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CASE REPORT

Anakinra suppresses familial Mediterranean fever crises in a colchicine-resistant patient

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ABSTRACT

We describe a 34-year-old male patient suffering from familial Mediterranean fever and experiencing an increase in both the frequency and severity of disease attacks, suggesting resistance to chronic treatment with colchicine. Since no alternative treatment is established, anakinra, an interleukin-1 receptor antagonist, was administered, not daily, as it has been previously reported, but only during crises, with successful outcome.

KEYWORDS

Anakinra, familial Mediterranean fever, interleukin-1 receptor antagonist

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease which mainly affects Armenians, non-Eshkenazi Jews, Turks and Arabs.[1] It has been also reported in other populations of the Mediterranean basin.[2] Due to the increasing number of immigrants from these countries, FMF should not be considered a rare disease throughout Europe. FMF is caused by mutations in the *MEFV* gene on chromosome 16p13.3 which encodes the protein pyrin/marenostrin, a protein which is expressed in the cytoplasm of mature neutrophils and monocytes.[3,4] The disorder is characterised by periodic episodes of fever, peritonitis, arthritis and erysipelatoid erythema and may be complicated by secondary amyloidosis. Colchicine is the recommended treatment as it has shown efficacy in the prevention of both acute attacks and secondary amyloidosis with a nonresponse rate of 5 to 10%.[5] In cases of colchicine resistance or intolerance, other medications, as the interferon-alpha, thalidomide, prazosin and etanercept, have shown efficacy, resolving the attack symptoms or even improving the symptoms of amyloidosis.[6-9] Anakinra, a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra), has been reported to be successful in everyday use, affecting both the severity and the frequency of FMF attacks.[10-13] Nevertheless, its favourable effect when administered only during crisis needs elucidation. Here, we report the effectiveness of anakinra in the remission of FMF attacks in a patient resistant to colchicine.

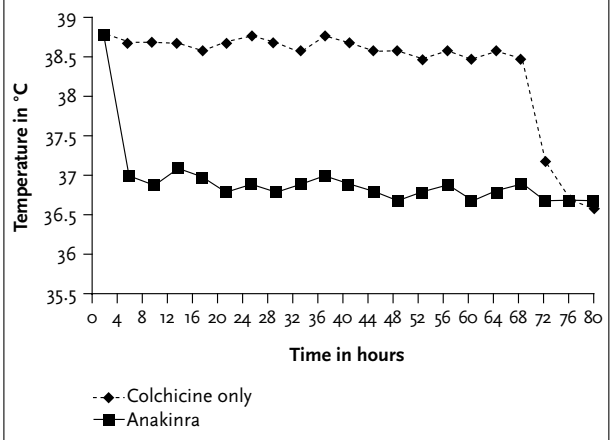
CASE REPORT

A 34-year-old male FMF patient, homozygous for pyrin M694V mutation,[2] was referred for signs attributed to colchicine resistance after several years of successful treatment. He reported more frequent attacks (ten episodes during the last year) characterised by more severe symptoms (worsening of the abdominal pain), despite being on treatment with colchicine at a high dose (2.5 mg). Each crisis lasted 70 to 72 hours and the abdominal pain, which was the initiating symptom, was accompanied by high fever (38.5 to 39°C) shortly afterwards. His renal function was normal, proteinuria was absent and there were no signs of organomegaly. His medical record was insignificant for arthritis or pleuritis. C-reactive protein (CRP) levels of >25 mg/dl (normal 0-0.5) and elevated white blood cell counts were repetitively measured during previous crises. As he experienced a severe impairment in his quality of life, and being aware of the reported efficacy of anakinra in the treatment of FMF patients resistant to colchicine, he asked to be given anakinra, as an additional treatment to colchicine. It was proposed to administer anakinra (Kineret, Amgen, USA) subcutaneously at a dose of 100 mg immediately after the onset of the abdominal pain, which was the initiating

symptom of the attack. Anakinra would be repeated after 24 hours according to the clinical course. No other medication which could affect the clinical course, such as analgesics or anti-inflammatory drugs, was recommended during the episodes. Colchicine was never withdrawn for reasons of secondary amyloidosis prevention and its dose was not altered. The overall procedure was approved by the Institutional First Internal Medicine Department Board and an informed consent was obtained from the patient.

The benefits of anakinra pulses were observed in the following six-month period. The patient reported only three minor episodes of FMF, with significant amelioration in the abdominal pain after the immediate use of anakinra according to the protocol described. His body temperature returned to normal values within an hour (*figure 1*). The only remaining symptom was a mild abdominal discomfort lasting for about 48 hours, which did not affect his daily or occupational activities. In two episodes, where the protocol was followed *lege artis*, the patient experienced immediate and lasting relief with a single dose of anakinra, given within 30 minutes of the onset of the episode, with no need for further palliative measures. Controversially, a single episode of inevitable deviation from the therapeutic protocol, a five-hour delay in the administration of anakinra, substantially decreased the efficacy of the regimen. Although this late first dose immediately relieved the febrile attack, a second 100 mg dose was repeated 18 hours later since a more severe abdominal discomfort (without fever) appeared. This second dose immediately cured the patient's crisis. As he was treated as an outpatient, we did not have the opportunity for a close laboratory follow-up.

Figure 1. *Representative pattern of fever during FMF attacks, before (dot line) and after (solid line) the introduction of anakinra in the patient, suggesting immediate response to anakinra*



The dotted line, representing crisis under colchicine monotherapy, is based on evaluation of patient's own observations. 0 denotes onset of symptoms.

CRP values were only available during the first episode, in particular 20 hours after the anakinra administration when the symptoms had already resolved. Thus, CRP was found to be significantly diminished (2.2 mg/dl) compared with available values observed during his previous FMF attacks (>25 mg/dl). No adverse reactions were observed. The benefit of anakinra introduction in FMF crisis is schematically represented in *figure 1*. There is also evidence that the frequency of the attacks after the introduction of anakinra (three crises over six months, mean 0.5) might have been reduced, when compared with the situation in the previous year (ten crises over 12 months, mean 0.9). However, if we combine both the frequency and severity of crises before and after the introduction of anakinra by scoring arbitrarily 2 for each month with a severe crisis, 1 for each month with a mild crisis and 0 for each month with no crisis and using Wilcoxon's test for unpaired samples, a statistically significant difference at $p<0.01$ is observed ($T1 = 87$, $T2 = 84$).

DISCUSSION

Our case report indicates that anakinra provides significant clinical benefit in the treatment of FMF attacks in nonresponders to colchicine. The initial concept was motivated by both previously published reports suggesting the efficacy of anakinra as a continuous daily medication and the patient's insistence, who, being a medical doctor himself, was desperately seeking an alternative treatment, as he experienced a continuous impoverishment of his quality of life. In fact, the patient himself insisted on the use of anakinra. Nevertheless, the administration protocol was proposed by our team. Anakinra was not used as a daily treatment, as it has been previously reported, but only during the episodes of the disease. This was repeated at three consecutive crises. Anakinra showed efficacy in all cases, especially when administered early.

Anakinra competitively inhibits IL-1 binding to the IL-1 receptor type 1 (IL-1RI) in a way that mimics the activity of endogenous IL-1Ra. This implies that even though recombinant IL-1Ra binds to IL-1RI with nearly the same affinity compared with IL-1, a 10- to 100-fold greater IL-1Ra molecular load is needed for the inhibition of IL-1 activity.[14] Taking this into consideration, we may hypothesise that the time-related efficacy of anakinra, which suggests a crucial role of IL-1β inhibition in the onset of the FMF inflammatory process, might be explained by the different IL-1β 'load' or, furthermore, by the different levels of inhibitors other than anakinra involved in the cytokine pathway. Based on this experience, we underline the necessity for the immediate administration of anakinra, as close to the initiation of symptoms as possible. However, generalised speculations can not be made from a single case.

Concerning autoinflammatory syndromes, anakinra has previously shown significant effectiveness in familial cold inflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous articular syndrome.[15,16] These related disorders are associated with heterozygous mutations in the *CIAS1* gene, which encodes the protein cryopyrin, a pyrin-like protein that plays an essential role in the regulation of IL-1β secretion through caspase-1 activation, sharing common characteristics with FMF.[17]

The exact function of pyrin, which plays a key role in FMF, is not well established. However, a negative regulatory role in the caspase-1 dependent production of IL-1β has been proposed, either through interaction of its N-terminal domain with ASC[4] or through inhibition of caspase-1 catalytic domains after the binding of pyrin β30.2 domain.[10] Consequently, the use of an IL-1β antagonist could be a rational choice in the treatment of FMF. Furthermore, there is no alternative to colchicine with established efficacy, thus urging for new medications for patients who have developed resistance or intolerance to colchicine. As a result, anakinra has been used in the treatment of such patients as a daily medication with significant reduction in both severity and frequency of the FMF attacks,[10-13] while the levels of amyloid and acute phase reactants were controlled.[10] Moreover, the fever attacks reappeared as soon as the drug was discontinued, enhancing the evidence of its efficacy.[10,11,13]

CONCLUSIONS

This case suggests that the addition of anakinra could be a potentially useful alternative therapeutic approach for FMF attacks in patients not responding to colchicine alone. The elevated cost of anakinra is moderated by its occasional use during crisis. As no alternative solution is established, treatment with anakinra could ameliorate the quality of life in patients resistant to colchicine. On-demand use of anakinra is suggested as soon as the first symptoms occur, with a second dose repeated 24 hours later if necessary without discontinuing colchicine. However, more longitudinal studies are needed to elucidate the clinical outcome and the short- and long-term efficacy of the on-demand anakinra use in FMF patients.

REFERENCES

1. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet. 2001;9:473-83.
2. Giaglis S, Papadopoulos V, Kambas K, et al. MEFV alterations and population genetics analysis in a large cohort of Greek patients with familial Mediterranean fever. Clin Genet. 2007;71:458-67.
3. The international FMF consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell. 1997;90:797-807.
4. Chae JJ, Komarow HD, Cheng J, et al. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. Mol Cell. 2003;11:591-604.
5. Lidar M, Schermann JM, Shinar Y, et al. Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetical, pharmacokinetic, and socioeconomic characterization. Semin Arthritis Rheum. 2004;33:273-82.
6. Tunca M, Akar S, Soytürk M, et al. The effect of interferon alpha administration on acute attacks of familial Mediterranean fever: A double-blind, placebo-controlled trial. Clin Exp Rheumatol. 2004;22:S37-40.
7. Seyahi E, Ozdogan H, Masatlioglu S, Yazici H. Successful treatment of familial Mediterranean fever attacks with thalidomide in a colchicine resistant patient. Clin Exp Rheumatol. 2002;20(4 suppl 26):S43-4.
8. Kataoka H, Kumagai H, Hanai H. Treating familial Mediterranean fever with prazosin hydrochloride. Ann Intern Med. 1998;129:424-5.
9. Mor A, Pillinger MH, Kishimoto M, Abeles AM, Livneh A. Familial Mediterranean Fever Successfully Treated With Etanercept. J Clin Rheumatol. 2007;13:38-40.
10. Chae JJ, Wood G, Masters SL, et al. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1 production. Proc Natl Acad Sci USA. 2006;103:9982-7.
11. Calligaris L, Marchetti F, Tommasini A, Ventura A. The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever. Eur J Pediatr. 2008;167(6):695-6.
12. Kuijk LM, Govers AM, Frenkel J, Hofhuis WJ. Effective treatment of a colchicine-resistant familial Mediterranean fever patient with anakinra. Ann Rheum Dis. 2007;66(11):1545-6.
13. Gattringer R, Lagler H, Gattringer KB, et al. Anakinra in two adolescent female patients suffering from colchicine-resistant familial Mediterranean fever: effective but risky. Eur J Clin Invest. 2007;37(11):912-4.
14. Dinarello CA. Biologic basis for interleukin-1 in disease. Blood. 1996;87(6):2095-147.
15. Hoffman HM, Rosengren S, Boyle DL, et al. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. Lancet. 2004;364:1779-85.
16. Thornton BD, Hoffman HM, Bhat A, Don BR. Successful treatment of renal amyloidosis due to familial cold autoinflammatory syndrome using an interleukin 1 receptor antagonist. Am J Kidney Dis. 2007;49:477-81.
17. Sutterwala FS, Ogura Y, Szczepanik M, et al. Critical Role for NALP3/CIAS1/Cryopyrin in Innate and Adaptive Immunity through Its Regulation of Caspase-1. Immunity. 2006;24:317-27.