CONCISE COMMUNICATION

DOI 10.1002/art.38777

Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study

Familial Mediterranean fever (FMF), the most common monogenic autoinflammatory disease, is characterized by recurrent self-limited attacks of fever and serositis. Between 5% and 10% of patients are resistant to or intolerant of colchicine, the current standard of care (1). Pyrin, the mutated protein in FMF, has an important role in the regulation of interleukin-1β (IL-1β) activation. This knowledge has led to the effective use of IL-1 inhibitors in >50 reported patients with colchicine-resistant FMF, including in one controlled study (2,3). In the present study we assessed the efficacy and safety of canakinumab, a selective, fully human anti–IL-1β monoclonal antibody with a terminal half-life of 50 days, in the treatment of children with colchicine-resistant FMF.

This 6-month, phase II, open-label, single-arm study (clinicaltrials.gov identifier NCT01148797) was conducted in 7 Caucasian children with FMF (5 boys and 2 girls; median age 9.5 years [range 6.8–14.9]) at 2 centers in Israel (Rambam Medical Center and Shaare Zedek Medical Center). The study was approved by the ethics committees at both hospitals, and informed consent was obtained from the parents/legal guardians of the participants. Patients were diagnosed according to the Tel-Hashomer criteria (4), with 2 exon 10 mutations on the MEFV gene (M694V/M694V in 5, M694V/V726A in 1, and M694V/M680I in 1). Participants were all colchicine resistant, having had ≥3 well-documented acute FMF attacks during the 3 months prior to screening despite treatment with colchicine at ≥1–2 mg/day (based on age) for at least 3 months.

Following successful screening, participants were enrolled in a 30-day run-in period. Those who experienced ≥1 investigator-confirmed FMF attack during this time were eligible for treatment. In addition to continuing daily colchicine treatment at the usual dosage, participants received 3 subcutaneous injections (4 weeks apart) of canakinumab 2 mg/kg (maximum 150 mg), with the first injection (day 1) administered during the next attack following the run-in period. The dose was doubled to 4 mg/kg (maximum 300 mg) if an attack occurred between the day 1 and day 29 visits. Day 86 was considered the end of the treatment period (4 weeks after administration of the last dose of canakinumab). Participants were followed up for another 2 visits (that occurred between day 126 and 160) or until an attack occurred (whichever occurred first). Attacks were then treated with acetaminophen and/or nonsteroidal antiinflammatory drugs only. The primary outcome measure was the proportion of participants with ≥50% reduction in the frequency of FMF attacks during the treatment period versus the pretreatment period. Secondary outcome measures included acute-phase reactant levels, health-related quality of life (Child Health Questionnaire—Parent Form 50 [CHO-PF50]) (5), physician’s global assessment of FMF control, time to attack following the last canakinumab injection (day 57), and safety and tolerability of canakinumab.

Six participants met the primary outcome measure with a ≥50% reduction (range 76–100%) in the rate of FMF attacks (Figure 1). The median 28-day time-adjusted attack rate decreased from 2.7 to 0.3 (89%). Three participants did not experience any attacks during the treatment phase. The canakinumab dose was doubled for the second and third injections in 2 participants: a responder who experienced 1 additional brief attack after dose escalation and the single nonresponder, who experienced 3 additional attacks (4 attacks overall). Compared with 34 attacks over 374 patient-days of followup during the pretreatment phase, only 8 attacks in 601 patient-days were reported during the treatment phase. The proportion of days that participants were experiencing an attack decreased from 24.2% to 3.6%. Eighteen of 34 attacks (53%) were rated as severe or very severe during the pretreatment phase, compared with 0 of 8 during the treatment phase. Following the first injection, clinical manifestations resolved the same day in 4 participants and within 24 hours in 3. Five participants developed an attack after the last canakinumab injection, within a median of 25 days (range 5–34).

Median C-reactive protein levels normalized by day 8 (from 74 mg/liter at baseline to 2 mg/liter on day 8 and 1.3 mg/liter on day 86), the erythrocyte sedimentation rate by day 29 (from 83 mm/hour at baseline to 17 mm/hour on days 29 and 86), and serum amyloid A levels by day 57 (from >500 mg/liter at baseline to 2.5 mg/liter on day 57 and 12.2 mg/liter on day 86). Health-related quality of life also improved, with an increase in CHO-PF50 summary scores for both the physical domain (from a median of 21 at baseline to 46 on day 86 [mean 50 in the healthy population]) and the psychosocial domain (31 to 40). The physician’s global assessment of FMF control at baseline was rated as very poor in 3 participants, poor in 3, and fair in 1. By day 86 this had improved to very good in 4 participants and good in 3.

Eleven adverse events (AEs) were reported in 4 participants; 2 were infections. All were mild except for 1 moderate streptococcal throat infection. There were no serious AEs, opportunistic infections, malignancies, or deaths. No significant laboratory abnormalities occurred, and formation of neutralizing antibodies to canakinumab was not observed. No participants discontinued the study or missed a treatment dose because of an AE.

The major limitation of this study, which was primarily a proof-of-concept study, was the small sample size. Of note, the proportion of complete responders (with no attacks) was lower than has been reported in studies of other autoinflammatory conditions treated with canakinumab, such as cryopyrin-associated periodic syndrome (6) and tumor necrosis factor receptor–associated periodic syndrome (7), but higher than has been reported in systemic juvenile idiopathic arthritis (8). This may be due in part to the selection, for the present study, of patients whose FMF was severe and resistant to colchicine treatment. The proportion of complete responders was slightly greater in this study than in a randomized trial of rilonacept treatment in a similar FMF population (3).
In summary, canakinumab was shown to be effective in treating pediatric patients with colchicine-resistant familial Mediterranean fever treated with canakinumab. Dose escalation was required in order to prevent attacks in some children. AEs were minor and manageable. All participants continued to receive canakinumab after the trial ended. A larger controlled study is needed to better evaluate the benefit of canakinumab in this population, including the optimal dose and interval of treatment, taking into account the high cost of IL-1 inhibitors.

Supported and sponsored by Novartis. Drs. Brik and Hashkes have received consulting fees, speaking fees, and/or honoraria from Novartis (less than $10,000 each). Drs. Brik, Bathol-Aviel, and Hashkes received research support from Novartis for the present study. Dr. Rachmilewitz-Minei is a former employee of Novartis.
AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hashkes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

Novartis facilitated the study design, helped with the data analysis, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Novartis.


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