



# Early Treatment of Systemic Juvenile Idiopathic Arthritis with Canakinumab and Complete Remission After 2 Years of Treatment Suspension: Case Report of an Adolescent Girl

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## Abstract

Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease characterised by fever and arthritis. We describe the case of a 14-year-old girl hospitalised with fever associated with rash, myalgia, arthralgia and polyarticular involvement. Examinations revealed increased levels of C-reactive protein, erythrocyte sedimentation rate, ferritin, triglycerides, leukocytes, neutrophils, lactate dehydrogenase, fibrinogen, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and  $\gamma$ -glutamyl transferase (GGT). Bone marrow biopsy showed polyclonal leukocyte activation. A genetic study revealed a heterozygous mutation of the *MEFV* gene, c.442G>C (E148Q), which is typical of familial Mediterranean fever. However, the genetic pattern was not associated with a history of recurrent fever, aphthous ulcers of the mouth, abdominal pain, arthralgia and rash. Therefore, a diagnosis of sJIA was made. The patient did not respond to non-steroidal anti-inflammatory drugs. Corticosteroids improved biochemical examinations; however, AST, ALT, GGT and glycaemia remained elevated and adverse effects of corticosteroid treatment became evident and therefore corticosteroids were withdrawn. Canakinumab (150 mg/4 weeks subcutaneously) was initiated. Biochemical data returned to normal values and clinical symptoms resolved. After 2.5 years of canakinumab treatment, complete disease remission allowed the prolongation of intervals between doses. When the intervals were longer than 10 weeks we discontinued the treatment. The patient is still in remission 2 years after canakinumab withdrawal.

## Key Points

An adolescent hospitalised with systemic juvenile idiopathic arthritis received early treatment with canakinumab.

The patient was treated for 2.5 years and is still in remission 2 years after canakinumab withdrawal.

Early introduction of canakinumab may help to rapidly taper corticosteroids and reduce corticosteroid adverse effects.

## 1 Introduction

Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease characterised by fever and arthritis associated with one or more of the following: hepatosplenomegaly, lymphadenopathy, serositis or rash [1]. The aetiology of sJIA is still unknown, but has a possible genetic background associated with environmental triggers [1].

A limited number of patients have a good response to non-steroidal anti-inflammatory drugs (NSAIDs): in a retrospective, single-centre cohort study it was reported that patients who respond to NSAIDs have the following characteristics at diagnosis:  $\leq 8$  years old, have an initial joint involvement  $\leq 5$  joints, have C-reactive protein (CRP)  $\leq 13$  mg/dL, and do not show macrophage activation syndrome (MAS) and serositis [2].

Most patients require corticosteroid treatment, and if they do not respond to corticosteroids they need to be treated with biological drugs [3]. However, anti-tumour necrosis factor (TNF)- $\alpha$  drugs, such as etanercept, adalimumab and infliximab, are less effective in sJIA than in other juvenile

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idiopathic arthritis (JIA) categories [3, 4]. Certainly, over recent decades, the clinical outcome of patients with sJIA has significantly improved. The early treatment of sJIA with interleukin (IL)-1 or IL-6 inhibitors is indicated in children with persistent active disease after 1 month of treatment with corticosteroids [5–7].

## 2 Clinical Case

We describe the clinical case of a 14-year-old girl who was hospitalized in October 2012 with fever ( $>39^{\circ}\text{C}$ ) associated with a transient rash, myalgia and arthralgia, and polyarticular involvement (knees, ankles, hands and feet dactylitis).

Biochemical examinations revealed the following: increased CRP (33.26 mg/dL), erythrocyte sedimentation rate (ESR) (86 mm/h), ferritin (9198 ng/mL), triglycerides (446 mg/dL), leukocytes (32,070), neutrophil count (29,100), lactate dehydrogenase (LDH) (760 U/L), fibrinogen (649 mg/dL), aspartate aminotransferase (AST) (146 IU/L), alanine aminotransferase (ALT) (741 IU/L) and  $\gamma$ -glutamyl transferase (GGT) (120 IU/L); haemoglobin levels were low (9.8 g/dL) (Table 1).

Tests for anti-nuclear antibodies (ANAs), extractable nuclear antigen antibodies (ENAs), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-*Saccharomyces cerevisiae* antibodies (ASCAs), anti-neutrophil cytoplasmic antibodies (ANCA) and lupus anticoagulant were negative. The Mantoux test and tests for IgM and IgG against parvovirus, Epstein–Barr virus (EBV), cytomegalovirus (CMV), adenovirus and indirect immunofluorescence assay (IFI) for Rickettsia were negative.

The patient underwent a bone marrow biopsy that showed polyclonal leukocyte activation, without signs of MAS or malignancy.

A genetic study of autoinflammatory diseases presenting with periodic fevers (familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase (MVK) deficiency and *NLRP3* mutations) revealed a heterozygous mutation of the *MEFV* gene, c.442G>C (E148Q), which is typical of FMF. However, the genetic pattern was not associated with a history of recurrent fever, aphthous ulcers of the mouth, abdominal pain, arthralgia and rash. Furthermore, other episodes did not occur in the subsequent years of follow-up of this patient. For this reason, a diagnosis of sJIA was made.

The patient started treatment with indomethacin tablets (3 mg/kg/day). However, significantly elevated CRP and ESR persisted and hepatocholangitis was documented by progressive increases in AST, ALT and GGT. As she had no response to NSAIDs, and EBV and CMV acute infection were excluded [8], on 13 October 2012, after 1 week of indomethacin treatment, intravenous prednisone 1 mg/kg/day was started, resulting in the progressive reduction of CRP, ESR, AST, ALT and GGT levels. However, 2 weeks later, AST, ALT, GGT and glycaemia increased and adverse effects related to corticosteroid treatment became evident (facies lunaris, hirsutism, striae rubrae on the legs and abdomen, and hypertension). Furthermore, the patient presented a depressive mood with suicide ideation. Neuropsychiatric counselling stressed the possible role of corticosteroids and suggested withdrawal of such treatment.

On 20 November 2012, after 1 month of corticosteroid treatment, the patient started treatment with canakinumab

**Table 1** Results of biochemical examinations

| Biochemical test                    | At admittance | After indomethacin | After 1 week of corticosteroids | After 2 weeks of corticosteroids | After canakinumab | At follow-up (October 2016) |
|-------------------------------------|---------------|--------------------|---------------------------------|----------------------------------|-------------------|-----------------------------|
| Leukocyte count (/ $\mu\text{L}$ )  | 32,070        | 30,890             | 21,000                          | 24,500                           | 4520              | 5800                        |
| Neutrophil count (/ $\mu\text{L}$ ) | 29,100        | 29,000             | 19,250                          | 22,000                           | 2540              | 3060                        |
| Hb (g/dL)                           | 9.8           | 9.5                | 10.0                            | 12                               | 13.2              | 13.5                        |
| CRP (mg/dL)                         | 33.26         | 34.2               | 8.5                             | 0.5                              | 0.5               | 0.05                        |
| ESR (mm/h)                          | 86            | 120                | 98                              | 32                               | 10                | 10                          |
| AST (IU/L)                          | 146           | 176                | 56                              | 145                              | 39                | 24                          |
| ALT (IU/L)                          | 741           | 820                | 62                              | 165                              | 34                | 18                          |
| GGT (IU/L)                          | 120           | 210                | 43                              | 132                              | 27                | 15                          |
| Ferritin (ng/mL)                    | 9198          | 9400               | 356                             | 205                              | 76                | 87                          |
| Triglycerides (mg/dL)               | 446           | 460                | 132                             | 150                              | 125               | 80                          |
| LDH (U/L)                           | 760           | 820                | 320                             | 298                              | 228               | 150                         |
| Fibrinogen (mg/dL)                  | 649           | 598                | 310                             | 295                              | 290               | 320                         |

ALT alanine aminotransferase, AST aspartate aminotransferase, CRP C-reactive protein, ESR erythrocyte sedimentation rate, GGT  $\gamma$ -glutamyl transferase, Hb haemoglobin, LDH lactate dehydrogenase

(150 mg/4 weeks subcutaneously), even though such treatment was still off-label, and corticosteroids were gradually tapered and stopped 7 weeks after canakinumab was started. Clinical and biochemical data significantly improved until the normalisation and resolution of clinical symptoms. After 2.5 years of canakinumab treatment, complete remission of the disease allowed prolongation of the intervals between canakinumab doses. When the intervals were longer than 10 weeks, after 4 years of therapy, the treatment was discontinued. The patient still remains in remission 2 years after canakinumab withdrawal.

### 3 Discussion

This case highlights the role of biological drugs in the treatment of sJIA, in particular anti-IL-1 $\beta$ . Canakinumab can contribute to ameliorating the lifestyle of adolescents affected by sJIA and the precocious introduction of this drug may help to rapidly taper corticosteroids and reduce their adverse effects.

The patient reached a complete and persistent remission, which was maintained during long-term follow-up without any further treatment.

The choice of canakinumab depended on the fact that the patient's clinical manifestations (with systemic more than articular symptoms, such as fever, rash and inflammatory markers) led us to choose an anti-IL-1 drug, as opposed to an anti-IL-6 drug. Moreover, the psychological frailty of the patient (i.e. suicidal ideation) required a drug with the least negative impact on quality of life and with mild adverse effects, e.g. at the injection site. One subcutaneous administration every 4 weeks was more tolerable and acceptable than a daily injection or an infusion every 14 days; the patient lived far from the centre at which the treatment was administered and travelling there required a 2.5 h journey each way. Finally, at the time of prescription, other biological drugs such as anakinra and tocilizumab were also off-label for paediatric use. Table 2 shows current therapies available for the treatment of sJIA in Europe [9–11].

### 4 Conclusion

This case report suggests the option of starting canakinumab early in the management of sJIA, in order to reduce the adverse effects of corticosteroids and to modify the natural history of the disease. In fact, prompt initiation of canakinumab can prevent articular and organ involvement and could stop the cytokine cascade that can require more complex treatments and could reduce their efficacy. The choice to treat in an early phase of sJIA can modify the natural

**Table 2** Drugs used in the treatment of systemic juvenile idiopathic arthritis [9–11]

| Drug        | Target | Route of administration | Main safety issues   | Safety monitoring  |
|-------------|--------|-------------------------|--|--|
| Canakinumab | IL-1   | SC                      | The most common AEs are upper respiratory tract infections. Serious infections have been observed. Some infections were unusual or opportunistic infections due to reduced white blood cell levels   | Monitor patients for signs and symptoms of infections during and after treatment. Canakinumab must not be used in patients with active or severe infection   |
| Anakinra    | IL-1   | SC                      | The most common AEs are headache, injection-site reactions and increased blood cholesterol   | Anakinra must not be used in people who are hypersensitive to anakinra, any of the other ingredients or proteins produced by <i>Escherichia coli</i> . Anakinra must not be started in patients who have neutropenia |
| Tocilizumab | IL-6   | IV                      | The most common AEs are upper respiratory tract infections, nasopharyngitis, headache, hypertension and abnormal liver function tests. The most serious AEs are serious infections, complications of diverticulitis and hypersensitivity reactions | Monitor patients for signs and symptoms of infections during and after treatment. Tocilizumab must not be used in patients with active or severe infection   |

AEs: adverse effects, *IL* interleukin, *IV* intravenous, *SC* subcutaneous

history of the disease and could allow complete remission without long-term morbidity.

Early canakinumab treatment may, therefore, be proposed as a treatment of choice in the management of sJIA.

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## Compliance with Ethical Standards

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**Conflict of interest** Maria Cristina Maggio, Saveria Sabrina Ragusa and Giovanni Corsello declare that they have no conflicts of interest.

**Informed consent** The consent of the parents of the patient is included in the hospital clinical documents.

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