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ADULT ONSET STILL'S DISEASE – CURRENT STATE OF KNOWLEDGE

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Abstract

Introduction: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology. AOSD lies at the crossroads of innate and adaptive immunity, highlighting the complexity of its pathogenesis. The heterogeneous clinical expression and the lack of specific diagnostic markers contribute to the difficulties in achieving a rapid and accurate diagnosis, necessitating a careful differentiation to exclude malignancies, infections, and other inflammatory conditions. There is no universally established treatment protocol, as new therapeutic options continue to emerge.

Aim of the study: The study aim is to analyse and summarize current state of knowledge about diagnosis and treatment strategies of Adult Onset Still's Disease.

Methodology: The PubMed database was searched to find scientific articles published between 2020-2025 with free full text available in which the term "Still's disease" appears in the title or keywords.

Conclusions: Adult-Onset Still's Disease is a complex autoinflammatory disorder driven by a dysregulated cytokine storm, with infections and genetic predispositions implicated as triggers. It presents variably, from systemic inflammation to chronic arthritis, and can lead to severe complications. While traditional treatments like NSAIDs, corticosteroids, and DMARDs have been used, biologic therapies targeting IL-1 and IL-6 have significantly improved outcomes. Ongoing research aims to refine diagnostics, identify biomarkers, and develop personalized treatments.

Keywords: Still's disease, AOSD

1. Etiopathology

The current perception of Still's disease tends to consider this disease as the archetype of non-familial or sporadic systemic autoinflammatory disorders. The pathophysiology of AOSD is a complex interplay between innate and adaptive immune mechanisms, with a central role played by a dysregulated cytokine storm.[1] This excessive inflammatory response is characterized by the overproduction of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ).[1] The inflammatory cascade is likely initiated by the recognition of danger signals, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[1] These signals are detected by Toll-like receptors (TLRs) expressed on innate immune cells, primarily macrophages and neutrophils, leading to their activation.[2] TLR engagement triggers the assembly of inflammasomes, particularly the NLRP3 inflammasome, which subsequently activates caspase-1, resulting in the excessive release of pro-inflammatory cytokines, such as IL-1β and IL-18.[3] Neutrophils play a crucial role in the pathogenesis of AOSD by perpetuating inflammation through the release of granule enzymes and antimicrobial proteins.[4] Additionally, an increased formation of neutrophil extracellular traps (NETs) has been implicated in further activating the NLRP3 inflammasome and pro-inflammatory macrophages, thereby amplifying the inflammatory response.[5] Some of those pathways are common between AOSD and other inflammatory diseases, which include: involvement of innate immune cells, especially neutrophils in AOSD, non-ulcer dyspepsia and spondyloarthritis; the central role of the NLRP3 inflammasome leading to caspase activation and overproduction of active IL-1β in AOSD, non-ulcer dyspepsia and Schnitzler syndrome; involvement of cytokines such as IL-18 and IL-6 in AOSD and Crohn's disease or IL-17 in AOSD and spondyloarthritis.[5]

It is still unknown what is the trigger of the disease. Cases of new-onset AOSD have been reported following COVID-19 and influenza vaccination.[6,7,8] Additionally, cytomegalovirus (CMV) infection has been identified as a potential trigger for AOSD onset or relapse.[9] Adenovirus, Human immunodeficiency virus (HIV), Mycoplasma pneumoniae, parvovirus B19, Epstein-Barr virus (EBV), rubella virus, measles morbillivirus (MeV), hepatitis virus, influenza virus, rubella, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are among the reported potential infectious triggers.[10] Genetic predisposition may also contribute to disease susceptibility, although AOSD is considered a multifactorial and polygenic disorder without a clear familial pattern.[11] Although no single gene has been identified as responsible for AOSD, multiple studies suggest a

genetic predisposition, particularly through polymorphisms in human leukocyte antigen (HLA) genes, including HLA-Bw35, HLA-B17, HLA-B18, HLA-B35, HLA-DR4, HLA-DR2, HLA-DRw6, and HLA-DRB1.[4] Strong associations have been reported with HLA-DRB1-12 and HLA-DRB1-15, while HLA-DR1 and HLA-DRB1-04 appear to be protective.[4] Variants in genes linked to other autoinflammatory diseases, such as MEFV (familial Mediterranean fever), TNFRSF1A (TRAPS), and NOD2 (granulomatous diseases), have been observed in AOSD patients, though their causal role remains unconfirmed.[4] Recent studies indicate increased mRNA expression of interferon-stimulated genes in the STING pathway (e.g., CGAS, NLRP4, STING1) in AOSD patients, particularly those with macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH).[4] IL-18 polymorphisms, especially at promoter position-607, have also been associated with disease susceptibility and severity.[4]

Adult-onset Still's disease is considered a continuum of systemic juvenile idiopathic arthritis (sJIA) based on multiple clinical, laboratory, and genetic similarities.[12] Both conditions present with high spiking fever, transient salmon-colored rash, arthritis or arthralgia, lymphadenopathy, hepatosplenomegaly, pharyngitis, and elevated ferritin levels.[12] Laboratory findings reveal similar inflammatory markers, including elevated erythrocyte sedimentation rate, C-reactive protein, hyperferritinemia, and neutrophilic leukocytosis.[13] Pathogenetically, both AOSD and sJIA are classified as autoinflammatory diseases driven by a cytokine storm, with IL-1, IL-6, and IL-18 playing central roles.[1] Genetic studies have identified shared susceptibility factors and similar gene expression profiles, particularly in response to IL-1 inhibitors.[4] AOSD may represent an undiagnosed or relapsing course of sJIA from childhood, with some patients exhibiting a polycyclic disease pattern.[5] Severe complications, including macrophage activation syndrome (MAS), occur in both diseases.[14] Reflecting this continuum, EULAR and PReS have recommended unifying both under the term Still's disease, emphasizing their fundamental similarity rather than an arbitrary age-based distinction.[15]

2. Epidemiology

AOSD, the adult counterpart of systemic juvenile idiopathic arthritis, is defined by symptom onset after the age of 16.[4] The incidence of AOSD is estimated at 0.16 to 0.4 cases per 100,000 persons annually.[2] The disease exhibits two peaks of onset, typically between 16–35 and 45–64 years of age,[2] with some studies suggesting a slight female predominance,[2] though others report no significant sex differences.[11] Geographical and ethnic variations in prevalence have been noted, with higher rates observed in Japanese populations compared to European cohorts,[5] and disparities in morbidity and mortality linked to racial and ethnic backgrounds in the United States.[3]

3. Clinical Presentation

Adult-Onset Still's Disease is characterized by a wide spectrum of clinical manifestations and diagnosis is often challenging due to the nonspecific nature of symptoms and the absence of distinctive serological markers.[11] However, several key clinical features are commonly observed in patients with AOSD - those are fever, skin rash and arthalgia or arthritis. Fever is

the cardinal symptom, occurring in 60–100% of AOSD patients.[13] Typically, it presents as a high, spiking fever,[10] often reaching ≥39°C (102.2°F) and appearing twice daily, with peaks in the morning and evening.[13] It may emerge abruptly and sometimes resolves spontaneously and it persists for at least one week.[11] In certain cases, fever may be the sole initial manifestation of AOSD.[11] The characteristic rash of AOSD is transient, maculopapular, and salmon-pink in color.[10] It commonly affects the proximal limbs and trunk.[13] Atypical persistent skin eruptions (APSEs), including linear or scratch-like lesions, may indicate alternative disease manifestations.[11] Persistent urticarial-like rashes may serve as a warning sign for hematological complications.[13] The rash frequently coincides with febrile episodes and may completely disappear during afebrile periods.[13] Both fever and rash correlate with disease activity.[13] Joint pain (arthralgia) is highly prevalent, affecting 70–100% of AOSD patients.[13] It frequently progresses to polyarthritis, involving both small and large joints, mimicking rheumatoid arthritis.[13] Arthritis may develop later in the disease course, with chronic forms leading to severe joint destruction, stiffness, and disability.[15] The most commonly affected joints include the wrists, knees, and ankles.[11] Additional common symptoms include pharyngitis or odynophagia, lymphadenopathy, hepatomegaly and/or splenomegaly and myalgia, though myositis and polymyositis are rare.[11] Other described rare symptoms include pleuritis, pericarditis, myocarditis, and abdominal pain.[13]

Laboratory findings include elevated inflammatory markers - increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are seen in all patients.[10] Another characteristic feature is hyperferritinemia - current findings suggest increased production by macrophages, liver and erythrocytes due to parallel erythrophagocytosis.[10] What is more, high circulating ferritin has a positive feedback mechanism that can further exacerbate its own inflammatory properties.[13] We additionaly observe neutrophilic leukocytosis (neutrophils (≥10,000/μL with ≥80% neutrophils). Abnormal liver function tests are detected mostly due to non-steroidal anti-inflammatory drugs (NSAIDs) or antibiotics and rarely due to fulminant hepatitis.[13] Rheumatoid factor (RF) and antinuclear antibodies (ANA) are typically negative.[16]

The clinical course of AOSD is highly variable and unpredictable, with three primary patterns: monocyclic - a single disease episode followed by remission, sometimes without treatment, polycyclic - recurrent disease episodes interspersed with remission periods lasting months or years and chronic- persistent inflammation with chronic arthritis and intermittent systemic

flare-ups.[5] Additionally, two major phenotypes of AOSD are recognized based on predominant symptoms. The first one is systemic phenotype characterized by high fever and skin rash, with a higher risk of severe complications.[10] Patients with this phenotype often present with high-grade fever (>39°C), abnormal liver function tests, thrombocytopenia, and hyperferritinemia.[10] There is also articular phenotype which predominantly involves joint symptoms, resembling classic rheumatoid arthritis.[17] Classification criteria such as Yamaguchi and Fautrel criteria are commonly employed in diagnosing AOSD.[10] Yamaguchi Criteria include major criteria (fever ≥39°C for ≥1 week, arthritis for ≥2 weeks, typical rash, leukocytosis ≥10,000/mm³ with ≥80% neutrophils) and minor criteria. Diagnosis requires at least five criteria, including at least two major ones, with exclusion of alternative causes.[10] Fautrel Criteria include major criteria (spiking fever ≥39°C, arthritis, transient erythema, pharyngitis, neutrophils ≥80%, glycosylated ferritin ≤20%) and minor criteria but lacks exclusion criteria.[10] Diagnosis requires either four major criteria or three major plus two minor criteria.[10]

4. Atypical cases and complications of Adult-Onset Still's Disease

Atypical disease trajectories may also be observed. AOSD primarily affects young adults, but cases with onset after 60 years, known as Elderly-Onset Still's Disease (EOSD), have also been reported.[18] EOSD tends to have a more severe disease course and higher complication rates compared to younger patients.[18] It more commonly presents with pleuritis and complications such as disseminated intravascular coagulation (DIC) and infections occur more frequently in EOSD.[18] Although severe acute kidney injury (AKI) is uncommon in AOSD, however cases of rapidly progressing AKI requiring hemodialysis have been reported, some of them associated with macrophage activation syndrome (MAS).[19] There are also reports of AOSD occurring alongside collapsing glomerulopathy, a severe variant of focal segmental glomerulosclerosis leading to renal failure.[20] TTP is a rare complication of AOSD, although some reports describe cases with extremely elevated ferritin levels (e.g., 32,696 ng/mL), suggesting concurrent TTP.[21] There was also described a case of non-infectious endocarditis associated with AOSD - 42-year-old male presenting with prolonged fever, sore throat, and knee arthralgia, along with mitral valve vegetations detected on transesophageal echocardiography, initially suspected to be infectious endocarditis, however, persistent fever and elevated inflammatory markers despite antibiotic therapy, combined with fulfillment of Yamaguchi criteria led to correct diagnosis.[22] A rare case described a patient with AOSD who developed GBS during a disease flare, recognizing GBS in AOSD patients with neurological symptoms is crucial for timely and appropriate treatment.[23] Beyond GBS, AOSD has been linked to neurological complications such as meningitis and encephalitis, frequently coexisting with MAS.[23] Another rare presentation of a disease is described in case report presenting a young male whose AOSD initially started with fever and myopericarditis, mimicking acute coronary syndrome, however coronary angiography revealed no significant findings, and AOSD was diagnosed after ruling out other causes.[24] Lymphadenopathy is a common feature of AOSD, but its histopathological presentation varies, encompassing mixed, diffuse, necrotic, and follicular patterns.[25] This

diversity can complicate differentiation from other reactive lymphadenopathies (e.g., lupus lymphadenitis) and lymphomas.[25] In summary, AOSD exhibits diverse clinical manifestations, and atypical cases or complications, such as those described above, require a high index of suspicion and thorough differential diagnosis. Understanding these rare presentations is crucial for early recognition and appropriate management of AOSD patients.

Some complications of Still's disease need to be described. Macrophage activation syndrome (MAS) is a severe, life-threatening complication of Adult-Onset Still's Disease that can develop at any stage of the disease.[15] It is classified as a secondary form of hemophagocytic lymphohistiocytosis (HLH) occurring in the context of rheumatic diseases and represents a hyperinflammatory syndrome driven by excessive activation of both innate and adaptive immune responses.[15] MAS should be suspected in patients presenting with persistent high fever unresponsive to standard treatment, splenomegaly, elevated or rapidly rising serum ferritin levels, often exceeding 10,000 ng/mL, serving as a key biomarker of MAS, cytopenias, hepatic dysfunction and intravascular coagulation activation, which may lead to disseminated intravascular coagulation (DIC).[15] Early identification of MAS is crucial, as it significantly impacts prognosis and treatment outcomes.[15] Other severe complications include disseminated intravascular coagulation (DIC), thrombotic microangiopathy, pulmonary hypertension, creeping hepatitis, and acute respiratory distress syndrome (ARDS).[11]

5. Traditional treatment

The traditional treatment strategies for AOSD include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS), and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[3] NSAIDs are often used as first-line therapy in patients with mild to moderate disease[10]; however, remission of fever and musculoskeletal symptoms is achieved in no more than 20% of cases with NSAID monotherapy.[11] Caution is required, as high doses of indomethacin and aspirin have been associated with fulminant liver failure in patients with elevated transaminases.[11] Nevertheless, NSAIDs may still be useful in the early diagnostic phase,[4] and high doses of indomethacin or ibuprofen can provide satisfactory symptom control.[4]

Corticosteroids are a cornerstone of Still's disease treatment, effectively controlling systemic and joint-related symptoms in 60–70% of patients.[11] As first-line therapy, they rapidly suppress inflammation, with an initial dose typically ranging from 0.5 to 1 mg/kg/day of prednisone.[11] Starting at ≥0.8 mg/kg/day has been associated with faster symptom resolution and fewer relapses.[11] In severe cases, such as macrophage activation syndrome (MAS), high-dose intravenous corticosteroids are recommended.[11] Once clinical symptoms subside and laboratory parameters normalize, gradual tapering is essential to minimize long-term adverse effects.[15] However, 40–45% of patients develop steroid dependence, leading to complications such as Cushing's syndrome, osteoporosis, and avascular necrosis.[11] To reduce corticosteroid exposure, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, are introduced in steroid-dependent patients.[3] In refractory cases, biologics targeting IL-1 and IL-6 pathways offer an effective alternative.[3] The growing use of biologics has led

to earlier intervention, improving outcomes and reducing corticosteroid-related toxicity.[3] While corticosteroids remain a key component of initial management, treatment strategies increasingly emphasize steroid-sparing approaches to achieve sustained remission with fewer side effects.[26]

Methotrexate, a conventional synthetic disease-modifying antirheumatic drug (csDMARD), plays a significant role in the treatment of Still's disease. It is primarily considered a second-line therapy for patients who do not respond to or cannot tolerate first-line treatment.[11] Methotrexate is particularly effective in managing joint involvement[15] and is often introduced before initiating biologic therapy.[16] Additionally, it serves as a steroid-sparing agent, reducing the need for long-term corticosteroid use.[11] Retrospective studies have reported clinical responses in most patients receiving methotrexate at doses of 7.5–17.5 mg/week, with some achieving complete remission.[11] However, evidence from randomized controlled trials (RCTs) remains limited.[15] Methotrexate's use requires careful monitoring due to its potential hepatotoxicity.[11] In cases of refractory disease or severe systemic manifestations, biologic agents targeting IL-1 and IL-6 are increasingly favored.[15] While methotrexate remains a valuable option for joint symptom control and corticosteroid reduction, its role is evolving in the era of biologic therapies.

Azathioprine, cyclosporine, and leflunomide have been utilized in specific clinical scenarios for the treatment of adult-onset Still's disease (AOSD), primarily as adjuncts before initiating biologic therapy. Azathioprine is mentioned as a potential option alongside methotrexate for steroid-dependent patients with refractory or polycyclic systemic AOSD.[3] Cyclosporine has been considered in patients with elevated liver enzymes receiving anakinra, though its role remains less established compared to other conventional DMARDs.[16] Leflunomide has been used mainly in patients with predominant joint involvement, often in combination with tocilizumab.[16] However, data on the routine use of these agents in Still's disease are limited, with methotrexate being the more frequently recommended conventional DMARD.[3] Further research and updated clinical guidelines are necessary to clarify their precise roles in disease management.

The primary goal of AOSD treatment is to control inflammation, alleviate systemic and joint symptoms, and prevent organ damage and MAS. While traditional therapies may be adequate for patients with a mild, self-limiting course, steroid-dependent cases and those with life-threatening complications require additional second-line treatments. Conventional approaches have proven insufficient for at least 30–40% of patients, particularly those with severe disease, highlighting a significant unmet need for targeted therapies.[10] Consequently, biologic agents are increasingly being used in cases refractory to conventional treatment.

6. Biological treatment

6.1 Interleukin-1 inhibitors

Interleukin-1 plays a central role in the pathogenesis of Still's disease, affecting both systemic juvenile idiopathic arthritis and adult-onset Still's disease.[26] Biologic therapies targeting IL-1 have demonstrated efficacy in patients with AOSD who are refractory to conventional treatments.[16] Anakinra, IL-1 receptor antagonist, is widely used in AOSD treatment and has demonstrated efficacy in multiple observational studies.[2] A meta-analysis of nine clinical studies suggests that anakinra can reduce or even stop glucocorticoid use without

triggering AOSD flares.[2] A randomized study in refractory AOSD patients compared anakinra to csDMARDs and more patients in the anakinra group achieved remission.[4] Different study found that 89.5% of AOSD patients experienced remission with biologics, with IL-1 inhibitors used in 68.4% of cases.[16] Anakinra appears more effective when administered early in the disease course, particularly in highly active systemic AOSD compared to isolated chronic arthritis.[17] Treatment is typically 100 mg/day, but due to its short half-life (6–8 hours), an increased dose of 200 mg/day (split into two administrations) may be required in some cases.[17] Common adverse effects include injection-site reactions and occasional hepatotoxicity, which is reversible upon treatment withdrawal.[17] Canakinumab was approved by the EMA and FDA for both sJIA and AOSD in 2016 based on the concept of the Still's disease continuum.[2] Trials have demonstrated improvement in clinical symptoms and laboratory findings following canakinumab administration and it is generally well tolerated with a favorable safety profile.[11] Rilonacept was successfully used in some refractory AOSD cases with predominant articular involvement as a steroid-sparing agent and has shown promise in reducing arthritis symptoms in AOSD patients, however currently FDA-approved only for recurrent pericarditis, not AOSD. [17,12] A switch from one IL-1 blocking agent to another is possible and recommended if response to treatment is lost or in the event of adverse effects.[17] The optimal dosing strategy for IL-1 inhibitors remains unclear, current dosing regimens are rigid, but adjusting the dose according to the patient's needs is often required.[17] Future research should address this issue to refine treatment guidelines. There is no standardized criterion for selecting the correct biologic agent or for discontinuing treatment once remission is achieved. However, cautious tapering after 6–12 months of sustained remission is suggested due to the high cost and injection burden.[17] This is typically done by gradually increasing the interval between injections.[15]

6.2 Interleukin-6 inhibitors

Interleukin-6 inhibitors, particularly tocilizumab and sarilumab, have emerged as effective therapeutic options for treating Still's disease, especially in cases refractory to conventional treatments or following IL-1 inhibitor failure.[10] Tocilizumab, an IL-6 receptor inhibitor, has demonstrated sustained efficacy for up to six years in refractory AOSD, including in patients unresponsive to corticosteroids or TNF and IL-1 inhibitors.[11] A phase III randomized, double-blind, placebo-controlled study confirmed its effectiveness in glucocorticoid-resistant AOSD.[17] Drug-free remission for tocilizumab ranged from 14.3% at a mean observation duration of 26.4 months to 72.7% at 18 months.[27] Another IL-6 inhibitor - sarilumab has also been reported to facilitate corticosteroid dose reduction.[10] Meta-analyses and Japanese studies further support the therapeutic role of IL-6 blockade in AOSD, including in the management of macrophage activation syndrome (MAS) and relapse prevention.[10] Although initially reserved for cases unresponsive to NSAIDs, corticosteroids, and conventional DMARDs, IL-6 inhibitors are increasingly incorporated earlier into treatment regimens.[3] Multidisciplinary discussion in specialized centers may be warranted for complex cases, particularly when considering IL-6 inhibitors as an alternative to IL-1 blockade.[28,15] While effective, IL-6 inhibitors have been associated with a higher incidence of infectious adverse events compared to IL-1 inhibitors, highlighting the need for careful monitoring in clinical practice.[15]

6.3 TNF-alfa, IL-18 and JAK inhibitors

Tumour necrosic factor-alfa inhibitors, including infliximab, etanercept, and adalimumab, were among the first biologic disease-modifying antirheumatic drugs (bDMARDs) used in adult-onset Still's disease (AOSD).[4] Their efficacy is primarily supported by observational studies and case reports, with no randomized controlled trials confirming their effectiveness and safety in Still's disease.[4] While generally well tolerated, their clinical benefit appears limited.[4] Some reports demonstrated rapid and sustained efficacy in joint and systemic symptoms, whereas larger cohort studies showed only 22–25% of patients achieving clinically inactive disease.[4] There have also been reports of disease exacerbation following etanercept administration, potentially linked to increased TNF-α levels.[11] Despite their historical role in AOSD management, TNF-alfa inhibitors are now considered less favorable compared to IL-1 and IL-6 inhibitors due to inconsistent efficacy.[4] Interleukin-18 (IL-18) inhibition is a novel therapeutic approach, tadekinig alfa, an IL-18 binding protein (IL-18BP), has been investigated in a phase II open-label, dose-escalation study assessing its safety and efficacy in AOSD.[10] Preliminary data suggest that prolonged treatment with tadekinig alfa may be beneficial in select patients, however, further research is needed to establish its long-term efficacy and safety profile.[10] Janus kinase (JAK) inhibitors have emerged as a potential therapeutic strategy for AOSD and related autoinflammatory diseases.[10] Baricitinib has shown variable results in refractory AOSD and undifferentiated systemic autoimmune disease,[3] while tofacitinib demonstrated efficacy in a Chinese cohort of 14 patients with refractory AOSD, including cases complicated by macrophage activation syndrome (MAS).[10] Preclinical studies suggest that JAK inhibition can mitigate inflammation and disease progression in HLH models.[10] A case report described successful combination therapy with anakinra and baricitinib in refractory AOSD, highlighting the potential role of JAK inhibitors in difficult-to-treat cases.[4] However, further studies are required to refine their place in the therapeutic landscape.

6.4 Other new biological therapies

In addition to IL-1, IL-6, TNF-α, IL-18 and JAK inhibitors, other biologic therapies have been considered or used in the treatment of AOSD, which include some of the following. Secukinumab, a humanized monoclonal antibody targeting IL-17A, is approved for the treatment of spondyloarthropathies, psoriatic arthritis, and psoriasis, however in one reported case of AOSD coexisting with spondyloarthritis, IL-17A inhibition led to complete remission of articular symptoms.[4] **Rituximab,** the monoclonal antibody targeting CD20 has been evaluated in limited case reports and series and while it has not provided significant evidence of efficacy, cases of successful treatment of refractory AOSD with rituximab have been described.[11] **Anti-CTLA-4, abatacept**, has been assessed in isolated case reports of refractory AOSD.[4] Similar to rituximab, there is insufficient evidence to support its broad effectiveness, though cases of successful treatment with abatacept have been reported.[4] Granulocyte-macrophage colony-stimulating factor **(GM-CSF) inhibitors, like mavrilimumab, are** being explored in autoimmune and inflammatory diseases, including AOSD.[15] GM-CSF has also been proposed as a potential biomarker for AOSD.[15] It is important to note that the efficacy of some of these therapies is based on limited data, such as case reports and small series, and further research is required to confirm their role in AOSD treatment. The current therapeutic approach primarily relies on IL-1 and IL-6 blockade.

7. Conclusion

Adult-Onset Still's Disease remains a complex and heterogeneous autoinflammatory disorder, with its pathogenesis driven by a dysregulated cytokine storm involving key inflammatory mediators such as IL-1, IL-6, and IL-18. While its exact trigger remains unknown, various infections and genetic predispositions have been implicated. The disease presents with a broad clinical spectrum, ranging from systemic inflammation with fever, rash, and organ involvement to a chronic arthritis-dominant phenotype. The course of AOSD is unpredictable, with potential life-threatening complications such as macrophage activation syndrome, disseminated intravascular coagulation, and severe organ dysfunction.

Historically, treatment relied on NSAIDs, corticosteroids, and conventional DMARDs such as methotrexate, but a significant proportion of patients experience steroid dependence or inadequate response. The advent of biologic therapies, particularly IL-1 and IL-6 inhibitors, has revolutionized disease management, offering more targeted and effective treatment options. Emerging therapies and novel biologics, provide promising alternatives for refractory cases. However, individualized treatment strategies and further research are essential to optimize outcomes.

As our understanding of AOSD continues to evolve, future efforts should focus on refining diagnostic criteria, identifying reliable biomarkers for disease activity, and developing more precise, personalized therapeutic approaches. The unification of AOSD and sJIA under the Still's disease continuum highlights the need for an integrated approach in managing these conditions. By advancing targeted therapies and improving early recognition, clinicians can enhance disease control, reduce complications, and improve the quality of life for patients affected by this challenging condition.

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