

## Discontinuation of Canakinumab following Clinical Disease Remission Is Feasible in Patients with Systemic Juvenile Idiopathic Arthritis

To the Editor:

The optimal duration of treatment in patients with juvenile idiopathic arthritis, especially systemic JIA (sJIA), is a major concern for parents and physicians alike. Innovative medicines have managed to control this otherwise potentially life-threatening condition<sup>1</sup>. However, questions remain regarding the duration and the best timing for cessation of treatment.

We report the results of a retrospective study describing the longterm outcome of children with sJIA treated with the antiinterleukin (IL)-1 $\beta$  monoclonal antibody canakinumab. In these children, treatment was discontinued following sustained clinical remission; we aim to identify potential relapse-associated risk factors.

This was a single-center retrospective case study conducted from January 2008 to January 2017 and including patients with sJIA (based on International League of Associations for Rheumatology criteria)<sup>2</sup> who had clinically inactive sJIA (clinical remission on medication/Wallace criteria)<sup>3</sup> for at least 2 years with canakinumab. Patients were monitored for up to 4 years [median time 3.4 yrs, interquartile range (IQR) 2.4–3.7] following attempted canakinumab withdrawal (the study period began at the time of canakinumab withdrawal). Demographics, clinical, and laboratory variables were recorded at the study onset. We also collected data on previous and concomitant medication exposure as well as clinical outcome following canakinumab discontinuation (remission-flare/American College of Rheumatology criteria; data not shown in full)<sup>4</sup>. Data were analyzed using SPSS 19.0. Differences were tested with the Mann–Whitney U test and Fisher’s exact test and a p value < 0.05 was set as the threshold for statistical significance. Our study was approved by the P. & A. Kyriakou Children’s Hospital Ethics and Research Committee (Ap. number ES4/i-345/2016-05). Written informed consent was obtained by the parent or legal guardian.

In a total of 12 patients (7 girls) with inactive sJIA (median age 8.5 yrs, IQR 3.7–11.3), canakinumab treatment was discontinued. Median disease duration at the time of canakinumab discontinuation was 3.8 years (IQR 2.7–6.4). All patients had received 4 mg/kg canakinumab at monthly intervals for at least 2 years. Median duration of treatment was 2.8 years (IQR 2.2–3.1). Discontinuation was gradual (spacing — 1 dose at 6 weeks and a subsequent dose at 8) in 75% of patients. All patients were taking corticosteroids when canakinumab was started (< 1 mg/kg prednisolone), and they were discontinued within 3 to 9 months. Ten out of 12 patients (84%) were taking methotrexate (MTX; mean dose: 12.5 mg/m<sup>2</sup>), one (8%) was taking leflunomide (20 mg), and one (8%) cyclosporine (1.5 mg/kg). They continued to take the same dose of synthetic disease-modifying anti-rheumatic drugs (DMARD) during treatment with canakinumab. Eight out of 12 patients (75%) had received at least 1 other biologic (b)DMARD before starting canakinumab: 2 (17%) anti-tumor necrosis factor- $\alpha$ , 1 (8%) abatacept, 2 (17%) tocilizumab, and 3 (25%) anakinra. Two out of the 12 patients (12.5%) had received at least 2 biologics prior to canakinumab, while 1 patient (8%) had received 3 biologics.

In 33% (4/12) of patients, canakinumab treatment was successfully stopped with no relapse. Out of these 4 patients (all taking MTX), 3 (75%) subsequently managed to stop MTX and remain in drug-free clinical remission (> 2 yrs). Eight out of 12 patients (75%) flared during the followup period. Median duration of remission following canakinumab withdrawal was 4.5 months (IQR 3.2–11.2). Six out of 8 patients (75%; 50% of the total) were restarted on canakinumab while a short course of steroids resolved the flare in the remaining 2 patients. Subgroup analysis showed that biologic-naïve patients [3/4 (75%) vs 1/8 (12.5%), p = 0.03] and patients with shorter median disease duration at the time of canakinumab discontinuation (1.8 vs 3.4 yrs, p = 0.04) had a higher chance of successful withdrawal. Patients who relapsed were more likely to do so within 6 months of canakinumab discontinuation; 7/8 (87.5%) relapsed in < 6 months versus 1/8 (12.5%) in more than 6 months (p = 0.02). The relapse percentages were

identical in the abrupt (62%) versus gradual discontinuation groups (67%; p = 0.07, data not shown). Age (p = 0.09) and sex (p = 0.08) did not affect clinical outcome (Table 1).

This was a retrospective analysis regarding discontinuation of canakinumab in patients with clinically inactive sJIA. In general, biologic-naïve patients demonstrate a swift and sustained response to IL-1 blockade<sup>5</sup>. Moreover, while multiple studies have shown clinical benefit of IL-1-targeted drugs such as recombinant IL-1Ra, not all patients responded equally well<sup>6,7</sup>; nonetheless in our study 3/12 patients who did not respond to IL-Ra responded to canakinumab. Moreover, the protocols in the aforementioned trials did not include a plan for tapering or stopping the drug once remission had been achieved<sup>8</sup>. On the other hand, a recently published study testing a stop strategy in patients with disease in remission at 3 months and at 2 years after the start of canakinumab showed promising results<sup>9</sup>. In accordance with other studies, timely initiation of an effective bDMARD appeared to be of importance in acquiring disease remission; the concomitant use of synthetic DMARD may be helpful in the effective withdrawal of bDMARD, but the numbers in our study were too small to draw a firm conclusion<sup>10</sup>. Our study demonstrated that canakinumab withdrawal is feasible in a proportion of patients with sJIA. Patients with shorter disease duration and no previous exposure to a bDMARD showed a higher chance of attaining longterm remission. Nonetheless, the required period of time in clinical disease remission while receiving canakinumab treatment prior to attempting discontinuation of the drug is still unclear.



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Table 1. Clinical characteristics of patients with sJIA associated with the ability to discontinue canakinumab.

Characteristics	Patients with sJIA Who Flared	Patients with sJIA Who Remained in Remission	p*
Male, 5 total, n (%)	3 (43)	2 (40)	0.1
Female, 7 total, n (%)	4 (57)	3 (60)	
Previous non-canakinumab biologic use	7/8 (87.5)	1/8 (12.5)	0.03
Disease duration at time of canakinumab discontinuation, yrs, median (IQR)	3.4 (2–5.2)	1.8 (1.3–3.4)	0.04
Age at time of canakinumab discontinuation, yrs, median (IQR)	8.9 (7.8–12.7)	9.2 (7.5–11.4)	0.09

\* Fisher’s exact test. sJIA: systemic juvenile idiopathic arthritis; IQR: interquartile range.

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