Biologics: Targets and Therapy

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REVIEW

Progress in Biological Therapies for Adult-Onset Still's Disease

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Abstract: Adult-onset Still's disease (AOSD) is a rare multifactorial autoinflammatory disorder of unknown etiology, characterized by an excessive release of cytokines triggered by dysregulated inflammation and articular and systemic manifestations. The clinical spectrum of AOSD ranges from self-limiting forms with mild symptoms to life-threatening cases and presents clinical and biological similarities with the juvenile form (sJIA). Nowadays, the advances in biologic agents no longer limit the treatment to NSAIDs, glucocorticoids, or conventional synthetic DMARDs. The blockade of IL-1 and IL-6 is effective in the treatment of systemic and articular inflammation of AOSD patients; however, novel compounds with different properties and targets are now available and others are being studied. In this review, starting from the pathogenesis of AOSD, we summarized the current and emerging biological therapies, possible effective agents for achieving AOSD control and remission.

Keywords: biologics, AOSD, IL-1 inhibitors, IL-6 inhibitors, small molecules, new treatment

Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology, with an estimated prevalence of 1 in 100,000 and an annual incidence of 0.16–0.40 per 100,000 depending on the population studied.[1] The overwhelming majority of cases present between the ages of 16–35 with a slight female predominance, however 10% of cases present after 50 years of age.[2]

AOSD has a heterogeneous clinical presentation. The main clinical features (spiking fever, arthritis, skin rash, and hyperferritinemia), as well as other minor features (sore throat, lymphadenopathy, hepatosplenomegaly, thrombocytosis, serositis, myalgia, neutrophilic leukocytosis, inflammatory anemia), characterized the disease.[3]

During the diagnostic process, Yamaguchi et al [4] and Fautrel et al[5] classification criteria for AOSD are actually used in clinical practice, although primarily designed for research. They include exclusion criteria such as infections, malignancies, and other autoimmune diseases with high sensitivity and specificity; so, they should be used only after a wide diagnostic framework.[6] Historically, AOSD phenotypes have been described based on the different evolution courses over time (monogenic, polycyclic, or chronic aspects) and on the type of symptoms (prominent systemic features or chronic arthritis).[7] This dichotomous classification distinguishes the systemic subtype characterized by high fever, skin rash, and higher risk to develop life-threatening complications, to the articular subtype with predominant joint pain and arthritis. These two phenotypes could also be predicted by some factors: high fever, hepatitis, and elevated serum levels of C-reactive protein and ferritin better associate with the systemic AOSD, while female gender, steroid dependence, and low ferritin level associate with the chronic AOSD.[1] In light of novel evidence about AOSD pathogenesis and the use of biological treatments, a different cytokine profile has been observed associated with distinct AOSD manifestations. The systemic subset, indeed, presents an excessive level of interleukin (IL)-1β and IL-18, while the chronic articular AOSD is principally driven by IL-6 and tumor necrosis factor (TNF)-α.[8] Several chemokines, including CXC-chemokine ligand 10 (CXCL10), CXCL13, and macrophage migration inhibitory factor (MIF)), the proteins S100 A8/A9 and A12 and the advanced glycation end products (AGEs) and their receptors (RAGE) have potential as new diagnostic biomarkers for AOSD, upon confirmation with larger patient groups.[9]

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Pathogenesis, Hyperinflammation, and Clinical Complications

Although the exact mechanisms involved in the pathogenesis of AOSD are unknown, significant progresses have been made to confirm the homology between AOSD and the systemic juvenile idiopathic arthritis (sJIA). Both conditions encompass many common clinical and biological findings as well as the disease onset and the clinical course result as undistinguishable from each other, suggesting a continuum of a single disease entity.[10]

The AOSD pathophysiology remains unclear. However, it is thought that factors including an imbalance in innate and adaptive immunity and an increase of inflammatory cytokines may contribute to disease development.[1] Aberrant IL-1 and IL-6 production, indeed, would favor the development of pathogenic adaptive T helper 17 (Th17) cell-mediated responses. Several infectious triggers, including viruses (*Parvovirus B19*, *Epstein Barr virus*, *Cytomegalovirus*) and bacteria (*Yersinia* and *Mycoplasma*), as well as genetic factors related to the HLA (HLA-Bw35, -B17, -B18, -B35, -DR2, -DR4, -DR5, -DQ1, DRw6, -DRB1, and -DQB1) are also believed to trigger the AOSD onset.[11]

The fundamental characteristic of AOSD pathogenesis is the neutrophil activation, responsible for the induction and regulation of inflammation. Neutrophil extracellular traps (NETs) play a pivotal role in the intense activation of macrophages and in stimulating the overproduction of several pro-inflammatory cytokines.[12] Specific Toll-like receptors (TLRs) and damage-associated molecular patterns (DAMPs) are reported to initiate and maintain the inflammatory response through the activation of NLRP3 inflammasomes, leading to caspase activation and overproduction of active IL-1β and IL-18.[13] These proinflammatory cytokines, in turn, lead to amplifying the inflammatory cascade through the exuberant production of downstream mediators, such as IL-6, IL-8, IL-17, TNF-α, and interferon (IFN)-γ, a so-called cytokine storm (Figure 1). Also, the inadequate resolution of the hyperinflammatory status can play a role in sustaining the cytokine storm. Similar to AOSD, excessive and uncontrolled systemic inflammation has been recognized as a hallmark of COVID-19, the current severe acute respiratory syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[14] This suggests a common link of the cytokine storm in both diseases' pathogenesis, although a recent study suggests differences in cytokine and soluble mediator profiles.[15] The levels of IL-6 and IL-10 are reported higher in severe COVID-19, while the expression of serum ferritin dramatically increased in AOSD. Interestingly, a misdirected immune response against SARS-CoV-2 virus may have led to the development of AOSD, according to a recent case report.[16]

The insufficient control of inflammatory activity in AOSD patients is even associated with a risk of serious and different complications. Secondary hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) is one of the most severe and life-threatening complications in predisposed AOSD patients.[17] Continuous high fever, lymphadenopathy, hepatosplenomegaly, and remarkably elevated levels of serum ferritin and IL-18 contribute to the clinical work-up of MAS patients. Moreover, MAS in AOSD entailed a greater risk of aggressive disease symptoms, difficulties in the response to treatment, and a mortality rate of 20–40%.[18] However, there is evidence that cytokine blockade, such as IL-1 and IL-18 inhibitions, might confer additional advantages in the treatment of MAS.[19,20] Other complications of AOSD included myocarditis, pericarditis, pulmonary hypertension, multiple organ failure and relapses.[21] Clinicians should be aware of these complications, because early recognition and prompt management can significantly reduce morbidity (and mortality). A recent and exhaustive review by Mitrovic and Fautrel[21] extensively describes the supportive measures and the immunomodulatory drugs useful to control these specific organ involvements in AOSD.

Conventional Treatments

The treatment of AOSD should be addressed to the different variety and severity of symptoms manifested. Clearly, the control of systemic inflammation and the prevention of MAS remain the main therapeutical purposes. For all severe AOSD-related complications, high-dose corticosteroids and supportive measures remain the first-line treatment. In case of inadequate response, combination with IL1 or IL-6 blockers is adequate.[21] Nowadays, the diffusion of new biological targeted therapies has extremely ameliorated the management of AOSD, as many approaches are now available and suitable for the diverse clinical manifestations and disease course.

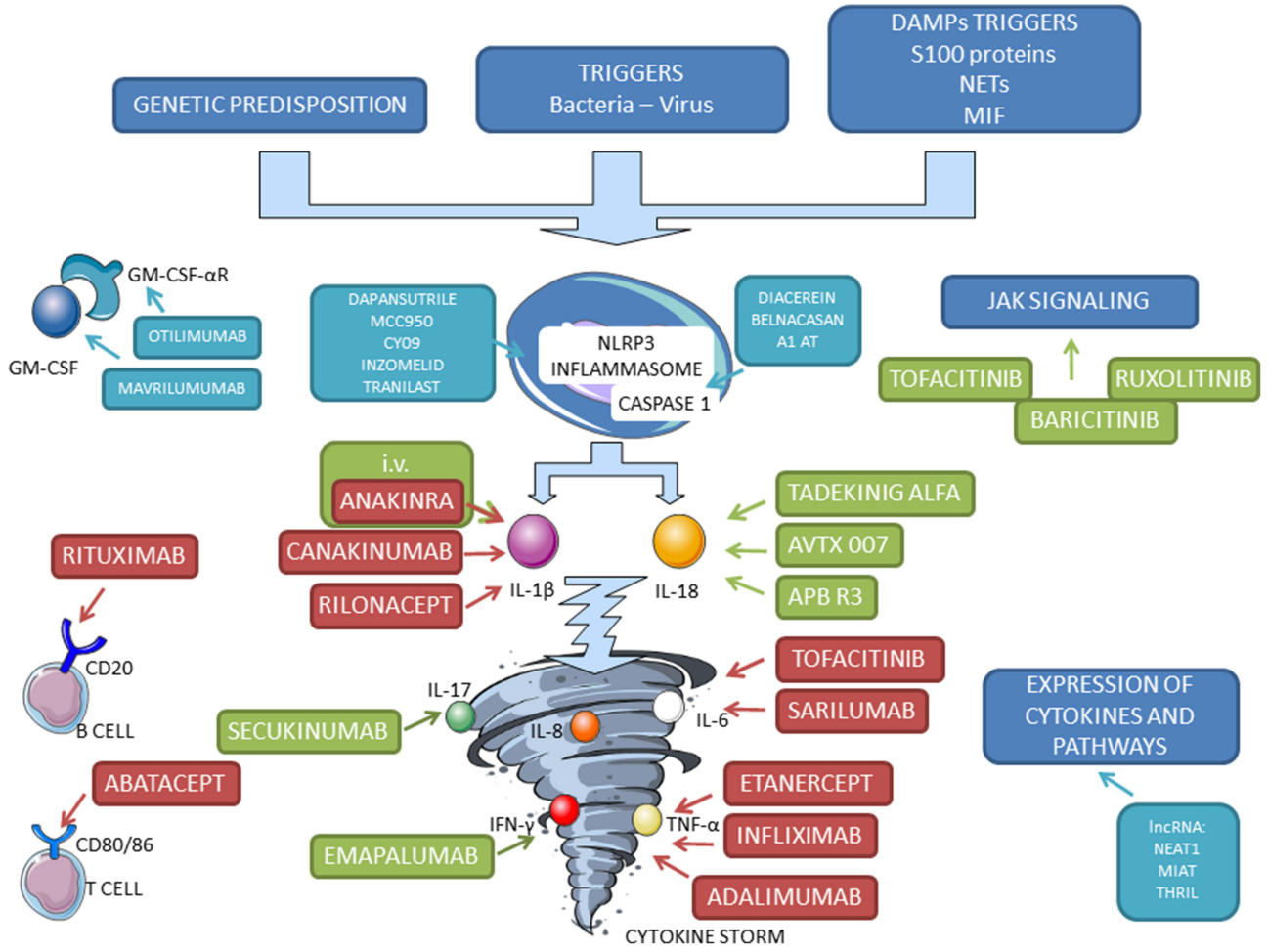

Figure 1 Scheme of pathogenesis of AOSD and identification of targets for old (red), new (green), and proposed (light blue) biological therapy.

Non-Steroid Anti-Inflammatory Drugs (NSAIDs), Glucocorticoids, and Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs)

NSAIDs represent the first line therapy, especially when systemic manifestations are almost absent.[22] However, nearly 20% of the patients present a self-limited disease and for most of them NSAIDs fail in control of the disease activity.[23] Nevertheless, NSAIDs should be used as a supportive treatment during the diagnostic process. Indeed, high dose indomethacin (150–250 mg/day) or ibuprofen 800 mg up to 4-times a day may control some of the inflammatory manifestations satisfactorily.[1,23] Of course, possible side-effects related to the prolonged employment of NSAIDs should be considered, such as gastrointestinal bleeding and for older patients the risk of renal or hepatic insufficiency.[24–26]

Glucocorticoids represent an efficient choice in approximately 80% of the patients at the initial dose of 0.5–1 mg/kg/day of methylprednisolone.[27] The response achievement is usually prompt and sustained on both articular and systemic manifestations. However, prolonged therapy with steroids should be avoided because of the risk of side-effects and adverse reactions including hypertension, diabetes, tachycardia, the possibility of early-onset osteoporosis, the occurrence of ecchymosis, and weight gain.[23] On the other hand, it should be considered that a quick reduction of steroid daily-intake may lead to disease relapses, thus the decrease of the posology should be done gradually. Sometimes, methylprednisolone can be insufficient in controlling the most severe manifestations, especially in those presenting with refractory forms or in patients who present with MAS features. In those cases, other types of glucocorticoids such as dexamethasone should be considered, in the same way as it is employed in the HLH-2004 protocol for the treatment of primary HLH.[28] However, a current defined posology for dexamethasone in severe AOSD has not been defined yet,

although the clinical decision should rely on a careful examination of the clinical manifestations and on the evaluation of serum biomarkers.

Regarding csDMARDS, they are typically considered glucocorticoid-sparing drugs and are usually added to glucocorticoids or NSAIDs to obtain an adequate disease control. Nowadays, their use is quite limited since biological DMARDs are preferred as second line therapy. Methotrexate and Cyclosporine A were the most frequently employed, especially for the treatment of the chronic articular pattern and for MAS, respectively, while data with azathioprine or leflunomide come from small case series or case reports and are scarce.[1]

Biological Agents

It was reported in different observational studies that 17–32% of AOSD patients can be resistant to both first-line corticosteroids and second-line csDMARDs.[23,29–31] Indeed, the systemic inflammation present in AOSD subjects depends on the increase of pivotal pro-inflammatory cytokines, such as IL-1, IL-6, IL-18, IL-17, and TNFα, which correlate with disease activity.[32] For this reason, nowadays, targeted biological treatments have emerged to be effective approaches for the management of AOSD, especially for the refractory form steroid-dependent or when severe manifestations occur.[23] However, there is no systematic criteria to select the correct drugs nor indications for biologics treatment suspension once clinical remission is achieved. In patients with systemic AOSD, response to IL-1 inhibitors must be expected within hours or days. It has been suggested that a cautious tapering of the drug could be attempted if clinical remission is maintained for at least 6–12 months.[33]

IL-1 Inhibitors

Anti IL-1 agents undoubtedly represent the milestone for the treatment of AOSD. To date, three IL-1 inhibitors are available for AOSD. IL-1 inhibitors have an overall satisfactory safety profile in AOSD. In terms of the risk of infection, treatment with anti-IL-1 agents seems to have an acceptable safety profile. Although the inhibition of IL-1 remains the gold standard in systemic AOSD and in the refractory forms,[34] other approaches should be considered.

Anakinra

Anakinra, a non-glycosylated form of human IL-1 receptor antagonist (IL-1Ra), acts as a pure receptor antagonist binding to the IL-1 receptor (IL-1RI) and preventing the activation of this receptor by either IL-1β or IL-1α.[35] Anakinra was firstly approved in 2001 for the treatment of rheumatoid arthritis, but the first employment in AOSD dates back to 2005 when the first cases were described.[36–38] As several studies report, it seems that anakinra is more effective if administered early in the disease course and it was proved to be more useful in patients with highly active systemic AOSD than in those with isolated chronic arthritis.[39] The confirmed effectiveness of anakinra was assessed in diverse observational studies by now.[40–44] Ortiz-Sanjuan et al[45] reported nearly 40 patients who experienced a marked reduction of the frequency of joint manifestations (from 87.8% at baseline to 41.5% after 12 months), of cutaneous rash (from 58.5% to 7.3%), fever (from 78% to 14.6%), lymphadenopathy (from 26.8% to 4.9%), and ferritin serum levels (from 63.4% to 36.6%) after 1year of therapy with anakinra. In addition, a general decrease of steroid daily intake was noticed ($p<0.01$). Similar results were achieved in a larger cohort of 136 consecutive AOSD patients that, after anakinra, exhibited a significant reduction of Pouchot's score from the baseline ($p<0.0001$) until the last follow-up period (12 months), with no major safety concerns.[46] Anakinra is usually administered at the dosage of 100 mg/day but given the short half-life (6–8 hours) in cases of insufficient response it can be increased to 200 mg, split into twice-daily administrations.[1] Treatment with anakinra has been associated with frequent injection-site reactions and occasionally severe cases of hepatotoxicity, reversible after treatment withdrawal.[44]

Canakinumab

Canakinumab is a fully human monoclonal antibody against IL-1β with a half-life of 26 days, which makes it possible to administer it at the dosage of 150 mg or 300 mg every 4–8 weeks. In 2016, canakinumab was approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for a license extension to treat both SJIA and AOSD, based on the concept of the Still's disease continuum.[11] In this context, in 2018, Feist et al[47] described the

efficacy and the safety of canakinumab in a subgroup of young adolescents with SJIA aged ≥16 years which were representative of an adult population. The phenotypic dichotomy of AOSD with the prevalence of systemic symptoms rather than polyarthritis reflects on the diverse possible therapeutical approaches. In this context, the CONSIDER trial (a multicenter, randomized, double-blind, placebo-controlled trial), which aimed to employ canakinumab in AOSD subjects with active joint involvement, did not achieve the primary endpoint (p=0.18) defined as the change in disease activity score (ΔDAS28>1.2).[48,49] These results pave the way to new therapeutical strategies, which should be tailored on each patient according to the clinical phenotype presented.

Rilonacept

Among other IL-1 inhibitors, it should be mentioned that Rilonacept (IL-1 trap molecule), a construct of two extracellular chains of the IL-1R complex (IL-1R plus IL1RAP), fused to the Fc portion of human immunoglobulin G1 (IgG1). Rilonacept can bind both IL-1β and IL-1α with high affinity and its half-life is longer than that of anakinra.[1] For this reason, it was successfully used at 160 mg/week in some refractory forms with a predominant articular involvement as a steroid-sparing agent.[50,51] However, Rilonacept is currently FDA-approved only for the treatment of recurrent pericarditis.

IL-6 Inhibitors

IL-6 is a pro-inflammatory cytokine downstream of IL-1, and it represents a therapeutic target as well for AOSD.

Tocilizumab

Tocilizumab (TCZ) is a humanized anti-IL-6 receptor antibody that recognizes both membrane-bound and soluble forms of IL-6 receptor, specifically blocking IL-6. It is administered subcutaneously at doses of up to 8 mg/kg every 2 weeks.[52] The efficacy of TCZ was proved in cases of refractory AOSD, especially when the chronic articular pattern was predominant.[53,54] However, the confirmation of its effectiveness on articular manifestation derived from a randomized clinical trial of 2018.[55] The same study also reported TCZ as acceptable in terms of safety.

Sarilumab

Sarilumab (anti IL-6Rα) is a fully human anti-IL-6Rα mAb that binds membrane-bound and soluble human IL-6Rα with high affinity.[56] So far, the efficacy of sarilumab in AOSD was reported only in one patient who was successfully treated after developing resistance to TCZ.[57] The rationale of switching to sarilumab in TCZ-resistant subjects derives from the data obtained from the ASCERTAIN EXTEND trial (NCT01146652) on patients affected by rheumatoid arthritis.[58] The hypothesis of using sarilumab in refractory cases relies on the fact that in systemic AOSD the high levels of IL-6 may overwhelm the neutralizing capability of TCZ, therefore the direct inhibition of the IL-6 receptor might help to reduce more thoroughly the pro-inflammatory activity of IL-6. The same trial (NCT01146652) evaluated the safety of sarilumab, showing that the incidence rate of adverse events of special interest was generally stable, without any signal for increased rate over time.

TNF-Alpha Inhibitors

Among TNF-α inhibitors, infliximab, etanercept, and adalimumab were the first biologicals used in single case reports or small series in the early 2000s.[59] The first employment of infliximab date to 2001, when it was administered i.v. at a dose of 3–5 mg/kg in three refractory Still's patients with success.[60] Other cases regarding the use of infliximab are reported in the literature.[61] Data with etanercept, the recombinant soluble form of the human 75-kDa TNF-receptor fusion protein, derive mostly from a small case series in which an improvement of the articular involvement has been observed after biweekly doses of 25 mg s.c in half of the patients with no occurrence of adverse reactions.[62] However, the convincing results with TNF-α inhibitors seen at the start were not confirmed by Fautrel et al,[63] who noticed a complete remission of symptoms only in five out of 20 patients treated with either infliximab or etanercept. Finally, data with adalimumab are mixed and scarce[64,65] and, for this reason, in AOSD other biological approaches are nowadays preferred to anti-TNF-alpha in terms of efficacy and safety. Indeed, a recent meta-analysis showed that the efficacy of TNFα inhibitors on

clinical and laboratory manifestations is significantly lower than that of other biologic treatments and the observed adverse reactions, including serious infections, may lead to TNFα inhibitors discontinuation.[66]

Other Therapeutical Approaches

Rituximab, a chimeric anti CD-20 monoclonal antibody, is approved for rheumatoid arthritis, but the experience in AOSD (administered at 375 mg/m^2 given twice at 4-week intervals) is limited and for selected cases.[67,68] Likewise, the employment of abatacept, a co-stimulation modulator that inhibits T-lymphocyte activation by binding to CD80 and CD86 and blocks the interaction with CD28, exhibited mixed and scarce results.[69,70] Concerning intravenous immunoglobulin (IVIGs) they were proved to be effective and well-tolerated at the usual dose of 2 g/kg in 2–5 days every month in half of the patients in two open-label studies;[71,72] however, they should be employed in selected cases or when life-threatening manifestations occur.

Novel Biologics Treatments

Alongside biologics that have now entered the therapeutic routine of AOSD patients, scientific efforts have produced new compounds with different pharmacokinetic and dynamic properties (Table 1). Oral small molecules such as JAK or new anti-cytokine have been developed, so AOSD patients refractory to a specific biologic drug could be easily switched to an alternative highly effective treatment.

IL-18 Inhibitors

IL-18 is a pro-inflammatory cytokine belonging to the IL-1 superfamily, whose activity is tightly regulated by natural IL-18 binding protein (IL-18BP). As previously described, elevated levels of IL-18 during the active phase of AOSD give it the role of a potential biomarker.[14] Actually, three IL-18 inhibitors are under evaluation; however, data on the clinical efficacy of IL-18 blockade is still limited.

Tadekinig Alfa

As recombinant human IL-18BP, tadekinig alfa binds IL-18 with a high affinity and in turn inhibits the secretion of TNF-α, IFN-γ, and IL-1.[73] The most comprehensive study is a Phase II clinical trial showing early clinical and laboratory efficacy independent of dosage (80 mg or 160 mg 3-times per week s.c.) in 23 patients with long-standing multidrug-resistant disease.[74] In fact, 50% of patients had previously been treated with csDMARD and with previous biologic agents in about one third of patients. The response rate was nearly 50% with an overall good safety profile. Similar to anakinra, the most frequent adverse event was injection site reaction; mild upper airway infections and arthralgia were also reported. A recent study evaluating the prolonged treatment with tadekining alfa reported a maintained clinical remission and dropped levels of free IL-18 in serum within 2 hours after injection.[75]

AVTX 007

AVTX 007 (formerly CERC 007, AEVI 007, or MEDI 2338) is a high affinity, fully human anti-IL-18 monoclonal antibody, being developed for the treatment of autoinflammatory diseases, potentially including AOSD, sJIA, and multiple myeloma. Early stage clinical development is underway in the USA (NCT04752371). The Phase I multicenter, open-label study plans to include 12 patients, six of whom will be administered AVTX-007 intravenous (i.v.) at a dose of 7 mg/kg. Based on safety results in the first cohort, six other participants will be administered a dose escalation or reduction of AVTX-007. Safety, tolerability, and efficacy will be evaluated.

APB R3

APB R3 is a long acting recombinant fusion protein composed of IL-18BP fused via a peptide linker to anti-human serum albumin Fab fragment (SAFA). SAFA is a platform technology to produce long-acting therapeutics by modifying antiserum albumin Fab avoiding lysosomal degradation and thereby prolonging the half life of the molecule. As at October 2021, early research of APB R3 is underway for the treatment of adult-onset Still's disease in South Korea.[76]

Table 1 Novel and Proposed Biologic Treatments for AOSD Patients

Novel Biologics	Type of Agents	Target	Indication	Status
Tadekinig alfa	Recombinant IL-18BP	IL-18	80 mg/160 mg 3-times per week s.c.	Phase II trial for AOSD
AVTX 007	Anti IL-18 mAb	IL-18	7 mg/kg i.v.	Phase I trail for AOSD
APB R3	IL-18BP/SAFA fusion protein	IL-18	na	Preclinical test for AOSD
Emapalumab	Anti-IFN-γ mAb	IFN-γ	6 mg/kg i.v., then 3 mg/kg every 3 days for 15 days, then twice-a-week for additional 2 weeks	Phase II trial for AOSD
Baricitinib	JAK1/2 inhibitor	JAK1/2	4 mg/day	Case reports
Tofacitinib	JAK1/3 inhibitor	JAk1/3	5 mg twice daily	Phase III trial for sJIA
Ruxolitinib	JAK1/2 inhibitor	JAK1/2	2.5 mg, 5 mg, or 10 mg twice daily depending on the body weight (≤10 kg, ≤20 kg, or >20 kg, respectively), oral	Case reports
Secukinumab	Anti IL17A mAb	IL-17A	na	Case reports
i.v. Anakinra	Recombinant IL-1RA	IL-1	300 mg/day	Case reports
Proposed Biologics				
Dapansutrile	Beta-sulfonyl nitrile	NLRP3	Oral	Phase II trial for gout
MCC950	Inflammasome assembly inhibitor	NLRP3	na	Preclinical studies
CY09	Inflammasome assembly inhibitor	NLRP3	na	Preclinical studies
Inzomelid	NLRP3 inhibitor	NLRP3	Oral	Phase I trial for adult CAPS
Tranilast	Anthranilic acid	NLRP3	0.3 g/day	Phase II trial for CAPS
Diacerein	Anthraquinone	Inflammasome complex	na	Preclinical studies
Belnacasan	Caspase 1 inhibitor	Caspase 1	na	Preclinical studies
A1-AT	Caspase 1 inhibitor	Caspase 1	na	Preclinical studies
Mavrilimumab	IgG4 mAb	GM-CSF-αR	na	Preclinical studies
Otilimumab	IgG1 mAb	GM-CSF	na	Preclinical studies
NEAT-1	lncRNA	PI3K/Akt/mTOR TRAF6-NF-kB	na	Preclinical studies
MIAT	lncRNA	TNF-α, IL-1β	na	Preclinical studies
THRIL	lncRNA	TNF-α	na	Preclinical studies

Abbreviations: IL, interleukin; BP, binding protein; s.c., subcutaneous; mAb, monoclonal antibody; i.v., intravenous; na: not available; IFN, interferon; JAK, janus kinase; RA, receptor antagonist; GM-CSF-αR, granulocyte-macrophage colony-stimulating factor alpha receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; lncRNA, long non-coding RNA.

Anti IFN-γ

IL-18 is a potent inducer of IFN-γ which has been found elevated in patients with macrophage activation syndrome complicating sJIA.[77] Recent reports[20,78] on the efficacy of an IFN-γ antibody (emapalumab) on cases of MAS

complicating sJIA has grown great expectations on the potential efficacy of novel therapeutic agent. However, data regarding the effectiveness and safety of the IFN-γ blockade in treating AOSD remain limited.

Emapalumab

Emapalumab is a fully human monoclonal antibody that neutralizes both free- and receptor-bound IFN-γ by inhibiting receptor dimerization and the signaling transduction.[79] The efficacy of emapalumab was recently assessed in a clinical trial enrolling 34 young patients with a diagnosis of primary HLH.[20] Although the 27 pretreated patients were reported to have worsened or reactivated disease, an unsatisfactory response, or adverse events, only 15% had fever, 70% thrombocytopenia, and 78% hyperferritinemia. However, the study by Locatelli et al[20] does not present convincing data for strong efficacy of emapalumab in patients with primary HLH. Recently, Gabr et al[80] reported that emapalumab effectively eliminated fever and improved laboratory outcomes of a patient with AOSD complicated by MAS.

JAK Inhibitors

Unlike the inhibition of targeted cytokines, Janus kinase (JAK) inhibitors can block a large variety of proinflammatory molecules through the competitive interaction with JAK region required for downstream JAK/STAT signaling. JAK inhibitors indeed prevent the effect of IL-6, IL-10, IFN-γ, IFN-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are strongly implicated in the AOSD pathogenesis.[81] Baricitinib and Ruxolitinib are more selective toward JAK1/2, while tofacitinib is more effective to JAK3.[82] Due to the modulating effect on the immune response, JAK inhibitors have a good chance of becoming a very promising treatment in heterogeneous disorders, such as AOSD. However, data regarding the effectiveness and safety of JAK inhibitors in treating AOSD remain limited to case reports.

Baricitinib

Baricitinib, a JAK1/2 inhibitor, was reported by Kacar et al[83] as effective in treating two AOSD patients refractory to csDMARDs and other biologics. The combination with anakinra effectively treated a patient with refractory AOSD;[84] this observation is partially confirmed by Gillard et al[85] in another case. The authors also reported two cases with a concomitant use of baricitinib and steroids but there was no response to therapy at the last follow-up.

Tofacitinib

Tofacitinib, a JAK1/3 inhibitor, has recently been approved by the FDA for polyarticular JIA and is currently under evaluation (5 mg twice daily) in a double-blind trial for sJIA (NTC03000439). At present, only case reports support the use of tofacitinib in Still's disease complicated by MAS,[86] as well as the studies on animal models of HLH.[87] Besides, a recent report revealed the successful use of tofacitinib in 14 patients with AOSD.[88]

Ruxolitinib

The JAK1/2 inhibitor ruxolitinib is known to significantly reduce the proliferation and activation of immune modulating IFN-γ and other cytokines on experimental murine models of HLH.[89] Therefore, ruxolitinib may be considered for patients with secondary HLH. Indeed, a pilot study in 12 children with secondary HLH showed a good clinical response after 28 days of oral treatment.[90] Partial response was also reported for two Still's patients with the concurrent use of steroids.[85]

Anti IL-17

An increase of IL-17 in AOSD has been reported[91] and is involved in the recruitment of neutrophils, thus contributing to the maintenance of the inflammatory phenotype.[92] Thus, the use of IL-17 inhibitors could be an effective and safe therapeutic option, especially in the chronic patients. However, more evidence and more treated cases are awaited.

Secukinumab

Secukinumab is a human monoclonal antibody that binds to and neutralizes IL-17A. It is currently approved in many countries to treat psoriasis, ankylosing spondylitis, non-radiographic axial spondyloarthritis (SpA), and psoriatic arthritis with a favorable safety profile. Mitrovic et al[93] reported a single case of an AOSD patient who achieved complete remission under secukinumab, after loss of efficacy to anakinra and MTX, after SpA onset. This observation could

suggest a phenotype shift rather than an overlap between the two diseases. Moreover, one has to keep in mind that the manifestations of SpA should be differentiated from the forms of Still's disease with chronic articular damage.

A New Strategy for Anti IL-1

The use of anti IL-1 agents is already known to give a fast and robust response in the majority of AOSD cases. Furthermore, both articular and systemic manifestations can respond to this approach, that has shown efficacy in specific organ involvements as well as in other systemic complications of diseases such as hyperinflammation, cytokine storm, and MAS.[32] In this context, on a larger series of patients with COVID-19 pneumonia, characterized by systemic hyperinflammation and cytokine storm, Pontali et al[94] reported the potential efficacy and safety of the early use of high doses of intravenous (i.v.) anakinra with or without glucocorticoids. We personally treated an AOSD patient with 1 mg/kg of oral prednisone and IL-1 inhibition with i.v. anakinra (100 mg every 8 hours) with clinical improvement in less than 24 hours [personal communication].

Proposal Future Treatments

Although anti-cytokine agents are characterized by a good safety profile that allows long periods of continued treatment, it would be reasonable to believe that the risks may outweigh the benefits once an inactive disease state is achieved. In these regards, new strategies for the treatment of the adult form of Still's disease are now under consideration.

NLRP3 Inflammasome Inhibitors

Great attention was recently addressed to the blockade of the inflammasome NLRP3 and its components, that are well-known to be involved in autoinflammatory processes. So far, different compounds able to bind NLRP3 and consequently the release of IL-1 have been investigated.

Dapansutrile

Dapansutrile (OLT1177), an orally active beta-sulfonyl nitrile, functions as a direct inhibitor of NLRP3 and it is currently tested in gout.[95] The first proof-of-concept, phase II trial on adult gouty patients was recently carried out in The Netherlands and dapansutrile was orally administered at variable dosages, eliciting a significant reduction of joint tenderness and swelling.[96] In addition, a dampening of pro-inflammatory cytokines, and in particular IL-6, was noticed. Despite the limitations of this preliminary study, the combination of its efficacy, the good safety profile, and the oral administration make dapansutrile a promising therapeutical option not only for gouty patients, but it is conceivable it could also be employed in AOSD, in particular in those patients having a predominant articular involvement.

Other NLRP3 Inflammasome Complex Inhibitors

By now, other blockers of NLRP3 or its components are under examination. MCC950 directly binds to the NACHT domain and inhibits the inflammasome assembly by hampering ASC oligomerization.[97] This compound was proven to reduce IL-1β production in vivo and in mouse models of CAPS.[98] A similar mechanism was described for CY09 which affects the NLRP3 ATPase activity hindering the assembly of NLRP3 itself.[99] On CAPS there are currently ongoing studies with Inzomelid (NCT04015076), another oral selective NLRP3 inhibitors, and tranilast (NCT03923140), an anthranilic acid able to bind the NACHT domain;[99] diacerein, an anthraquinone compound, may downregulate both NLRP3/caspase-1/IL-1β either the IL-6/pSTAT3 axis,[100] while belnacasan (VX-765) and A1-AT target directly the caspase I component blocking the IL-1β release.[95,101] Despite the studies on these inflammasome inhibitors currently being at an early stage, it is conceivable they could have future employment in Still's disease.

Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Another target that has been investigated in recent times is GM-CSF.[102] GM-CSF can upregulate neutrophils and macrophages, can induce the formation of NETs, and in turn enhances the production of pro-inflammatory cytokines by binding to its receptor.

Mavrilimumab and Otilimab

In this context, mavrilimumab (CAM-3001), an IgG4 monoclonal antibody (mAB), and otilimab (MOR-103), an IgG1 mAB, can bind the GM-CSF-alpha receptor and GM-CSF, respectively, preventing the release of pro-inflammatory cytokines. Both otilimab and mavrilimumab were proved to be effective and safe in rheumatoid arthritis patients, providing a significant reduction of DAS28-CRP in the clinical trials carried out by now.[103–105] In addition, mavrilimumab was recently employed for the treatment of severe COVID-19 pneumonia, relying on the fact that the inhibition of GM-CSF could curb the hyperinflammation provoked by the virus.[106] For this reason, it is conceivable these inhibitors could be used for treating both the chronic articular pattern and the systemic form of Still's disease.

Long Non-Coding RNAs

Recently, the expression signature of long non-coding RNAs (*lncRNAs*) in AOSD patients was investigated to understand whether they could correlate with the disease phenotype. *LncRNAs* are known to be central regulators of the immune responses[107–110] and their expression is associated to certain pathways or cytokines that contribute to AOSD pathogenesis. For example, *NEAT-1* (nuclear enriched abundant transcript 1) levels, detected in serum samples of AOSD patients, strongly correlate with the expression of other *lncRNAs* after cyclosporine or anti IL-6, while they were not observed before starting the treatments. *NEAT-1* can upregulate the PI3K/Akt/mTOR and TRAF6-NfkB axis and in turn regulates the production of IL-6, IL-17, and TNF- α. Similarly, *MIAT* (myocardial infarction associated transcript) was described as a suppressor on TNF-α and IL-1β, while, on the other hand, *THRIL* (TNF-alpha and hnRNPL-related immunoregulatory lincRNA) was found to upregulate TNF-α; in AOSD indeed, high levels of *MIAT* and a low expression of *THRIL* were observed in comparison to healthy controls.[111]

Taken together these results suggest that, according to the different type of *lncRNA* signature detected, it is possible to understand the axis, or the group of cytokines mostly involved in AOSD pathogenesis and, thus, managing properly the patients contributing to the treat-to target strategy.

Conclusions

Recent advances in biologic drug development have had a major impact on AOSD patients in terms of improved quality-of-life and coping strategies. Specific inhibition of IL-1 and IL-6 is now considered a safe and effective therapy to better control the disease. As reported in this work, there are currently a number of biological agents, possible effective targets for achieving AOSD control and remission. The early and targeted blockade of the inflammation is critical for treatment, and early biological therapies in an appropriate window-of-opportunity is expected in the near future.

Disclosure

The authors report no conflicts of interest in this work.

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