Efficacy of Continuous Interleukin 1 Blockade in Mevalonate Kinase Deficiency: A Multicenter Retrospective Study in 13 Adult Patients and Literature Review

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ABSTRACT. ***Objective.*** To report efficacy and tolerance of interleukin 1 blockade in adult patients with mevalonate kinase deficiency (MKD).

Methods. We retrospectively collected data on 13 patients with MKD who had received anakinra (n = 10) and canakinumab (n = 7).

Results. Anakinra resulted in complete or partial remission in 3/10 and 5/10 patients, respectively, and no efficacy in 2/10, but a switch to canakinumab led to partial remission. Canakinumab resulted in complete or partial remission in 3/7 and 4/7 patients, respectively.

Conclusion. These data support frequent partial responses, showing a better response with canakinumab. The genotype and therapeutic outcomes correlation should help in the personalization of treatment. (J Rheumatol First Release January 15 2018; doi:10.3899/jrheum.170684)

Key Indexing Terms:
MEVALONATE KINASE DEFICIENCY HEREDITARY AUTOINFLAMMATORY DISEASES
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Mevalonate kinase deficiency (MKD; OMIM 260920) is a rare monogenic autosomal recessive autoinflammatory disease, characterized by the early onset of febrile attacks accompanied by an array of symptoms[1,2,3]. The number of known patients with MKD is estimated to be > 300 throughout the world, with a worldwide distribution[3]. Classic antiinflammatory or immunosuppressant drugs have exhibited only limited or no efficacy. The pathophysiology of MKD remains only partially understood, but the involvement of interleukin (IL) 1 is well established. MKD leads to a lack of isoprenoid products. In its absence, phosphatidylinositol-3-kinase activity promotes unchecked

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Toll-like receptor (TLR)-induced inflammatory responses. Binding of pyrin to its inhibitory 14-3-3 proteins, which are responsible for constitutive pyrin inflammasome activation and increased IL-1β secretion, is diminished[3,4,5]. Another pathway is mediated by mitochondrial desoxyribonucleic acid and reactive oxygen species through the nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome. In addition, defective autophagy led to the accumulation of damaged mitochondria in monocytes, which primes monocytes for IL-1β hypersecretion[6].

Two anti-IL-1 drugs are available in France: anakinra, a recombinant homologue of the human IL-1 receptor antagonist, and canakinumab, a human anti-IL-1β monoclonal antibody[7]. Reports on the use of these newly available drugs involved only case reports or small case series, more often in pediatric patients and within limited followup periods. Therefore, applicable experience with these drugs in this newly recognized rare disease remains limited.

We report on the use of anakinra and canakinumab in adult French patients with MKD and describe the evolutionary efficacy and tolerance of these drugs.

MATERIALS AND METHODS

We selected 5 patients from a previously reported cohort diagnosed with MKD in adulthood who had received anakinra or canakinumab and had sufficient data[8]. Briefly, in our cohort, patients > 16 years of age at diagnosis were identified with genetic analysis or received enzymatically proven diagnoses because of family history of MKD or typical clinical features in France and Belgium, from January 2000 to December 2014. We also included patients referred to the reference center for autoinflammatory diseases for whom anti-IL-1 therapy was introduced or continued into adulthood. All patients were treated after multidisciplinary consultation meetings, which included the opinions of doctors involved in the network of French reference centers for autoinflammatory diseases. Complete response (CR) was defined as the absence of both clinical symptoms and inflammatory biological syndrome (C-reactive protein level ≤ 10 mg/l). Partial response (PR) was defined by a decline of both the symptoms and the frequency of attacks, but with persistence of some clinical manifestations and/or abnormal laboratory findings. Failure was defined by absence of any substantial effect on disease activity. Loss of efficacy (LOE) was considered if a patient had a transient CR, followed by recurrent typical attacks. Our study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles, and approval from our institution's research ethics board (Comité de Protection des Personnes Nord Ouest III) has been obtained for this retrospective study. Categorical variables were reported as percentages, and continuous variables were expressed as median (range).

RESULTS

Thirteen patients with MKD were included, 8 of whom were diagnosed in adulthood (Table 1). Anti-IL-1 therapy was introduced or continued in all patients into adulthood. Three patients exhibited homozygosity for V377I (n = 2) and A148T (n = 1) mutations. The other 10 patients exhibited compound heterozygosity for the V377I mutation, in combination with I268T (n = 2), del 631-633 (n = 2), R176K, G335D, G305A, A147T, T342I, or T243Yfs*34 (n = 1 each) mutations.

Continuous treatment with anakinra was used in 10 patients [16 mos (3–47)], resulting in CR in 3/10 patients (30%), PR in 5/10 patients (50%), and no efficacy in the other 2 patients (20%). LOE was noted in patients 1 and 6 after 3 and 5 months, respectively. Six patients (60%) experienced injection-site reactions, infections, and/or weight gain. Patient 5 had recurrent pulmonary infections favored by an acquired bronchiectasis; anakinra could be continued with subcutaneous immunoglobulin replacement therapy. Patient 7 had recurrent bronchitis and nasopharyngitis that led to anakinra discontinuation.

Canakinumab was used in 7 patients [18 mos (4–60)]. CR was observed in 3/7 patients (43%), with secondary LOE in 1/7 (14%), and PR in the other 4 patients (57%). One patient had recurrent pulmonary infections favored by chronic obstructive pulmonary disease that led to canakinumab discontinuation. Notably, in patients 4 and 5, canakinumab allowed for sustained PR after the failure of > 10 drugs, including anakinra. The patient with the homozygous A148T mutation maintained CR to anakinra. Both patients who harbored the heterozygous del 631-633 mutation exhibited failure with anakinra.

DISCUSSION

Our study on 13 adult patients with MKD shows that continuous IL-1 targeting is an effective treatment, but most often only offers PR or a rapid LOE in longterm use. Moreover, in the 4 patients treated sequentially with anakinra then with canakinumab, the latter exhibited better, but mostly partial, efficacy. Finally, 2 rarely or never-reported molecular defects, the A148T and the del 631-633 mutations, seem to have particular treatment outcome profiles with CR and failure of anakinra, respectively.

Most of the literature data are related to anakinra, with a CR observed in 12.5–30%, PR in 50–87.5%, and no efficacy in 0–20% of the cases[2,7,9,10] (Table 2). Among the 10 patients who had discontinued anakinra in a French retrospective study, 2 patients had experienced LOE, 2 had adverse drug reactions, and 3 patients discontinued treatment at their request. Anakinra was not only responsible for injection site reactions (39%) and injection site pain (36%) but also for weight gain (11%), liver toxicity (7%), and severe infections (5.1%)[11].

Regarding canakinumab, CR was obtained in 50–80% of the cases, with PR in remaining patients[2,7] (Table 2). In the retrospective French observational study by Galeotti, *et al*, canakinumab lowered the clinical score more than anakinra in 3 out of 4 patients sequentially treated with both drugs[7]. Canakinumab had better cutaneous tolerance (4%), but the patients experienced mild respiratory infections (17%) and liver toxicity (9%)[11]. Canakinumab corrected the upregulated levels of interferon and myeloid-related inflammatory responses, with a longer and larger response than with anakinra[12]. A multicenter study of canakinumab in MKD is

Table 1. Main clinical features and outcomes of mevalonate kinase deficiency patients treated with antiinterleukin 1 therapy.

Patients, Sex	Age at First Symptoms/at Diagnosis	*MVK* Gene Mutations	Symptoms (mean flare frequency/yr)	Previous Treatments	Antiinterleukin 1 Therapy (age at treatment start)	Outcome
Patient 1, male	1 yr/33 yrs	V377I, V377I	Fever, arthralgia and myalgia, rash, pharyngitis, splenomegaly (2)	Corticosteroids, methotrexate, colchicine	Anakinra 100 mg/d (34 yrs)	Complete remission, then loss of efficacy within 3 mos
Patient 2, female	2 yrs/27 yrs	A148T, A148T	Fever, diarrhea, abdominal pain, polyarthritis, skin rash, pharyngitis, conjunctivitis (12)	NSAID, penicillamine, sulfasalazine, methotrexate, statin, corticosteroids, colchicine	Anakinra 100 mg/d (36 yrs), then 2/wk after 41 mos	Complete remission within 47 mos
Patient 3, male	NR/34 yrs	V377I, I268T	Fever, abdominal pain, diarrhea, arthralgia, aphthous ulcers (3)	Hydroxychloroquine, statin, colchicine	Canakinumab 150 mg/8 wks (44 yrs)	Partial remission, discontinued after 2 injections at patient's request
Patient 4, female	3 yrs/16 yrs	V377I, del 631-633	Fever, diarrhea, arthralgia and myalgia, enlarged lymph nodes, oral aphthous ulcers (24)	NSAID, corticosteroids, thalidomide, intravenous immunoglobulins, methotrexate, etanercept, adalimumab, infliximab, statins, colchicine, lenalidomide, mycophenolic acid, azathioprine, rituximab, pegylated interferon, abatacept	Anakinra 100 mg/d (19 yrs)	No efficacy, severe injection site reactions, discontinued after 18 mos
					Canakinumab 150 mg/6 wks (24 yrs), then 300 mg/4 wks	Complete remission, then loss of efficacy within 12 mos, and then partial remission with increased dosage. Discontinuation after 43 mos because of a desire for pregnancy
Patient 5, female	7 yrs/25 yrs	V377I, del 631-633	Fever, enlarged lymph nodes, polyarthralgia, asthenia, oral aphthous ulcers, rash (6)	NSAID, colchicine, cyclosporine, methotrexate, azathioprine, intravenous immunoglobulins, infliximab, adalimumab, etanercept, abatacept, mycophenolic acid, lenalidomide, thalidomide	Anakinra 100 mg/d (33 yrs)	No efficacy, severe injection site reactions, discontinued after 12 mos
					Canakinumab 150 mg/8 wks (38 yrs), then 150 mg/4 wks and 150 mg/3 wks	Partial remission after 18 mos, but recurrent infections
Patient 6, female	18 mos/8 yrs	V377I, R176K	Fever, pharyngitis, enlarged lymph nodes, hepatosplenomegaly, abdominal pain (17)	Corticosteroids, NSAID	Anakinra 100 mg/d (21 yrs)	Complete remission, then loss of efficacy within 5 mos, and injection site reactions, discontinued after 18 mos
					Canakinumab 150 mg/ 8 weeks (24 yrs)	Partial remission, injection site reactions, discontinued after 46 mos because of a desire for pregnancy
Patient 7, female	Childhood/ Childhood	V377I, I268T	Fever, vomiting, abdominal pain, arthralgia, genital ulcers, splenomegaly, enlarged lymph nodes (17)	Corticosteroids, NSAID, colchicine, pentoxifylline	Anakinra 100 mg/d (27 yrs), then every 2 d	Partial remission, but recurrent infections, discontinued after 14 mos
Patient 8, male	5 mos/13 yrs	V377I, G335D	Fever, abdominal pain, arthralgia, headaches, oral aphthous ulcers, asthenia, diarrhea, enlarged lymph nodes (12)	Corticosteroids, colchicine	Anakinra 100 mg/d (21 yrs)	Partial remission, severe injection site reactions, discontinued after 10 mos
					Canakinumab 150 mg/ 8 wks (22 yrs)	Partial remission after 6 mos
Patient 9, female	1 mo/4 yrs	V377I, G305A	Fever, headaches, abdominal pain, vomiting, asthenia, arthralgia, oral aphthous ulcers, skin rash, enlarged lymph nodes (3)	Corticosteroids, aspirin, NSAID, etanercept	Canakinumab 150 mg/ 8 wks (18 yrs)	Complete remission after 13 mos

Table 1. Continued.

Patients, Sex	Age at First Symptoms/at Diagnosis	*MVK* Gene Mutations	Symptoms (mean flare frequency/yr)	Previous Treatments	Antiinterleukin 1 Therapy (age at treatment start)	Outcome
Patient 10, female	1 mo/5 yrs	V377I, A147T	Fever, abdominal pain, enlarged lymph nodes, oral aphthous ulcers, skin rash (24)	Etanercept	Canakinumab 150 mg/4 wks (11 yrs), then every 6 wks after 8 mos, every 8 wks after 4 mos, every 10 wks after 6 mos, then on demand after 20 mos	Complete remission after 60 mos
Patient 11, male	6 yrs/40 yrs	V377I, T243Yfs*34	Fever, headaches, abdominal pain, myalgia, arthralgia, enlarged lymph nodes (2)	Corticosteroids, colchicine	Anakinra 100 mg/d (40 yrs)	Partial remission, but recurrent pulmonary infections and weight gain, discontinued after 6 mos
Patient 12, male	18 mos/39 yrs	V377I, T342I	Fever, hepatosplenomegaly, skin rash, abdominal pain, polyarthritis, oral aphthous ulcers, pharyngitis, enlarged lymph nodes, uveitis, mental retardation, epilepsy, aseptic meningitis (4)	Corticosteroids, aspirin, azathioprine, colchicine	Anakinra 100 mg/d (39 yrs)	Partial remission after 20 mos
Patient 13, female	40 yrs/41 yrs	V377I, V377I	Fever, polyarthralgia, abdominal pain, oral aphthous ulcers, enlarged lymph nodes (24)	Corticosteroids, methotrexate, statin	Anakinra 100 mg/d (48 yrs), then every 2 d after 24 mos	Partial remission after 35 mos

NSAID: nonsteroidal antiinflammatory drugs; NR: not reported.

ongoing (ClinicalTrials.gov, NCT02059291). Anti-IL-1 therapy is currently introduced as a first-line agent in 71% of cases when biologic therapy is required because of severe MKD, but 50% (5/10) of cases discontinued anakinra as a result of lack of efficacy[13]. These results should generate a decrease in ineffective and/or harmful drugs, such as in our historical patients 4 and 5. Canakinumab has recently been approved by the American Food and Drug Administration and the European Medicines Agency in MKD.

Some patients may require higher dosage of canakinumab as shown in 1 of our patients. Higher dosage of anakinra could also exhibit better response, but because of its daily and often painful injections, our practice is to prefer a switch to canakinumab.

Limited data are available on the phenotype-genotype correlation and even less on the genotype and therapeutic outcomes correlation. Although this short series does not provide a firm treatment outcome analysis according to molecular defects, the only patient who showed a sustained CR under anakinra harbored the homozygous A148T mutation. Inversely, both patients who harbored the del 631-633 mutation were the only patients to exhibit a failure with anakinra. These 2 patients were already reported in the article from Bader-Meunier, *et al*[14]. Enzymatic activity was < 2% in 1 patient, and not measured in her sister. Because the V377I mutation, which was found in 10 other patients, was not associated with this unfavorable outcome, we hypothesized that the failure of anakinra may be related to the del 631-633 mutation. Moreover, ter Haar, *et al* found that patients with the V377I mutation, compared to patients without the V377I mutation, less often exhibited continuous disease courses, and severe gastrointestinal or musculoskeletal involvement[2]. Their 4 patients who exhibited the compound heterozygous V377I/I268T mutation and received a biologic therapy showed PR with anti-IL-1 therapy, as in our 2 patients.

The evaluation of the efficacy of treatment could be impaired by a possible publication bias and the natural evolution of MKD, because there is a significant decrease in the severity and frequency of attacks with increasing age[8,15]. The available data are reassuring regarding the longterm safety of anti-IL-1 therapy: the rate of adverse drug reactions declined with the longterm use of anakinra, and canakinumab is well tolerated in cryopyrin-associated periodic syndromes[16,17].

The few reports on IL-1 blockade in MKD currently support its efficacy, but with frequent PR and with a better response to canakinumab compared with anakinra. The possible correlation between the genotype and the treatment outcome should help in the personalization of treatment, which requires larger multicenter prospective studies. Some studies indicate that MKD is a multicytokine disease, through TLR2/TLR4-dependent cytokine production[2,18,19]. This could explain the partial efficacy of anti-IL-1 drugs in most patients with MKD and could argue for the assessment of

Table 2. Literature data on continuous antiinterleukin 1 efficacy in mevalonate kinase deficiency.

Study, yr	Study Population	Complete Response, n (%)	Partial Efficacy, n (%)	No Response, n (%)	Median Followup, mos
Anakinra					
Galeotti, *et al*, 2012[7]	8 pediatric and adult patients	1 (12.5)	7 (87.5)	0 (0)	12
Kostjukovits, *et al*, 2015[9]	12 pediatric patients (literature review, after exclusion of cases reported by Galeotti, *et al*)[7]	3 (25)	7 (58)	2 (17)	8 (1 missing data)
Ter Haar, *et al*, 2016[2]	19 patients (Eurofever Registry)	3 (16)	13 (68)	3 (16)	Not reported
Deshayes, *et al*, present study	10 adult patients	3 (30)	5 (50)	2 (20)	16
Canakinumab					
Galeotti, *et al*, 2012[7]	6 pediatric and adult patients	3 (50)	3 (50)	0 (0)	14
Ter Haar, *et al*, 2016[2]	5 patients (Eurofever Registry)	4 (80)	1 (20)	0 (0)	Not reported
Arostegui, *et al*, 2017[12]	8 pediatric and adult patients	4 (50)	4 (50)	0 (0)	24
Deshayes, *et al*, (present study)	7 adult patients	3 (43)	4 (57)	0 (0)	18
Total	75	24 (32)	44 (58.7)	7 (9.3)	15

other cytokine-targeting drugs. Although it has been used in very few patients with MKD who were refractory to anakinra, anti-IL-6 therapy has already been tried with success[20].

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