Effects of interleukin-1 antagonists on *de novo* and pre-existing damage in patients with familial Mediterranean fever

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Abstract

Objective

Colchicine is the mainstay of familial Mediterranean fever treatment and interleukin (IL-1) antagonists are the treatment of choice in resistant patients. We aimed to investigate efficacy of IL-1 antagonists in the prevention of damage, as well as the causes of treatment failure.

Methods

A total of 111 patients fulfilling Euro fever and Tel-Hashomer criteria and treated with IL-1 antagonists were included in the study. Patients were grouped according to their recent damage status: no damage, pre-existing damage and de novo damage that developed under IL-1 antagonist treatment. The degree of damage was determined using the Auto Inflammatory Disease Damage Index (ADDI). Total damage score was calculated separately as its original definition and with excluding chronic musculoskeletal pain, creating the modified ADDI (mADDI).

Results

Forty-six patients (43,2 %) had damage according to the mADDI. Damage was commonly observed at musculoskeletal, renal and reproductive domains. Median duration of treatment was forty-five months. Two patients developed de novo damage: one musculoskeletal and one reproductive in this time-period. Five patients had a worsening of their damage while using IL-1 antagonists. De novo damage with IL-1 antagonist treatment was associated with acute phase protein levels.

Conclusion

We evaluated change in damage accrual while using IL-1 antagonists in patients with FMF. Physicians should pay attention to controlling inflammation to prevent further damage, especially in those with pre-existing damage.

Key words

familial Mediterranean fever, damage, anakinra, canakinumab, IL-1 antagonists, treatment efficacy

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Received on September 29, 2022; accepted in revised form on March 29, 2023.

Competing interests: none declared.

Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease, characterised by self-limiting attacks of fever, serositis, arthritis and skin rash. FMF is an autosomal recessive inherited disease resulting from MEFV gene mutations. MEFV encodes a protein called pyrin which is involved in the regulation of critical components of the innate immune system (1).

MEFV mutations disrupt regulation of pyrin inflammasome, causing uncontrolled activation of caspase-1, which induces the release of potent proinflammatory cytokines, interleukin (IL)-1, IL-18 and activation of gasdermin D pyroptotic pathway (2). Mechanisms of inflammatory eruptions manifesting as attacks are partially understood. However, severity, frequency and involved sites are determined by environmental and genetic factors, such as M694V, the most commonly detected variant, leads to more severe and difficult-to-treat disease (3). FMF attacks reduce quality of life and drastically impair work productivity of affected individuals (4). Although FMF is thought to have an excellent prognosis with appropriate treatment, delayed diagnosis, inattentive care, and non- compliance with treatment might lead to serious complications. The most severe complication of FMF is amyloid A (AA) amyloidosis, which results from deposition of AA fibrils in the kidneys, gastrointestinal tract, heart, and other organs. AA amyloidosis is a fatal condition that almost always occurs in untreated or inadequately treated patients which develops as an unfortunate consequence of chronic uncontrolled inflammation. (5). Apart from AA amyloidosis, chronic inflammation might cause damage in the reproductive, gastrointestinal, and musculoskeletal organ systems and might affect growth (6-8). Objective and comprehensive evaluation of the damage is crucial for the determination of long-term outcome and efficacy of used treatments (9).

FMF treatment aims to improve quality of life by reducing the frequency, duration and severity of attacks and to suppress chronic inflammation to prevent damage in the long term. Colchicine, an inhibitor of microtubule polymerisation and neutrophil chemotaxis, is the mainstay of FMF treatment as it prevents both attacks and AA amyloidosis (10). However, 5–10% of patients do not respond well to colchicine and another 30% show partial response (11). Additionally, 20% of patients show colchicine intolerance or dose limiting adverse effects which decreases efficacy of treatment (12, 13). In this regard, biologic therapy represents a major ground-breaking tool in the management of patients with colchicine resistant (crFMF) and intolerant patients. Interleukin (IL)-1 antagonists like anakinra and canakinumab, were found to yield a good clinical response and favourable safety profile (14, 15). However, subclinical inflammatory activity may not be fully controlled with these agents as evidenced by elevated C reactive protein (CRP) and serum amyloid A (SAA) levels (16) despite these treatments raising concerns for the development of complications in the long term. To fulfil this unmet need, we performed a study to evaluate the change in damage accrual with use of IL-1 antagonists in the long term in patients with FMF.

Materials and methods

FMF patients diagnosed with Eurofever criteria and also fulfilled Tel Hashomer criteria (17, 18) and had been treated consistently with IL-1 antagonists for at least 3 years were enrolled in this cross- sectional study. Adherence to treatment was investigated from electronic drug registry and nonadherent patients were excluded from the study. Demographic data, the course of illness (severity, duration, frequency, and type of attacks), comorbid conditions, and treatments were recorded. Complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), 24- hour urine protein excretion, liver, and kidney function tests were recorded for each patient at attack-free periods. Genotype data were acquired for all patients. Activity of FMF is evaluated according to frequency of attacks, patient global assessment (PGA) and the Autoinflammatory Disease Activity Index (AIDAI) during each visit (19).

As a rule of our specialised autoinflammatory clinic, the treatment decision is made by the joint decision of the patient and the doctor after the patient is informed about the evidence-based treatment options. However, our centre admits referred FMF patients who were prescribed biologic agents beforehand. Colchicine is prescribed to all patients immediately after diagnosis, and patients are warned of the importance of adherence to treatment at each visit.

Colchicine resistance was defined as having one or more attacks per month or persistent inflammation in attack-free periods despite the regular use of maximum tolerated dose of colchicine (20). Persistent inflammation was defined as consistently elevated CRP levels measured in between attacks.

Damage accrual was determined with Autoinflammatory Disease Damage Index (ADDI), which consists of 18 items; sub-fertility/infertility, amenorrhea, amyloidosis, proteinuria, renal insufficiency, growth failure, pubertal delay, developmental delay, serosal scarring, cognitive impairment, elevated intracranial pressure, central nervous system involvement, hearing loss, ocular involvement, joint restriction, bone deformity, osteoporosis, and musculoskeletal pain. In original form these components are grouped into 8 categories (reproductive, renal/amyloidosis, developmental, serosal, neurological, auditory, ocular, and musculoskeletal damage). We also used mADDI to evaluate the damage with excluding musculoskeletal pain because of the subjectivity of this item (21). Patients who married before IL-1 antagonist treatment, had their first sexual experience before IL-1 antagonist treatment, and had additional diseases that may be the cause of infertility were not accounted for disease-related infertility. Urine protein excretion and acute phase reactants were tested in each visit. Osteoporosis was screened for every patient using DEXA scanning. Serosal scarring was screened in each patient with either abdominal ultrasonography or computed tomography. All other parameters were tested in patients with compatible findings in clinical and laboratory evaluations. AA amyloidosis was confirmed with minor salivary gland, kidney, or rectal biopsies if there were suggestive findings. Patients were grouped according to their recent damage status at the initiation of IL-1 antagonists as; no damage, pre-existing damage, and *de novo* damage which developed under IL-1 antagonist treatment. Treatment efficacy was evaluated for the prevention of *de novo* damage and change in pre-existing damage with treatment. Institutional ethics committee approved the study and written informed consent was obtained from all participants.

Statistical analyses were performed using SPSS software (v. 17.0 for Windows; SPSS Inc., Chicago, IL, USA). The qualitative variables were expressed as numbers, percentages and were compared with chi-square test. The quantitative variables were investigated using the Kolmogorov-Smirnov and Shapiro-Wilk tests to determine normality distribution and expressed as averages or medians, as applicable with their corresponding standard deviations or interquartile ranges. Quantitative variables were compared with either student t or Mann-Whitney U-tests depending on their distribution of normality. *p*-values less than 0.05 were considered as statistically significant throughout the analysis.

Results

A total of 111 patients (53.2% female, 46.8% male; mean age of 38±11.5 years) were included in the study (Table I). The median duration of disease was 18 years (min-max: 4–59 years) and median IL-1 antagonist treatment duration was 45 months (min-max: 53–120 months). Forty-six patients (43.2%) had a type of damage according to items listed in the mADDI at the last assessment. Thirty-nine (37%) of them had damage prior to IL1 antagonists, five of them showed increase in damage score, whereas two patients had *de novo* damage under IL-1 antagonist treatments. Comparison of clinical, genetic, and laboratory features of FMF patients with respect to their damage status was summarised in Table I. The most common objective damage item was AA amyloidosis (n=28) followed by joint deformity and impaired fertility. Twenty-three patients with pre-existing damage and six patients with increased damage had constantly high CRP levels while receiving colchicine and IL-1 antagonist treatments. Median levels of CRP levels were 4,0 mg/L (min-max: 1-30) in patients without any damage, 7 (2-40) for patients with pre-existing damage and 14 (min-max: 3-40) for patients with increased damage.

An increase in mADDI scores was observed in five patients who administered IL-1 antagonist therapy after a median duration of three years and occurred in musculoskeletal (n=3), renal (n=1) and reproductive systems (n=2, Table II). One patient showed both infertility and declined renal function while treated with IL-1 antagonist.

Sex, M694V homozygous mutation, smoking, disease duration and total time of IL1A treatment did not significantly affect damage score. Patients without damage have significantly higher rate of fever, peritonitis and arthritis attacks. mADDI score was also significantly associated with age, levels of acute phase proteins in the inter attack period and clinical activity of the patients. Patients with damage were significantly older (35.6±11.06 *vs.* 42.3±10.0 years, p=0.004). Also, patients who have increased damage/*de novo* damage with IL1A treatment have higher CRP and sedimentation levels in inter attack period (p=0.017, p=0.001 in order, Fig. 1). Also, patients with pre-existing damage have a lower AIDAI score when compared to patients without any damage (p=0.024).

Osteoporosis was diagnosed in two participants but one of them did not have DEXA scan before treatment, so this patient was not considered to have *de novo* damage. Likewise, a patient who had infertility was not considered to have *de novo* damage owing to her marriage after the commencement of IL-1 antagonist treatment.

In two patients with biopsy-proven amyloidosis proteinuria was progressed under anakinra and then canakinumab but ADDI scores were not affected as glomerular filtration rates (GFR) were remained stable. Both patients were switched to tocilizumab without improvement in proteinuria. One of them-

Table I. Demographic features of all participants.

	No damage n=67	Preexisting damage n=67	*De novo*/ increased damage n=7	*p*-value
Age (years, median(min-max))	**33 (19-79)**	**39 (27-63)**	31 (22-62)	**0.004**
Sex (number of females(%))	34 (50.7)	25 (56)	28 (28.5)	0.17
Duration of disease (years(min-max))	40 (3-59)	56 (3-38)	43 (10-41)	0.33
Duration of IL-1 antagonist treatment (months, median)	40 (38-120)	50 (36-100)	44 (36-90)	0.103
Fever, n (%)	26 (40)	**5 (12)**	2 (28)	**0.02**
Peritonitis, n (%)	24 (39)	**2 (5)**	2 (28)	**0.002**
Pleuritis, n (%)	25 (40)	**5 (13)**	2 (28)	**0.023**
Arthritis, n (%)	20 (32)	6 (16)	2 (28)	0.241
Skin rash, n (%)	6 (11)	6 (16)	0	0.392
Myalgia, n (%)	16 (26)	**2 (5)**	2 (28)	**0.03**
Inter attack CRP (mg/L, median(min- max))	**4 (1-30)**	7 (1-40)	**14 (3-40)**	**0.017**
Inter attack sedimentation (mm/hour, median(min-max))	15 (2-60)	16 (4-75)	**30 (23-60)**	**0.001**
AIDAI score(median(min-max))	**3 (0-9)**	**1 (0-9)**	3 (0-24)	**0.024**
Mutations (n)				
M694V/M694V	26	14	2	
M694V/any	44	38	4	0.41
M694V/M680I	3	4	1	
M680I/any	11	9		

p-values that are statistically significant and groups causing this difference are in bold in the table. n: number of patients, IL-1: interleukin1.

Table II. Frequency of each new damage item according to ADDI with IL-1 antagonist treatment.

Pre-existing damage (n=44)		Progression of pre-existing damage (n=5)	*De novo* damage (n=2)
Infertility (n)	4	2 [a]	1
Non-amyloid proteinuria (n)	18	1	0
Amyloidosis (n)	23	1 [b]	1 [c]
Renal insufficiency (n)	11	0	1 [d]
Serosal scarring (n)	1	0	0
Joint deformity (n)	9	3	1
Osteoporosis (n)	12	1	1 [e]
Musculoskeletal pain (n)	23	6	3 [f]

N: number of patients, **a**: one of these patients had first sexual intercourse after IL-1 antagonist treatment, so infertility may present before. **b**: this patient did not respond IL-1 antagonist cycling and dose escalation and switched to tocilizumab. **c**: diagnosed while on IL-1 antagonist d: emerged after 4 years of ÌL-1 antagonist treatments in an AA amyloidosis patient. **e**: patient's bone scan did not exist prior to initiation of IL-1 antagonist treatment. **f**: non-specific, non-localised chronic musculoskeletal pain.

had remission with tocilizumab with stable GFR levels between 60-70% and ~ 2 g/day proteinuria. Although complete remission could be achieved in other patients, supply of tocilizumab was impaired after six months. Eventually, during follow-up, four patients died, all with pre-existing damage, two from COVID-19 pneumonia and two from complications of amyloid kidney disease.

Discussion

In our study we found that 39% of patients already had a type of damage before the initiation of IL-1 antagonist therapy and 10.8% of them progressed after the treatment. Development of damage is significantly associated with uncontrolled inflammation and clinical activity score. Unfortunately, two patients developed *de novo* damage and five patients had worsening of ADDI damage scores despite the use of IL-1 antagonists. Moreover, in two patients' proteinuria was progressed without increasing ADDI score due to inherent limitation of scoring system. We found that the main reason of worsening under IL-1 antagonists was the inadequate control of inflammatory activity and reluctance in treatment modification.

The European League Against Rheumatism (EULAR) recommends FMF treatment to achieve the control of acute attacks, minimise chronic and subclinical inflammation, prevent complications, and provide an acceptable quality of life (22). Colchicine is very effective for obtaining both clinical and laboratory remission and prevents severe complications in majority of patients (22). However, 10% of patients are colchicine non-responders and another 30% are partial responders who continue to suffer from attacks (23). Previous studies demonstrated that subclinical inflammation is evident in almost a quarter of patients if assessed with CRP (24-26) and 45% if assessed by Serum AA (27) despite the regular use of colchicine. Moreover, side effects such as diarrhoea, elevation in transaminases, and cytopenia hamper maintenance of optimal doses in one fifth of patients (13). IL1 antagonists are the treatment of choice in FMF patients with colchicine resistance and intolerance (28-30). However, in our study, we found that substantial number of patients already had damage at the initiation of IL-1 antagonists, suggesting a delay in these treatments. Therefore, patients should be carefully monitored for colchicine resistance and intolerance, and IL-1 inhibitors must be commenced before the occurrence of irreversible complications.

IL-1 antagonists are highly effective in the prevention of attacks, suppression of inflammatory markers to a degree, and probably development of AA amyloidosis, but their long-term efficacy is largely unknown (14, 16, 31). CLUSTER trial evaluated the efficacy and safety of canakinumab to treat patients with crFMF during a 72-week period. They reported good control of disease without occurrence of a new damage (16). However, in the same study, up to 25% of patients had CRP levels of ≥10 mg/L and almost 90% of patients had SAA levels of ≥10 mg/L at the end of 2 years (16). In another study inflammatory markers found to be higher than healthy control subjects in FMF patients despite the use of IL-1 antagonists (32). Also in another study,

44 patients were analysed retrospectively when dichotomised to subgroups according to creatinine levels, they showed improvement of renal functions after mean 21 months' treatment with IL-1 antagonists (33). In our study, we found that damage was associated with age and chronic inflammation, and we determined that the primary culprit of damage was exposure to inflammation. Despite the treatment with IL-1 antagonists, 6.3% of our patients developed new damage or progression of damage under these treatments. In our report, CRP and sedimentation levels were higher in patients who have damage under IL-1 antagonist treatments. Therefore, elevated acute phase protein levels between attacks should be considered as an indicator of uncontrolled disease activity (24). Therefore, even in patients receiving IL-1 antagonists, careful monitoring is warranted for the development of new damage or worsening of the pre-existing damage.

FMF has an excellent prognosis if clinical and laboratory remission is obtained. It is reported that more than 50% of patients suffer from at least one complication of this disease (20). Any study systematically evaluated efficacy of IL-1 antagonists in FMF patients with pre-existing damage to date. In our study we found that patients with pre-existing damage are at risk of worsening in ADDI damage scores. Therefore, potential damage items should be monitored in all patients to decide on therapeutic changes and those with pre-existing damage should be carefully monitored for the risk of clinical and laboratory worsening, and their treatments need to be modified until complete control of inflammatory activity. Currently, there are limited number options available, like increasing the drug doses, cycling between IL-1 antagonists and switching to an IL-6 antagonist, tocilizumab.

There is an unmet need for new treatment options and guidelines for the management of crFMF patients on IL-1 antagonists. The ADDI index was developed for the comprehensive assessment of damage accrual and widely used in clinical studies (9). This scoring system provide numeric scoring of damage status in autoinflammatory diseases and provide an important convenience in clinical practice. Also, standardisation of damage in autoinflammatory diseases have an advantage about assessing efficacy of treatment. Although it is a useful measurement, it still has some limitations. In our study group, two patients diagnosed with extensive amyloidosis prior to IL-1 antagonist treatment had worsening in proteinuria, and serum amyloid A levels. Tocilizumab, an IL-6 blocker, was added to the treatment because of unresponsiveness to dose escalation of IL-1 blockers and colchicine. However, it was not reflected in the ADDI score, even though these two patients had a clear progression in damage and a decision for a change in the treatment modality. Hence, ADDI may not be adequate for quantifying severity of damage, and parameters may need to be redefined, such as the level of proteinuria and number of damaged joints (not counting the presence or absence of a specific damage item). For these limitations, we evaluated damage items individually for the assessment of actual progression.

Two patients had new damage and five of them had progression of damage with IL-1 antagonists according to mADDI. Three patients described nonspecific musculoskeletal pain. As a damage item, musculoskeletal pain is defined as non-inflammatory pain that impaired daily activities and is scored as "1" in ADDI which has the same weight as proteinuria (9). It is difficult to assess the association of musculoskeletal pain with actual damage. Since muscle pain is very common, affected by many factors and not objective in terms of causality, it should be discussed to whether include this item to damage evaluations. Since our study includes an important claim, development of new damage under IL-1 antagonist therapy, we did not find it appropriate to count those patients who only had musculoskeletal pain while using IL-1 antagonists in the *de novo* damage category. In a previous report about risk factors associated with damage in FMF, they showed causality and association of some risk factors with chronic damage domains except musculoskeletal pain (20). Other damage indexes such as vasculitis damage index or SLICC/ACR do not include such a subjective item (25,34). Of note, FMF also has some musculoskeletal attack types like myalgia, arthralgia, and arthritis. In clinical practice, it is hard to differentiate frequent musculoskeletal attacks with damage.

Damage was significantly associated with age, but not with duration of disease. Although it is not an expected result, we thought that this difference is caused from study population. All damage markers were carefully assessed and other medical conditions leading to same clinical scenario was excluded.

We have some important limitations in our study. First, this is a cross sectional study and not performed as a prospectively designed study. Secondly, we did not include paediatric patients and developmental delay cannot be determined. Efficacy of IL-1 antagonists in terms of prevention of *de novo* damage might be superior in children due to shorter disease duration. Also, patients were enrolled from a single centre and although our centre is dedicated to care of auto inflammatory patients, site-specific approaches might be responsible for the outcome. There is a new registry system for auto inflammatory diseases from 24 countries and 4 continents collect baseline and follow-up data which include demographics, patient history, symptoms, trigger/risk factors, therapies, and healthcare information for monogenic autoinflammatory diseases. Studies from larger-scale cohorts like the AIDA registry may provide more reliable data (35). Third, a study had limitations of all retrospective studies that warrant further multicentre prospective studies.

In conclusion, our results highlight the importance of persistent inflammation and higher clinical activity in the progression of the FMF related damage. Elevated acute phase proteins in the inter- attack period are an independent predictor of future damage. Persistent inflammation and increased number/duration of attacks are the main causes of damage and may be an insidious indicator of uncontrolled disease. Therefore, clinicians should be responsive to control disease activation and levels of acute phase proteins to prevent damage.

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