Received: 6 October 2023 | Revised: 19 February 2024 | Accepted: 29 April 2024

DOI: 10.1111/1756-185X.15192

International Journal of Rheumatic Diseases

WILEY

LETTER TO THE EDITOR

Experience on the long-term use of canakinumab in mevalonate kinase deficiency: A case series

Dear Editor,

We really appreciated the article "Long-term efficacy of canakinumab in hyperimmunoglobulin D syndrome" recently published by your Journal.[1] Indeed, although the treatment has been approved for hyperimmunoglobulin D syndrome (or mevalonate kinase deficiency – MKD), scarce data are available from real-world experiences. The "cluster" clinical trial for drug approval showed that the response to canakinumab is less predictable in MKD than in other autoinflammatory disorders, and several patients only show a partial response. To further describe long-term experience with canakinumab in MKD, we would like to share our experience on its use at the Rheumatology Service of the Institute for Maternal and Child Health IRCCS Burlo Garofolo Hospital in Trieste, Italy.

Patient 1 is a 34-year-old woman with MKD (c16_34del/V377I genotype) who has been treated with canakinumab for 8 years after initial use of steroids and anakinra. Currently, symptoms are well controlled with canakinumab that she takes only during severe attacks, because of a recurrence of skin herpes during the treatment. Mild attacks are effectively controlled with steroid therapy.

Patient 2 is a 13-year-old girl affected by MKD (V377I/V377I genotype) with recurrent inflammatory episodes despite canakinumab (100–150 mg every 4 weeks). Therefore, it was proposed to treat relapses with anakinra tapering canakinumab every 6 weeks.

Patient 3 is a 23-year-old man affected by MKD (V377I/I268T genotype) on therapy with canakinumab (150 mg every 4–6 weeks) since the age of 13 after initial treatment with anakinra and steroids.

Patient 4 is a 20-year-old man affected by MKD (homozygous G336S variation). His episodes were at first treated with glucocorticoids, with a partial response. Over the years, episodes became more severe, thus, canakinumab was started (150 mg every 4 weeks), with a good response. Occasionally, he still needs steroids to better control his symptoms.

Patients 5 and 6 are two siblings with MKD (both have homozygosis of V377I variant and also heterozygosis of the V132I one).

Patient 5 is an 18-year-old woman, who received the diagnosis of MKD at the age of 5, after an initial suspicion of PFAPA. Episodes were well controlled by glucocorticoids although recurrent episodes inevitably limited her school and social life. Thus, when she was 14, she started canakinumab (150 mg every 4 weeks) with a good response.

Patient 6 is a 6-year-old boy. At 13 months, he was referred to our service because of recurrent episodes of fever with refusal to walk or seat and marked fatigue. As for his sister, analysis confirmed the diagnosis of MKD. When he was 3 years old, he started canakinumab (75 mg every 4 weeks), with a good response. Nonetheless, this treatment progressively lost its effectiveness; therefore, it was gradually switched to anakinra.

Patients' characteristics are summarized in Table 1.

The main challenge in the management of periodic fevers syndromes (PFS) is to suppress inflammation and relieve symptoms. Conventional treatments, such as oral steroids, non-steroidal anti-inflammatory drugs, and methotrexate are usually the first choices of treatment, but they often provide just symptomatic relief.[2] Therefore, biological drugs are often needed to control inflammation after the failure of conventional treatments.[2] Anti-interleukin 1 (IL-1) drugs are approved for the treatment of PFS with a favorable safety and tolerability.[2,3] The 2021 EULAR/American College of Rheumatology recommendations state that in children with MKD, an anti-IL1 therapy is generally required.[4–6]

Two patients (1 and 3) were initially treated with anakinra. While in patient 1, it was at first effective in controlling symptoms, patient 3 did not respond to the treatment from the beginning. For the other patients, canakinumab was the anti-IL1 drug of choice after the development of cortico-dependance or cortico-resistance because they entered a clinical trial. Compared with anakinra, canakinumab was likely safe and in some cases even more effective. Moreover, the monthly administration was much less stressful. Patients 1 and 2 are now reducing the administrations. The first one gets on-demand canakinumab during severe attacks, while the second takes canakinumab every 6 weeks and on-demand anakinra in case of severe attacks with short-lasting triggers. The on-demand use of anakinra has already been reported to be effective in treating short relapses of familial Mediterranean fever,[7] and this use has been recommended at the onset of MKD's flares.[4] Instead, data on the effectiveness of on-demand canakinumab are lacking. In our experience, patient 1 benefited from its use. Patients 2 and 6 instead, after an initial benefit lost the response to canakinumab, while anakinra maintained its

TABLE 1 Patients' characteristics.

	Genotype	Age at onset and symptoms	Response to steroids	Previous ANK treatment and response	Duration of CKB therapy and dosage	Side effects of CKB	Current treatment
1	c16_34del/V377I	Infancy; recurrent fever, malaise, asthenia, abdominal pain	Good, but poor tolerance (irritability, panic attacks)	During acute attacks. Efficacy reduced after 5 years	8 years 150 mg every 2 months	Skin herpes	CKB as needed and steroids for mild attacks
2	V377I/V377I	In the first month of life; recurrent fever, abdominal and chest pain, diarrhea, sinusitis /bronchitis, arthralgia	Initially good (for 8 years), then cortico-dependence	For 1 year with only partial efficacy	4 years 100–150 mg every 4 weeks	Cystic acne during adolescence	CKB every 6 weeks and ANK during acute attacks
3	V377I/I268T	In the first month of life; recurrent fever, sore throat, abdominal pain, diarrhea	Good but with cortico-dependence	Discrete response with persistent musculoskeletal symptoms during interictal periods	10 years 150 mg every 4–6 weeks	None	CKB every 6 weeks
4	G336S/G336S	In the first 6 months of life; recurrent, abdominal pain, diarrhea, pharyngotonsillitis	Partial	None	9 years 150 mg every 4 weeks	None	CKB every 4 weeks; occasionally steroids
5	V377I/V377I plus V132I	From the age of 4 months; recurrent fever, pharyngotonsillitis, oral aphthosis, arthralgias, sinusitis /bronchitis, abdominal pain	Good	None	4 years 150 mg every 4 weeks	Cystic acne during adolescence	CKB every 4 weeks
6	V377I/V377I plus V132I	After the first year of life, recurrent fever, refusal to walk or seat	Partial	None	3 years 75 mg every 4 weeks	None	Gradual switch to ANK

Abbreviations: ANK, Anakinra; CKB, Canakinumab.

effectiveness during flares. As in patients 1 and 4, the long-term use of glucocorticoids remains possible, without a shortening of the intervals between episodes.

The evidence of excessive production of interleukin-1β (IL-1β) in MKD is the basis for the use of canakinumab in this condition, with the aim of limiting all the IL-1β-related clinical manifestations.[2,6] Some authors suggested that an impaired prenylation of RhoA protein could be responsible for the IL-1β hypersecretion in MKD, through an increased activity of autoinflammatory pathways, as Rac1/PKB signaling and inflammasome-mediated routes.[8]

Canakinumab was administered at a regular dosage (2 mg/kg every 4 weeks for patients <40 kg, 150 mg every 4 weeks for patients >40 kg).[5] We did not register significant effects, as reported in the literature.[1,5,9]

Actually, it is not yet clear why some mutations lead to one phenotype rather than others. The most common variant is V377I mutation in the compound heterozygosis and it has been mainly reported in the milder phenotype, but also in asymptomatic patients or in those with severe manifestations.[10] According to the study by Houten et al. the incidence of the disease based on allele frequency in the study population should be higher than actually observed.[11] The authors give as a possible explanation a reduced penetrance of V377I homozygosity which would lead to a milder phenotype of MK deficiency, which could be diagnosed as PFAPA, or no disease phenotype.[11]

Moreover, it is hypothesized that in addition to the two mutated alleles, other possible modifiers and epigenetic factors are present.[12]

In our patients, no correlation was found between genotype and response to treatment with canakinumab. Interestingly, two siblings had the same mutation; however, the response to the drug was consistently different. In fact, patient 6 had a poor response to canakinumab as well as patient 3, although they present different genetic mutations.

In general, MKD is much more clinically heterogeneous than other autoinflammatory diseases.

In clinical practice, doctors usually try different treatments before finding the one which fits best for the patient. At adult age, MKD is usually milder and it is easier to control symptoms.

Although there are several studies and case reports on the use of canakinumab to control inflammation and prevent complications of autoinflammatory fevers, our case series reports a longer follow-up, demonstrating the long-term effectiveness of canakinumab.[13,14] The average duration of treatment with canakinumab in our patients is about 6 years, with patient 3 with the longest follow-up of 10 years.

In conclusion, we presented a case series of patients with MKD, treated with canakinumab for a time greater than 5 years, demonstrating its safety and its long duration term results.

AUTHOR CONTRIBUTIONS

FB and CT wrote the manuscript, SP and AT cared for patients and discussed the clinical report, MG performed genetic analyses and corrected the manuscript draft, AT promoted and supervised the study.

ACKNOWLEDGMENTS

The authors would like to thank Martina Girardelli for the relevant contribution in patients' genetic analysis and the revision of the final version of the manuscript.

FUNDING INFORMATION

This work was supported by the Ministry of Health, Rome – Italy, in collaboration with the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste – Italy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Francesca Burlo[1]
Cristina Tumminelli[1]
Serena Pastore[2]
Andrea Taddio[1,2]
Martina Girardelli[2]
Alberto Tommasini[1,2]

[1]*Department of Medicine, Surgery, and Health Sciences, University of Trieste, Trieste, Italy*
[2]*Institute for Maternal and Child Health, "IRCCS Burlo Garofolo", Trieste, Italy*

Correspondence
Alberto Tommasini, Department of Medicine, Surgery, and Health Sciences, University of Trieste, Trieste, Italy.
Email: alberto.tommasini@burlo.trieste.it

ORCID

Francesca Burlo https://orcid.org/0000-0002-8915-5855

REFERENCES

1. Ozdemir Isik O, Karadag DT, Tekeoglu S, Yazici A, Cefle K, Cefle A. Long-term efficacy of canakinumab in hyperimmunoglobulin D syndrome. *Int J Rheum Dis*. 2023;27:e14857. doi:10.1111/1756-185X.14857
2. Hur P, Lomax KG, Ionescu-Ittu R, et al. Reasons for canakinumab initiation among patients with periodic fever syndromes: a retrospective medical chart review from the United States. *Pediatr Rheumatol Online J*. 2021;19(1):143. doi:10.1186/s12969-021-00605-2
3. Kuemmerle-Deschner JB, Gautam R, George AT, Raza S, Lomax KG, Hur P. Systematic literature review of efficacy/effectiveness and safety of current therapies for the treatment of cryopyrin-associated periodic syndrome, hyperimmunoglobulin D syndrome and tumour necrosis factor receptor-associated periodic syndrome. *RMD Open*. 2020;6(2):e001227. doi:10.1136/rmdopen-2020-001227
4. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology Points to consider for diagnosis, management and monitoring of the Interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis

factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the Interleukin-1 receptor antagonist. *Arthritis Rheumatol*. 2022;74(7):1102-1121. doi:10.1002/art.42139
5. 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):1908-1919. doi:10.1056/NEJMoa1706314
6. Mulders-Manders CM, Simon A. Hyper-IgD syndrome/mevalonate kinase deficiency: what is new? *Semin Immunopathol*. 2015;37(4):371-376. doi:10.1007/s00281-015-0492-6
7. Sag E, Akal F, Atalay E, et al. Anti-IL1 treatment in colchicine-resistant paediatric FMF patients: real life data from the HELIOS registry. *Rheumatology (Oxford)*. 2020;59(11):3324-3329. doi:10.1093/rheumatology/keaa121
8. Van der Burgh R, Pervolaraki K, Turkenburg M, Waterham HR, Frenkel J, Boes M. Unprenylated RhoA contributes to IL-1β hypersecretion in mevalonate kinase deficiency model through stimulation of Rac1 activity. *J Biol Chem*. 2014;289(40):27757-27765. doi:10.1074/jbc.M114.571810
9. Tsitsami E, Papadopoulou C, Speletas M. A case of hyperimmunoglobulinemia d syndrome successfully treated with canakinumab. *Case Rep Rheumatol*. 2013;2013:795027. doi:10.1155/2013/795027
10. Rodrigues F, Philit JB, Giurgea I, et al. AA amyloidosis revealing mevalonate kinase deficiency: a report of 20 cases including two new French cases and a comprehensive review of literature. *Semin Arthritis Rheum*. 2020;50(6):1370-1373. doi:10.1016/j.semarthrit.2020.03.005
11. Houten SM, van Woerden CS, Wijburg FA, Wanders RJ, Waterham HR. Carrier frequency of the V377I (1129G>a) MVK mutation, associated with hyper-IgD and periodic fever syndrome, in The Netherlands. *Eur J Hum Genet*. 2003;11(2):196-200. doi:10.1038/sj.ejhg.5200933
12. Messer L, Alsaleh G, Georgel P, et al. Homozygosity for the V377I mutation in mevalonate kinase causes distinct clinical phenotypes in two sibs with hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS). *RMD Open*. 2016;2(1):e000196. doi:10.1136/rmdopen-2015-000196
13. Malcova H, Strizova Z, Milota T, et al. IL-1 inhibitors in the treatment of monogenic periodic fever syndromes: from the past to the future perspectives. *Front Immunol*. 2021;11:619257. doi:10.3389/fimmu.2020.619257
14. Jeyaratnam J, Simon A, Calvo I, et al. Long-term efficacy and safety of canakinumab in patients with mevalonate kinase deficiency: results from the randomised phase 3 CLUSTER trial. *Rheumatology (Oxford)*. 2022;61(5):2088-2094. doi:10.1093/rheumatology/keab696