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A comprehensive review on adult onset Still's disease

Roberto Giacomelli[a,*], Piero Ruscitti[a], Yehuda Shoenfeld[b,c]

[a] Rheumatology Section, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[b] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel
[c] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

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ABSTRACT

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology usually affecting young adults; spiking fever, arthritis and evanescent rash are commonly observed during the disease. Other frequently observed clinical features include sore throat, hepatomegaly, splenomegaly, lymphadenopathy and serositis. Furthermore, AOSD patients may experience different life-threating complications. Macrophage activation syndrome (MAS) has been reported up to 15% of AOSD patients and it is considered to be the most severe complication of the disease being characterised by high mortality rate. During AOSD, laboratory tests reflect the systemic inflammatory process showing high levels of erythrocyte sedimentation rate and C-reactive protein. In addition, the ferritin levels are typically higher than those observed in other autoimmune, inflammatory, infectious, or neoplastic diseases. Analysing AOSD disease course, 3 different clinical patterns of AOSD have been identified: i. monocyclic pattern, characterised by a systemic single episode; ii. polycyclic pattern, characterised by multiple, ≤ 1 year lasting, flares, alternating with remissions; iii. chronic pattern, related to a persistently active disease with associated polyarthritis. At present, AOSD therapeutic strategy is aimed at targeting pro-inflammatory signs and symptoms, preventing organ damage and life-threating complications and minimising adverse effects of treatment. However, the treatment of AOSD remains largely empirical, lacking controlled clinical trials. High dosages of corticosteroids are usually the first line therapy when the systemic symptoms predominate. Despite this treatment, a large percentage of patients experiences several flares with an evolution toward the chronic disease course and up to 16% of patients die during the follow up, due to AOSD-related complications. On these bases, in the last years, biological agents have been successfully used in refractory cases. Finally, multiple recent lines of evidence have suggested new insights in AOSD pathogenesis unmasking further therapeutic targets. In fact, small molecules, used in experimental MAS models, might represent new therapeutic options.

1. Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology usually affecting young adults. It is typically characterised by spiking fever, arthritis, evanescent rash and hyperferritinemia [1,2]. Still's disease was named after description, in 1897, of 22 children affected by systemic onset juvenile idiopathic arthritis (sIJA), by George Still [3]. Subsequently, in 1971, Eric Bywaters reported 14 adult patients, affected by skin rash, fever, polyarthritis, whose clinical picture strongly resembled the paediatric Still's disease, thus defining AOSD [4]. At present, despite the poor outcome in several patients, AOSD remains a multisystemic disorder of unknown etiology, difficult diagnosis, scarcely studied compared with other rheumatic diseases [1–5]. Due to the relatively low number of studies, the pathogenesis of the disease as well as the optimal management of patients are still not fully elucidated.

In this review, we focus on the pathophysiological steps leading to disease, clinical picture, diagnosis, possible therapeutic strategies of AOSD in the biologics era. We aim to provide useful information for physicians managing these patients.

2. Methods

We designed a comprehensive search of literature on AOSD, by a review of reports published in indexed international journals until up 31/12/2017. We followed proposed guidelines for preparing

* Corresponding author. Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L'Aquila, Delta 6 Building, Via dell'Ospedale, 67100, L'Aquila, Italy.
E-mail address: roberto.giacomelli@cc.univaq.it (R. Giacomelli).

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Table 1
Epidemiology of AOSD.

Epidemiology	
Incidence	0.16–0.4/100000 people
Prevalence	1-34 cases/1 million people
Gender distribution	equally distributed
Age of onset	bimodal peak at ages 15–25 and 36–46 years

AOSD, adult onset Still's disease.

biomedical narrative review [6]. MedLine (*via* PubMed) and Embase databases were searched. The bibliography of relevant articles was also hand-searched for identification of other potentially suitable studies.

3. Epidemiology

The available epidemiologic results report AOSD incidence in a range between 0.16 and 0.4/100000 people and estimated prevalence rate between 1 and 34 cases/1 million people (Table 1) [7,8]. Although in some series women seem to be more affected than men, AOSD is considered to be equally distributed between genders [9,10]. AOSD usually affects young people with a bimodal peak at ages 15–25 and 36–46 years [7–10]. However, an old age onset, after the age of 60 years, has been also reported [11–13].

4. Pathogenesis of AOSD

AOSD may be categorised as a multigenic autoinflammatory disorder at the crossroads of autoinflammatory and autoimmune diseases, due to its complex pathogenesis, involving both innate and adaptive immune system [2]. It is generally accepted that unknown factor(s), acting as second hit, may trigger a pathologic process in genetically susceptible patients finally leading to the activation of an aberrant inflammatory response, which is responsible of AOSD development, as summarised in Fig. 1 [1,2,5,11].

4.1. Genetic susceptibility

Although a familial trend has not been reported in AOSD, some genetic studies showed an association of the disease with different susceptibility genes [16–20]. Some associations between AOSD and HLA antigens have been reported, including HLA-B17, -B18, -B35, -DR2 and -DR4 [14]. In addition, AOSD patients show a more frequent association with both HLA-DRB1*12 and -DRB1*15 [15]. Recent papers suggested associations between HLA-Bw35 and HLA-DRB1*14 with a mild, self-limiting disease and association with HLA-DRw6 in patients experiencing joint involvement [16,17]. Furthermore, HLA-DRB1*1501 (DR2) and HLA-DRB1*1201 (DR5) were associated with chronic disease course of AOSD, whereas HLA-DQB1*0602 (DQ1) was more frequently expressed in patients with chronic and systemic AOSD [18]. More recently, polymorphisms in both interleukin (IL)-18 gene and in macrophage migration inhibitory factor (MIF) gene were proposed to contribute to the disease susceptibility [19,20]. Three haplotypes of IL-18, S01, S02 and S03, composed of 13 genetic polymorphisms covering 2 distinct promoter regions, were determined for 28 AOSD patients [19]. The Authors reported that the frequency of diplotype configuration of S01/S01 was significantly higher in AOSD patients and were associated with a higher IL-18 production compared with healthy controls [19]. Furthermore, both −173 G/C single nucleotide polymorphism (rs755622) and −794 $CATT_{5–8}$ repeat (rs5844572) polymorphism in the MIF functional promoter have been reported in AOSD [20]. The frequency of MIF -794 $CATT_5$ allele was increased in patients and was associated with a higher production of MIF compared with healthy controls. In AOSD patients, a high frequency of −794 $CATT_7$ containing MIF genotypes was observed in those with liver dysfunction. Haplotype analysis also revealed a high representation of the MIF haplotype defined by −173*C/-794 $CATT_5$ (C5) in AOSD patients, suggesting that functional promoter polymorphisms in the MIF gene may contribute to the disease susceptibility and/or in the clinical presentation [20]. Finally, the analysis of 4 hereditary periodic fever syndromes genes in AOSD has been recently performed [21]. Authors performed Sanger sequencing and quantitative analysis of all the coding regions of MEFV, TNFRSF1A, MVK and NLRP3 in 40 AOSD patients. Three rare variants in MEFV were identified and were associated with a severe disease

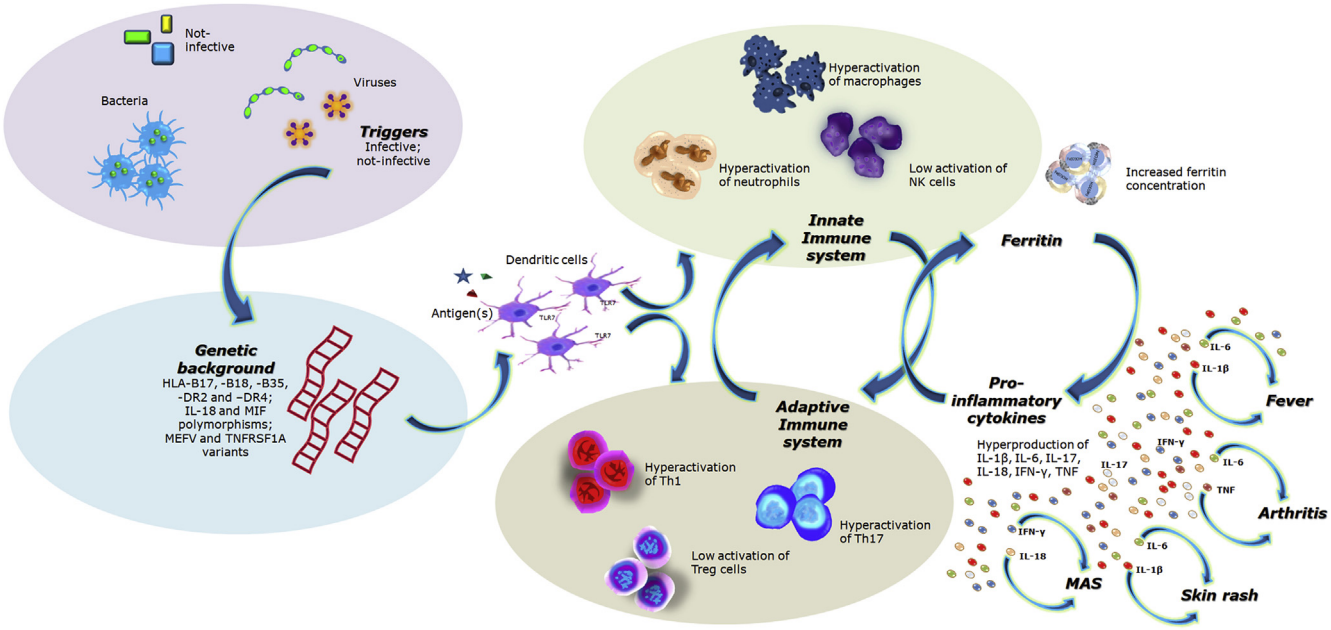

Fig. 1. AOSD may be categorised as a multigenic autoinflammatory disorder at the crossroads of autoinflammatory and autoimmune diseases, due to its complex pathogenesis, involving both innate and adaptive immune system. It is generally accepted that unknown factor(s), acting as second hit, may trigger a pathologic process in genetically susceptible patients finally leading to the activation of an aberrant inflammatory response, which is responsible of AOSD development.

course. Furthermore, 5% of patients, experiencing a more severe disease course, carried a pathogenic variant of TNFRSF1 [21].

4.2. Trigger factors

A possible infectious etiology of AOSD has been proposed due to the similarity between AOSD clinical presentations and infections [2]. Seasonality has also been reported in AOSD and this variation has been reported as an argument for an infectious trigger [5]. A large number of viruses, including rubella, measles, echovirus 7, coxsackievirus B4, cytomegalovirus and Epstein–Barr virus have been suggested to trigger AOSD pathogenesis activating the aberrant response of the immune system [22–24]. Some bacteria have considered to be involved, such as mycoplasma pneumonia, chlamydia pneumonia, yersinia enterocolitica, brucella abortus and borrelia burgdorferi [25–27]. More recently, both solid cancers and haematological malignancies have been proposed as possible triggers of AOSD, *via* the same pathogenic pathways reported for macrophage activation syndrome (MAS) development, a severe life-threating complication of AOSD [2,28]. However, it must be pointed out that, no unique pathogenic trigger has been clearly defined, suggesting the possibility that multiple environmental triggers may be a role in AOSD.

4.3. Innate immune system, a major pathogenic step

Activated cells of the innate immunity play a major role in AOSD pathogenesis. Many markers reflecting the activation of these lineages were studied in these patients [2,5,29–33]. Toll-like receptor (TLR) 7 ligation may promote the recruitment of neutrophils and thus the increasing pro-inflammatory response [33]. Interestingly, it has been shown that TLR7-MyD88 pathway was overexpressed in the dendritic cells of AOSD patients, transcripts and protein levels of TLR7-signalling molecules, including MyD88, TRAF6, IRAK4 and IFN-α, were up-regulated. Furthermore, expression levels of TLR7 in dendritic cells positively correlated with pro-inflammatory cytokines [33]. It has been reported that CXCL-8, formerly IL-8, a chemokine produced by macrophages and neutrophils, recruiting and activating neutrophils at the site of inflammation, was increased in sera of AOSD patients [30–32]. CD64 (FcγRI) is a high-affinity receptor for monomeric IgG1 and IgG3 expressed by mononuclear phagocytes leading to internalisation of immune complexes and cytokines release [34]. Interestingly, neutrophils of AOSD patients showed up-regulation of CD64, which correlated with active disease [35]. Macrophage-colony stimulating factor (M-CSF) was reported to be increased in the sera of AOSD patients [36]. This cytokine is involved in proliferation, differentiation and survival of macrophages. M-CSF also increases phagocytic, chemotactic as well as cytotoxic activities of these cells [39]. In addition, other markers of macrophages were reported in AOSD, including calprotectin, MIF and soluble CD163 (sCD163) [37,38,40]. Calprotectin is a calcium-binding cytosolic protein of the neutrophils and macrophages, secreted during the activation of these cells [41]. Calprotectin levels were higher in the sera of 25 AOSD patients compared with controls. In this study, calprotectin also showed a significant association with disease severity, C reactive protein (CRP) and ferritin [40]. MIF levels were significantly increased in the sera of 57 AOSD patients and correlated with clinical disease severity [37]. Furthermore, sCD163, a molecule exclusively expressed on cells of the monocytic lineage, was increased in active AOSD patients [38]. Higher sCD163 levels were observed in 34 active AOSD patients compared with inactive patients [38]. Recently, the possible role of Nod-like receptor 3 or cryopyrin (NLRP3) in AOSD pathogenesis has been proposed. Inflammasomes are cytosolic multiprotein complexes activated after the recognition of various stimuli, PAMPs (pathogen-associated molecular patterns) or DAMPs (damage-associated-molecular patterns) and responsible for pro-IL-1β and pro-IL-18 activation [42–45]. During AOSD, significantly higher mRNA levels of NLRP3 inflammasome signalling were observed in patients compared with healthy controls [44]. NLRP3 expression was also correlated with disease activity in AOSD patients [45]. Finally, it has been observed that the frequency and the cytotoxic functions of NK cells were impaired in AOSD patients [46,47]. NK cells frequencies and NK cell cytotoxicity were investigated in 45 AOSD patients and resulted lower in active AOSD patients than in inactive patients and controls [46]. NK cell cytotoxic functions, evaluated by co-incubation of effector cells with target cells at different effector-to-target ratios, were significantly lower in AOSD patients when compared with controls. These parameters of NK cells were newly evaluated in patients after treatment and both low NK cell proportion and cytotoxic dysfunction were improved [47]. In this context, it has been proposed that the pro-inflammatory cytokines produced during AOSD, mainly IL-18, may decrease the NK cell activity [48,49]. Remarkably, an impairment of NK cell cytotoxicity has been reported as part of MAS pathogenesis, a potential fatal complication of AOSD [50].

4.4. The involvement of the adaptive immune system

Different works have suggested the involvement of adaptive immune system in AOSD pathogenesis [1,2,5,51]. Increased concentrations of α-soluble receptor of IL-2 (CD25) may suggest T cell activation and proliferation in AOSD patients [18,52]. IL-4-producing T cells in sera, skin and synovial tissues in AOSD patients have been reported, reflecting a Th1 polarization of $CD4^+$ T cells [31]. Furthermore, IFN-γ and IL-4-producing Th cells were increased in active AOSD and correlated with disease severity [32]. During AOSD, the differentiation of naïve T cells into Th17 cells is supported by AOSD pro-inflammatory *milieu* and IL-18 synergises with IL-23 promoting IL-17 production by IL-23-primed $CD4^+$ T cells [49,53]. During AOSD, high frequencies of circulating Th17 cells were reported in active AOSD patients and correlated with severity score, serum ferritin levels and different pro-inflammatory cytokines [53,54]. As far as the role of circulating $CD4^+$ $CD25^{high}$ regulatory T cells (Treg) is concerned, recently, circulating Treg cells frequencies and levels of transforming growth factor-β (TGF-β) were evaluated in 52 AOSD patients [55]. Significantly lower levels of circulating $CD4^+CD25^{high}$ Treg cells and serum TGF-β were found in AOSD patients and were inversely correlated with disease severity. Interestingly, AOSD patients with monocyclic course showed significantly higher frequency of circulating Treg cells and TGF-β compared with chronic patterns, suggesting the association between Treg cells and better prognosis [55].

4.5. Aberrant production of pro-inflammatory cytokines

The aberrant immune system activation leads to the production of several pro-inflammatory cytokines, although it is not possible to observe a specific AOSD profile [56]. Despite the lack of association between polymorphisms of IL-1β genes and AOSD susceptibility [57], IL-1β were significantly higher in sera of patients compared with healthy subjects [58]. To date, it must be pointed out that peripheral blood mononuclear cells of healthy subjects may secrete large amounts of IL-1β and express genes of innate immunity, after incubation with sera from sIJA patients, the juvenile counterpart of AOSD [58]. IL-1β production results mainly by caspase-1 activity through the inflammasome activation and it is responsible for systemic inflammation and destruction of cartilage and bone [59–61]. In addition, the pivotal role of IL-1β derived from several reports reporting the clinical usefulness of anti-IL-1 treatments in AOSD [62–64]. Interleukin-18 is a pro-inflammatory cytokine released by inflammasome and its levels were higher in AOSD sera, synovial biopsies, lymph nodes when compared with healthy controls [65–67]. In addition, it has been suggested that hepatic macrophages may produce a high amount of IL-18, thus contributing to AOSD-related hepatitis [68]. IL-18 may also trigger Th1 response inducing the secretion of IFN-γ by cytotoxic $CD8^+$ and NK cells [69]. This feature has suggested that IL-18 may play a major role

in MAS initiation. In fact, high IL-18 levels may predict the development of MAS in AOSD, pointing out its possible pathogenic role in patients experiencing the complication [70]. During AOSD, it has been shown that IL-6 levels were increased both in salmon-colored skin rash and in sera of patients, correlating with disease activity [31,32,71,72]. IL-6 may also be responsible for some clinical features of AOSD, such as fever and joint manifestations, and for the increased production of acute-phase proteins by the liver [30,71,72]. It has been also reported the increased production of IL-17 in AOSD [53,54]. This cytokine is produced by Th17 cell in response to their stimulation with IL-23 amplifying inflammation, stimulating production of neutrophil-recruiting chemokines and enhancing granulopoiesis [53,54]. Tumor necrosis factor (TNF) levels were increased in the sera and tissues from AOSD patients, although not correlating with disease activity [30,51]. TNF type 2 soluble receptor levels correlated with CRP and have been proposed as an activity marker [51]. Finally, some chemokines may be involved in AOSD pro-inflammatory process [73–75]. Recently, it has been reported that CXCL9, CXCL10, CXCL11, CXCL13 were increased in AOSD and were correlated with markers of disease activity, suggesting pathogenic and clinical markers [74,75].

4.6. The "Hyperferritinemic Syndrome", the additional pathogenic role of ferritin

Recently, it has been proposed that AOSD, MAS, catastrophic antiphospholipid syndrome and septic shock, sharing similar clinical and laboratory features and characterised by very high level of serum ferritin, may be included under a common umbrella named "Hyperferritinemic Syndrome" [76]. During these conditions, the hyperferritinemia may not only be considered a consequence of inflammatory process, but it may be involved in a vicious loop exacerbating the inflammatory proprieties of ferritin [77]. In fact, ferritin synthesis is regulated, in addition to iron availability, by different cytokines, largely over-expressed in AOSD patients [77–80]. In experimental model, hepatic stellate cells treated with increasing dosages of ferritin showed the production of pro-inflammatory molecules, independently of the iron concentration [81]. Ferritin is an intracellular iron storage protein including 24 subunits: heavy (H) subunits and light (L) subunits, on the basis of their molecular weight [82,83]. The H-/L-subunits ratio may change, depending on specific tissue and physiologic status of the cell. In normal condition, ferritin enriched with L subunits (L-ferritin) has been found within liver and spleen; on the contrary, the ferritin enriched with H subunits (H-ferritin), may be mainly observed within heart and kidneys [82–84]. In this context, increased H-ferritin and number of macrophages expressing H-ferritin have been shown in AOSD inflammatory infiltrates of affected tissues, suggesting a pathogenic role [85–88]. H-ferritin may have a role in inflammatory disorders by its specific link to TIM-2, a member of the T cell immunoglobulin and mucin-domain (TIM) gene family, a family of cell surface molecules involved in the regulation of immune responses [89,90]. Although this receptor was considered a defined marker of Th2 cells, in an inflammatory *milieu*, different cells, including macrophages, may express it [91]. The H-ferritin/TIM-2 binding may suggest a possible link between H-ferritin and inflammatory pathogenic process [77,81,89].

5. Clinical features

AOSD typically manifests with a symptomatic triad characterised by spiking fever, arthritis and maculo-papular salmon-pink evanescent skin rash (Table 2) [1–5].

5.1. Fever

AOSD accounts up to 20% of fevers of unknown origin and almost all patients experience high spiking fever [92–94]. AOSD fever generally exceeds 39 °C and is transient, lasting under 4 h. It shows commonly a quotidian or twice quotidian pattern with the highest temperatures observed in the late afternoon or early evening [1–5]. The fever usually shows an abrupt onset resembling an infectious syndrome, and, sometime, the temperature may return to normal value even without antipyretic treatment. In AOSD, fever often precedes the onset of other manifestations [11].

Table 2
Clinical and laboratory features of AOSD.

Clinical and laboratory Features	Frequency
Fever	93–100%
Arthritis	86–100%
Skin rash	58–87%
Myalgias	13–84%
Splenomegaly	35–79%
Lymphadenopathy	28–74%
Sore throat	27–74%
Liver involvement	21–62%
Pleurisy	8–53%
Weight loss	5–44%
Pericarditis	6–38%
Abdominal pain	5–38%
Hyperferritinemia	69–93%
Increased CRP	96–100%
Increased ESR	87–99%
Neutrophilic leukocytosis	74–94%
Liver abnormalities	36–74%
Inflammatory anaemia	18–68%

AOSD, adult onset Still's disease; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; AST, aspartate amino transferase: ALT, alanine amino transferase.

5.2. Musculoskeletal disease

Joint involvement is a common sign; arthralgia and arthritis mainly involving wrists, knees and ankles are frequently reported in AOSD [5]. At the start of the disease, these symptoms may be mild and transient [11]. However, subsequently, patients may experience a chronic destructive symmetrical polyarthritis [94,95]. Pericapitate or carpometacarpal joint narrowing may also occur, after 6 months of disease, with a possible progression to carpal ankylosis, in subsequent years. In this context, it has been reported that the joint fluid aspiration may show an inflammatory fluid with neutrophil predominance [14]. Myalgias are also a common musculoskeletal AOSD feature, usually they are generalised and associated with exacerbations of fever [2,11].

5.3. Skin disease

A large percentage of AOSD patients may show an evanescent salmon-pink erythema which may be associated with an erythematous maculopapular eruption, predominantly found on the proximal limbs and trunk, appearing during the febrile attacks. Some patients, with usually more severe outcome, may experience this eruption for many weeks [96,97]. The histopathology of this rash shows a mixed inflammatory infiltrate, surrounding the perivascular areas and without epidermal changes, strongly differs from the persistent rash, in which the eruption shows 2 main findings: i. a pattern of dyskeratosis in the superficial layers of the epidermis without accompanying basilar dyskeratosis; ii. a sparse superficial dermal infiltrate often containing neutrophils but without vasculitis [98–100].

5.4. Splenomegaly and lymph nodes involvement

Both splenomegaly and mild-severe enlargement of cervical lymph nodes (LNs) are frequently observed in AOSD patients and lymphoma should be always considered in the differential diagnosis of this clinical

picture [101,102]. In the histological analyses of LNs samples, different patterns are observed [88,103]. The atypical paracortical hyperplasia pattern, characterised by paracortical hyperplasia with vascular proliferation and mixed cell infiltration, and the burnt out histiocytic pattern, characterised by exuberant paracortical hyperplasia with vascular proliferation and extensive sinus macrophages infiltration, are the most common histological features [103].

5.5. Liver involvement

A large percentage of patients shows liver abnormalities, hepatomegaly and increased value of hepatic enzymes [104,105]. The abnormal liver enzymes are usually related to mild cytolysis, but severe cytolysis may occur. Pseudo-angiocholitis, jaundice and acute hepatitis leading to hepatic failure have been rarely reported [106–108]. In the available literature, liver pathologic changes could not identify the specific cause of liver damage in AOSD, thus pathologic examination of liver biopsy samples is usually unnecessary for management of the patients [108–110]. Complete recovery of hepatic involvement may be observed in all patients. Liver dysfunction may be associated with non-steroidal anti-inflammatory drugs (NSAIDs) treatment [2,11,14].

5.6. Other signs and symptoms

Other non-specific symptoms may be observed in AOSD. Patients may show, early during the course of the disease or during disease flare, signs and symptoms of sore throat [2]. It has been suggested to be related to a viral infection (triggering the disease) or to crico-arytenoid joints inflammatory involvement of or to aseptic non-exudative pharyngitis [111]. AOSD patients may experience different cardio-pulmonary features including fibrosis, pleural and pericardial effusions [2,5,11,112–115]. AOSD may also affect kidney, interstitial nephritis, subacute glomerulitis, renal amyloidosis and collapsing glomerulopathy have been reported [116–119]. It is also possible to recognise neurological manifestations, such as cranial nerve paralyses and seizures [120–124]. However, it must be pointed out that these rare manifestations are mainly described in single-case reports, thus limiting the external validity of these findings.

6. Complications

AOSD patients may experience different complications affecting their clinical picture, management and prognosis (Table 3) [125].

6.1. MAS, the life-threating evolution of AOSD

MAS occurrence may complicate AOSD course and, considering common clinical and pathogenic features, it has been proposed that AOSD and MAS may be part of the same disease spectrum, in which AOSD should be considered the milder form [125]. MAS has been reported up to 15% of AOSD patients and it is considered to be the most severe complication of the disease with high mortality rate ranging from between 10 and 41% [126,127]. Infections, medications and flares of AOSD are considered the most common MAS triggering factors [128]. MAS clinical picture includes continuous high fever, hepatosplenomegaly and histopathological evidence, typically in the bone marrow, of haemophagocytosis by activated macrophages [128,129]. During AOSD, the change of fever pattern to a non-remitting pattern should alert physician in evaluating the possible evolution toward this complication [130,131]. Analysing predictive factors of MAS occurrence in a large cohort of AOSD patients, the evidence of lymphadenopathy and liver involvement were associated with occurrence of this complication [132]. In fact, mild-severe enlargement of LNs and liver abnormalities may be observed in AOSD patients due to not only to a widespread accumulation of inflammatory cells in these organs, but also to the occurrence of haemophagocytosis, which may be observed also in liver and peripheral lymphoid tissues [128]. The presence of abdominal pain, at the time of AOSD diagnosis, was also reported to be a predictor of MAS occurrence [132]. Furthermore, different works have reported serum ferritin levels higher in those AOSD patients complicated by MAS [126,127,133,134]. Finally, in clinical setting, MAS may be misdiagnosed due to the immunosuppressive treatments used to control disease flare [125].

Table 3
Main complications of AOSD.

Complications	Characteristic clinical picture
Macrophage activation syndrome	Non-remitting high fever, hepatosplenomegaly and histopathological of haemophagocytosis
Disseminated intravascular coagulopathy	Non-remitting high fever and purpuric or petechial rash
Thrombotic thrombocytopenic purpura	Microangiopathic haemolytic anaemia, thrombocytopenia and multiple organ failure
Diffuse alveolar haemorrhage	Haemoptysis, coughing and progressive dyspnoea
Pulmonary hypertension	Shortness of breath, chest pain, swelling and cyanosis
Aseptic meningitis	Vomiting, headache and firm neck pain

AOSD, adult onset Still's disease.

6.2. Other severe complications

Several other severe complications have been reported in AOSD, including disseminated intravascular coagulopathy (DIC), thrombotic thrombocytopenic purpura (TTP) and diffuse alveolar haemorrhage (DAH) [125].

AOSD patients may experience the occurrence of DIC, a life-threatening complication caused by an uninhibited activation of the coagulation system [135]. The clinical presentation of DIC during AOSD shows non-remitting fever and purpuric or petechial rash [125]. These patients may closely mimic sepsis, leading to treatment with only antimicrobials and delaying management with immunomodulators [136]. Serum soluble adhesion molecules and soluble thrombomodulin may indicate endothelial cell damage in AOSD complicated by DIC [137]. TTP-associated AOSD has been documented, it is characterised by a microangiopathic haemolytic anaemia, thrombocytopenia and multiple organ failure [125]. TTP belongs to the category of thrombotic microangiopathies, which may be distinguished in primary and secondary, in which an underlying factor such as autoimmune diseases, neoplasia and drug treatment, may be identified [138]. TTP is associated with a severe deficiency of the von Willebrand factor-cleaving protease, ADAMTS13, leading to an excessive platelet aggregation and microvascular occlusion [139–141]. DAH is characterised by the accumulation of red blood cells in the alveolar spaces and it has been also described in AOSD [142,143]. Haemoptysis, coughing and progressive dyspnoea are common symptoms, evolving to an acute respiratory failure [143]. Non-specific chest radiography, decreased haemoglobin and haemorrhagic bronchoalveolar lavage fluid are typical DAH features [144]. In AOSD patients, other complications are pulmonary hypertension, characterised by shortness of breath, chest pain, swelling and cyanosis [114,115], and aseptic meningitis, associated with vomiting, headache and firm neck pain [123,124].

7. Laboratory findings

During AOSD, laboratory findings usually show increased ESR and CRP, neutrophilic leukocytosis, inflammatory anaemia and thrombocytosis [145,146]. Liver abnormalities, mainly a mild to moderate increases, are also common. In addition, serum ferritin levels are higher compared with those observed in other autoimmune, inflammatory, infectious or neoplastic diseases, characterised by a decreased

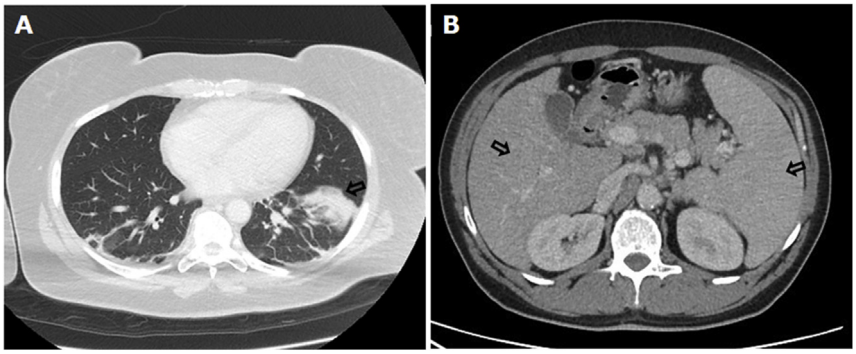

Fig. 2. AOSD is characterised by multi-visceral involvement, in this figure, AOSD pneumonia (A, arrow), splenomegaly and hepatomegaly (B, arrows) are shown by CT images.

glycosylated ferritin (< 20%) [147–150]. Although the poor specificity, a 5-fould increase of serum ferritin levels are strongly suggestive of AOSD and it is generally considered a useful marker to assess the disease activity and to predict MAS occurrence [151,152]. In addition to hyperferritinemia, common findings in MAS during AOSD include peripheral blood cytopenia, raised liver enzymes and hypertriglyceridemia [153–155]. Typically, in MAS-related AOSD, ESR may be relatively low due to the presence of hypofibrinogenemia. A trend in falling ESR with persistence of high CRP levels should be carefully evaluated in AOSD management in assessing MAS occurrence [154,155].

8. Clinical imaging

The clinical workup before the AOSD diagnosis included the exclusion of potential mimickers and chest X-rays and abdominal ultrasound scan are usually performed [126,132,133]. Computed tomography (CT) and/or PET/CT exams may be further added to the diagnostic workup of these patients showing multi-visceral involvement (Fig. 2), such as deep LNs, splenomegaly, hepatomegaly and serous effusions [156,157]. In the case of fever of unknown origin, 18FDG-PET–CT may support the diagnosis of AOSD [157,158]. In these patients, 18FDG-PET–CTs may show hypermetabolism in LNs and glands [159]. As far as joint evaluation is concerned, during the early phase of AOSD or flare, the conventional radiography was reported to be normal or displaying a soft-tissue swelling or mild periarticular demineralization of the involved joints [2]. Subsequently during chronic pattern of the disease, patients may develop a distinctive pattern of intercarpal and carpometacarpal joint space narrowing, mainly bilateral, leading to typical pericapitate ankylosis and/or joint erosions [14,160,161].

9. Diagnosis and classificative criteria

AOSD is a clinical diagnosis, and in the absence of a definitive diagnostic test, often necessitates the exclusion of potential mimickers, mainly infectious, neoplastic, autoimmune and autoinflammatory diseases [162,163]. As detailed in Fig. 3, the clinical workup should include the exclusion of infections by blood cultures and, in the MAS patients, bone marrow cultures, serology, PCR analyses, chest X-rays and abdominal echography. The possible differential diagnosis should be evaluated with malignancies by chest X-rays, abdominal echography and blood samples. In the case of further suspicion of malignancies, CT and/or PET/CT should be added to the diagnostic work up. About patients with possible hematologic cancers, bone marrow examination and LN biopsy should be considered. Autoimmune diseases may be excluded by blood tests, antinuclear antibodies, anticitrullinated peptids autoantibodies, rheumatoid factor, ANCA and for the exclusion of systemic vasculitides tissue biopsy and arteriography. Finally, the possible differential diagnosis with autoinflammatory diseases by the execution of gene analyses should be performed [132,133].

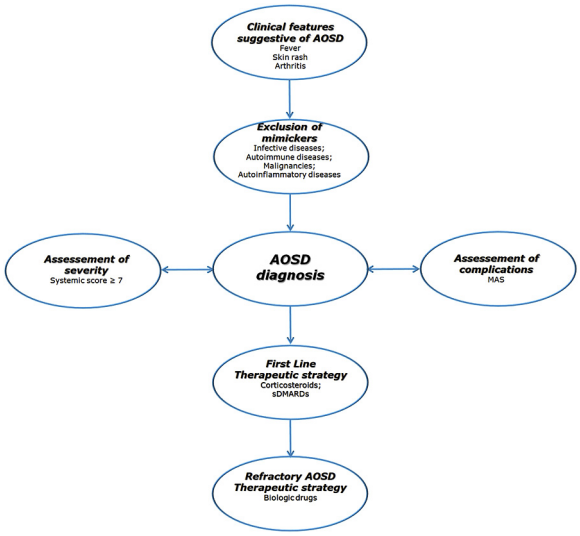

Fig. 3. AOSD is a clinical diagnosis, and in the absence of a definitive diagnostic test, often necessitates the exclusion of potential mimickers, mainly infectious, neoplastic, autoimmune and autoinflammatory disease. At the time of diagnosis, the assessment of severity by using systemic score and complications may identify patients at higher risk of poor prognosis. The lack of clinical response with the first-line corticosteroids and second-line sDMARDs may identify refractory AOSD patients in which biologic drugs may be considered.

Different diagnostic criteria have been proposed for AOSD diagnosis (Table 4), based on the combination of clinical and laboratory findings. The Yamaguchi's criteria are the most sensitive (93.5%), followed by Cush's (80.6%) and Calabro's (80.6%) [164–167]. Subsequently, Fautrel's Criteria have been proposed with the evaluation of glycosylated ferritin fraction providing 80.6% sensitivity and 98.5% specificity [168]. However, some limitations have been pointed out in all these criteria. In fact, the sensitivity of the Yamaguchi's criteria is reduced by the large number of clinical conditions that should be excluded whereas Fautrel's set of diagnostic criteria requires measurement of glycosylated-ferritin, which is not always available in many health care facilities [162].

10. Course and prognosis

According to the disease course as described by Cush JJ et al. [166], it is possible to categorise AOSD patients into 3 different clinical patterns (monocyclic, polycyclic, and chronic) as shown in Fig. 4. A monocyclic course is defined as a single episode for more than 2 months but less than 1 year followed by sustained remission through the entire follow-up period. A polycyclic course is characterised by recurrent systemic flares with remissions between flares. A chronic course is

Table 4
Classificative criteria of AOSD.

Classificative criteria		
Cush JJ [166]	Yamaguchi M [167]	Fautrel B [168]
Probable AOSD: 10 points during 12 weeks observation	5 criteria, at least 2 major	4 major criteria or 3 major and 2 minor
Definite AOSD: 10 points during 6 months of observation	Exclusion criteria: infections, malignancies, rheumatic diseases	
2 points each:	Major criteria:	Major criteria:
Quotidian fever > 39 °C	Fever > 39 °C, intermittent, 1 week or longer	Spiking Fever > 39 °C
Transient rash	Arthralgia > 2 weeks	Arthralgia
WBC > 12000/mL and ESR > 40 mm/h	Typical rash	Transient rash
Negative ANA/RF	WBC > 10000/mL (> 80% Neutrophil granulocytes)	Neutrophil granulocytes ≥ 80%
Carpal ankylosis		Glycosylated ferritin < 20%
1 point each:	Minor criteria:	Minor criteria:
Onset age > 35 years	Sore throat	Maculopapular rash
Arthritis	Lymphadenopathy and/or splenomegaly	WBC > 10000/mL
Sore throat	Liver abnormalities	
RES involvement or liver abnormalities	Negative ANA/RF	
Serositis		
Cervical or tarsal ankylosis		

AOSD, adult onset Still's disease; ESR, erythrocyte sedimentation rate; RES, reticuloendothelial system; WBC, white blood count; ANA, antinuclear antibody; RF, rheumatoid factor.

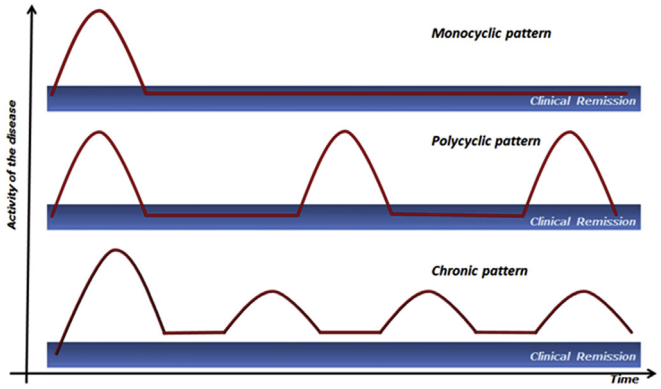

Fig. 4. AOSD patients may be stratified according to different disease courses: i. the monocyclic course is defined as a single episode followed by sustained remission through the entire follow-up period; ii. the polycyclic course is characterised by recurrent systemic flares with remissions between flares; the chronic course is defined as at least one episode of persistent symptoms.

defined as at least one episode of persistent symptoms lasting longer than 1 year [166]. At present, only few studies tried to focus on the prognostic factors in these patients [52,95,101,102,148]. Although mostly derived from a single centre and based on a limited number of patients, it has been suggested that polyarthritis and joint erosions at disease onset may predict a chronic progression and poor functional prognosis [2,5]. Furthermore, high fever at disease onset may correlate with monocyclic AOSD [95]. In this context, it has been also proposed the assessment of AOSD patient by using the systemic score [14]. This score assigns 1 point to each of 12 manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis > 15000/mm^3, sore throat, myalgia, and abdominal pain (maximum score: 12 points). The prognostic value of this score has been recently investigated [133]. In that study assessing a large cohort of AOSD patients, high systemic score was predictive of a more severe outcome. Specifically, a cut-off of 7.0 of systemic score, at the time of diagnosis, was correlated with a high risk of AOSD-related death, suggesting a more severe subset of patients [133].

11. Treatments

At present, the treatment of AOSD patients remains empirical. Available evidence on treatment is mainly derived from small retrospective case series and not from prospective, double-blind, randomised trials (Table 5) [169,170]. The optimal management of AOSD has been recently discussed, suggesting that some refractory patients may benefit from biologic drugs [171,172].

11.1. First line therapies

In different studies, NSAIDs failed to control the symptoms of AOSD and a large percentage of patients experienced adverse events [173–175]. Therefore, NSAIDs risk/benefit *ratio* does not seem to be favourable in AOSD. However, the temporary use of NSAIDs may be helpful during diagnostic workup [1–5]. In this context, the use of indomethacin (150–250 mg/day) has been proposed [14,172]. Corticosteroid therapy is considered the first-line of treatment for AOSD, inducing a clinical response in about 60% of patients [2,171,176]. Corticosteroids should be started at a dosage of 0.5–1 mg/kg/day, but intravenous high-dosages corticosteroids may be considered, if severe visceral involvement and/or MAS occur [176,177]. High dosages seem to be more efficient in controlling the disease. Patients treated with high prednisone dosages (≥ 40 mg, 0.8 mg/kg, daily) showed quicker resolution of AOSD signs and symptoms with subsequent less relapses compared with those received a lower dosage [104,176]. The response to corticosteroids is rapidly reported within few days [171,176]. Usually, the tapering of corticosteroids should start after 4–6 weeks of therapy, when the symptoms and the inflammatory laboratory parameters are normalised. However, steroid dependency may occur until up to 45% of AOSD patients and should be carefully evaluated in the management of these patients [2,176]. Interestingly, it has been observed that splenomegaly, low glycosylated ferritin levels, elevated ESR and young age at onset of AOSD may predict steroid dependency, suggesting the early addition of a steroid-sparing agent [173].

11.2. Second line therapies

Methotrexate (MTX) is the most frequently administered sDMARD in AOSD, mainly for its steroid-sparing effect [178,179]. It has been reported that MTX, at dosage of 7.5–17.5 mg/week, reduced daily corticosteroid intake in 26 steroid-dependent AOSD patients [180]. In this study, after adding MTX, 69% attained a complete remission and 39% discontinued corticosteroids [180]. The liver involvement, which often complicates AOSD patients, should not contraindicate MTX therapy, although a continuous monitoring of transaminases would be needed [179]. If MTX is not able to control the disease, other sDMARDs may be considered. However, few data have suggested a beneficial use of hydroxychloroquine, intravenous immunoglobulin and/or cyclosporine A in AOSD patients [181–183].

Table 5
Main studies assessing the efficacy of biologic drugs in AOSD.

Author	Year	Country	Study design	Patients	Biologic drug used	Clinical Response
IL-1 blockade						
Lequerre et al. [191]	2008	France	Observational study	15	Anakinra	73.3%
Laskari et al. [197]	2011	Greece	Observational study	25	Anakinra	96%
Nordstrom et al. [196]	2012	Finland, Norway, Sweden	Randomised study	12	Anakinra	50%
Iliou et al. [190]	2012	Greece	Observational study	10	Anakinra	100%
Giampietro et al. [189]	2013	France	Observational study	28	Anakinra	85.7%
Gerfaud-Valentin et al. [95]	2014	France	Observational study	6	Anakinra	83.3%
Cavalli et al. [187]	2015	Italy	Observational study	16	Anakinra	100%
RossiSemeraro et al. [192]	2015	France	Observational study	35	Anakinra	88.6%
Ortiz-Sanjuán F et al. [194]	2015	Spain	Observational Study	41	Anakinra	46.3%
Dall'Ara et al. [188]	2016	Italy	Observational study	11	Anakinra	100%
Vitale et al. [193]	2016	Italy	Observational study	78	Anakinra	91.1%
Sfriso et al. [10]	2016	Italy	Observational study	35	Anakinra	94.3%
Colafrancesco et al. [198]	2017	Italy	Observational study	140	Anakinra	81.4%
TNF blockade						
Husni et al. [210]	2002	USA	Observational study	12	TNFi	58.3%
Fautrel et al. [214]	2005	France	Observational study	20	TNFi	85%
Sfriso et al. [10]	2016	Italy	Observational study	41	TNFi	46.3%
IL-6 blockade						
Puèchal et al. [205]	2011	France	Observational study	14	Tocilizumab	78.6%
Suematsu et al. [207]	2012	Japan	Observational study	12	Tocilizumab	91.66%
Elkayam et al. [209]	2013	Israel	Observational study	15	Tocilizumab	100%
Bannai et al. [202]	2014	Japan	Observational study	7	Tocilizumab	100%
Cipriani et al. [208]	2014	Italy	Observational study	11	Tocilizumab	100%
Ortiz-Sanjuán F et al. [194]	2014	Spain	Observational study	34	Tocilizumab	64.7%
Song et al. [204]	2016	Korea	Observational study	14	Tocilizumab	85.7%
Li et al. [203]	2017	China	Observational study	8	Tocilizumab	100%
IL-18 blockade						
Gabay et al. [215]	2018	France, Germany, Switzerland	Randomised study	23	Tadekinig alfa	47.8%

11.3. Refractory AOSD

The lack of clinical response with the first-line corticosteroids and second-line sDMARDs may identify refractory AOSD patients [184], although a validated definition is still missing. In these patients, biologic agents may be considered and, recently, a meta-analysis of observational studies has shown that such drugs may induce a clinical response and a complete remission in a large percentage of AOSD patients [185]. In this context, it has been proposed that AOSD may be categorised into 2 different subsets; patients presenting with systemic features and patients presenting with a prominent joint involvement [186]. High fever, increased levels of CRP and liver enzymes are typical features of "systemic AOSD" and may allude a clinical response to IL-1 or IL-6 antagonists. "Rheumatic AOSD", characterised by a predominant joint involvement would better respond to TNF-inhibitors or IL-6 antagonist [186]. Furthermore, biologic drugs have shown different additional benefits in the management of refractory AOSD patients, including a reduction of the number of flares and a significant steroid-sparing effect [184–187].

11.4. IL-1 antagonists

Three IL-1 antagonists are available, a recombinant antagonist of the IL-1 receptor (IL-1Ra, anakinra), a human monoclonal antibody directed against IL-1β (canakinumab), and a soluble IL-1 trap fusion protein (rilonacept). Several works showed the efficacy of anakinra, used at 100 mg/day *via* subcutaneous injection, in refractory AOSD patients [187–193]. In these studies, anakinra treated patients experienced the disappearance of symptoms within a few days and the normalisation of the inflammatory markers within 2–4 weeks. Furthermore, corticosteroids could be tapered and discontinued in these patients [194–197]. Recently, these findings were confirmed in a large cohort of AOSD patients, in which good clinical response and safety profile were observed, after 3 months of treatment with anakinra [198]. In these studies, a self-limited injection-site erythema was the most common adverse event reported during anakinra treatment [194–198]. In some patients, if the disease is well controlled, a progressive dose reduction could be proposed spacing subcutaneous injections of anakinra [176]. If insufficient response to anakinra is observed, rilonacept and canakinumab may be considered; they have a longer half-lives and may be administered every week or every 8 weeks, respectively [199]. Both drugs have been reported to be effective in case series assessing AOSD patients [200,201]. In this context, the results of ongoing clinical trial (ClinialTrial.gov, NCT02204293), assessing the efficacy of canakinumab are awaited to fully clarify this topic. This trial is aimed at investigating the efficacy of canakinumab in AOSD patients with active joint involvement. In this study, AOSD patients would be randomised to receive canakinumab, in a dose of 4 mg/kg body weight up to a maximum of 300 mg every 4 weeks, or placebo. At week 24, patients achieving the primary endpoint of significant reduction of disease activity could be included in an open-label phase of the study and treated with canakinumab every 4 weeks for further 2 years.

11.5. IL-6 antagonist

Tocilizumab is a humanised monoclonal antibody directed against the IL-6 receptor that was used to treat refractory AOSD patients, at a dosage of 5–8 mg/kg every 2–4 weeks [202–205]. Usually, tocilizumab-treated patients experienced a good clinical response. Tocilizumab should be considered as an alternative to IL-1 antagonists, particularly when joint involvement is associated with systemic symptoms [171,172]. In fact, the mean disease activity score (DAS)28, used to evaluate the activity of the disease with chronic articular AOSD, decreased during the follow-up of the observational studies [206–208]. Furthermore, the corticosteroid-sparing effect and the good safety profile of this drug have been reported [205–209]. Interestingly, it has been also described that clinical effect of tocilizumab could persist for 6 months after its discontinuation [208].

11.6. TNF-inhibitors

TNF-inhibitors, infliximab, etanercept, and adalimumab, have been

employed to treat refractory AOSD [210–214]. In 20 chronic AOSD patients treated with infliximab and etanercept [214], 5 patients experienced complete remissions (1 with etanercept and 4 with infliximab), 11 achieved partial remissions and TNF-inhibitors failed to control the disease in the remaining 4 patients. At last visit, after a mean follow-up of 13 months, 11 patients had discontinued TNF-inhibitor due to insufficient efficacy and 4 due to side effects. Furthermore, switching from one drug to another failed to show an additional clinical benefit [214]. At present, TNF-inhibitors could be of interest mainly in the management of chronic poly-articular disease [186].

11.7. The possible therapeutic role of IL-18 blockade

During AOSD, IL-18 could be considered to be a pivotal pathogenic mediator and different studies have documented high levels of IL-18 during active AOSD [65–70]. On these bases, a clinical trial (ClinicalTrial.gov, NCT02398435) aimed to assess safety and efficacy of tadekinig alpha, an IL-18-binding protein, has been designed [215]. In this study, AOSD patients were randomised to receive either 80 mg or 160 mg of tadekinig alpha for 12 weeks. After 3 weeks, the patients defined as non-responders (CRP levels did not decrease by ≥ 50% from baseline values or absence of temperature normalisation) could be up-dosed to 160 mg for an additional 12 weeks. The primary endpoint was safety and secondary endpoint included the efficacy. Twenty AOSD patients were enrolled and assessed during the study. A good safety profile was observed at the end of the study. Furthermore, clinical response, defined as ≥70% decrease of serum CRP and ferritin levels, was observed in a percentage of patients, suggesting tadekinig alpha as a possible new therapeutic option for AOSD [215].

11.8. Looking forward, new therapeutic options from experimental models

Recently, multiple lines of evidence have suggested the role of janus kinases (JAK) inhibitors in the management of inflammatory diseases [216–218]. Interestingly, the efficacy of ruxolitinib, a JAK inhibitor with a selectivity for subtypes JAK1 and JAK2, has been reported in animal models of MAS, the most common complication of AOSD [219–221]. In these experimental models, ruxolitinib induced an improvement of survival rate associated with an improvement of peripheral blood cytopenia, reduction of pro-inflammatory molecules and a decrease of infiltrating pro-inflammatory macrophages [219–221]. Considering that MAS is the most common complication of AOSD, it could be possible to speculate the possible future clinical usefulness of these new therapeutic strategies targeting JAK pathways.

12. Conclusions

AOSD is a rare systemic inflammatory disease challenges for diagnosing and treating, characterised by spiking fevers, arthritis and evanescent rash, associated with high levels of ferritinemia. Although its pathogenesis is largely unknown, the pivotal role of the pro-inflammatory cytokines, IL-1β, IL-18, IL-6, IL-17 and TNF, and of ferritin in perpetuating the inflammatory vicious loop have been reported. At present, AOSD therapeutic strategy is aimed at targeting pro-inflammatory signs and symptoms, preventing organ damage and life-threating complications, minimising the adverse effects of treatment. However, as the current information on treatment efficacy was mainly obtained from small retrospective case series and not from prospective double blinded randomised trials, the treatment of AOSD remains empirical and further randomised controlled trials are surely needed to optimise the therapeutic strategy of these patients. Finally, given that multiple recent lines of evidence have suggested new insights in AOSD pathogenesis, new therapeutic targets have been highlighted, thus possible improving AOSD management, in the next future.

Conflicts of interest

The authors have declared that no competing interests exist.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jaut.2018.07.018.

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