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CLINICAL STUDY

Canakinumab as monotherapy for treatment of familial Mediterranean fever – first report in Central and Eastern Europe region

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ABSTRACT

Autoinflammatory disorders (AID) are characterized by spontaneous attacks of acute inflammation with a broad spectrum of clinical symptoms. Ongoing inflammation and reoccurrence of acute flares can lead to the development of amyloidosis. One group of AID is represented by monogenic periodic fever syndromes while familial Mediterranean fever (FMF) is the most common form of AID from this group. Its prevalence in Central and Eastern Europe was reported to be very low. We report a case of FMF patient with a very severe clinical course of FMF and intolerance to colchicine, which is a gold standard for FMF treatment. The clinical effect of the application of anakinra was insufficient and accompanied with side effects and low tolerability. Switching to canakinumab (human monoclonal antibody against IL-1β) at dose of 150 mg every 4 weeks induced a rapid remission of the disease activity and inflammatory markers. However, due to relapse of acute flares after three weeks from application, the escalation of dose to 300 mg every 4 weeks induced a complete remission of symptoms and significantly improved the quality of life. This is the first report of successful canakinumab administration in FMF patient in Central and Eastern Europe, a region with very low incidence of FMF *(Tab. 1, Ref. 16)*. Text in PDF *www.elis.sk.*

KEY WORDS: autoinflammation, monogenic periodic fever syndromes, familial Mediterranean fever, amyloidosis, colchicine-resistant disease, canakinumab.

Introduction

Autoinflammatory disorders (AIDs) represent an interesting group of genetically inherited immunodeficiency disorders characterized by uncontrolled spontaneous activation of innate immune reactivity. Recurrent uncontrolled onsets of systemic inflammatory response without any evident infectious origin are typically associated with a broad spectrum of clinical symptoms from fever to serositis, arthralgias/arthritis, skin rashes or general fatigue. A specific subgroup of AID is represented by monogenic periodic fever syndromes with an underlying mutation in the genes involved in the regulation of inflammatory cascade (1, 2). The spectrum of new AID is expanding, and newly described genetic causes are reported every year. Familial Mediterranean fever (FMF) is the most common form of monogenic AIDs all over the world with very high incidence in specific geographical areas. On the other hand, the prevalence in Central and Eastern European (CEE) countries was reported to be very low (3). Due to its rare incidence, FMF is usually forgotten to be a part of differential diagnostic algorithms of recurrent fever, and the diagnosis is confirmed with a long-time delay. The late diagnosis of FMF is associated with the development of organ complications, e.g. amyloidosis. There are only few case reports or case report studies published from CEE region, so it is possible that many FMF patients remain unrecognized (3–5).

The standard treatment of FMF patients is colchicine, which is able to decrease the reoccurrence of flares, achieve control over the ongoing spontaneous inflammation and prevent the development of organ amyloidosis. However, 5 – 10 % of patients are resistant or even intolerant to the treatment with colchicine (6). Since the central role in the spontaneous inflammation flares is played by interleukin 1β (IL-1β), the therapeutic blockade of this cytokine represents another important therapeutic strategy for these patients. Up to now, there are three molecules available on the market, namely anakinra (recombinant antagonist of IL-1 receptor), rilonacept (fully human dimeric fusion protein consisting of extracellular domain of both IL-1 receptor components) and finally, canakinumab (fully human monoclonal antibody against IL-1β) (Tab. 1) (7). Despite the increasing number of reports about the use of all the three biologicals in the successful management of various periodic fever syndromes, and according to the summary

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Tab. 1. Biologicals against interleukin 1β and their selected characteristics (adapted from Moll et al, 2013 (7)).

	Interleukin-1 inhibiting biologicals		
Molecule	**Anakinra**	**Rilonacept**	**Canakinumab**
Characterization of molecule	Recombinant antagonist of human IL-1 receptor	Human dimeric fusion protein (extracellular domain of both IL-1 receptor components)	Fully monoclonal human antibody against IL-1β
Target	IL-1α, IL-1β	IL-1α, IL-1β, IL-1Ra	IL-1β
Biological half-life	4 hours	67 hours	21-28 days
Indications	CAPS	CAPS	CAPS, FMF, HIDS, TRAPS
Age limitation	none	≥ 12 years	none

CAPS – cryopyrin-associated periodic syndrome, FMF – familial Mediterranean fever, HIDS – hyperimmunoglobulinemia D syndrome, IL-1 – interleukin 1, IL-1Ra – interleukin 1 receptor antagonist, TRAPS – TNF-receptor associated periodic syndrome

of product characteristics, only canakinumab is indicated for the treatment of FMF.

Clinical study

We report a case of a 36-year-old man of Caucasian ethnicity with the history of recurrent abdominal pain accompanied with mildly increased fever. His clinical problems started to appear approximately at the age of 17 years. Acute attacks of pain lasted approximately 3 days and were accompanied with the increase in non-specific inflammatory markers (C-reactive protein over 100 mg/L) and negative procalcitonine. Abdominal ultrasound performed during the acute flare did not reveal any pathological findings and no fluid in abdominal cavity was detected. The periods between the pain attacks were accompanied with fatigue, arthralgia and vasculitis-like symptoms on shin. Microbiological examinations were completely negative and did not explain the problems. There was no response to antibiotic treatments prescribed by general practitioners and the analgesics showed only partial clinical response. After three years of duration of the problems, the patient underwent a gastrofibroscopic examination with the findings of *Helicobacter pylori*-associated antral gastritis, which was treated according to the standard protocols but without any significant effect on the reoccurrence of abdominal pain. The stool was of normal consistence and examination of urine did not yield any pathological finding. A colonoscopic examination showed incipient inflammatory signs following the diagnosis of ulcerative colitis, and a treatment with 5-aminosalicylic acid was initiated. However, neither this therapy improved the clinical status. The control endoscopic examination did not show any pathologic finding in upper and lower parts of gastrointestinal tract. MR-enterography yielded normal results. Thereafter, appendectomy was performed but recurrent abdominal pain persisted. The patient underwent different dietetic interventions, but none succeeded in relief of pain. The serological tests for coeliac disease and stool for faecal calprotectin were negative; porphyria was also excluded. Respiratory symptoms were not present. Four years after the beginning of the symptoms, an intensive back pain emerged besides the abdominal attacks. They responded to subcutaneous applications of morphine only. Family history was negative for any of immune-mediated diseases. No oedemas of the skin, face, or extremities were presented.

Normal levels of immunoglobulins, C3, and C4 components of the complement system, normal antigenic and functional levels of C1-inhibitor were disclosed by laboratory investigations. Inflammatory markers returned usually to increased levels between the attacks (C-reactive protein between 7.3 – 18.9 mg/L). Taking into account the recurrent abdominal pain of short duration, negative findings of the previously performed examinations and laboratory testing, and increase in inflammatory markers during abdominal pain, the diagnosis of familiar Mediterranean fever was suggested and genetic analysis performed. The analysis of *MEFV* gene revealed a pathological missense mutation in exon 10 p.Met694Val (c.2080A>G) in a heterozygous state and the disease-associated variant p.Glu148Gln (c.442G>C) in a compound heterozygosity. The examination of serum amyloid A between the flares was 13.2 – 35.8 mg/L. The diagnostic delay between the first symptoms and genetic confirmation of the disease was almost 17 years. The treatment with colchicine was initiated; however, it was withdrawn due to intolerance and side effects (myalgia, acceleration of fatigue, and elevation of creatinine kinase) after two weeks despite its partial effect on the clinical course and symptoms. Subsequently, the application of anakinra, 100 mg per day (body weight 116 kg), was started. It led to a partial relief of symptoms and abdominal pain. Despite this treatment, milder abdominal attacks were still present and chronic fatigue together with lower limbs pain and arthralgia persisted. Application of anakinra was accompanied by local reactions and inflammation in the application site. Moreover, severe headache and hypertension (requiring combined antihypertensive therapy) was also present. Serum amyloid A (the highest value 158 mg/L) and C-reactive protein remained elevated despite the application of anakinra and intermittent use of non-steroidal anti-inflammatory drugs. Due to intolerance of colchicine, partial efficacy of anakinra with systemic and local side effects and persistence of chronic fatigue, high frequencies of flares and persistent elevation of serum amyloid, the treatment with canakinumab was started. The initial dose was 150 mg every 4th week. Surprisingly already after the 1st dose, the patient reported a significant relief from fatigue and arthralgia; no abdominal pain attack was also noticed within three weeks after the application. Unfortunately, in the 4th week after the first canakinumab application, acute flare reappeared. However, the application of 2nd dose of 150 mg that followed after 4 weeks, induced disappearance of symptoms and pain. After three weeks, another flare appeared and therefore the escalation of the dose to 300 mg every 4 weeks was introduced. This dose was able to induce a complete remission of symptoms till the next application. The regular application of 300 mg of canakinumab finally led to the achievement of control over the diseases that was expressed with remission of clinical symptoms and normalization of inflammatory

markers (C-reactive protein less than 5 mg/l and serum amyloid A 3.69 mg/L). The quality of life has significantly improved and patient has become able to return back to work and normal life.

Discussion

Familial Mediterranean fever is the most common disease out of all monogenic autoinflammatory diseases. The treatment is aimed at the prevention of painful attacks (resulting from serositis) and development of organ amyloidosis. The treatment with non-steroidal anti-inflammatory drugs or corticosteroids could be also used during the acute flare, although it is usually not effective. The gold standard in clinical management of FMF is colchicine with several suggested modes of action (e.g. inhibition of neutrophil chemotaxis through a direct effect on cytoplasmic microtubules, a reduction in the expression of adhesion molecules on white blood cells and endothelial cells etc.) (8). If tolerated well, it is a life-long therapy. It has been used for both adults and children with titration of the applied dose. Its full clinical effect and dose adjustment could be seen usually within several weeks to months after the beginning of its application. Its administration should start once the diagnosis of FMF is confirmed by genetic analysis and must be taken daily, since a missing dose may lead to the attack. In the population with high prevalence of FMF, it can be used also as a diagnostic test, however, in other geographical settings its diagnostic use is not recommended (1, 2).

Approximately 5 – 10 % of patients did not show a sufficient response to colchicine or yielded a significant side effects requiring its withdrawal. Another possibility is the use of biologicals against IL-1β (anakinra, rilonacept, canakinumab). The use of these medicaments is usually indicated in patients with insufficient response to colchicine, those with persistent high serum concentration of amyloid, patients suffering from severe side effects of colchicine therapy, and in cases with associated vasculitis or renal involvement (8). The mode of action of available biologicals differs. Anakinra and rilonacept are targeting especially IL-1α and IL-1β while anakinra inhibits the receptor for IL-1 and rilonacept neutralises IL-1 in the blood. On the other hand, canakinumab, a fully human monoclonal antibody, binds selectively to IL-1β. Canakinumab is the first biological therapy approved by FDA (Food and Drug Administration) and EMEA (European Medicines Agency) for FMF patients (10). Its application leads to rapid remission of symptoms and suppresses the markers of inflammation. Its efficacy and safety were confirmed by case reports, case report series or even double-blind, randomized, placebo-controlled studies in both children and adults. Clinical response and full remission were observed in the majority of involved patients (11–15). Moreover, in certain cases, the drug administration interval was safely increased during the remission from 4 to 6–8 weeks (15). Several authors recommend for colchicine-resistant FMF patients to start with a short half-life molecule (anakinra) to assess the efficacy of such approach before long half-life IL-1 blocking strategies (canakinumab) are indicated (16).

Conclusions

Although the gold standard for the treatment of FMF is colchicine, its narrow therapeutic window makes its application ineffective in a great proportion of patients. Nowadays, fortunately, other alternative treatments can be considered. Our case report confirms an excellent clinical response to canakinumab in FMF patient intolerant to both, colchicine and anakinra. Application of canakinumab should be recommended for patients with Familial Mediterranean fever, who are resistant or intolerant to colchicine or for those with insufficient response to the treatment with colchicine. We would like to increase the awareness of FMF also in regions where low incidence and prevalence are reported.

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