

The Efficacy of Anakinra in Colchicine-Resistant Familial Mediterranean fever: a Case Report

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Abstract

Familial Mediterranean Fever (FMF) is an inherited autoinflammatory disease whose standard treatment is colchicine, which prevents attacks and inflammatory complications in 80 to 90% of cases. The overall rate of non-response is around 10-20%. Anti-cytokine therapies have been shown to be promising in the treatment of this disease in case of resistance to colchicine. We report the efficacy of an il-1 receptor antagonist (anakinra) in the control of febrile seizures in a child with colchicine-resistant fmf and the main reasons for considering colchicine resistance.

Introduction

Familial Mediterranean Fever (FMF) is an inherited autoimmune disease characterized by recurrent episodes of fever with sterile peritonitis, pleural inflammation, arthritis and / or rash similar to erysipelas (1). Although colchicine is the standard prophylactic therapy for this condition, some patients do not respond to or tolerate its side effects. Anakinra represents a therapeutic alternative for these refractory fmfs in order to avoid a dark renal prognosis. Our objective is to report our experience through a case that illustrates the efficacy of this molecule in a child with colchicine-resistant fmf both clinically and biologically, with irrefutable benefits on quality of life.

Case

Child born in July 2005, admitted for recurrent fever associated with abdominal pain evolving since the age of 2 years.

The clinical onset was in this patient, with protracted inflammatory episodes repeating every two to three weeks. Each episode resulted in high fever, abdominal pain associated with chest pain and myalgia leading to multiple hospitalizations from a young age.

Biological tests revealed marked inflammation (sedimentation rate vs, 95 mm at first hour, C - reactive protein (CRP), 100 mg / l, hyperleucocytosis at 15680 per cubic millimeter) and platelets at 508,000 Cells / mm³.

The patient has benefited from a multitude of complementary immunological, infectious and radiological examinations.

In 2012, the diagnosis of fmf was made by the team of pediatric rheumatology, selected according to the yalcinkaya criteria and confirmed genetically by the detection of the m694v / m694i mutation in the heterozygous composite state.

The child was started on analgesic and antispasmodic treatment with colchicine at the beginning at a dose of 1 mg / day without any improvement, with persistence of biological signs of inflammation, which necessitated the increase of the dose to 1.5 mg / day.

The evolution was marked by the accentuation of the painful accesses in frequency and intensity affecting the quality of life, the sleep, the growth and the schooling of the child.

The renal balance remained normal. Diabetic side effects such as diarrhea with episodes of dehydration occurred with colchicine.

This inefficiency of colchicine led us to propose treatment with anakinra at a dose of 1 mg / kg in October 2013 in combination with colchicine at a dosage reduced by 50%. No adverse effects were observed. His symptoms resolved after a few weeks. The levels of inflammation markers: crp and ferritin decreased (Figures 1 and 2). The efficacy of anakinra persisted in the months following immediate improvement with complete remission after 6 months to date. No adverse effects were observed with a 4 years follow-up.

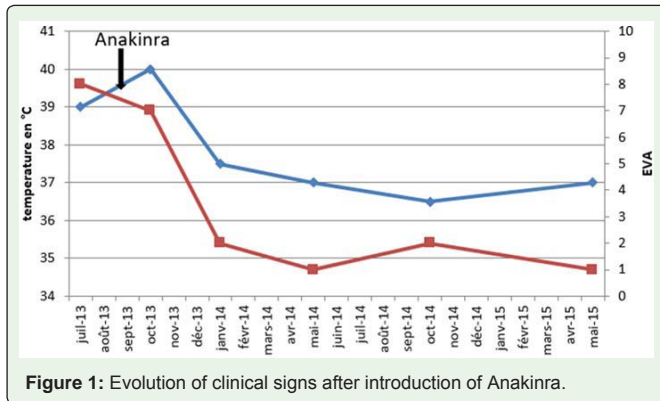


Figure 1: Evolution of clinical signs after introduction of Anakinra.

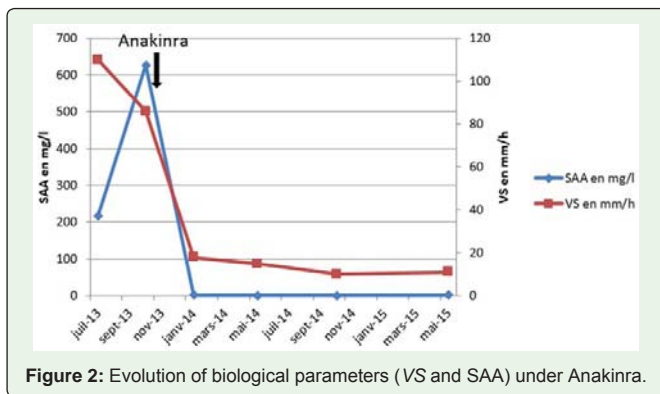


Figure 2: Evolution of biological parameters (VS and SAA) under Anakinra.

Discussion

Anakinra (kineret) is part of the new class of biotherapies, having an antagonistic action on the interleukin [1] receptor (il1), thus blocking this cytokine. This molecule is used for the treatment of cryopyrin-associated periodic syndrome (caps), as well as adult and juvenile forms of still’s disease.

Fmf is an autosomal recessive disease linked to mutations of 2 alleles of the mefv gene, encoding a protein called pyrine (or marenostrin). Although its exact function is not yet well known, it is clear that the major role of pyrin is in the regulation of inflammation through its interaction with the inflammasome [2]. His mutation therefore leads to uncontrolled activation of il-1 and clinical manifestations of autoignition. The indication of a treatment acting against the effects of il-1 could be effective in this disease from where the interest of the anakinra.

In recent years, anakinra’s interest in the colchicine-resistant forms of Familial Mediterranean Fever (fmf-cr) has become major. To date, about twenty publications have shown a beneficial effect of anakinra in the treatment of fmf-cr, with clinical and biological improvement, including reduction of seizure rate and serum level of inflammatory proteins [3,4].

Most of the publications around anakinra and fmf concern isolated clinical cases in which this molecule has shown high and rapid efficacy [5-7]. A series of 7 patients (including 5 in pediatric age) treated with anakinra (5 patients) or canakinumab (2 patients) was recently reported, confirming a good efficacy of these agents, both on the recurrence of seizures and vasculitis situations Severe [8].

The efficacy of anakinra has been observed in both patients with an inadequate colchicine response but also in patients with reactive amyloidosis, renal failure and transplantation [9].

Our patient received anakinra because of the severity of his symptoms and resistance to colchicine. Treatment with anakinra has shown a rapid and lasting effect, suggesting that it is an important therapeutic tool for pediatric rheumatologists and should be considered as second-line treatment.

In the management of fmf, the objectives are to prevent clinical attacks and suppress chronic subclinical inflammation and its sequelae, especially secondary amyloidosis [10].

Colchicine remains the mainstay of the treatment whose efficacy has been demonstrated since 1974 by zemer et al. [11]. Resistance to colchicine is on average between 10 and 20% of patients [10] and more frequently observed in patients with the most severe mefv genotypes (m694 v) as confirmed by a recent French study [12].

In most cases, the main reasons for considering colchicine resistance in the pediatric population are severe and persistent clinical symptoms and poor compliance with high doses of colchicine [11,13]. The 10 to 20% of patients who resist colchicine treatment is a major problem.

The suggested therapeutic alternatives were the use of thalidomide, interferon alpha, intravenous colchicines and tnf inhibitors [14,15]. However, no treatment has proved effective in these patients.

Conclusion

Anakinra is an effective treatment option for fmf patients. Nevertheless, prospective studies must be performed to evaluate the dosage and efficacy as well as the safety of anakinra while codifying alternative treatments for colchicine resistance.

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