## Efficacy and safety of canakinumab in familial Mediterranean fever in Japan: a single-centre retrospective study

Sirs,

Familial Mediterranean fever (FMF) predominantly impacts Mediterranean populations and involves inflammatory episodes caused by MEFV gene mutations (1, 2). Although colchicine is effective mostly, 10-15% of patients exhibit resistance or intolerance (3-5). Recent Japanese studies have examined the efficacy and safety of canakinumab (6, 7), but they did not differentiate between typical and atypical cases or address outcomes after dosage increases. This study assessed canakinumab, an IL-1β inhibitor, in colchicine-resistant Japanese patients, including dosage adjustments for typical and atypical FMF cases.

This study evaluated canakinumab in colchicine-resistant or -intolerant FMF patients at Nagasaki University Hospital from 2017 to 2022. Patients were classified as having typical or atypical FMF using the Tel-Hashomer criteria, with resistance defined as inadequate symptom control and intolerance as adverse reactions necessitating discontinuation. The Ethics Committee approved the study, and informed consent was obtained. Data on demographics, clinical history, canakinumab dosage, treatment duration, and attack frequency were collected. Canakinumab was administered subcutaneously at 150 mg every four weeks, with adjustments to 300 mg based on response. Primary outcomes were attack frequency reduction and safety, analysed using Wilcoxon signed-rank, Fisher's exact tests, and a mixed-effects model for intra-subject correlations ($p<0.05$).

The results are summarised in Figure 1. In a study of 30 FMF patients at Nagasaki University Hospital, participants were categorised into typical (n=18) and atypical (n=12) groups. Supplementary Table S1 presents the clinical characteristics and treatment outcomes. Typical FMF patients, mostly female (83.3%), had a higher attack frequency (2 attacks/month) than the atypical group (female: 41.7%, 0.4 attacks/month), with a significant reduction over 48 weeks (Fig. 1 A-B). No significant changes were seen in serum CRP and SAA levels (Fig. 1C-F). Genetic analysis identified various mutations, with L110P/E148Q being the most common. The study also examined drug retention over 80 weeks, noting that 10 patients discontinued treatment due to insufficient response or adverse events. The typical group had more discontinuations from adverse effects. Retention rates between the two groups were similar when excluding those who discontinued due to adverse events (typical: 64.3%, atypical: 75%). In the dose escalation group (n=14), the retention rate at approximately 60 weeks, excluding those who discontinued due to adverse events, was 57.1%. Backgrounds of these patients are detailed in Supplementary Table S2.

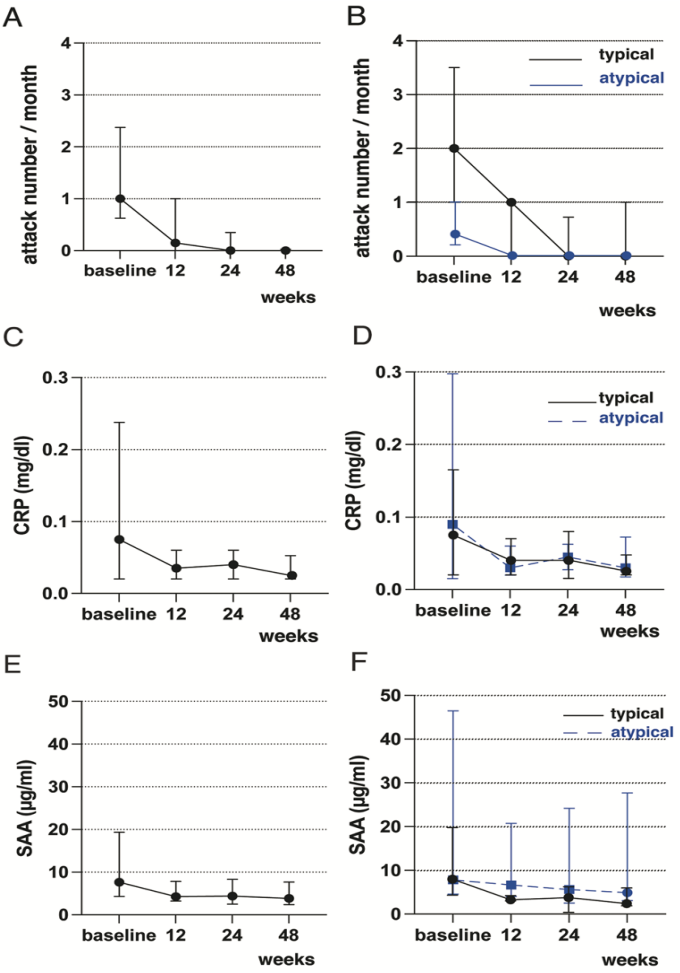


**Fig. 1.** Longitudinal analysis of fever attack frequency and changes in attack-free C-reactive protein (CRP) levels in serum amyloid A (SAA) in patients with typical and atypical FMF over 48 weeks. The analysis was conducted over a 48-week period and demonstrated a significant reduction in attack frequency in both patient groups.
**A**: Fever attack frequency for all patients. **B**: Distinct trajectories between typical and atypical FMF over 48 weeks. **C-F** displays the progression of the attack-free inflammatory markers CRP and SAA in patients with FMF.
**C** and **E** illustrate the general trend for all patients, whereas **D** and **F** provide a comparative view between typical and atypical FMF. Error bars indicate interquartile range.

This study provides a comprehensive evaluation of the efficacy and safety of canakinumab in treating both typical and atypical FMF in a Japanese cohort, by examining its impact over a 48-week period. This study marks the first detailed account of long-term adherence and effectiveness of escalated dosage regimens in these patients. This study revealed no significant differences in attack frequency between the typical and atypical FMF groups, suggesting that canakinumab is uniformly effective across diverse clinical presentations. The mutation analysis highlighted a distinct genetic landscape in this population, with a notably lower frequency of the M694I mutation compared to the national data (8, 9), which may influence disease severity and response to treatment. The effectiveness of canakinumab, reflected through a substantial reduction in attack frequency without significant changes in inflammatory markers, such as CRP and SAA, underscores its potential as a treatment for those resistant or intolerant to colchicine. We observed that the retention rate for patients who underwent a dose increase to 300 mg of canakinumab was approximately 50% after 60 weeks. This finding is significant, as previous research suggests that escalating the dose from 150 to 300 mg can induce remission in an additional 30% of patients (10). Our results confirmed that increasing the dose is beneficial for those who do not respond to the standard dose, particularly in patients resistant or intolerant to colchicine.

Y. Tsuji[1], *MD, PhD*
T. Koga[1], *MD, PhD*
T. Tomokawa[2], *MD*
M. Umeda[1], *MD, PhD*
N. Iwamoto[1], *MD, PhD*
A. Kawakami[1], *MD, PhD*

# Letters to the Editors

[1]*Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki;*
[2]*Sasebo Chuo Hospital, Rheumatic and Collagen Disease Center, Sasebo, Japan.*

*Please address correspondence to:*
*Tomohiro Koga*
*Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences,*
*Nagasaki University Graduate School of Medical Sciences,*
*1-7-1 Sakamoto,*
*Nagasaki 852-8501, Japan.*
*E-mail: tkoga@nagasaki-u.ac.jp*

*Competing interests: T. Koga, M. Umeda and A. Kawakami have received honoraria for lectures from Novartis Pharmaceuticals. The other authors have declared no competing interests.*



## References

1. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-64. https://doi.org/10.1016/s0140-6736(97)09408-7
2. LIVNEH A, LANGEVITZ P, ZEMER D *et al*.: The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996; 26(3): 612-27. https://doi.org/10.1016/s0049-0172(96)80012-6
3. LIDAR M, SCHERRMANN JM, SHINAR Y *et al*.: Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. *Semin Arthritis Rheum* 2004; 33(4): 273-82. https://doi.org/10.1053/s0049-0172(03)00137-9
4. OZEN S, KONE-PAUT I, GÜL A: Colchicine resistance and intolerance in familial Mediterranean fever: definition, causes, and alternative treatments. *Semin Arthritis Rheum* 2017; 47(1): 115-20. https://doi.org/10.1016/j.semarthrit.2017.03.006
5. MIGITA K, ASANO T, SATO S, KOGA T, FUJITA Y, KAWAKAMI A: Familial Mediterranean fever: overview of pathogenesis, clinical features and management. *Immunol Med* 2018; 41(2): 55-61. https://doi.org/10.1080/13497413.2018.1481579
6. TOMOKAWA T, KOGA T, ENDO Y, MICHITSUJI T, KAWAKAMI A: Efficacy and safety of canakinumab for colchicine-resistant or colchicine-intolerant familial Mediterranean fever: A single-centre observational study. *Mod Rheumatol* 2022; 32(4): 797-802. https://doi.org/10.1093/mr/roab048
7. YOSHIDA S, SUMICHIKA Y, SAITO K *et al*.: Effectiveness of colchicine or canakinumab in Japanese patients with familial Mediterranean fever: a single-center study. *J Clin Med* 2023; 12(19): 6272. https://doi.org/10.3390/jcm12196272
8. MIGITA K, UEHARA R, NAKAMURA Y *et al*.: Familial Mediterranean fever in Japan. *Medicine* (Baltimore) 2012; 91(6): 337-43. https://doi.org/10.1097/md.0b013e318277cf75
9. KOGA T, SATO S, MISHIMA H *et al*.: Next-generation sequencing of the whole MEFV gene in Japanese patients with familial Mediterranean fever: a case-control association study. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S35-41.
10. DE BENEDETTI F, GATTORNO M, ANTON J *et al*.: Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med* 2018; 378(20): 1908-19. https://doi.org/10.1056/nejmoa1706314