Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation

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Abstract
Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever and inflammation. The most severe complication of FMF is the development of AA amyloidosis, which can be life threatening. The only current effective treatment for FMF is colchicine. Regular prophylactic treatment with colchicine at a dose of 1–2 mg daily prevents or substantially reduces the clinical manifestations of FMF in at least 90% of cases. However, ~10% of patients are reported to be resistant or non-responsive to colchicine and in these cases there is no consensus as to which second line agents should be used. We describe the first case, to our knowledge, of a patient with FMF and end-stage renal failure due to AA amyloidosis, successfully treated with IL-1 receptor blockade. Our data suggest that the IL-1 receptor antagonist Anakinra (Kinera1; r-metHuIL-1 ra) may represent a safe and effective therapy for the treatment of colchicine-resistant FMF, in patients requiring renal replacement therapy, with dialysis or transplantation.

Keywords: Anakinra; colchicine; familial Mediterranean fever; interleukin-1 receptor antagonist

Introduction
Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever and inflammation affecting serosal surfaces, joints and skin. FMF is the most common of the hereditary periodic fever syndromes, a group of diseases that include tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), the hyper IgD and periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndromes (CAPS) [1]. The gene responsible for FMF, MEFV, was identified through positional cloning in 1997. The function of the protein product of MEFV, pyrin, is not yet fully understood although a number of subtle abnormalities of leukocyte function have been noted in patients with FMF. At its N-terminal, the protein contains a pyrin death domain (PYD). Members of the death domain superfamily play important roles in the assembly and activation of apoptotic and inflammatory complexes by homotypic protein–protein interactions. Proteins with PYDs are involved in modulation of IL-1β production, apoptosis and NF-κB signalling and have been implicated in CAPS as well as FMF [2].

FMF predominantly affects populations arising from the Eastern Mediterranean, and its prevalence in the Turkish population has been estimated to be 1/1073. The most serious and life-threatening complication of FMF is AA amyloidosis. The amyloid fibrils are derived from cleavage fragments of the circulating acute phase reactant, serum amyloid A (SAA) protein, which is synthesized by hepatocytes under the transcriptional regulation of IL-1, IL-6 and TNF. It is thought that the exceptionally high incidence of AA amyloidosis in untreated FMF is secondary to the intense inflammatory response that accompanies disease flares on a background of subclinical inflammation [3]. Prior to widespread use of colchicine prophylaxis, up to 60% of patients with FMF died of amyloidosis, while more recently it has been reported in 12.9% of a large Turkish series. Current treatment centres on complete, sustained control of the underlying inflammatory disease thus reducing the supply of the amyloid fibril precursor, SAA [4,5].

The only current effective treatment for FMF is colchicine, a serendipitous discovery made by Goldfinger in 1972. Regular prophylactic treatment with colchicine at a dose of 1–2 mg daily prevents or substantially reduces the clinical manifestations of FMF in at least 90% of cases. However, ~10% of patients are reported to be unresponsive to colchicine [6], and in these cases there has been no consensus on which second line agents to use. We report here...
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Fig. 1. Course of inflammatory parameters in serum (CRP mg/l; SAA mg/l) and dose (mg/week) of administered Anakinra (Kinerec®; r-metHuIL-1ra) in the patient with FMF during haemodialysis (period: day -350 until time point 0) and after renal transplantation (time point 0 until day 600). Increase of inflammatory parameters after transplantation is due to reactivation of FMF with subsequent increase in the dose of Anakinra due to the development of acute Banff II rejection and central venous catheter infection with bacteraemia.

the first case of a patient with ESRF due to amyloidosis successfully treated with IL-1 blockade.

Case Report

In 1993, a Turkish male presented to our institution at the age of 30 years with nephrotic range proteinuria (14 g/24 h) and impaired renal function (GFR of 44 ml/min). He had a history of intermittent febrile episodes over the previous 4 years. A percutaneous renal biopsy was performed, revealing amyloid deposits of AA type. In addition, rectal biopsies and a fat aspirate also demonstrated deposits of AA amyloid. In view of his symptoms and ethnicity, a clinical diagnosis of FMF complicated by AA amyloidosis was made and he was commenced on colchicine 1.5 mg daily. In view of his proteinuria, he was also started on an ACE inhibitor. He appeared to respond to colchicine with a complete remission of his fever attacks, and the nephrotic syndrome went into partial remission (4.5 g/24 h). Over the next decade, he remained free of symptoms but his renal function continued to deteriorate slowly.

In 2004, he represented with fevers and refractory nephrotic syndrome with massive proteinuria (36 g/24 h) and renal failure. Up to admission, he had remained on regular colchicine and an ACE inhibitor. He underwent a medical nephrectomy with indomethacine and commenced intermittent haemodialysis. His diagnosis of FMF was strongly corroborated by the finding that he was homozygous for MEFV M694 V, the genotype associated with the most severe clinical disease and the highest risk of developing amyloidosis. Over the following months, he had recurrent attacks of fever, arthralgia, peritonitic abdominal pain and diarrhoea despite increasing his colchicine to 2.0 mg/day. Extensive investigations failed to demonstrate any alternative cause of his symptoms, and he was felt to have developed colchicines-resistant FMF.

In February 2006, we discontinued colchicine and started treatment with the IL-1 receptor antagonist Anakinra (Kinerec®; r-metHuIL-1ra). As he was on dialysis, 100 mg was administered subcutaneously three times weekly after haemodialysis. His clinical symptoms and inflammatory parameters (Figure 1) both resolved within a couple of days. In May 2006, he received a cadaveric kidney transplant with standard protocol immunosuppression from our unit (tacrolimus, mycophenolate and prednisolone). There was immediate good graft function.

With restoration of a near normal GFR (55 ml/min), his FMF became active again. This was assumed to be due to renal clearance of Anakinra, and his symptoms and inflammatory markers settled when Anakinra was increased to the standard dose regime of 100 mg daily (Figure 1).

Discussion

Primary therapeutic strategy in FMF is the use of colchicine [7], which reduces the inflammatory response by preventing activation, de-granulation and migration of neutrophils, binding β-tubulin and leading to β-tubulin–colchicine complexes [6]. Primary or acquired colchicine resistance is thought to be associated with an inadequate colchicine mononuclear cell concentration and has been attributed to a disturbed activity of p-glycoprotein pump in granulocytes [8] and, on the other hand, to competitive inhibition of colchicine metabolism via the CYP 450 system [9]. Therefore, several other drugs like anti-TNF-α preparations, interferon-α and thalidomide have been used as new treatment options for FMF in recent years.

Several case reports reported on the resolution of symptoms after the use of the IL-1 receptor antagonist Anakinra in multi-system inflammatory diseases [10]. Chae recently treated a FMF patient with the M694 V/M694 genotype
and systemic amyloidosis with Anakinra as an adjunctive therapy. The patient demonstrated control of both the serum Amyloid A and CRP over several months [2]. The beneficial effect of Anakinra in an otherwise refractory FMF patient heightens interest in the role of pyrin in the regulation of cytokine processing.

The patient we described above, is to the best of our knowledge the first patient with FMF on haemodialysis who has received the IL-1 antagonist Anakinra for the treatment of inflammatory symptoms. With the reduced dose of 100 mg sc and after each dialysis session, it was noted that the injection given was found to be safe, effective and without side effects, like neutropaenia. The relief of symptoms was evident within a very short period of time; this was also accompanied by a rapid decline of inflammatory parameters like SAA and CRP (Figure 1). After transplantation, the dose of Anakinra had to be increased; this was due to normal transplant function. There was no noted increase in the infection rate and no evidence for a drug interaction between Anakinra and the immunosuppression used. In summary, we perceived evidence that the IL-1 antagonist Anakinra might be a safe and effective substance for the treatment of colchicines-resistant patients with FMF on haemodialysis, as well as after successful kidney transplantation. We therefore conclude that prospective studies on a larger number of patients are necessary to prove this hypothesis.

Conflict of interest statement. None declared.

References

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