O, Palazzo E, Blétry O, et al. Fatal infectious complications in 2 patients with adult onset Still disease. Rev Med Interne 1996;17:407–9.
[191] Manganelli P, Fietta P, Zuccoli P. Adult-onset Still's disease with respiratory distress syndrome, polyserositis and disseminated intravascular coagulation: a case with a fatal outcome. Clin Exp Rheumatol 2003;21:139.
[192] Gianella S, Schaer DJ, Schwarz U, Kurrer M, Heppner FL, Fehr J, et al. Retinal microangiopathy and rapidly fatal cerebral edema in a patient with adult-onset Still's disease and concurrent macrophage activation syndrome. Am J Hematol 2008;83:424–7.
[193] Domingues RB, da Gama AMC, Caser EB, Musso C, Santos MCS. Disseminated cerebral thrombotic microangiopathy in a patient with adult's still disease. Arq Neuropsiquiatr 2003;61:259–61.
[194] Masuyama A, Kobayashi H, Kobayashi Y, Yokoe I, Sugimura Y, Maniwa K, et al. A case of adult-onset Still's disease complicated by thrombotic thrombocytopenic purpura with retinal microangiopathy and rapidly fatal cerebral edema. Mod Rheumatol 2013;23:379–85.
[195] Hong YH, Lee CK. A case of adult onset Still's disease with systemic inflammatory response syndrome complicated by fatal status epilepticus. Rheumatol Int 2008;28:931–3.
[196] 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 2010;62:2530–5.
[197] Koizumi R, Tsukada Y, Ideura H, Ueki K, Maezawa A, Nojima Y. Treatment of adult Still's disease with dexamethasone, an alternative to prednisolone. Scand J Rheumatol 2000;29:396–8.
[198] 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 1999;26:373–8.
[199] Mitamura M, Tada Y, Koarada S, Inoue H, Suematsu R, Ohta A, et al. Cyclosporin A treatment for Japanese patients with severe adult-onset Still's disease. Mod Rheumatol 2009;19:57–63.
[200] Vignes S, Wechsler B, Amoura Z, Papo T, Francès C, Huong DL, et al. Intravenous immunoglobulin in adult Still's disease refractory to non-steroidal anti-inflammatory drugs. Clin Exp Rheumatol 1998;16:295–8.
[201] Permal S, Wechsler B, Cabane J, Perrot S, Blum L, Imbert JC. Treatment of Still disease in adults with intravenous immunoglobulins. Rev Med Interne 1995;16:250–4.
[202] Emmenegger U, Frey U, Reimers A, Fux C, Semela D, Cottagnoud P, et al. Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes. Am J Hematol 2001;68:4–10.
[203] Liozon E, Ly K, Aubard Y, Vidal E. Intravenous immunoglobulins for adult Still's disease and pregnancy. Rheumatology (Oxford) 1999;38:1024–5.
[204] Husni ME, Maier AL, Mease PJ, Overman SS, Fraser P, Gravallese EM, et al. Etanercept in the treatment of adult patients with Still's disease. Arthritis Rheum 2002;46:1171–6.
[205] Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
[206] Cavagna L, Caporali R, Epis O, Bobbio-Pallavicini F, Montecucco C. Infliximab in the treatment of adult Still's disease refractory to conventional therapy. Clin Exp Rheumatol 2001;19:329–32.
[207] Kraetsch HG, Antoni C, Kalden JR, Manger B. Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. Ann Rheum Dis 2001;60:55–7.
[208] Kokkinos A, Iliopoulos A, Greka P, Efthymiou A, Katsilambros N, Sfikakis PP. Successful treatment of refractory adult-onset Still's disease with infliximab. A prospective, non-comparative series of four patients. Clin Rheumatol 2004;23:45–9.
[209] Fautrel B, Sibilia J, Mariette X, Combe B. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis 2005;64:262–6.
[210] Benucci M, Li GF, Del Rosso A, Manfredi M. Adalimumab (anti-TNF-alpha) therapy to improve the clinical course of adult-onset Still's disease: the first case report. Clin Exp Rheumatol 2005;23:733.
[211] Kaneko K, Kaburaki M, Muraoka S, Tanaka N, Yamamoto T, Kusunoki Y, et al. Exacerbation of adult-onset Still's disease, possibly related to elevation of serum tumor necrosis factor-alpha after etanercept administration. Int J Rheum Dis 2010;13:e67–9.
[212] Agarwal S, Moodley J, Ajani Goel G, Theil KS, Mahmood SS, Lang RS. A rare trigger for macrophage activation syndrome. Rheumatol Int 2011;31:405–7.
[213] Aikawa NE, Ribeiro AC de M, Saad CGS, Pereira RMR, Levy M, Silva CA, et al. Is anti-TNF switching in refractory Still's disease safe and effective? Clin Rheumatol 2011;30:1129–34.
[214] Koné-Paut I, Piram M. Targeting interleukin-1β in CAPS (cryopyrin-associated periodic) syndromes: what did we learn? Autoimmun Rev 2012;12:77–80.
[215] Hoffman HM. Therapy of autoinflammatory syndromes. J Allergy Clin Immunol 2009;124:1129–38.
[216] Rudinskaya A, Trock DH. Successful treatment of a patient with refractory adult-onset still disease with anakinra. J Clin Rheumatol 2003;9:330–2.
[217] Vasques Godinho FM, Parreira Santos MJ, Canas da Silva J. Refractory adult onset Still's disease successfully treated with anakinra. Ann Rheum Dis 2005;64:647–8.
[218] Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum 2005;52:1794–803.
[219] Kalliolias GD, Georgiou PE, Antonopoulos IA, Andonopoulos AP, Liossis S-NC. Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial. Ann Rheum Dis 2007;66:842–3.
[220] Kötter I, Wacker A, Koch S, Henes J, Richter C, Engel A, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum 2007;37:189–97.
[221] Lequerré T, Quartier P, Rosellini D, Alaoui F, De Bandt M, Mejjad O, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis 2008;67:302–8.
[222] Laskari K, Tzioufas AG, Moutsopoulos HM. Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study. Arthritis Res Ther 2011;13:R91.
[223] Giampietro C, Ridene M, Lequerre T, Costedoat Chalumeau N, Amoura Z, Sellam J, et al. Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. Arthritis Care Res 2013;65:822–6.
[224] Nigrovic PA, Mannion M, Prince FHM, Zeft A, Rabinovich CE, van Rossum MAJ, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 2011;63:545–55.
[225] DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Juvenile Idiopathic Arthritis Disease-specific Research Committee of Childhood Arthritis Rheumatology and Research Alliance, Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res 2012;64:1001–10.
[226] Nordström D, Knight A, Luukkainen R, van Vollenhoven R, Rantalaiho V, Kajalainen A, et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. J Rheumatol 2012;39:2008–11.
[227] Moulis G, Sailler L, Astudillo L, Pugnet G, Arlet P. May anakinra be used earlier in adult onset Still disease? Clin Rheumatol 2010;29:1199–200.
[228] Gattorno M, Piccini A, Lasiglié D, Tassi S, Brisca G, Carta S, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2008;58:1505–15.
[229] Kontzias A, Efthimiou P. The use of Canakinumab, a novel IL-1β long-acting inhibitor, in refractory adult-onset Still's disease. Semin Arthritis Rheum 2012;42:201–5.
[230] Petryna O, Cush JJ, Efthimiou P. IL-1 Trap rilonacept in refractory adult onset Still's disease. Ann Rheum Dis 2012;71:2056–7.
[231] Ruperto N, Quartier P, Wulffraat N, Woo P, Ravelli A, Mouy R, et al. Paediatric Rheumatology International Clinical Trials Organisation, A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum 2012;64:557–67.
[232] Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396–406.
[233] 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;19:69–72.
[234] Matsumoto K, Nagashima T, Takatori S, Kawahara Y, Yagi M, Iwamoto M, et al. Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. Clin Rheumatol 2009;28:485–7.
[235] Sumida K, Ubara Y, Hoshino J, Suwabe T, Hiramatsu R, Hasegawa E, et al. Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab. Clin Rheumatol 2010;29:1191–4.
[236] Perdan-Pirkmajer K, Praprotnik S, Tomšič M. A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature. Clin Rheumatol 2010;29:1465–7.
[237] Sakai R, Nagasawa H, Nishi E, Okuyama A, Takei H, Kurasawa T, et al. Successful treatment of adult-onset Still's disease with tocilizumab monotherapy: two case reports and literature review. Clin Rheumatol 2012;31:569–74.

[238] Kobayashi M, Takahashi Y, Yamashita H, Kaneko H, Mimori A. Benefit and a possible risk of tocilizumab therapy for adult-onset Still's disease accompanied by macrophage-activation syndrome. Mod Rheumatol 2011;21:92–6.
[239] Thonhofer R, Hiller M, Just H, Trummer M, Siegel C, Dejaco C. Treatment of refractory adult-onset Still's disease with tocilizumab: report of two cases and review of the literature. Rheumatol Int 2011;31:1653–6.
[240] Puéchal X, DeBandt M, Berthelot J-M, Breban M, Dubost J-J, Fain O, et al. Tocilizumab in refractory adult Still's disease. Arthritis Care Res 2011;63:155–9.
[241] Cipriani P, Ruscitti P, Carubbi F, Pantano I, Liakouli V, Berardicurti O, et al. Tocilizumab for the treatment of adult-onset Still's disease: results from a case series. Clin Rheumatol 2013;33:49–55.
[242] Elkayam O, Jiries N, Dranitzki Z, Kivity S, Lidar M, Levy O, et al. Tocilizumab in adult-onset Still's disease: the Israeli experience. J Rheumatol 2014. http://dx.doi.org/10.3899/jrheum.130881 [Epub ahead of print].
[243] De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. PRINTO, PRCSG, randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385–95.

Oxidative stress, FOXO3A and developing vitiligo

Vitiligo is an acquired disorder resulting from the loss of functional melanocytes and clinically it is characterized by asymptomatic depigmented macule or patch. There are several pathogenic hypotheses for vitiligo including autoimmune, intrinsic defect of melanocytes and defective defense against oxidative stress. FOXO3A is the forkhead members of the class O (FOXO) transcription factors, it has an important role in cell cycle regulation, DNA repair and protects from oxidative stress. A recent study by Ozel Turkcu U, *et al.* (**Gene 2014 Feb 15;536(1):129-34**), investigated FOXO3A gene polymorphisms and FOXO3A protein levels, activities of superoxide dismutase (SOD) and catalase antioxidant enzymes in vitiligo patients and healthy controls. In addition, the levels of plasma advanced oxidation protein products (AOPP) in subjects were evaluated to understand the possible role of protein oxidation in disease etiology. Their cohort included 82 vitiligo patients and 81 unrelated healthy controls. They have demonstrated a significant relationship between rs4946936 polymorphism of FOXO3A gene and vitiligo/active vitiligo patients ($p=0.017$; $p=0.019$ respectively), but not for rs2253310 ($p>0.05$). SOD activity and AOPP levels of vitiligo patient were increased compared with control group, whereas FOXO3A levels and catalase enzyme activity of vitiligo patient were decreased compared with control group ($p<0.05$). Their study indicates that rs4946936 of FOXO3A gene might be associated with susceptibility to vitiligo and that oxidative stress may have a role in the pathogenesis of vitiligo.

Yaron Zafrir, MD