Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure

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Abstract

Background. Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder, for which systemic AA amyloidosis is the major complication revealed most of the time by renal abnormalities. Current treatment is daily colchicine that prevents both recurrent inflammatory attacks and amyloidosis deposition in most patients. However, some patients still develop amyloidosis and renal failure. Functional studies suggest that interleukin (IL)-1 is implicated in the inflammatory reaction in FMF and therefore, IL-1 inhibitors could be a new approach to treat FMF. The aim of this series study was to evaluate anakinra in patients with FMF complicated with amyloidosis and renal failure.

Methods. We studied a series of adult patients with FMF complicated with amyloidosis and treated with anakinra in one reference centre were reviewed. A search for published patients with FMF associated amyloidosis treated with anakinra was performed by screening PubMed.

Results. We report four cases of patients with FMF-associated amyloidosis treated with anakinra and discuss the clinical pertinence of its use in these particular clinical settings.

Conclusions. Anakinra has a strong effect on both inflammatory attacks and general status in patients with FMF-associated amyloidosis. It may contribute to changing the prognosis of these patients. Long-term studies are needed to appreciate the effect of anakinra or other IL-1 inhibitors on the natural history of amyloidosis in these patients.

Keywords: AA amyloidosis; colchicine; familial Mediterranean fever; interleukine-1 inhibitors; renal failure

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease associated with mutations in the MEFV gene, affecting mostly the Mediterranean populations (Armenians, Arabs, Jews and Turks) [1]. It is characterized by recurrent episodes of fever and serosal or cutaneous inflammation. The major complication of FMF is the development of secondary (AA) amyloidosis. Amyloidosis primarily manifests as a nephropathy characterized by proteinuria of nephrotic range, uraemia and finally end-stage renal failure necessitating chronic dialysis and renal transplantation [1]. Daily colchicine prevents both attack recurrence and amyloidosis in most patients affected with FMF and remains so far the first-line treatment of FMF [2]. In patients who do not tolerate colchicine or fail to respond, second-line agents, as interferon-alpha, thalidomide and tumour necrosis factor inhibitors have been used with limited response on preventing inflammatory flares, and there is no data on their effects to prevent the occurrence of amyloidosis [3–5]. Anakinra is an analogue of the natural interleukin (IL)-1-receptor antagonist that targets type I IL-1-receptor and thus blocks the effect of IL-1β, which is thought to be activated in FMF [6]. It is administered subcutaneously once a day or several times a week. The main side effect is erythematous painful spots at the injection sites after the first administrations. Experience with IL-1β blocking agents in FMF is so far poor. A recent case series emphasizes the usefulness or anakinra in several situations where colchicine has failed [7]. We report here the efficacy of anakinra in four patients with FMF.
complicated with amyloidosis and chronic renal failure, which highlights the use of this drug in these settings.

Materials and methods

The medical records of four patients with FMF complicated with AA amyloidosis were reviewed by the French national centre for AA amyloidosis and FMF (K.S.S. and G.G.). The main clinical characteristics of these patients and their genotypes for MEFV gene and the evolution after anakinra are summarized in the Table 1.

Patient 1

A 55-year-old woman of Sephardic origin presented at our institution in 2007 with a history of FMF, proteinuria and moderate renal failure. AA amyloidosis was proven by salivary gland biopsy. MEFV gene analysis showed that the patient was homozygous for the M694V mutation. She developed diarrhoea, which was attributed to hyperthyroidism success-fully treated with radioactive iodine. Meanwhile, proteinuria increased to a nephrotic range (900 mg/mmol of creatinine in 2009, 765 mg/mmolC in February 2010) despite a daily dose of 2 mg of colchicine, while estimate glomerular filtration rate by the Modification of Diet in Renal Disease formula decreased progressively (55 mL/min in 2007, 40 mL/min in 2010). Then diarrhoea recurred. An endoscopy of the whole colon disclosed a terminal ileitis. Biopsy revealed non-specific slight inflammation without evidence for Crohn’s disease but showed amyloid deposits. It was decided to use infliximab to target both FMF and inflammatory bowel disease. She did not appear to respond to this regimen after 6 months and remained with frequent FMF attacks requiring hospital stay, diarrhoea and deteriorating renal function, whereas her C-reactive protein (CRP) level was never under 20 mg/L. In February 2010, anakinra 100 mg/day was started and colchicine was stopped after a few weeks of anakinra. Since this change, she had no more attacks and was seen only as outpatient; diarrhoea had partially regressed. CRP level decreased from 45 mg/L the day before beginning anakinra to 6 mg/L (Normal range < 5) 5 days later and in normal range 1 month later; since then, CRP level was permanently < 5 mg/L. Her renal function was stable with an estimated glomerular filtration rate of ~30 mL/min and proteinuria was at 520 mg/mmolC in July 2011 (after 17 months of anakinra).

Patient 2

A 27-year-old patient from Armenian origin had been on chronic haemodialysis for a year for end-stage renal disease associated with FMF. The patient was homozygous for the M694V mutation of the MEFV gene. Despite colchicine 1 mg/day, he remained very symptomatic with subin-stant abdominal attacks, high CRP and serum amyloid A (SAA) levels (33 times the normal range and 23 times the normal range, respectively) and severe inflammatory anaemia. An abdominal computed tomography scan examination suggested diffuse colitis that was not confirmed by

Table 1. Main characteristics of patients with FMF-associated amyloidosis treated with anakinra

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Genotype</th>
<th>Associated clinical manifestations</th>
<th>Treatment modalities</th>
<th>Clinical effect</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>F</td>
<td>55</td>
<td>M694V/M694V</td>
<td>Hyperthyroidism, recurrent abdominal attacks, chronic diarrhoea, moderate renal failure, weight loss</td>
<td>100 mg/24 h</td>
<td>Complete remission of attacks, partial effect on constitutional symptoms, normalization of CRP level</td>
<td>17</td>
</tr>
<tr>
<td>Case 2</td>
<td>M</td>
<td>27</td>
<td>M694V/M694V</td>
<td>End-stage renal failure, 1 year on chronic haemodialysis</td>
<td>100 mg/24 h, 3×/week</td>
<td>Complete clinical remission, normalization of CRP level</td>
<td>7</td>
</tr>
<tr>
<td>Case 3</td>
<td>F</td>
<td>27</td>
<td>M694V/V726A</td>
<td>End-stage renal failure, 5 years on chronic haemodialysis</td>
<td>100 mg/24 h, 3×/week</td>
<td>Complete remission of attacks, strong effect on constitutional symptoms, normalization of CRP level</td>
<td>18</td>
</tr>
<tr>
<td>Case 4</td>
<td>F</td>
<td>61</td>
<td>M694V/M694V</td>
<td>End-stage renal failure, 6 years on chronic haemodialysis Renal transplantation</td>
<td>100 mg/24 h</td>
<td>Complete remission of attacks, partial effect on constitutional symptoms, normalization of CRP level</td>
<td>8</td>
</tr>
<tr>
<td>Belkhir et al. [8]</td>
<td>F</td>
<td>68</td>
<td>M694V/M694V</td>
<td>Recurrent attacks</td>
<td>100 mg/48 h</td>
<td>Partial remission</td>
<td>0, 5</td>
</tr>
<tr>
<td>Moser et al. [9]</td>
<td>M</td>
<td>43</td>
<td>M694V/M694V</td>
<td>Moderate renal failure Recurrent attacks</td>
<td>100 mg after dialysis 3×/week</td>
<td>Complete remission</td>
<td>7</td>
</tr>
<tr>
<td>Alpay et al. [10]</td>
<td>F</td>
<td>52</td>
<td>M694V/M694V</td>
<td>End-stage renal failure, dialysis and transplantation</td>
<td>100 mg/24 h</td>
<td>Complete clinical remission of both diseases. After 18 months of anakinra, proteinuria reappeared Clinical remission, normalization of CRP level</td>
<td>18</td>
</tr>
<tr>
<td>Bilginer et al. [11]</td>
<td>F</td>
<td>Child</td>
<td>M694V/M694V</td>
<td>Associated Behçet’s disease</td>
<td>1 mg/kg/24 h</td>
<td>Complete remission</td>
<td>18</td>
</tr>
<tr>
<td>Hennig et al. [12]</td>
<td>M</td>
<td>35</td>
<td>Not declared</td>
<td>Pneumonia with opacities in chest X-ray attributed to FMF in a renal transplant patient</td>
<td>100 mg/24 h</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>
endoscopy. Colic biopsies showed AA amyloidosis. Anakinra 100 mg was started 3 days a week with a frank clinical improvement: disappearance of abdominal attacks, decrease of CRP at 12 mg/L (Normal range < 5) 2 weeks after the beginning of anakinra and normalization of CRP and SAA levels after 6 weeks of anti-IL-1, rise of haemoglobin level which allowed stopping erythropoietin. With 4 months follow-up of anakinra, only slight neutropenia was observed that remained >1.10^9/L, there were no severe infectious complication (one rotavirus diarrhoea and one haemophilus bronchitis that did not required hospitalization). Renal transplantation is now under consideration for this patient.

**Patient 3**
A 27-year-old woman from Turkish origin who had FMF-associated amyloidosis had renal failure since she was 9 years old and has been on chronic haemodialysis for 5 years. Despite colchicine 1 mg/day, she had frequent abdominal attacks, one of them leading to a blank colloscopy. Echocardiography revealed a large interventricular septum suggestive of amyloidosis with altered left ventricular function. Troponine level was in normal range and brain natriuretic peptide level was 4738 ng/L (Normal range < 100). Anakinra 100 mg was started 3 days a week in May 2010 with an excellent clinical response: disappearance of attacks, weight gain and improvement of the general status and a frank decrease of CRP from 95 mg/L before anakinra to 1 mg/L 7 weeks after the beginning of this treatment. Echocardiography showed a normalization of the left ventricular function 11 months later. Whereas renal transplantation was so far contraindicated because of poor general status and uncontrolled inflammation, it is now under consideration.

**Patient 4**
A 61-year-old woman of Sephardic origin was diagnosed with FMF-associated amyloidosis at the age of 39 years. She had renal failure since she was 18 years old and has been treated with haemodialysis for 6 years. Despite maximal dose of colchicine according to renal failure, FMF remained active with a high number of abdominal attacks and chronic rise of serum CRP. She developed heart diastolic dysfunction without echocardiographic signs of amyloidosis. Recurrent diarrhoea and bloody stools led to an endoscopic examination of the colon, which disclosed a non-specific erythematous appearance of the sigmoid colon. This severe medical condition had a profound negative impact on her mood and her quality of life. Anakinra 100 mg was started 3 days a week in May 2010 with an excellent clinical response: disappearance of attacks, improvement of the general and mental status. After anakinra, CRP level decreased from 189 mg/L to 1 mg/L within 3 months. Four months later, the patient was transplanted and remained free of attacks after 6 months. No severe infection occurred.

**Discussion**
We report here four patients with FMF complicated with amyloidosis who were treated with the IL-1 inhibitor anakinra. Despite colchicine at maximal dose according to renal failure, FMF attacks were still frequent in all of these patients as well as constitutional symptoms (weight loss, poor nutritional status and depressive mood). In all of them, the switch from colchicine to anakinra led to a dramatic effect characterized by both remission of attacks and improvement of constitutional symptoms. Patients 1 and 2 have not been hospitalized since anakinra was started. Patient 4 who was on chronic haemodialysis for 6 years and had a poor general status contraindicating renal transplantation, achieved successful transplantation 3 months after the introduction of anakinra. Patient 3 who was on chronic haemodialysis for 5 years is now being considered for renal transplantation as well as Patient 2. Moreover, the acute-phase inflammatory response completely normalized in our four patients with a mean delay of 2 months. The evolution of proteinuria under anakinra was not possible for three of the four patients because of anuria.

To our knowledge, only five additional single cases of patients with FMF associated with amyloidosis and treated with anakinra have been published in the literature [8–12]. The main characteristics of these five patients are given in Table 1. All are adult patients except one who is affected both with FMF and Behçet’s disease. In all patients, attacks were still present despite colchicine and disappeared completely under anakinra with a longer follow-up of 20 months. Thus, they have very similar characteristics to those of our four patients. In eight of these nine patients, molecular testing showed homozygosity for the M694V mutation in MEFV gene, the last one was a compound heterozygote for the M694V and V726A mutations. Homozygosity for the M694V mutation is usually thought to be associated with a more severe FMF phenotype [13], with amyloidosis and for some authors with resistance to colchicine [14].

A recent review classified the reasons for using IL-1-targeting drugs in FMF patients into four categories: [1] incomplete control of FMF disease activity despite colchicine treatment; [2] high SAA levels and/or renal complications despite colchicine treatment; [3] impossibility to use colchicine for the treatment of FMF because of severe side effects; [4] FMF in association with vasculitis. We think that our patients with FMF associated with amyloidosis and renal failure held concurrently several criteria of these four categories.

Although colchicine pharmacokinetics has not been extensively characterized, chronic renal failure enhances the risk for drug–drug interaction of colchicine with several drugs including the frequently used macrolide antibiotics [15, 16]. In patients with renal transplantation, colchicine interacts with cyclosporin, which may lead to serious complications [17]. However, a recent pharmacological study showed a colchicine dose reduction algorithm to prevent colchicine toxicity secondary to drug–drug interaction including cyclosporine that would help to manage colchicine in transplanted patients [18]. Anakinra is potentially an immunosuppressive drug that should be used a priori cautiously in transplanted patients [19]. Cytopenia is a potential side effect but is usually mild. One published case reported no serious adverse effects in a patient with renal transplantation for FMF-associated amyloidosis [9]. Another instructive case of successful treatment with anakinra was reported in a patient who acquired FMF mutations after allogeneic bone marrow transplantation (BMT) and who presented intolerance and resistance to colchicine treatment [20]. Anakinra has shown no toxicity in allogeneic BMT in the prevention of graft-versus-host disease, which suggests that it may be used in other contexts of immunosuppression, such as renal transplantation [21]. Clinical experience remains, however limited, and anakinra should be used cautiously in the context of immunosuppression. Vaccination against pneumococcus is recommended before the administration of anakinra. The administration 3 days a week in three of our patients was governed by the rhythm of haemodialysis. Moreover, it has been shown in other autoinflammatory diseases such as cryopyrinopathies at a steady state that the dose of 100 mg 3 times a week of anakinra was sufficient to control the disease. The pharmacokinetics of anakinra is not well known in patients with end-stage renal failure, thus the dose should be...
carefully thought in these patients and haemogram should be closely controlled such as Patient 2 whose neutropenia became under 1000/mm$^3$ after increasing the dose of anakinra from 100 mg three times a week to 100 mg four times a week.

Our patients also had permanently high CRP levels despite colchicine, which normalized after anakinra. This effect probably accounts for frank improvement of the general status and weight gain. This improvement was the most important clinical change that led to considering renal transplantation in patients whose general status was so far not compatible with this treatment.

The impact of anakinra on the development of systemic amyloidosis cannot be evaluated because of the short follow-up. As systemic amyloidosis is mainly determined by the level and duration of inflammation, the effect of anakinra is promising.

**Conclusion**

Although colchicine treatment is safe and prevents both recurrent attacks and amyloidosis in the large majority of FMF patients, other treatments are needed in some specific situations. The situations where a drug other than colchicine could be indicated remain to be defined thoroughly, the resistance to colchicine is so far not precisely defined. We suggest that anakinra, and potentially other IL-1 targeting drugs, may replace colchicine in FMF complicated with amyloidosis and chronic renal failure, especially in patients on chronic haemodialysis. This substitution would thus combine the benefits of anakinra on the control of inflammation and the loss of secondary effects of colchicine. Further studies are necessary to evaluate the safety and efficacy of IL-1 antagonists in FMF patients and its effect on preventing amyloidosis deposition or recurrence of amyloidosis on renal transplant.

**Conflict of interest statement.** None declared.

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Received for publication: 25.5.11; Accepted in revised form: 8.8.11