Pathogenesis, disease course, and prognosis of adult-onset Still’s disease: an update and review

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Abstract

Objective: Adult-onset Still’s disease (AOSD) is a rare but clinically well-known polygenic systemic autoinflammatory disease. In this review, we aim to present frontiers in the pathogenesis, clinical features, diagnosis, biomarkers, disease course, prognosis, and treatment in AOSD.

Data sources: We retrieved information from the PubMed database up to July 2019, using various search terms and relevant words, including AOSD and Still’s disease.

Study selection: We included data from peer-reviewed journals. Both basic and clinical studies were selected.

Results: Pathogenesis of AOSD involves genetic background, infectious triggers, and immunopathogenesis, mainly the activation of macrophages and neutrophils followed by a cytokine storm. Diagnosis and prognosis evaluation of AOSD is still challenging; therefore, there is an urgent need to identify better biomarkers. Biologic agents, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α antagonists in the treatment of AOSD, have good prospect.

Conclusion: This review highlights the advances in pathogenesis, potential biomarkers, disease course, and treatment in AOSD.

Keywords: Adult-onset Still’s disease; Biomarkers; Disease course; Pathogenesis; Treatment

Introduction

Adult-onset Still’s disease (AOSD) is a rare but clinically well-known multi-systemic autoinflammatory disorder. It is typically characterized by a high spiking fever, an evanescent skin rash, polyarthralgia, sore throat, leukocytosis, and hyperferritinemia.[1-3] AOSD was first defined by Bywaters[4] in 1971 after description of fourteen adult patients whose clinical manifestations closely resembled the systemic juvenile idiopathic arthritis (previously named Still’s disease). The incidence of AOSD has been reported at 0.16 (per 100,000 persons) in France,[5] 0.22 in Japan,[6] and 0.4 in northern Norway.[7] AOSD usually affects young adults, and the median age at diagnosis is 36 years old.[8] Females seem to be more affected in some studies, accounting for approximately 70% of the patients with AOSD,[8] while in a recent study AOSD is considered to have a similar incidence in men and women. Asian patients are reported to have a significantly higher in-hospital mortality rate.[9]

Progresses have been achieved in the complex pathogenesis of AOSD in the last few decades. In this review, we focus on the frontiers in the pathogenesis arising from recent studies, and aim to update information about disease course and prognosis in AOSD.

Pathogenesis

The etiology of AOSD is still unclear, while there is evidence that various mechanisms contribute to the pathogenesis of AOSD, mainly including genetic susceptibility, infectious triggers, activation of inflammation, and deficient resolution of inflammation [Figure 1].

Genetic background

AOSD is categorized as a multigenic disorder.[10] Familial trend has not been reported for AOSD yet, but some studies have found that genetic susceptibility and polymorphisms were associated with AOSD. Associations of AOSD patients and human leucocyte antigen (HLA) antigens, including HLA-Bw35 (first described), -B17, -B18, -B35, -DR2, -DR4, -DR5, -DQ1, -DRw6, -DRB1, and -DQB1 have been described in different ethnic groups.[11-15] Polymorphisms in genes of interleukin-18
(IL-18), serum amyloid A1, and macrophage inhibitory factor (MIF) may affect the susceptibility of patients with AOSD.\textsuperscript{[16-19]} But there are no significant associations of FcγR or Mediterranean fever gene polymorphisms with AOSD.\textsuperscript{[20-22]}

**Infectious triggers**

It has long been suspected that infections, especially viral infections, are potential triggers of AOSD due to the similar symptoms between them. AOSD patients often present similar manifestations with viral infections, including abrupt high fever, sore throat, and rash before the onset or relapse of disease.\textsuperscript{[10,23]} Over the past decades, many cases have reported infection with pathogens in AOSD patients, including rubella virus, measles morbillivirus, mumps virus, Epstein-Barr virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, cytomegalovirus (CMV), parvovirus B19, adenovirus, echovirus, human herpesvirus 6, influenza virus, para-influenza viruses, coxsackievirus, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Borrelia burgdorferi*.\textsuperscript{[124-20]} However, data based on a cohort study is lacking. Recently, a study consisting of 100 AOSD patients has investigated the presence of antibodies against virus, virus DNA load, and nucleic acid sensors (IFI16 and AIM2).\textsuperscript{[130]} It shows that CMV infection is strongly related to the initiation or amplification of inflammatory responses in AOSD. It is suggested that viral infection may trigger the initiation or relapse of AOSD.\textsuperscript{[30]}

**Activation of inflammation**

The activation and amplification of inflammation, characterized by a cytokine storm, is the hallmark of AOSD.\textsuperscript{[13,10,31]} It has been recognized that the initiation and facilitation of inflammation are mainly driven by innate immune cells while adaptive immune cells also participate in it. Among them, macrophage and neutrophil activation play a major role in the pathogenesis of AOSD.\textsuperscript{[10]} Natural killer (NK) cells and T cells are also reported to be involved in the amplified inflammatory response.

**Macrophage Activation**

Many biomarkers reflecting macrophage activation are increased in patients with AOSD and correlated with disease activity, including macrophage-colony stimulating factor and interferon-γ (IFN-γ).\textsuperscript{[32,33]} Their activation is triggered by danger signals such as pathogen-associated molecular patterns or damage-associated molecular patterns (DAMPs).\textsuperscript{[31,34]} The role of several DAMPs in AOSD pathogenesis have been well illustrated, including high mobility group box 1, advanced glycation end products, S100 proteins, soluble CD163, MIF, and neutrophil extracellular traps (NETs).\textsuperscript{[34]} These danger signals initiate...
macrophages activation via specific Toll-like receptors, and then facilitate activation of NACH, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasomes. Upon activation, NLRP3 inflammasomes upregulate caspase-1 activity, leading to the proteolytic cleavage of pro-IL-1β and IL-18 to its bioactive and mature forms from their ex- forms.31,35,36 Then IL-1β and IL-18 further promote immune cells to produce a large amount of pro-inflammatory cytokines, including IL-6, IL-8, IL-17, and tumor necrosis factor (TNF)-α, as well as IL-1β and IL-18 themselves.31,35-37 These cytokines activate downstream pathways and thus contribute to an amplified inflammatory response, which is called a cytokine storm. Macrophage activation leads to increased release of ferritin. It is well recognized that AOSD is characterized by high levels of ferritin in serum, called “hyperferritinemic syndrome.” Ferritin is produced by macrophages, liver cells, and Kupfer cells,38 and is now discovered to play a role as a pro-inflammatory cytokine.39 It can activate an iron-independent signaling cascade, resulting in phosphatidylinositol 3-kinase - nuclear factor kappa-B (PI3K-NFκB) activation and dramatically enhanced expression of pro-inflammatory mediators like IL-1β, inducible nitric oxide synthase, regulated upon activation normal T cell expressed and secreted factor, inhibitor of NF-κB, and intra-cellular adhesion molecule 1 in hepatic stellate cells.39 Furthermore, ferritin synthesis is also regulated by the bursting pro-inflammatory cytokine in AOSD, such as IL-1β.40,41 Ferritin sub-units are divided into heavy (H) sub-units and light (L) sub-units, and ferritin enriched with L-sub-units (L-ferritin) is found in liver and spleen in the normal condition.42,43 In some AOSD patients with macrophage activation syndrome (MAS), increased levels of H-ferritin and its imbalance with L-ferritin are found in bone marrow and liver, and H-ferritin levels are correlated with disease severity.44 Similarly, enhanced tissue H-ferritin expression and a strong infiltrate of CD68+/H-ferritin+ cells are found in the lymph nodes and skin of AOSD patients. Moreover, a positive correlation between H-ferritin levels as well as CD68+/H-ferritin+ cells number and disease severity is reported.45,46 Therefore, it is hypothesized that ferritin could be involved in amplifying inflammation of AOSD as an oxygen radical donor or by an unknown mechanism that is yet to be determined.47 More studies need to be carried out.

**Neutrophil Activation**

Neutrophil activation is also a hallmark of AOSD. CD64 (FcyR1), a neutrophil activation marker, is upregulated in active AOSD.48 CXC-chemokine ligand 8 (ex-IL-8), a primary chemokine known to be involved in neutrophils recruitment and activation, is also elevated in AOSD patients.49 Recently, evidence of increased NET formation in AOSD has been first proved.37,50 NETs are weblike structures released by neutrophils in both infectious and non-infectious inflammatory conditions. NETs are composed of chromatin filaments coated with histones, DNA, and granular proteases.51,52 The spontaneous enhancement of NETs in AOSD is dependent on the high level of reactive oxygen species.171 Moreover, the function of NETs in AOSD is to activate NLRP3 and macrophages in AOSD.172 Thus, a novel link between neutrophils and macrophages is established by NET formation in AOSD.

**NK Cells Deficiency**

Lower percentages, decreased absolute numbers and defective cytotoxic function of NK cells have been reported in AOSD, which may contribute to persistent macrophage and lymphocyte activation.53,54 In acute AOSD, NK cells also have a stronger ability to secret IFN-γ; moreover, their expression of IL-12 and IL-15 receptors are also upregulated, which promotes their IFN-γ production.54 NK T cell deficiency is also present in active AOSD and is found to be correlated with NK cell dysfunction.55

**T Cells Imbalance**

Significant higher IFN-γ-producing Th1 cells and Th1/Th2 cells ratio have been found in peripheral blood in AOSD patients. Notably, a positive correlation between Th1 cell level as well as Th1/Th2 ratio and serum IL-18 levels is found.56 Increased concentrations of α-soluble receptor of IL-2 (CD25) in AOSD may suggest the pathogenetic role of T cell activation in AOSD.57 Th17 cells are also elevated in active untreated AOSD patients, and correlated with the disease activity score and pro-inflammatory cytokine levels.58 Th17 cells may contribute to the pathogenesis of AOSD by producing the pro-inflammatory cytokine IL-17 to stimulate neutrophil recruitment. Decreased proportions of CD4+, CD4CCR7+, CD4+CD62L-, and CD8+CD62L- cells and increased proportions of CD8+ naïve T cells are found in AOSD patients. Moreover, proportions of CD4+ effector memory T cells, CD8+ naïve T cells, and CD8+ effector memory T cells are significantly associated with the systemic score.59

**Deficient resolution of inflammation**

Deficiency in resolution of inflammation has been hypothesized to play a role in the pathogenesis of AOSD.3,31 However, the hypothesis lacks sufficient supporting data. A study published in 2010 discovered a diminished level of circulating CD4+CD25high Foxp3 Treg cells and the transforming growth factor-β in AOSD patients, and the level was inversely correlated with disease activity of AOSD and on the rise after clinical remission.60 No other data of deficiency in anti-inflammatory cytokines in patients with AOSD has ever been reported. Conversely and surprisingly, levels of immune-suppressive cytokines are mostly found to be increased in AOSD and may act as a potential biomarker. IL-10, a classical anti-inflammatory cytokine, shows elevated serum levels in AOSD, and the levels of IL-10 are associated with disease activity.61 Similarly, a significantly higher level of IL-37 and its positive correlation with disease activity are detected in serum in AOSD patients.62 IL-37 can attenuate the production of IL-1β, IL-18, IL-6, and TNF-α in peripheral blood mononuclear cells from patients with AOSD.62 According to the above results, it is suggested that there exists a feedback loop from pro-inflammatory cytokines to the upregulation of anti-inflammatory cytokines.62

**Clinical Features and Diagnosis**

Four symptoms of AOSD are cardinal: fever, arthritis or arthralgia, skin rash, and leukocytes >10,000/mm3 with
neutrophils >80%. Other manifestations are sore throat, odynophagia, myalgia, myositis, lymphadenopathy, splenomegaly, pericarditis, myocarditis, pleuritis, lung disease, and hepatitis. Life-threatening complications may also be present, including pulmonary arterial hypertension, fulminant hepatitis, MAS, disseminated intravascular coagulopathy, myocarditis, acute respiratory syndrome, and thrombotic microangiopathy. Main laboratory findings include elevated erythrocyte sedimentation rate and C-reactive protein levels. Mild to moderate liver abnormalities are common. Anti-nuclear antibodies and rheumatoid factor are mostly negative.

The current recognized diagnosis of AOSD is based on clinical manifestations and still lacks specific diagnostic tests. Exclusion of mimickers is extremely necessary, mainly including infectious, malignant, autoimmune, and some other autoinflammatory diseases. Several diagnostic criteria have been proposed, and two of them are validated in clinical practice and research: the Yamaguchi and Fautrel criteria. Yamaguchi criteria is most widely used. A combination of Yamaguchi criteria with glycosylated ferritin (GF) ≤20% can reach a diagnostic sensitivity of 98.2% and specificity of 98.6%.

Biomarkers for AOSD

Serum ferritin

As discussed, serum ferritin is a biomarker of AOSD, while its specificity is poor. Four systemic diseases can be included in the “hyperferritinemic syndrome.” AOSD, MAS, catastrophic anti-phospholipid syndrome, and septic shock. High serum ferritin levels are closely correlated with disease activity and associated with systemic pattern, recurrent flares, occurrence of MAS, and poor prognoses. Aside from total ferritin levels, the GF level has also been investigated. The normal GF level is >50% total ferritin level, but it decreases to 20% to 50% in inflammatory condition owing to the ferritin production. In AOSD, GF level can even drop to under 20%. A combination of ferritin >5 × upper limit of normal and GF ≤20% can reach a diagnostic specificity of 92.9%.

Cytokine levels

Serum pro-inflammatory cytokine levels like IL-1B, IL-18, IL-6, TNF-α, and IFN-γ are elevated in AOSD and are associated with disease activity. Among them, the role of IL-18 as a biomarker of AOSD is mostly studied. Evidences have suggested that IL-18 is a potential biomarker to diagnose AOSD and assess disease activity. High levels of IL-18 are associated with RHL, hepatitis, steroid dependence, and systemic pattern. Moreover, increased IL-1B is also associated with systemic pattern, whereas high levels of IL-6 are associated with arthritic pattern. Serum anti-inflammatory cytokines, such as IL-10 and IL-37, are also elevated in AOSD and can be used as biomarkers to assess disease activity of AOSD.

Other potential biomarkers

Other biomarkers, including DAMPs, microRNAs, and chemokines, have been proposed in different studies [Table 1]. These biomarkers may shed new insights into pathogenesis and treatment of AOSD.

Disease Course and Prognosis

Several AOSD disease courses have been described. A phenotypic trichotomy illustrates three different clinical courses of AOSD: (i) monocyclic/self-limited course, defined as a single episode (2 months to 1 year) followed by sustained remission throughout the whole follow-up period; (ii) polycyclic/intermittent course, with recurrent systemic flares between remissions; (iii) chronic course, at least one episode of persistent symptoms lasting longer than 1 year. The chronic course is the most frequent one. We notice that this definition of AOSD disease course is strongly based on the follow-up time, and it does not clearly illustrate the condition of treatment during remission. Yet another description takes the condition of drug withdrawal into account: the monocyclic course is either self-limited or includes drug-free remission, in which treatments after remission can be progressively tapered and finally stopped without relapse after a few months. The recurrent or polycyclic course is characterized by AOSD relapses after a few months or years under immunomodulatory treatment or after its discontinuation.

Recent data have suggested that these three patterns may be grouped into only two: a systemic form and a chronic articular form. This phenotypic dichotomy may be more useful in applying different treatments for patients with AOSD.

As introduced above, severe life-threatening complications or even death can occur in AOSD, and some patients have poor response to corticosteroid treatment. However, few studies have focused on the prognostic factors of these situations in AOSD. In 2009, a study analyzed clinical features and prognosis of 61 cases of AOSD in China. It defined the cyclic course as a favorable outcome of AOSD and the chronic course or death as an unfavorable outcome. It has shown that pleuritis, interstitial pneumonia, elevated ferritin levels, and failure of fever to subside after 3 days of prednisolone at 1 mg kg⁻¹ d⁻¹ are unfavorable prognostic factors for patients with AOSD.

So far there is no exact report of the long-term survival rate for AOSD based on large samples. In a long-term follow-up study of Still’s disease (eight AOSD patients followed up for 14 ± 5 years), two AOSD patients died. In the retrospective study of 61 AOSD cases mentioned above, patients with disease duration over 2 years present a mortality of 12%.

Treatment

Before the biologic era, treatment options were limited to nonsteroidal anti-inflammatory drug (NSAIDs), corticosteroids, and conventional disease-modifying antirheumatic drugs (CDMARDs). The efficacy and safety of NSAIDs are not satisfying, but it can be used as a temporary supportive treatment. Corticosteroid
therapy is used as the first-line treatment for AOSD, with an initial dosage at 0.5 to 1.0 mg/kg per day.[1,91] To a large extent, the duration of treatment is based on the patients’ response to the drugs and disease course. The response to corticosteroids is rapid within few days.[3,29] Usually, the tapering of corticosteroids starts after 4 to 6 weeks of therapy,[3] when the symptoms and the inflammatory laboratory parameters are normalized. Polycyclic and chronic AOSD need a long-term continuous treatment. Patients with severe visceral involvement or MAS should achieve intravenous, high-dosages corticosteroids.[1] Methotrexate (MTX) is still frequently used in AOSD for its steroid-sparing effect. If MTX fails to control the disease, other cDMARDs may be taken into consideration.[3] In a few retrospective studies, cyclosporine A has been proved to be as effective as MTX in the treatment of AOSD patients with both systemic and chronic articular involvement.[89,92] Azathioprine can be effective in controlling cutaneous eruptions or acute pericarditis in systemic AOSD.[89] Tacrolimus is also suggested to be useful in refractory AOSD in a report of six cases.[93] Other DMARDs like hydroxychloroquin, leflunomide, sulfasalazine (SSZ), cyclophosphamide, and intravenous immunoglobulin have also been applied with various response rates, but most of them seem to be ineffective and have more frequent adverse events.[89] Notably, the use of SSZ may trigger the onset of MAS in AOSD.[94]

In patients lacking clinical response with corticosteroids or cDMARDs (refractory AOSD), biologic agents should be applied.[93] Cytokine inhibitors targeting IL-1β, IL-6, TNF-α, and potentially IL-18 can suppress the inflammatory response in AOSD.[96,97] TNF-α blockers are the first biologic agents used for AOSD, but they turn out to be of limited efficacy and must be reserved for patients with chronic articular AOSD.[98] IL-1β inhibitors are now the

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**Table 1: Potential biomarkers of AOSD.**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Diagnostic ability</th>
<th>Disease activity</th>
<th>Clinical features</th>
<th>Prognosis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calprotectin</td>
<td>Sensitivity: 63.0%</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>[103]</td>
</tr>
<tr>
<td>S100A8/A9</td>
<td>Sensitivity: 69.4%</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>[104]</td>
</tr>
<tr>
<td>S100A12</td>
<td>–</td>
<td>+</td>
<td>NA</td>
<td>For polycyclic/chronic articular pattern</td>
<td>[105]</td>
</tr>
<tr>
<td>AGE and sRAGE</td>
<td>–</td>
<td>+</td>
<td>Skin rash, sore throat, serositis</td>
<td>–</td>
<td>[107]</td>
</tr>
<tr>
<td>HMGB1</td>
<td>–</td>
<td>+</td>
<td>Skin rash, sore throat, serositis</td>
<td>–</td>
<td>[107]</td>
</tr>
<tr>
<td>sCD163</td>
<td>–</td>
<td>+</td>
<td>Sore throat, myalgia, splenomegaly, pleuritis</td>
<td>For macrophage activation syndrome (MAS)</td>
<td>[109]</td>
</tr>
<tr>
<td>MIF</td>
<td>–</td>
<td>+</td>
<td>Sore throat, myalgia, splenomegaly, pleuritis</td>
<td>–</td>
<td>[109]</td>
</tr>
<tr>
<td>ICAM1</td>
<td>–</td>
<td>+</td>
<td>NA</td>
<td>For hepatic dysfunction and DIC</td>
<td>[110]</td>
</tr>
<tr>
<td>miR-134</td>
<td>–</td>
<td>+</td>
<td>NA</td>
<td>For systemic inflammatory pattern</td>
<td>[111]</td>
</tr>
<tr>
<td>miR-142-5p+miR-101-3p</td>
<td>Sensitivity: 88.24%</td>
<td>+</td>
<td>miR-101-3p: fever, sore throat and arthralgia</td>
<td>–</td>
<td>[112]</td>
</tr>
<tr>
<td>+miR-29a-3p</td>
<td>Specificity: 80.49%</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>CXCL10, CXCL13</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>–</td>
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<td>CXCL12, CXCR4</td>
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<td>+</td>
<td>NA</td>
<td>–</td>
<td>[114]</td>
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<tr>
<td>CXCL9, CXCL10, and CXCL11</td>
<td>–</td>
<td>+</td>
<td>CXCL9 and CXCL10: skin rash</td>
<td>–</td>
<td>[115]</td>
</tr>
<tr>
<td>IL-33 and sST2</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>[116]</td>
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<tr>
<td>GLK and GLK expressing T cells</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>[117]</td>
</tr>
<tr>
<td>HO-1</td>
<td>Sensitivity: 84.8%</td>
<td>+</td>
<td>NA</td>
<td>For HPS</td>
<td>[119]</td>
</tr>
<tr>
<td>Specificity: 83.3%</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[120]</td>
</tr>
<tr>
<td>Serum β2-microglobulin</td>
<td>–</td>
<td>+</td>
<td>NA</td>
<td>For HPS</td>
<td>[119]</td>
</tr>
<tr>
<td>DNI</td>
<td>Sensitivity: 82.1%</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>[120]</td>
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<tr>
<td>Specificity: 84.6%</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[122]</td>
</tr>
<tr>
<td>(rule out sepsis)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neutrophil CD64</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>[48]</td>
</tr>
<tr>
<td>Monocyte CD64</td>
<td>–</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>[121]</td>
</tr>
</tbody>
</table>

AOSD: Adult-onset Still’s disease; AGE: Advanced glycation end product; sRAGE: Soluble receptor for AGE; HMGB1: High mobility group box-1; sCD163: Soluble CD163; MIF: Macrophage migration inhibitory factor; ICAM1: Intra-cellular adhesion molecule 1; CXCL: CXC-chemokine ligand; CXCR: CXC-chemokine receptor; IL: Interleukin; sST2: Soluble suppression of tumorigenicity 2; GLK: Germinal center kinase-like kinase; HO-1: Heme oxygenase-1; DNI: Delta neutrophil index; +: Yes; –: No; NA: Not available; miR: Micro-RNA; HPS: Hemophagocytic syndrome.
primary choice for treating autoinflammatory diseases, and anakinra is the first one to show convincing and sustained efficacy in treating both systemic and articular AOSD.\(^{99,100}\) It is reported that tocilizumab is the only IL-6 antagonists used in refractory AOSD patients, and the clinical response is strong, rapid and sustainable, with a corticosteroid-sparing effect.\(^{91,102}\) Recently a retrospective study enrolling 27 AOSD patients has shown that biologic treatment may depend on the phenotypic dichotomy: a substantial response for tocilizumab in chronic articular type and anakinra in systemic type.\(^{87}\)

**Conclusions**

In the past decades, progress has been made in the possible etiology of AOSD and identification of its diagnostic and prognostic biomarkers. Yet no reliable prediction of the treatment response and outcome of AOSD is available. Given the recent insights in AOSD pathogenesis and a better understanding of its disease course, new therapeutic targets, and clinical management may be approved to improve the outcome of AOSD in the future.

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**Conflicts of interest**

None.

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3. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on the etiology of AOSD and identification of its disease course, new therapeutic targets, and clinical management may be approved to improve the outcome of AOSD in the future.\(^{87}\)


