Concise report

Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency

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Abstract

Objective. To describe the efficacy and safety of IL-1-targeting drugs, anakinra and canakinumab, in patients with mevalonate kinase deficiency (MKD).

Methods. A questionnaire was sent to French paediatric and adult rheumatologists to retrospectively collect information on disease activity before and after treatment with IL-1 antagonists from genetically confirmed MKD patients. We assessed the frequency of crises and their intensity using a 12-item clinical score built for the purpose of the study.

Results. Eleven patients were included. Anti-IL-1-targeting drugs were used continuously in all but one patient who received anakinra on demand. Daily anakinra (nine patients) or canakinumab injections every 4–8 weeks (six patients, in four cases following anakinra treatment) were associated with complete remission in four cases and partial remission in seven. The median score during MKD attacks decreased from 7/12 before treatment to 3/12 after anakinra and 1/12 after canakinumab. The number of days with fever during attacks decreased from 5 before treatment to 3 after anakinra and 2 after canakinumab. Marked decrease of C-reactive protein and serum amyloid A protein were recorded. Side effects were mild or moderate; they consisted of local pain and inflammation at injection site, infections and hepatic cytolysis.

Conclusion. Continuous IL-1 blockade brings substantial benefit to MKD patients. Controlled trials are necessary to further assess the clinical benefit and treatment modalities in these patients.

Key words: mevalonate kinase deficiency, hyper-IgD syndrome, interleukin-1, anakinra, canakinumab, auto-inflammatory disease.

Introduction

Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory disease caused by mutations of the MVK gene, which compromise isoprenoid and cholesterol biosynthesis. Depending on the residual MVK activity, the clinical spectrum ranges from mild forms of hyper-IgD syndrome (HIDS) to lethal forms of mevalonic aciduria (MA) [1–3]. HIDS generally manifests before the age of 3 years and is characterized by recurrent and lifelong episodes of fever and inflammation, which last for 5–7 days. Other clinical manifestations include lymphadenopathy, headaches, abdominal pain, vomiting, hepatosplenomegaly, various skin rashes and transient arthritis. Patients with MA typically suffer from severe psychomotor retardation, progressive cerebellar ataxia, typical dimorphic features, severe growth retardation and progressive visual impairment. The lifelong recurrent attacks cause major alteration of the quality of life. Furthermore, MKD is associated with an increased risk for life-threatening bacterial infections [2] and secondary AA amyloidosis [4].

Data on therapeutic options for MKD, including statins (HMG-CoA reductase inhibitors), high-dose glucocorticoids [5] and anti-TNF agents [2, 3, 6, 7], are currently limited and rely generally on case reports and small series. In MK-deficient peripheral blood mononuclear
cells, the shortage of isoprenoid end products increases IL-1β secretion [8], suggesting that targeting of the IL-1 signalling may be a potential therapy for HIDS patients. Some case reports and global disease surveys reported success with anakinra, a recombinant, non-glycosylated homologue of the human IL-1 receptor antagonist that inhibits binding of IL-1α and IL-1β to the IL-1 receptor [3, 9–13], and canakinumab, a human monoclonal antibody directed against IL-1β [2], but most of these studies do not specify the exact treatment modalities. More recently, in a prospective observational study, anakinra treatment of eight HIDS patients on demand at the onset of crisis reduced the duration and severity of attacks but did not decrease the frequency of attacks [14].

Here, we present 11 MKD patients who were treated with anakinra and/or canakinumab. Based on these cases and those published by others, we discuss the possible indications of IL-1-targeting drugs in MKD patients.

Patients and methods

We used an e-mail survey among the members of the French Paediatric Society for Paediatric Rheumatology (SOFREMIP) and e-mails to reference centres for systemic diseases to identify MKD patients who received anti-IL-1-targeting drugs. Clinical features, complications, course of disease and response to therapy were recorded using a questionnaire. Data on anti-IL-1 treatments included the type of biologic, the dose and administration procedure, and the effect on individual symptoms. A clinical symptom score and a global physician’s visual analogical scale were used to assess the response to treatment. The clinical symptom score was established retrospectively by the sum of the following 12 clinical disease manifestations (one point for each present item): fever (38°C or more), cervical lymphadenopathy, aphthae, skin rashes, arthralgia, arthritis, myalgia, nausea/vomiting, abdominal pain, diarrhoea, headaches and throat pains. The first score refers to the visit before IL-1 inhibitor treatment and the second score is a global evaluation of the period under treatment. Furthermore, we recorded the evolution of CRP and serum amyloid A (SAA) before and during anti-IL-1 treatment, as well as treatment-associated side effects. The CRP and SAA were measured between crises. The study was in accordance with French regulations; no ethical committee was required for this retrospective study.

Results

We identified 11 patients from six centres. Six patients had been reported in previous publications [2, 10, 15]; however, their outcome under biologic treatment was not thoroughly analysed. Eight patients were classified as HIDS and three patients as MA because they presented at least one of the following: severe psychomotor retardation, progressive cerebellar ataxia, typical dysmorphic features and progressive visual impairment [16]. All patients carried two MVK mutations and had a severe inflammatory feature with at least two attacks per month under ongoing treatments. The demographic and genetic features are summarized in Table 1. Proteinuria (>0.3 g/24 h) without amyloidosis was present in two patients; patient 10 had a pauci immune glomerulonephritis, and patient 7 had a mild (0.75 g/24 h) and transient proteinuria.

Treatments administrated before anti-IL-1 treatment were steroids (9/11 patients), NSAIDs (8/11 patients), statins (1/11 patients), etanercept (4/11 patients), colchicine (3/11 patients), IVIG (3/11 patients) and adalimumab (1/11 patients). Patient 10, received treatment with CYC, aspirin, AZA, ciclosporin and sirolimus for pauci immune GN, which required kidney transplantation [10].

The choice for using either anakinra or canakinumab as first-line resulted from a discussion between the physicians and the parents and took into account the patient’s preferences.

High frequency of attacks hindering the quality of life and persistent systemic inflammation with increased risk for complications such as AA amyloidosis were the main reasons for initiating anti-IL-1 therapy. Five patients received anakinra alone, two patients canakinumab alone and four patients started with anakinra and were later switched to canakinumab. The median duration (range) of anti-IL-1 treatments was 15 (4–72) months: 11 (2–72) months for anakinra and 14 (10–21) months for canakinumab. The doses of anakinra varied from 1 to 5 mg/kg/day. In some patients the dose was gradually modified according to patients’ responses to treatment. In patients 3 and 11, the dose of anakinra was gradually tapered to three injections per week, at 3 and 2 mg/kg, respectively. The doses of canakinumab ranged from 2 to 7 mg/kg every 8 weeks in five cases. Patient 5 received canakinumab at a dosage of 7 mg/kg every 4 weeks. Anti-IL-1-targeting drugs were used continuously in all patients but one patient (patient 7) who received anakinra on demand the first day and the following 7 days of an attack.

The evolution of clinical score and frequency of attacks at baseline and during anti-IL-1 treatments (anakinra and canakinumab) are shown in the Fig. 1. Partial clinical remission, defined by a decline of both the symptoms and the frequency of attacks, was obtained in seven of nine patients on anakinra and three of six patients on canakinumab. Complete clinical remission (no attack and no inflammatory syndrome) was obtained in one of nine patients on anakinra and three of six patients on canakinumab. The number of days with fever during attacks decreased from 5 before treatment to 3 after anakinra and 2 after canakinumab. CRP decreased during anti-IL-1 treatment in all patients. Complete normalization of CRP levels was achieved in one of seven patients receiving anakinra and five of six patients receiving canakinumab. Haemoglobin levels (range) increased from 9.9 (7.9–12.1) g/dl before treatment to 10.8 (10–15.5) g/dl after anakinra and 13.6 (9.9–15.5) g/dl after canakinumab. SAA protein levels were monitored in three patients. The median (range) SAA level decreased from 253.5 (0–846) mg/l before treatment to 13.5 mg/l after treatment with anti-IL-1 treatments. One patient with severe MA (patient 6) partially responded to anakinra. She underwent successful allogenic bone marrow transplantation from an
HLA-identical sister [15]. Four patients were switched from anakinra to canakinumab. Reasons for discontinuation of anakinra were to obtain a more convenient dosing schedule and to avoid injection site reaction. In three of the four patients, treatment with canakinumab lowered the clinical score more than anakinra. One patient received anakinra on demand the first day of an attack and the following 7 days. He experienced this treatment during only two attacks where the clinical score, the duration of attacks and the inflammatory markers decreased.

Seven patients received anti-IL-1-targeting drugs without additional medication. Patient 3 and 11 were on combined therapy with NSAIDs and paracetamol, respectively. Patient 5 received adalimumab because the disease was not controlled with anakinra alone at 5 mg/kg/day. This association, theoretically not recommended, was not successful; however, no secondary effects were observed. Both drugs were discontinued and switched to canakinumab, which induced partial control of the disease. Patient 2, with partial response on canakinumab, received additionally a single dose of CSs (bethamethasone 0.2 mg/kg) the first day of crises, which reduced their duration. Patient 10, who had kidney transplantation before anakinra treatment, still received his immunosuppressive treatment (steroids, sirolimus and ciclosporin).

Overall, both anakinra and canakinumab were well tolerated. The side effects of anakinra treatment were injection site inflammatory reactions (four patients), an episode of shivers and hypothermia after the first injection (one patient) and bacterial pneumonia (one patient). The side effects of canakinumab treatment were injection site reaction (one patient), recurrent pharyngitis (one patient) and transient hepatitis in patient 5 when the dose of canakinumab was increased to 7 mg/kg every 4 weeks. Furthermore, one patient who also received high-dose corticoids had a transient hepatitis without confirmation of viral or autoimmune aetiology. No safety issues emerged from haematological monitoring and urine analyses.

Discussion

We report marked clinical effect of IL-1 blockade in 11 patients with MKD who were treated with anakinra or canakinumab, administrated continuously in all but one patient, with various schemes of administration. Even though the retrospective character of this study bears many possible sources of bias and heterogeneity, our observations show that all patients with MKD had an improvement of disease activity under IL-1-targeting drugs with regard to the reduction of a clinical score during attacks, the reduction of the duration and frequency of attacks, and the decreased biological inflammation. However, complete clinical and biological remission was obtained in only one of nine patients on anakinra and three of six on canakinumab.

The choice of continuous anti-IL-1 treatment in 10 of 11 cases here contrasted with the way MKD patients were treated in a recent prospective study, where Bodar et al. [14] used anakinra on demand at the onset of crises in eight HIDS patients. They report a clinical response...
defined by a more than 50% reduction in duration of attacks, but no changes were observed with regard to the frequency of attacks. The decision for one or the other option could take into account the patient’s desire for treatment-free days during remission vs fewer attacks. More importantly, additional studies are necessary to compare the advantage of either treatment modality with respect to the reduction of long-term complications such as AA amyloidosis, infections or treatment-associated long-term side effects.

Our three patients with the most severe phenotype had partial remission with continuous anakinra. In contrast, Bodar et al. [14] reported no remission of symptoms in two patients with continuous anakinra treatment. Lower doses of anakinra (2 mg/kg/day vs 3–5 mg/kg/day in our study) may at least, in part, explain these differences. Thus further trials should address questions about pharmacokinetics and the dose-dependent response of IL-1-targeting drugs in MA. We do not recommend the combination of a TNF inhibitor and an IL-1 inhibitor, which can be dangerous and seems not to be effective.

Overall, treatments were well tolerated, injection site reaction being the most frequent secondary effect reported. We observed one bacterial infection, which was non-complicated, especially when taking into account MKD patients who are at high risk for severe sepsis [2].

There is no standard therapy for MKD. The main goals of an effective treatment should include a complete control of systemic inflammation, a prevention of secondary complications and a marked improvement of the quality of life. Some preliminary recommendations for the use of anti-IL-1 treatment in MKD could be raised from our brief experience and from a few reports from the literature. We do not recommend the use of anti-IL-1 as first-line treatment, because the cost-effectiveness and safety of these drugs are still unknown. NSAIDs and a short course of steroids could be sufficient in patients with only a few attacks and without subclinical inflammation (e.g. normal CRP and SAA) between attacks. The use of anti-IL-1 treatment could be recommended to patients with a high frequency of attacks, especially those who experience more than 12 attacks per year and have detectable continuous subclinical inflammation. Higher dosages and a shortened interval between injections for long-lasting drugs (canakinumab) should be advised in patients with suboptimal response to standard doses.

Altogether, patients published by us and others indicate that IL-1-targeting drugs may be good candidates when looking for an effective treatment of patients with severe MKD, and encourage further exploration of their efficacy in controlled trials. Whether long-lasting drugs should be used as a first choice, or only after having confirmed the clinical benefit of silencing the IL-1 pathway with...
short-acting drugs or when compliance problems are encountered needs to be discussed.

**Rheumatology key messages**

- Long- and short-acting IL-1-targeting drugs are well tolerated in MKD.
- Long-lasting IL-1-targeting drugs should be used preferably as a second-line treatment in MKD.

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**References**