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Editorial

Biological agents in the management of adult-onset Still's disease

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1. Clinical and biological manifestations of adult-onset Still's disease

Adult-Onset Still's disease (AOSD) is a rare (incidence ranges between 1 and 10 per million inhabitants) autoinflammatory disease that is characterized by a clinical triad, including high-spiking fever, arthralgias (± arthritis) and erythematous evanescent skin rash. These clinical manifestations are sometimes associated with sore throat, lymphadenopathies, hepato-splenomegaly, and serositis. Clinical presentation is highly variable, including monocyclic remitting disease, polycyclic inflammatory flares interspaced by quiescent periods, and chronic inflammatory manifestations. Chronic arthritis leading to joint destruction and ankylosis may represent the predominant clinical presentation in chronic AOSD. Life-threatening complications such as myocarditis and macrophage activation syndrome (MAS) can occur. Some biological abnormalities are highly suggestive of AOSD, including leukocytosis with neutrophilia and hyperferritinemia. Nonetheless, none of the clinical and laboratory features are specific of AOSD and the diagnosis should be considered only after careful exclusion of other diseases such as autoimmune and infectious diseases, and malignancies. Approximately twenty-five years ago, Yamaguchi et al. have established diagnostic criteria based on above-mentioned clinical and biological signs and exclusion diagnosis that are still largely used [1]. A children counterpart of AOSD, currently termed systemic onset juvenile idiopathic arthritis (SoJIA) shares similar manifestations but is ten times more frequent than AOSD. Sir George Frederic Still initially described SoJIA in 1897, followed by the first description of AOSD seven decades later by Bywaters [2].

2. AOSD pathogenesis

The etiology of AOSD is still obscure and little is known about its pathophysiology. Elevated levels of many proinflammatory cytokines, including interleukin (IL)-8, IL-18, tumor necrosis factor (TNF)-α and IL-6 have been detected in the serum and tissues of patients. The disease is characterized by a Th1 polarization of CD4+ T cells, neutrophils and macrophage activation, and NK cell dysfunction. Although specific genetic markers have not been identified yet, AOSD shares common clinical and biological manifestations with autoinflammatory monogenic conditions characterized by periodic fever, in which excessive IL-1 signaling has been demonstrated such as cryopyrinopathies and familial Mediterranean fever. Given these similarities and the absence of overt markers of autoimmunity or infection, AOSD has been classified within the spectrum of autoinflammatory disorders (reviewed in [3]).

3. Management of AOSD

The low prevalence of AOSD has been a major limitation for the development of clinical trials, and thus its management has remained largely empirical. First line treatment comprises non-steroidal anti-inflammatory drugs (NSAIDs) that are usually replaced by corticosteroids once the diagnosis is established. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), especially methotrexate, are often used in case of resistance to corticosteroids or as corticosteroid sparing agents. Despite the use of csDMARDs, AOSD can remain active and high dose glucocorticoids are sometimes required to control inflammatory manifestations. The demonstration that biologic DMARDs (bDMARDs) such as IL-1 and IL-6 antagonists are effective in SoJIA has been considered by many clinicians as indirect evidence of the efficacy of these agents in AOSD. In the next paragraphs we will review the effect of bDMARDs in AOSD.

Tumor necrosis factor (TNF)-α inhibitors were the first bDMARDs that have been used in AOSD. In the early 2000s, three small cohorts of corticosteroid resistant and/or csDMARDs refractory patients demonstrated the efficacy of infliximab in AOSD [4]. Both systemic and articular manifestations improved, along with inflammatory biological markers. The effect of etanercept in refractory AOSD has been examined in an open-label prospective study including mainly patients with arthritis [5]. Among 12 patients included in this study, 7 responded to etanercept. Systemic manifestations improved in one-third of the patients. A French survey described induction of complete remission of AOSD by etanercept in 1/10 cases [6]. Literature is far too scarce to draw any conclusion about the effect of adalimumab on AOSD [7]. TNF-α inhibitors showed a favorable safety profile with injection site reactions (ISR) as the only side effect described in a few cases.

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Tocilizumab, a monoclonal humanized anti-IL-6R antibody, has proven to be efficacious in a phase 3 randomized placebo-controlled clinical trial in NSAID and corticosteroid resistant SoJIA [8]. No clinical trial was performed in AOSD but many case reports and retrospective studies were published that were recently reviewed [9]. In this systematic review, the overall remission rate was estimated at 85.4%. Both clinical and biological features of AOSD were well controlled by tocilizumab, which also showed a marked corticosteroid-sparing effect. Except for a few cases of MAS of unknown cause, but that may be attributed to the treatment, tocilizumab was safe. Finally, IL-6 antagonism was also beneficial in patients who failed to respond to other bDMARDs.

The rational regarding the use of agents targeting IL-1 has been provided by *ex vivo* studies showing that peripheral blood mononuclear cells from healthy donors cultured in the serum from patients with SoJIA produced increased levels of IL-1β. The results led to the use of anakinra in a few patients with refractory SoJIA patients with marked efficacy [10]. These results were confirmed in a randomized placebo controlled clinical trial [11]. Two phase 3 randomized placebo-controlled clinical trials with canakinumab, a fully human monoclonal anti-IL-1β antibody, showed significant benefit of canakinumab as compared to placebo [12]. Cases of MAS have been reported in patients treated with canakinumab even in those with well-controlled SoJIA [13]. The efficacy of rilonacept, a fusion protein that includes IL-1R sequences and binds to IL-1, was studied in two randomized double-blind placebo-controlled trials. The first study showed sustained improvements regarding articular and systemic manifestations in the open label extension despite the absence of significant differences between rilonacept and placebo in the 4-week double-blind phase [14]. In the second study, time to achieve a clinical response was significantly shorter in the rilonacept than in the placebo arm [15]. Junge et al. extensively reviewed numerous case reports, case series and national surveys that described the effect of anakinra on AOSD, and also mentioned a few publications reporting the use of rilonacept or canakinumab in this disease [16]. Rilonacept allowed at least partial remission in all 11 treated cases with refractory AOSD, some of which failed to respond to anakinra. Canakinumab showed a good efficacy, although in a limited number of cases, with complete or partial remission rates of 70% and 20%, respectively [16]. A phase 2 randomized placebo controlled clinical trial is in progress and may provide important information regarding the efficacy of canakinumab in AOSD (NCT02204293). Anakinra led to complete or partial remission in respectively 73% and 18% of cases. It was effective on articular and systemic manifestations, but extra-articular manifestations seemed more rapidly and completely controlled, while arthritis could persist. Moreover, glucocorticoids could be tapered or stopped in more than half of anakinra-treated AOSD patients [16]. The first published randomized clinical trial testing the efficacy of a bDMARD in cortico-dependant AOSD compared anakinra to csDMARDs in 22 patients [17]. Remission was achieved in 6/12 anakinra-treated patients at week 24 as compared to 2/10 patients on csDMARDs.

Recent evidence indicates that IL-18 represents an interesting target in the management of AOSD. IL-18 is a pro-inflammatory cytokine belonging to the IL-1 family, the activity of which is tightly regulated at two levels. First, IL-18 is produced as a biologically inert pro-peptide that requires to be processed by caspase 1 to become activated and subsequently released out of the cells. Second, IL-18 bioactivity is regulated by IL-18 binding protein, a naturally occurring inhibitor present at high levels in the circulation. IL-18BP binds with high affinity to mature IL-18, thus preventing its interaction to its cell surface receptors. Several studies have reported the presence of elevated IL-18 levels in AOSD patients in correlation with active phases of the disease. However, these data did not distinguish IL-18 complexed with IL-18BP from free unbound IL-18. Recently, by using an ELISA that specifically recognizes free IL-18, we showed that serum levels of free IL-18 were elevated in AOSD and correlated with clinical signs of disease activity as well as with ferritin levels [18]. Of note, elevated serum levels of free IL-18 were also found in SoJIA and MAS patients [19].

The effect of IL-18 targeting in AOSD has been examined in a recent multicenter, open-label, dose-escalating, phase 2 clinical trial with recombinant human IL-18BP (tadekinig α) [20]. Twenty-three patients with active AOSD despite corticosteroids and/or DMARDs, sometimes with a past history of bDMARDs treatment, were enrolled. Ten and thirteen patients were assigned to receive subcutaneous injections of 80 mg and 160 mg of tadekinig α three times per week, respectively. After three weeks, half of patients from both groups achieved predefined response criteria, including a reduction of at least 50% of baseline CRP levels and normalization of body temperature. Among the patients initially treated with 80 and 160 mg tadekinig α, 50% and 58%, respectively, displayed a reduction of 70% or normalization of CRP levels or a normalization of ferritin levels and at least a 20% decrease of joint count at week 12. At week 3, patients who did not respond to 80 mg tadekinig α were up-titrated to 160 mg. Treatment with tadekinig α significantly decreased skin rash and was associated with a glucocorticoid sparing effect. In addition, several biomarkers of disease activity, including ferritinemia, neutrophilia, IL-6, S100A12, S100A8/9, transaminases, decreased significantly with tadekinig α. Injection site reactions were the most frequent adverse event.

4. Conclusion

Due to its rarity, prospective controlled clinical trials are scarce in AOSD and therapy remains essentially empirical. Recent data regarding the efficacy of IL-6 and IL-1 antagonists in SoJIA provided indirect evidence of the efficacy of these agents in AOSD. Indeed, the evidence regarding the efficacy of these agents in AOSD rely primarily on case series and retrospective reports. Despite these limitations, canakinumab was recently licensed for the treatment of AOSD by the EMA. Targeting IL-18 with Tadekinig α has shown promising results in a recent phase 2 clinical trial.

Disclosure of interest

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