New insights in systemic juvenile idiopathic arthritis—from pathophysiology to treatment

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Systemic juvenile idiopathic arthritis (SJIA) is characterized by the clinical features of remitting fever, a typical skin rash and arthritis. Many patients show frequent flares or persistent disease activity with significant morbidity and serious complications. Recent investigations in the pathophysiology of SJIA have focused on mediators of the innate immune system. Especially IL-1β, IL-6 and IL-18 as well as phagocyte-specific S100-proteins (S100A8, S100A9 and S100A12) are correlated with disease activity and secondary complications. Beside IL-6 all these molecules are secreted by a so-called alternative pathway. A loss of control of the alternative secretory pathway seems to be involved in release of pro-inflammatory proteins leading to the inflammatory process of SJIA. These insights lead to new promising treatment approaches, like application of recombinant anti-IL-1 receptor antagonist or anti-IL-6 receptor antibodies in patients resistant to conventional anti-inflammatory treatment. First case studies show improvement and remission on therapy in a substantial portion of these patients. In this review, we summarize the current knowledge of pathophysiology and experiences in the treatment of SJIA.

KEY WORDS: Systemic juvenile idiopathic arthritis, Innate immune system, Treatment, Calgranulin, Calprotectin.

Introduction

In 1897, George Frederic Still summarized his observations on 12 children with systemic juvenile idiopathic arthritis (SJIA) [1]. It was the first systematical description of this typical systemic inflammatory disease in childhood presenting the clinical characteristics of SJIA. SJIA is one of the most severe systemic inflammatory diseases in childhood. Many patients show frequent flares or persistent disease activity with significant morbidity and serious complications, especially those children with a therapy-resistant course. Most patients need combined treatment with glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) for years [2]. Over the last decades SJIA has been assigned to the large group of autoimmune diseases, however, no specific autoantigens or autoantibodies have been identified so far. In contrast, activation of the innate immune system dominates the clinical picture of SJIA. Novel data about the pathogenesis of SJIA underline the relevance of an uncontrolled innate immune system as an important mechanism of the disease indicating that SJIA is primarily an auto-inflammatory rather than an autoimmune disease. These insights lead to new promising treatment approaches, like application of recombinant anti-IL-1 receptor antagonist or anti-IL-6 receptor antibodies in treatment-resistant courses of SJIA with at least preliminary success.

SJIA is defined as a subtype of juvenile idiopathic arthritis (JIA), characterized by the clinical features of remitting fever, a typical erythematous skin rash and arthritis. SJIA is a typical disease of childhood, and in contrast to the other subtypes of JIA shows no preference regarding gender or time of disease onset in the first decade of life. Beginning of SJIA in adolescents is rare and adult onset is reported only in a few cases. In Europe, the incidence of JIA is about 10:100000/yr of which SJIA represents 6-20% [3, 4]. The International League of Associations for Rheumatology classified SJIA as an arthritis in children starting before 16 yrs of age associated with a daily quotidian fever of 39°C (or more) persisting for more than 2 weeks and at least one of the following clinical features of systemic inflammatory origin: an evanescent rash, lymphadenopathy, hepatosplenomegaly or serositis (e.g. pleuritis or pericarditis) [5, 6]. The outstanding clinical feature that distinguishes SJIA from other subtypes of JIA is remitting fever up to more than 39°C. The second clinical sign of certain diagnostic value in SJIA is a more or less typical transient cutaneous rash (Fig. 1A). Arthritis completes the trias that often confirms the diagnosis of SJIA. In the beginning, arthritis may be present with an oligoarticular and asymmetric pattern. However, in most cases with remitting or persisting disease activity, arthritis progresses to polyarticular disease. Many children with SJIA show frequent relapses or persisting systemic disease activity accompanied with the risk of significant chronic morbidity, as there are joint destruction, chronic pain on motion or immobilization, significant growth retardation and the risk of severe infections. Independent of the disease course secondary macrophage activation syndrome (MAS) is a well-known complication in SJIA.

In this review, we summarize the current knowledge of pathophysiology and experiences in the treatment of SJIA.

New aspects of pathogenesis of SJIA

Patients with SJIA do not show signs of lymphocyte-mediated antigen-specific immune responses. The typical clinical signs of SJIA are rather associated with granulocytosis, thrombocytosis and up-regulation of acute-phase reactants indicating an uncontrolled activation of the innate immune system. Both during initial manifestation as well as during flares of SJIA there is an early activation of the vascular endothelium with expression of leucocyte adhesion molecules like E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and subsequent recruitment of a perivascular infiltrate of neutrophils and pro-inflammatory activated monocytes [7]. Important pro-inflammatory cytokines secreted by these phagocytes are tumour necrosis factor-α (TNF-α), IL-1 and IL-6.

Cytokine networks in SJIA

TNF plays a central role in different experimental models of arthritis [8] and specific blockade of TNF has been shown to be very efficient in various forms of rheumatoid arthritis [9]. However, compared with other forms of JIA, patients with SJIA show a limited response to anti-TNF treatment [10].
Recent data indicate a prominent role of IL-1 in SJIA. Serum of SJIA patients induces the transcription of genes of the innate immune system including IL-1 in peripheral blood mononuclear cells (PBMCs). In addition, activated monocytes from patients with SJIA secrete significantly higher amounts of IL-1β in comparison with monocytes of healthy controls, whereas release of TNF-α and IL-6 was not significantly different in both groups [11]. In addition, another member of the IL-1 cytokine family, IL-18, shows very high serum concentrations with high specificity for SJIA compared with other forms of JIA [12, 13]. Active IL-1β is secreted by several inflammatory cell types including monocytes and macrophages. IL-1 acts on the bone marrow and stimulates granulopoiesis resulting in neutrophilia of the peripheral blood. IL-1 receptors of the brain activate the thermoregulation of the hypothalamus and lead to fever. IL-1β also activates IL-1 receptors on endothelial cells that may cause cutaneous rash in SJIA and result in the production of IL-6 [14]. IL-6 on the other hand stimulates hepatocytes and induces the production of several acute-phase proteins like C-reactive protein and serum amyloid A. Serum levels of IL-6 are markedly elevated in patients with SJIA and correlated with systemic features of the disease, especially with periods of fever and platelet counts as well as severity of joint involvement [15]. In synovial fluid of SJIA patients, IL-6 concentrations were significant higher than in other subtypes of JIA [16]. Growth impairment, increased osteoclastogenesis and reduced osteoblast activity can be induced by chronic overexpression of IL-6, shown in IL-6 transgenic mice and reflect skeletal changes similar to patients with SJIA [17]. In persisting disease activity of SJIA serum IL-6 concentrations are negatively correlated with insulin-like growth factor-1 (IGF-1) and IGF-binding protein 3, while growth hormone productions remain correlated with insulin-like growth factor-1 (IGF-1) and IGF-2 [23].

Serum levels of IL-6 are markedly elevated in patients with SJIA compared with other forms of JIA [12, 13]. Active IL-1β and IL-6 was not significantly different in both groups [11]. First clinical experiences with IL-6 receptor antibody treatment revealed efficacy regarding control of disease activity in SJIA [21, 22] (see subsequently).

Adult-onset Still’s disease (AOSD) is the analogous of SJIA and is also characterized by spiking fever, rash and arthritis. In patients with AOSD, elevated levels of cytokines, as IL-1, IL-6; TNF-α and IFN-γ were found in active disease [23]. In accordance with these findings effective treatment has been reported in recent years even in AOSD with biologic agents, like anti-TNF-α, anti-IL-1 and anti-IL-6 [23].

The pathogenesis of MAS, a typical complication in SJIA, is unknown. However, there are clinically similar features in primary haemophagocytic lymphohistiocytosis (HLH) and MAS. Pancytopenia with haemophagocytosis, liver dysfunction, coagulopathy and fever can be explained by the effects of pro-inflammatory cytokines as well, like TNF-α, IL-1, IL-6 and IFN-γ [24]. Mutations in perforin, a protein with regulatory effects in lymphocyte, natural killer (NK) cell and macrophage apoptosis, are the underlying cause in some forms of HLH. A decreased expression of perforin may thus lead to a persistent pro-inflammatory activation of these cells and induction of pro-inflammatory cytokines in MAS [25]. In SJIA patients, significant decrease in perforin expression could be determined in CD8+ cells and NK cells compared with polynuclear JIA patients or control donors. Autologous stem-cell transplantation leads to normal expression of perforin even in SJIA patients [26]. A direct role of perforin in the pathogenesis of SJIA, however, is not clear so far.

**Phagocyte-specific S100-proteins in SJIA**

The predominant role of the innate immune system in SJIA is furthermore underscored by the high expression and serum concentrations of the calcium-binding proteins S100A8, S100A9 and S100A12, which are specifically secreted during activation of neutrophilic granulocytes and monocytes. The extraordinarily high range of serum concentrations in SJIA is closely associated with disease activity and can be found neither in other forms of inflammatory arthritis, nor in other auto-immune or infectious diseases [27–29]. In addition, expression of S100A8 and S100A9 show a significant activation of the epithelial layer of the skin during the early phase of SJIA indicating a pro-inflammatory role of epithelial cells in SJIA as well (Fig. 1B) [28]. S100A8, S100A9 and S100A12 exhibit pro-inflammatory effects on leucocytes and endothelial cells, and are thus likely to be directly involved in the inflammatory process of SJIA [30–32]. S100A12 seems to be a member of a novel inflammatory signalling pathway involving RAGE (receptor for advanced glycation end products) as a receptor transducing pro-inflammatory signals in endothelial cells and phagocytes [33, 34]. S100A12 induces the expression of adhesion molecules as well as pro-inflammatory cytokines on endothelial cells in a nuclear factor-κB (NF-κB)-dependent manner. Effects of S100A12 on endothelium in vitro resulted in an increased mRNA expression of VCAM-1, ICAM-1, IL-8 and monocyte chemotactic protein-1 (MCP-1) in human microvascular endothelial cells [35]. Direct effects of S100A12 on expression of IL-1 and IL-6 have not been described so far. In addition, inflammatory responses in murine models of inflammation can be blocked by anti-S100A12 or anti-RAGE antibodies [33]. In contrast to S100A12, S100A8 and S100A9 have not been shown to bind to RAGE. After release by activated phagocytes complexes of both proteins bind specifically to endothelial cells [31]. Potential ligands on endothelial cells (ECs) released from activated phagocytes and endothelial cells. These observations are confirmed on recent treatment experiences in SJIA-patients with chronic disease activity. Treatment with IL-1 receptor antagonist reduces the clinical and laboratory features of disease activity in SJIA patients showing resistance to conventional therapy including blocking of TNF [11]. First clinical experiences with IL-6 receptor antibody treatment revealed efficacy regarding control of disease activity in SJIA [21, 22] (see subsequently).

![Fig. 1. (A) Acute rash at the onset of SJIA. (B) Expression of S100A9 by keratinocytes and infiltrating phagocytes (immunoperoxidase staining, red) in skin biopsy of the acute rash in active SJIA.](https://academic.oup.com/rheumatology/article-abstract/47/2/121/1789048/122)
are heparansulphate proteoglycans or carboxylated N-glycans expressed by ECs after activation [36, 37]. The significant role of S100A8/S100A9 for leucocyte recruitment is further underscored by the finding that S100A8/S100A9 increases the binding capacity of the integrin receptor CD11b/CD18 on leucocytes to ICAM-1 on endothelium [38]. S100A8/S100A9 induces a thrombogenic, inflammatory and apoptotic response in human ECs [31, 32]. In addition, cell junction-associated proteins were down-regulated in ECs after treatment with S100A8/S100A9 resulting in a dose-dependent increase of the endothelial permeability [32]. Murine S100A8 activates phagocytes in a Toll-like-receptor 4 (TLR-4)-dependent manner and induces expression of TNF, IL-1β and IL-12 [39]. On the other hand, IL-1 but not IL-6 induces mRNA-expression and secretion of S100A8/S100A9 in human monocytes [40, 41]. However, at present, one cannot decide whether secretion of IL-1β, IL-6 or S100-proteins is a primary or secondary step in the cause-and-effect chain of SJIA.

Alternative secretory pathway

The specific over-expression of IL-1, IL-18, S100A8, S100A9 and S100A12 points to a novel aspect regarding the pathogenesis of SJIA. All these molecules are secreted by a so-called alternative pathway which is different from the classical intracellular transport mechanism via endoplasmatic reticulum and Golgi complex used by other cytokines. This pathway includes activation of the nucleotide receptor P2X7, an efflux of potassium from the cell which results in the influx of calcium ions and the activation of phospholipases and lysosomal exocytosis. The initial activation of IL-1 and IL-18 includes a proteolytic cleavage of inactive pro-cytokines by a multiprotein complex called inflammasome. The uncontrolled activation of the inflammasome and cleavage of pro-IL-1 by caspase-1 have been shown to be important molecular mechanisms in different inherited auto-inflammatory syndromes resulting in spontaneous fever attacks [42, 43]. In contrast to IL-1 and IL-18, S100-proteins are not processed by caspase 1 prior to release [40]. Thus, a loss of control of the alternative secretory pathway downstream of caspase 1 seems to be involved in release of pro-inflammatory proteins leading to the inflammatory process of SJIA (Fig. 2). In this regard, the pathogenesis of SJIA shows more similarities with auto-inflammatory diseases than with classical antigen-driven autoimmune diseases. However, it is conceivable that there may be a relationship between the clinical and prognostic heterogeneity of SJIA patients and different pathogenic mechanisms related to alternative secretory pathways.

Present treatment options for SJIA

The aim of drug therapy in SJIA is the effective suppression of uncontrolled systemic and local inflammation to attain disease remission and to avoid chronic disease complications. Acute phases of systemic disease, at initial manifestation or during acute flares, are the domains of glucocorticoid-treatment. To reduce steroid-related morbidity combined therapy with disease-modifying drugs is recommended in most patients. Most long-term experience exists with methotrexate, 10–20 mg/m² body surface/week [44, 45]. Alternatively treatment with azathioprine, 2 mg/kg body weight/day is feasible [46, 47]. Some experience exists in the treatment with cyclosporine A or thalidomide in SJIA patients, most of them with persisting active disease despite use of glucocorticoids and methotrexate. However, controlled clinical trials are lacking [48, 49]. In these open case studies improvement is reported in the majority of patients. In a recent surveillance study of 329 patients, half of whom had SJIA, who were treated with cyclosporine A, the authors conclude that cyclosporine A may have a less-favourable efficacy profile than MTX and etanercept, whereas the frequency of side-effects may be similar [50]. In cases of persisting disease activity beside combined therapy with glucocorticoids and disease-modifying drugs TNF-blockade with etanercept is still recommended for patients with SJIA [10, 51, 52]. However, published studies report a reduced response to this treatment regimen in only 30% of patients with SJIA compared with more than 70% in other subtypes of JIA [51].

Despite these established treatment approaches in SJIA about 50% of SJIA-patients reveal persisting disease activity or remitting flares or depend on high-dose steroids [52, 53]. Therefore, SJIA was the first auto-immune disease in childhood for which an international treatment protocol of autologous stem-cell transplantation (ASCT) was established for patients refractory to conventional therapy. More than 50% of these patients reached complete remission. However, flares were observed in 28% of patients after ASCT. In addition, ASCT showed a high treatment-related morbidity and mortality in SJIA (9%) [54, 55].

Novel cytokine-directed treatment strategies

Recent insights into the molecular mechanisms underlying SJIA led to clinical approaches in blocking IL-1 and IL-6 to suppress inflammation in SJIA.

The most promising results have been published so far for therapeutic strategies targeting IL-1. In preliminary studies including SJIA-patients with chronic disease activity, who have been resistant to conventional disease-modifying drugs including TNF-blockade, treatment with IL-1 receptor antagonist (anakinra) led to rapid and sustained remission within a few days [11, 56]. Nine SJIA-patients with active inflammation and disease duration between 29 an 144 months resistant to a combination of prednisolone and methotrexate or TNF-blockade were treated...
with recombinant IL-1 receptor antagonist as a daily subcutaneous injection with 2 mg/kg/day. After a follow-up of 2–12 months all patients responded to therapy and became afebrile within the first week of treatment. Active arthritis completely resolved in 6/8 patients and improved in the remaining two. Leucocytosis and thrombocytosis resolved in all patients, ESR reached normal values in 8/9 patients, and haemoglobin levels increased to normal levels in 6/8 patients [11].

Therapy with an anti-IL-6-receptor antibody (tocilizumab) revealed good response in two phase II studies [21, 22].

Eleven children with steroid-dependent course of SJIA were treated within an escalating dose trial of a recombinant human anti-IL-6 receptor monoclonal antibody. Intravenous doses of 2–8 mg/kg were administered 3 times in a 2-week interval. Two weeks after the third treatment 10/11 children reached a response of 50% improvement and 7/11 children of 70% improvement according the JIA core set of improvement criteria [21]. In another open-label phase II trial 18 patients with active SJIA were enrolled. All patients received prednisolone >0.2 mg/kg/day and 12 patients had been treated with methotrexate <20 mg/m²/week. Patients were treated in three groups with a single dose of 2, 4 and 8 mg/kg tocilizumab. Eleven out of 18 patients reached a 30% improvement and 8/18 patients achieved ≥50% improvement. Clinical improvement was observed for up to 8 weeks [22].

In summary, new treatment options with specific blocking of pro-inflammatory mediators of the innate immune system reveals significant improvement and induce remission in SJIA patients with a so far treatment-resistant course of the disease and thus reduce the risk of secondary complications.

Currently, other IL-1 inhibitors have been developed, like a long-acting soluble receptor fusion protein or antibodies and first open-label studies are on their way but only preliminary short-time results have been presented so far [57].

Perspectives

Up to now SJIA is a burdensome disease in childhood with a high risk of relevant disease complications and mortality. Future efforts, therefore, aim at early registration of risk factors of treatment resistant courses in SJIA and the early induction of stable remission by verifying novel molecular targets for future therapeutic strategies.

Recent investigations have focused on mediators of the innate immune system in the pathophysiology of SJIA. Especially IL-1β, IL-6 and IL-18 as well as phagocyte-specific S100-proteins (S100A8, S100A9 and S100A12) are correlated with disease activity and secondary complications in SJIA. First case studies by blocking some of these mediators show improvement and remission on therapy in many patients. During the next years controlled studies have to define advantage, position in treatment protocols and patient characteristics indicative for use of these novel therapies as well as side-effects and their ability in establishing long time remission in SJIA.

Rheumatology key messages

• Activation of innate immunity plays an important role in the pathophysiology of SJIA.
• Accordingly, blockade of IL-1 and IL-6 shows promising effects in SJIA patients resistant to conventional treatment.

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References


