

Treatment advances in systemic juvenile idiopathic arthritis

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Abstract

Systemic juvenile idiopathic arthritis (JIA) is an autoinflammatory condition that is distinct from other forms of childhood arthritis. Recently, biologic agents that specifically inhibit the cytokines interleukin (IL)-1 and IL-6 have demonstrated remarkable clinical effectiveness and confirmed the importance of these cytokines in the disease process. Future studies are likely to optimize the care of children with systemic arthritis and further elucidate the disease pathogenesis.

Introduction

The advent of biologic therapeutic agents with highly specific molecular targets has dramatically improved clinical outcomes for many patients and has profoundly changed the field of rheumatology over the last 15 years. In addition to providing marked clinical benefit, these new therapeutic agents can help confirm the pathogenic role of their molecular targets in disease processes. Recent developments in the treatment of systemic JIA demonstrate both of these beneficial features of biologic agents.

Characteristics of systemic JIA

JIA comprises a heterogeneous collection of conditions that all begin prior to age 16 years, persist for at least 6 weeks, and have an unknown etiology [1]. Systemic JIA is one of seven categories of JIA and represents the childhood-onset equivalent of adult-onset Still disease. For many years, systemic JIA has been distinguished as being clearly different from the other categories of JIA. Systemic JIA has a distinct clinical phenotype that typically includes once-daily high-spiking fevers accompanied by one or more of the following: evanescent rashes, generalized lymphadenopathy, hepatosplenomegaly, and serositis [1]. These “systemic features” are often more clinically significant than the arthritis component at the time of disease onset. Historically, a significant minority of patients with systemic JIA develops a severe, destructive polyarthritis that

frequently persists even after the systemic features may subside [2,3]. This particular disease phenotype likely represents the most disabling of all the different manifestations of JIA.

Systemic JIA appears to be best classified as an “autoinflammatory” disease, rather than an autoimmune disease [4-7]. The distinction between autoimmune and autoinflammatory is made according to the immune cells thought most responsible for the underlying disease pathology. When the adaptive immune response cells are most responsible, as typically evidenced by auto-reactive antigen-specific T lymphocytes and high-titers of auto-antibodies produced by B lymphocytes (e.g. type I diabetes mellitus), the disease is termed autoimmune. When the innate immune system (e.g. monocytes and neutrophils) is the predominant cause of disease (e.g. familial Mediterranean fever), this is termed an autoinflammatory condition.

In contrast to the other categories of JIA, systemic JIA is very strongly associated with macrophage activation syndrome (a form of secondary hemophagocytic lymphohistiocytosis), a potentially fatal disorder manifested by marked cytopenia, liver dysfunction, coagulopathy, central nervous system disorders, and, in its most extreme forms, multiple organ dysfunction syndrome. There is debate over whether macrophage activation syndrome is a complication of systemic JIA or rather the most severe

manifestation of systemic JIA among a subset of those children who are genetically predisposed [7-12].

Treatment of systemic JIA

Systemic JIA has been treated with large doses of systemic glucocorticoids (e.g. prednisone) given chronically in order to attempt to achieve disease control. In some cases, adequate disease control could not be obtained, even with the use of high-dose glucocorticoids. In other cases, the numerous adverse drug effects from prednisone (e.g. excessive weight gain, osteoporosis and fracture, hypertension, hyperglycemia, cataracts, avascular necrosis of the bone, growth suppression, and infections) were nearly as harmful as the disease itself. Traditional therapeutic agents used to spare the use of glucocorticoids in many rheumatologic diseases (e.g. methotrexate) are not very effective against systemic JIA [13,14]. Even the tumor necrosis factor inhibitors, which proved to be a landmark development in the treatment of rheumatoid arthritis, polyarticular JIA [15,16], and other autoimmune diseases, failed to provide benefit for most patients with active systemic features [14,17,18].

The precise pathogenesis of systemic JIA remains incompletely understood. Nevertheless, the pro-inflammatory cytokines IL-1 β and IL-6 were implicated in several translational studies [7,9,19-23] and were identified as potential therapeutic targets. Subsequently, IL-1 and IL-6 inhibitors have demonstrated remarkable effectiveness for many patients with systemic JIA.

Inhibition of IL-1

IL-1 β had been suspected to be a primary driver of systemic JIA disease activity. The first published report of successful therapy of systemic JIA with IL-1 inhibition occurred in 2004 with the case report of remarkable response in two patients whose severe disease manifestations were previously refractory to other therapies [24]. Around this same time, other investigators found that serum from children with systemic JIA induced the transcription of IL-1 β related genes in the peripheral blood mononuclear cells of healthy controls [19]. Based in part on this finding, these investigators treated systemic JIA with the IL-1 inhibitor anakinra and produced a dramatic clinical response, including disease remission in seven of nine patients who were refractory to prior therapies [19].

These encouraging initial reports led to a marked increase in the use of anakinra for the treatment of systemic JIA in clinical practice, as reported in several case series. An early report showed a remarkable response to treatment with anakinra in 10 of 21 patients and suggested that there may be a better response to anakinra therapy among patients with active arthritis in only a few joints, compared to those

with arthritis in many joints [25]. Other case series published around this time showed remarkable benefit among many, but not all, users of anakinra [26,27]. A larger retrospective case series of 46 patients with systemic JIA was limited to children who received anakinra as part of their initial glucocorticoid-sparing treatment regimen. This study revealed that anakinra produced a complete clinical response among 59% of patients [28]. Contrary to long-standing treatment practices, 10 children in this report received anakinra as monotherapy (without concurrent systemic glucocorticoid use), and 80% of these 10 had a complete response. Subsequently, in 2011, a small, placebo-controlled, randomized trial was published that demonstrated the efficacy of anakinra for the treatment of systemic JIA [29]. In this study, 8 of 12 patients who received anakinra achieved the primary outcome of the study (absence of fever and overall 30% improvement in clinical status), compared to 1 of 12 patients who received placebo.

In addition to anakinra, other IL-1 inhibitors have been developed and subsequently studied for systemic JIA. Canakinumab was recently shown to be very efficacious against systemic JIA in a randomized, placebo-controlled trial [30]. In this study, 67% of subjects experienced at least 70% clinical improvement and 30% achieved clinically inactive disease 29 days after a single subcutaneous dose of canakinumab. Later in the study, a substantial proportion of patients were able to successfully significantly decrease their systemic glucocorticoid doses according to pre-specified clinical parameters. Another IL-1 inhibitor, rilonacept, appears to be very efficacious for systemic JIA also, as evidenced by the results of a long-term extension of an exploratory study [31], as well as preliminary results from a placebo-controlled randomized clinical trial [32].

Unsurprisingly, IL-1 inhibitors appear to be similarly effective for the treatment of adult-onset Still disease as for systemic JIA, as evidenced by one small randomized study of anakinra [33] and uncontrolled reports of the use of anakinra [27,34], canakinumab [35], and rilonacept [36].

Inhibition of IL-6

While inhibition of IL-1 with anakinra was being adopted in North America and Europe for the treatment of systemic JIA, inhibition of IL-6 was producing dramatic clinical benefit in Japan. An early report published in 2005 showed an abrupt reduction in disease activity in 10 of 11 patients who received IL-6 inhibition with tocilizumab, a monoclonal antibody against the IL-6 receptor [37]. In 2008, a placebo-controlled randomized trial was published demonstrating the efficacy of tocilizumab [38], and the long-term open label extension of this trial showed sustained effectiveness for most patients [39]. In 2012, the TENDER trial was published and demonstrated

results similar to the Japanese study among patients located in Europe and North and South America [40]. There was a remarkable response among most children who received tocilizumab; 71% of patients improved clinically by at least 70% within 3 months of starting tocilizumab, compared to 8% who received placebo. During the open-label extension phase of the trial, 28% of patients had clinically inactive disease one year after initiating tocilizumab.

Similar to the IL-1 inhibitors, IL-6 inhibition with tocilizumab appears to effectively treat adult-onset Still disease too, as suggested by numerous uncontrolled observations of previously treatment-refractory patients [41,42].

Safety

Fortunately, all of the new IL-1 and IL-6 inhibitors mentioned appear to be relatively safe, with the primary worrisome adverse effect being an increased rate of infection. This infection risk has not yet been fully characterized, but it appears reassuring, particularly when considering the relative risks compared to children with systemic JIA who are alternatively being treated with high doses of glucocorticoids, which are known to significantly increase the risk of infection [43].

Periodic monitoring of blood cell counts and liver enzyme levels is indicated for patients receiving IL-1 or IL-6 inhibitors. It appears that abnormalities in these tests are more frequent with tocilizumab treatment compared to the other mentioned biologic agents [40].

In the clinical trials of canakinumab and tocilizumab, there were deaths observed as a result of macrophage activation syndrome [30,40]. This likely reflects the severity of the underlying disease among patients enrolled in these studies; however, some authors speculate that IL-1 or IL-6 inhibitors may promote the development of macrophage activation syndrome in some patients [44,45]. Irrespective of a possible casual association, the use of IL-1 and IL-6 inhibitors clearly does not necessarily prevent the development of macrophage activation syndrome. Nevertheless, the observation that anakinra can effectively treat macrophage activation syndrome in many patients is reassuring [46,47].

One worrisome observation has been a possible recent increase in the development of serious pulmonary conditions, such as pulmonary arterial hypertension, among children with severe systemic JIA. Whether these pulmonary conditions, which are not typically associated with systemic JIA, are a result of treatment with IL-1 or IL-6 inhibitors or whether they are a result of severe disease

and/or macrophage activation syndrome is currently unclear and warrants further investigation [48].

Treatment recommendations

In direct response to these recent advances in therapy, the American College of Rheumatology updated their treatment recommendations for systemic JIA in 2013 [14]. Biologic agents that inhibit IL-1 (anakinra or canakinumab) or IL-6 (tocilizumab) are recommended as the first glucocorticoid-sparing therapies for children with active systemic features. This is in contradistinction to the other categories of JIA, for which a variable trial of non-biologic agents (primarily methotrexate) is recommended prior to the use of biologic agents [49]. Additionally, in some instances, IL-1 or IL-6 inhibitors are considered appropriate to use prior to or in the absence of systemic glucocorticoids [14]. This is a significant departure from the treatment approach that has been used for several decades and may diminish the adverse effects of glucocorticoids commonly associated with the treatment of systemic JIA.

Current controversies and future directions

Some investigators have hypothesized that the systemic JIA disease process is initially driven by IL-1 β for a variable period of time. This is then followed by a chronic disease phase in which IL-1 β plays a less key role [7]. However, currently the clinical evidence is not strong enough to support or refute this hypothesis. In the aforementioned large case series of patients treated with anakinra as the first glucocorticoid-sparing agent, there appeared to be a significant reduction in the proportion of children who developed the chronic polyarthritis manifestations of the disease [28]. An earlier case series reported that children with established polyarthritis had a worse clinical response to treatment with anakinra; those without active systemic features did not exhibit a poorer response, although the number of such patients was very small [25]. In the published clinical trial of canakinumab, children with polyarthritis generally exhibited a robust response to treatment that was similar to those without polyarthritis. A differential response to therapy based on the presence or absence of systemic features could not be evaluated, because all children enrolled in the trial had active fever [30]. As further clinical and translational studies are performed, the role of IL-1 β and its possible transient importance earlier in the systemic JIA disease process will become more certain.

In contrast, according to clinical trial results thus far, IL-6 inhibition may be effective at any stage in the disease process. Secondary analyses of the most recent tocilizumab clinical trial revealed no differences in response rates between those patients with and without active

systemic features or those with and without chronic polyarthritis [50].

Anakinra, canakinumab, and rilonacept all inhibit IL-1 in different ways that may prove clinically important and subsequently inform investigators about the role of IL-1 β in systemic JIA. The role or importance of IL-1 α , which is currently poorly understood, may also become clearer. Anakinra is a receptor fusion protein of the naturally occurring IL-1 receptor antagonist and effectively blocks soluble IL-1 β and IL-1 α . Canakinumab is a monoclonal antibody against IL-1 β and does not bind IL-1 α . By binding IL-1 β , canakinumab decreases endogenous production of IL-1 receptor antagonist. Rilonacept is a fusion protein comprising portions of the IL-1 receptor and IL-1 receptor accessory protein. Rilonacept effectively binds IL-1 β , IL-1 α , and IL-1 receptor antagonist. If significant differential clinical effects are observed among these different IL-1 inhibitors, then these may provide further insights into the pathogenesis of disease.

There are differential treatment responses to the IL-1 and IL-6 inhibitors in children with systemic JIA that appear to be attributable to currently unknown patient characteristics. Both clinical trials of canakinumab and tocilizumab enrolled patients who had previously failed treatment with anakinra, and there did not appear to be a major difference in clinical response based upon prior anakinra use [50]. One possible explanation could be inadequate dosing of anakinra, as it appears that smaller children require a higher dose per kilogram of body weight than older children or adults [28]. Alternatively, there may be true differential effectiveness in individual patients. If this is true, then identifying why particular patients respond best to a particular therapeutic agent may further inform our understanding of the pathogenesis of systemic JIA. An ongoing observational comparative effectiveness study of the initial treatment of systemic JIA that will assess clinical outcomes for children treated with IL-1 inhibitors, IL-6 inhibitor, methotrexate, or systemic glucocorticoids alone may help answer important questions about treatment [51].

Another area of significant interest is the treatment of macrophage activation syndrome. Anakinra has been shown to be effective in the treatment of macrophage activation syndrome in uncontrolled reports [46,47]. To date, similar reports have not been published about canakinumab or tocilizumab. If future studies demonstrate differences in the relative effectiveness of treating macrophage activation syndrome, this will very likely influence clinical practice and inform investigators about the pathogenesis of this disease manifestation.

In summary, there have been several recent exciting developments in the treatment of systemic JIA. Highly effective biologic therapies are benefiting patients clinically and providing investigators with clues about the underlying mechanisms of disease. Much remains to be learned about the disease pathogenesis and the optimal treatment of patients.



Abbreviations

IL, interleukin; JIA, juvenile idiopathic arthritis.

Disclosures

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