Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children and systemic juvenile idiopathic arthritis (sJIA) accounts for 6–15% of the patients. It was found that there was spontaneous expression of IL-1β in patients with sJIA. Canakinumab (ACZ885, Canakinumab) is a human anti-IL-1β monoclonal antibody. Its mode of action is based on the neutralization of IL-1β signaling which may result in the suppression of inflammation process in patients with disorders of autoinflammatory origin including sJIA. In addition to its use in the treatment of CAPS (cryopyrin-associated periodic syndromes) and acute gouty arthritis flares in many countries, the drug provides significant advantages over existing competitive therapies, including monthly SC administration and favorable safety profile.

Keywords: anti-interleukin-1 • canakinumab • systemic juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children [1]. JIA stands for a group of diseases with arthritis lasting more than 6 weeks with no apparent cause and with disease onset prior to age 16 [2]. Eight heterogeneous categories are defined with differences in clinical presentation, course, prognosis and response to treatment. Systemic JIA, the most severe JIA subtype, is characterized by chronic arthritis; intermittently high, spiking fever; maculopapular rash; hepatosplenomegaly; lymphadenopathy; serositis and a marked increase in the level of acute-phase reactants [3–5]. sJIA accounts for 6–15% of all Caucasian JIA cases [6]. The clinical course of sJIA is heterogeneous. In some patients, the arthritis develops months after the onset of systemic symptoms. This is in part reflected by differences in the International League of Associations for Rheumatism definition [6]. sJIA can be a monophasic and mild disease with mainly systemic features, a relapsing disease or a more chronic disease with some or all the features either from the onset or with arthritis occurring within a few months after the onset of systemic features [7]. The pathophysiology of the disease includes both activation of the innate and adaptive immune system. Laboratory and clinical observations have shown a major pathogenic role of the innate immunity and in particular of 3 cytokines: interleukin (IL)-6, IL-1 and IL-18 [8–10]. Pascual et al. [11] found that there was spontaneous expression of IL-1β in peripheral blood mononuclear cells of sJIA patients.

Innate immunity abnormalities lead to a distinct group of pathologic conditions known as autoinflammatory diseases, in which monocytes and neutrophils, rather than lymphocytes, are the predominant effector cells [12]. These diseases have clinical features like sJIA including recurrent fevers and multisystem inflammation that usually affects the joints, skin, gastrointestinal tract and eyes, and are complicated by amyloidosis in the long term [12].

Interleukin-1 (IL-1) is a proinflammatory cytokine produced by a variety of cell types, particularly mononuclear phagocytes, in response to injury, infection and inflammation. The biological activity of IL-1 is encoded by two distinct genes, IL-1α and IL-1β [13]. The observed biological activities

Canakinumab: new treatment choice for systemic juvenile idiopathic arthritis

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of IL-1β are mediated through the type I receptor, which is ubiquitously expressed and binds both IL-1β and IL-1α [14]. IL-1 induces numerous downstream mediators implicated in the inflammatory process including, chemokines, cytokines, including IL-1 itself, IL-6 and tumor necrosis factor alpha (TNF-α), cyclooxygenase 2 leukocyte adhesion molecules, acute phase proteins, neutrophilic response, thrombocytosis as well as extracellular matrix components fibronectin, and collagen types I, III and IV [15]. Several endogenous mechanisms exist that limit IL-1 activity, one of which is the IL-1 receptor antagonist (IL-1Ra), binding but not signaling through, the type I receptor.

Gene association and expression studies have shown that sJIA is a multifactorial disease. This is associated with polymorphisms of the innate response genes [16–18]. There has been one report a weak association with HLA in a small cohort [19]. The involvement of IL-6, IL-1β, and IL-18 may account for some of this heterogeneity thus these cytokines are seen as candidates for anticytokine therapy [20–22]. IL-1β seems to be a major mediator of the inflammatory cascade especially important in systemic onset JIA. Systemic onset JIA patients’ mononuclear cells spontaneously produce large amounts of IL-1β and sera of the patients could provoke IL-1β synthesis in cultures of mononuclear cells from healthy controls making this cytokine an interesting target for therapy of this disease [11]. Use of IL-1 blockade in the treatment of sJIA was recommended in the 2013 ACR treatment Recommendations for JIA [23]. Currently, three different biologic inhibitors of the IL-1β pathway are available: anakinra, an IL-1 receptor antagonist; canakinumab, a human IL-1β antibody and rilonacept, an IL-1 receptor fusion protein.

In the study by Lequerre et al. [24], 35 (20 with juvenile, 15 with adult onset Still’s disease) patients were treated with anakinra (1–2 mg/kg (maximum 100 mg) daily s.c.). Systemic symptoms (fever, rash) disappeared in 25 patients (14 with juvenile, 11 with adult onset Still’s disease) and 50% of the patients were able to reduce the corticosteroid dose. In an international multicenter series report, anakinra was used as a first-line disease-modifying therapy in 46 sJIA patients. Complete response to initial therapy was observed in 59% of patients, while another 39% exhibited a partial response in an average of 14 months. Inactive disease was achieved in 8 of 10 on anakinra monotherapy [25]. Treatment is limited especially due to considerable local injection site reactions. This reaction rarely limits its use of treatment in sJIA patients (when cooling, or local corticosteroids on the skin are applied).

In the recent study, 20 patients were conducted, at the 3-month time point, 85% of the patients showed an adapted ACR Pedi 90 response or had inactive disease; 75% of the patients achieved this response while receiving recombinant IL-1Ra alone [26].

Rilonacept is an IL-1R/IL1RacP/Fc-fusion protein with a prolonged plasma half-life compared with anakinra. It is blocking soluble IL-1β, thereby preventing the binding of IL-1β to its cell-bound receptor. In an open-label phase of a randomized controlled double-blind study in 24 patients with systemic arthritis aged 5–20 years, it demonstrated an impressive effect [27]. Adapted ACR Pediatric 30, 50 and 70 response rates at 3 months from start of study were 78.3, 60.9 and 34.8%, respectively; response was generally maintained over the study duration [27]. Serious adverse events were seen including, macrophage activation syndrome (MAS), pulmonary fibrosis, anemia and relapse in the study [27]. Anakinra and rilonacept received US FDA approval for treatment rheumatoid arthritis and cryopyrin-associated periodic syndromes (CAPS), respectively [28]. They have not to receive approval for the treatment of sJIA yet [28].

Canakinumab in SJIA

Pharmacodynamics

Canakinumab is a human anti-IL-1β monoclonal antibody that binds specifically to human IL-1β. It neutralizes the bioactivity of human IL-1β through the prevention of its binding to the IL-1β receptor. Therefore, canakinumab treatment would likely exert a broad spectrum of anti-inflammatory effects and impact the remodeling processes associated with long term chronic injury and inflammation. Due to its potency and selectivity for IL-1β, low potential for immunogenicity and long duration of action, canakinumab is a promising therapeutic agent for patients with IL-1β driven inflammatory diseases [29,30].

Canakinumab binds with high affinity and specificity to human IL-1β (binding dissociation constant of 40 pmol/l) [29]. Canakinumab does not cross-react with IL-1α or the interleukin-1 receptor antagonist (IL-1ra) [29]. By binding to IL-1β, canakinumab prevents IL-1β interacting with IL-1 receptors. These results in the inhibition of down-stream events of IL-1 signaling, including IL-1β-induced gene activation, the production of markers of inflammation such as the acute-phase proteins serum amyloid A (SAA) and C-reactive protein (CRP), and the mobilization of neutrophils and platelets from the bone marrow [29]. Canakinumab normalized the production rate of IL-1β in a clinical study in patients with CAPS [30]. The production of IL-1β was fivefold higher in patients with the disease versus healthy subjects (31 vs 6 ng/day). Treatment with intravenous canakinumab 10 mg/kg returned the rate of IL-1β production in patients with CAPS to normal levels within 8 weeks. Levels of IL-1ra, which were also elevated in the patients with CAPS, returned to normal...
limits within 8 days of initiation of canakinumab treatment. CRP and SAA levels, which were elevated at baseline in previously untreated patients with CAPS, returned to normal within 8 days of canakinumab treatment and were maintained within normal limits for the remainder of a 2-year, Phase III trial [31]. Elevated counts of neutrophils, lymphocytes, and platelets returned to normal with canakinumab treatment in clinical studies involving patients with CAPS [30].

**Pharmacokinetics & metabolism**
In addition to the trials on healthy subjects, the pharmacokinetics of canakinumab has been evaluated in CAPS and sJIA patients.

The mean terminal elimination half-life (t\(\frac{1}{2}\)) of canakinumab was long (26 days) in adults [32]. The serum clearance of canakinumab was estimated to be 0.174 l/day in a typical CAPS patient weighing 70 kg but can vary depending on the bodyweight [32]. Apparent clearance per kg body weight (CL/F per kg) was comparable between the sJIA and CAPS population (0.004 l/d per kg) [32].

Following a single (initial) subcutaneous canakinumab 150 mg administration in CAPS patients, canakinumab was slowly absorbed from the injection site reaching a maximum serum concentration (C\(\text{max}\)) of 15.9 ± 3.52 μg/ml in approximately 7 days. Accordingly, the ka value estimated by the pharmacokinetic-binding model was low (0.3 day\(^{-1}\)) [33]. The incomplete bioavailability of canakinumab injected subcutaneously is likely due to proteolytic degradation within the reticuloendothelial system following uptake from the interstitial tissue rather than the blood as the drug transits the lymphatics to the thoracic duct. The 63–70% subcutaneous bioavailability of canakinumab is in line with the bioavailability estimates of other IgG type monoclonal antibodies [33].

The pharmacokinetic properties of canakinumab in pediatric patients were similar to those in adults. C\(\text{max}\) values of 7.7–13.6 μg/ml were reached after 2–7 days in children treated with a single subcutaneous dose of canakinumab 150 mg or 2 mg/kg [34]. The canakinumab t\(\frac{1}{2}\) in children (23–26 days) was similar to that in adults [34].

As canakinumab is a human IgG with a large molecular size (~150 kDa), negligible renal excretion is expected and impairment of renal function is not likely to influence the pharmacokinetics. Secretion into the bile is not a significant contributor to the elimination of IgG antibodies [33].

Canakinumab exhibits dose-proportional pharmacokinetics, when given both as an intravenous infusion (0.3–10 mg/kg) and as a single subcutaneous injection (150–300 mg) [33]. Long-term pharmacokinetic and pharmacodynamic assessments were performed in the CAPS and sJIA trials [30,35,36]. There was no evidence of time-dependent alteration of the pharmacokinetic profile in any of the studies. Peak serum concentrations (C\(\text{max}\)) mean 16 mg/ml, were reached after approximately 7 days in adult patients treated with a single subcutaneous dose of 150 mg canakinumab [33]. In sJIA patients after repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was observed to be 1.6-fold of single use. Steady state was reached after 110 days. The overall predicted mean (±SD) for C\(\text{min}\), C\(\text{max}\), and AUC\(\text{ss}\) were 14.7 ± 8.8 μg/ml, 36.5 ± 14.9 μg/ml and 696.1 ± 326.5 μg*d/ml, respectively [32].

The AUC\(\text{ss}\) in each age group was 692, 615, 707 and 742 μg*d/ml for 2–3, 4–5, 6–11 and 12–19 years old, respectively. When stratified by weight, a lower (30–40%) median of exposure for C\(\text{min}\) was found (11.4 vs 19 μg/ml) and AUC\(\text{ss}\) was (594 vs 880 μg*d/ml) for the lower bodyweight category (<40 kg) versus the higher bodyweight category (>40 kg) was observed [32].

**Clinical efficacy**

**Phase I studies**
A Phase I study (NCT004212260) is currently ongoing in Japan [37]. In addition, canakinumab has been used in a large number of patients and healthy volunteers and in very few of them have been associated with side effects [37]. Infections, gastrointestinal disorders and vertigo were reported side effects. In clinical studies for CAPS, RA and sJIA, the patients have not any anticanakinumab antibodies [38,39]. No formal studies investigating interactions between canakinumab and other pharmaceutical agents, including IL-1 blockers has been found [37].

**Phase II studies**
Ruperto et al. were conducted a Phase II, multicenter, open-label study in sJIA in 2012 [40]. In the study, the patients were evaluated using standardized measurement of ACRpedi30 improvement as well as fever at day 15 and every other week until a disease flare. 60% of the patients with sJIA treated in this study experienced an improvement in symptoms, meeting at least an adapted ACR Pedi 50 within 15 days of canakinumab administration, with four achieving inactive disease status [40].

Median estimated time to relapse was 56 days (95% CI: 32–100) for doses less than 3 mg; 60 days (38–95) for the 3 mg dose and 90 days (45–181) for doses greater than 3 mg/kg, with a 19, 17 and 7% probability of relapse within one month, respectively. Injections were well-tolerated, and no serum antibodies against canakinumab were detected. The recorded adverse
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Figure 1. Pediatric ACR* responses and inactive disease at day 15. Inactive disease: no active arthritis, fever, rash, serositis, hepatomegaly or lymphadenopathy attributable to systemic juvenile idiopathic arthritis, normal C-reactive protein and physicians global assessment indicating no disease activity.

Data taken from [20].

Phase III studies

In the placebo controlled, double-blind, randomized Phase III study conducted by Ruperto et al. [20], the initial efficacy and safety of canakinumab administration was assessed over a four week period in patients with relapsing sJIA. A randomized two-part study Phase III study was then initiated to evaluate the sustained efficacy of canakinumab in patients between 2–19 years of age and have active sJIA. The ability to taper steroids was assessed in the open label part 1, for a maximum duration of 32 weeks, and the time to relapse during canakinumab treatment was assessed in the subsequent withdrawal double-blind part 2 where 50 patients from part I switched from canakinumab to placebo and 50 continued on canakinumab. An open-label extension Phase III clinical trial was initiated in order to assess the long-term efficacy, safety and immunogenicity of canakinumab in patients with sJIA. Patients (minimum age of two years) who responded to treatment with canakinumab but clinically deteriorated afterwards, was retreated with 4 mg/kg sc every four weeks for a maximum of two years [20].

84% of the patients on the drug achieved clinical measure of improvement (ACRpedi30) at day 15, in contrast to 10% on placebo (Figure 1), and these values were sustained at day 29 (Figure 2). In another randomized controlled study, 34% achieved ACR100 and 77% achieved ACRpedi30 response in the open label phase (called part I) and then proceeded to the randomized placebo controlled phase (called part II). In total, 74% of patients on canakinumab remained flare free, compared with 25% on placebo. Both studies have been published together [20].

Safety & tolerability

Over 2300 subjects including approximately 250 children (aged 2 to 17 years) have been treated with canakinumab in interventional studies in patients with CAPS, sJIA, gouty arthritis or other IL-1β mediated diseases, and healthy volunteers. A total of 201 sJIA patients aged 2 to 20 years have received canakinumab in clinical trials. The safety and efficacy of canakinumab in CAPS and sJIA patients under 2 years of age have not been established [22]. Russo et al. [41] were to determine the short and long term efficacy and safety of canakinumab therapy in 10 children with CAPS. There were no serious or severe adverse events during the study period. Three children developed four infections (chickenpox, pneumonia and infective gastroenteritis) [41]. In Phase II study, only two patients with sJIA reported serious adverse events related to canakinumab: one had an Epstein-Barr virus infection, and the other had a hematoma, prolonged activated partial thromboplastin time, gastroenteritis, and syncope [40]. Canakinumab injections were well tolerated and there were no reports of severe injection site reactions.

Macrophage activation syndrome is a life-threatening disorder that develops in approximately 10% of children with sJIA [42]. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of sJIA, as these are known triggers for MAS. Based on clinical trial experience, it can be hypothesized that canakinumab does not appear to increase the incidence of MAS in sJIA patients. In Phase II study, MAS was not observed in any of 23 patients [40]. Whereas, in Phase III trial, 5 patients had MAS after canakinumab [20]. In 2012, reactive macrophage
activation syndrome was reported in a patient with adult-onset Still’s disease after canakinumab therapy [43].

Canakinumab effects on the development of malignancies are not known. However, there is a possible increased risk of malignancies in patients receiving immunosuppressive agents, including canakinumab [44]. On the other hand, the molecular signature in cancer displays similarities to dysregulated inflammatory response. IL-1β targeting agents could potentially be used in inflammation-promoted malignancies such as lung cancer [45]. Adverse drug reactions were showed in Table 1.

Regulatory affairs
In addition to its use in CAPS in the United States, the European Union and many other countries, canakinumab has recently been approved in the United States, the European Union, Russia and the Philippines for the treatment of sJIA (as monotherapy or in combination with methotrexate). Canakinumab is also approved for the treatment of acute gouty arthritis attacks in the European Union and several other countries.

Canakinumab costs in Europe >120,000 euros/year, and that is more than 5–6 times the costs of the other possible biological therapeutics (e.g., anakinra or tocilizumab) for therapy of sJIA. Since there are no head to head comparison studies available, proving that canakinumab is better than these other possible therapeutics, this will definitely affect treatment choices by health care providers.

Future perspective
Canakinumab has been shown to be effective in autoinflammatory diseases like Familial Mediterranean Fever, Hyper Immunoglobulin D Syndrome, TNF Receptor Associated Periodic Syndrome, Schnitzler Syndrome and Behçet disease evidenced by some case reports and/or exploratory studies.

There is increasing interest in evaluating the effects of canakinumab in various autoinflammatory diseases. Additional studies of canakinumab as a treatment option for different kinds of diseases including this indication are ongoing.

The results of the studies and experiences among canakinumab use in sJIA patients imply that it will be one of the cornerstones of sJIA treatment in particular for the patients that do not respond to conventional treatments. Especially, canakinumab is recommended for patients with continued disease activity after treatment with steroid, metotrexate or anakinra or tosilizumab according to ACR recommendations.

Conclusion
In conclusion, systemic JIA lacks the classic features of autoimmune disease such as autoantibodies and HLA associations, and cells of the innate immune system are strongly implicated in this disease.

Canakinumab is seen as effective and safe in treatments of both sJIA and CAPS. Recently ongoing studies indicate that the molecular signature in most chronic diseases, including cancer, myocardial infarctus and diabetes mellitus, displays similarities to dysregulated inflammatory response. Results from the trials are expected to advance our knowledge regarding the clinical value of IL-1 blockers.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership of options, expert testimony, grants or patents received or pending, or royalties.

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<th>Table 1. Summary of adverse drug reactions from pivotal systemic juvenile idiopathic arthritis clinical trials.</th>
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<td><strong>Reaction</strong></td>
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<td>Infections and infestations</td>
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<td>Gastrointestinal disorders</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>• Mild</td>
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1Lower respiratory tract infections, upper respiratory tract infections, viral infections, urinary tract infections, gastroenteritis. Reproduced with permission from [44] © Novartis.
Executive summary

Mechanism of action
- Canakinumab is a human anti-IL-1β monoclonal antibody that binds specifically to human IL-1β. It neutralizes the bioactivity of human IL-1β by prevention of its binding to the IL-1β receptor.

Pharmacokinetics
- Canakinumab has a long half-life of 26 days and, therefore, can be administered even bimonthly for CAPS and monthly for sJIA.
- Following a single (initial) subcutaneous canakinumab 150 mg administration in CAPS patients, canakinumab was slowly absorbed from the injection site reaching a maximum serum concentration (Cmax) of 15.9 ± 3.52 μg/ml mg/ml in approximately 7 days.
- The pharmacokinetic properties of canakinumab in pediatric patients were similar to those in adults.

Clinical efficacy
- Canakinumab improved articular and systemic features of sJIA with significant reduction of the number of inflamed joints, prompt resolution of fever and reduction of acute phase reactants, and allowed reduced steroid. In the Phase III study 45% of sJIA patients were able to taper from 0.34/mg/kg/day to 0.05 mg/kg/day, and 33% were able to discontinue corticosteroids entirely.

Safety
- Canakinumab is generally safe and well tolerated in clinical trials as evidenced by very few discontinuations, and a slightly increased rate of nonserious infections of the upper respiratory tract.
- Canakinumab injections were well tolerated and there were no reports of severe injection site reactions.

Dosage & administration
- Recommended dose of canakinumab for patients with a body weight ≥7.5 kg is 4 mg/kg (with a maximum of 300 mg) administered every 4 weeks as a single dose via subcutaneous injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.

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