Interferon-α as a Treatment Modality for Colchicine-Resistant Familial Mediterranean Fever

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ABSTRACT. ***Objective.*** Previous reports on interferon-α (IFN-α) were conflicting with respect to its efficacy in familial Mediterranean fever (FMF) refractory to colchicine treatment. We investigated the effect of IFN-α in patients with colchicine-resistant FMF.

Methods. In a prospective, patient self-controlled, open-label study evaluating the safety and efficacy of IFN-α in patients with FMF with a severe phenotype, refractory to intensified (oral plus intravenous) colchicine therapy, we advised patients to subcutaneously inject IFN-α, 3 million international units, at the onset of the FMF attack. Attacks not treated with IFN-α of the same patients and in the same sites served as control attacks. Features of each attack were recorded in a questionnaire, eventually used to compare between IFN-α-treated and non-treated attacks.

Results. Ten patients with a total of 80 attacks were recruited. Compared to 22 untreated attacks, a > 20% and > 50% reduction in the duration of the attacks was noted in 100% and 90% of the 58 IFN-α-treated attacks, respectively ($p < 0.001$ for both). The severity (degree of pain) of the IFN-α-treated attacks was attenuated by > 20% and > 50% in 88% and 49% of these attacks, respectively ($p < 0.001$ for both). The most common drug-related adverse events were chills and fatigue.

Conclusion. Early intervention with IFN-α injections was associated with reduced attack length and/or severity in a substantial number of bouts, with an acceptable cost of adverse events. (First Release June 1 2008; J Rheumatol 2008;35:1362–5)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER INTERFERON-α COLCHICINE TREATMENT

Familial Mediterranean fever (FMF) is an autoinflammatory disease, characterized by attacks of peritoneal, pleural, and synovial inflammation and gradual development of amyloidosis[1,2]. Attacks last typically between 24 and 72 hours and resolve spontaneously. During attacks the patients are febrile, incapacitated, and confined to bed, and have agonizing pain. Colchicine, introduced in the early 1970s, is the only effective therapy for prevention of FMF attacks. No effective alternative prophylactic treatment is currently available, subjecting 10% of the patients (around 15,000 worldwide), who are colchicine-resistant, to recurrent uncontrolled attacks. Such patients can receive only symptomatic and supportive therapy, mainly analgesia, using nonsteroidal antiinflammatory drugs (NSAID) or opioid compounds, with only a partial, transient, or poor response. A recent survey revealed that colchicine nonresponders are not different from colchicine responders in clinical, in demographic, or in FMF gene (*MEFV*) features. The only abnormality found was a reduced level of colchicine in the mononuclear cells of the nonresponders[3]. This finding suggested that failure to respond to colchicine is probably related to a genetic defect, separate from that causing FMF, perhaps located in cells of the mononuclear lineage. Currently, the only proven management for nonresponders consists of the addition of weekly intravenous (IV) colchicine (1 mg) to the oral colchicine regimen. However, even this modality has a limited success[4].

Interferon-α (IFN-α) is a naturally occurring species-specific immunomodulatory glycoprotein, which increases macrophage and natural killer cell phagocytic activity and augments lymphocyte-specific cytotoxicity. It is produced by many cell types, predominantly T and B lymphocytes, and exerts both antiviral and antineoplastic activity, features used clinically for these purposes (e.g., against hepatitis C virus infection, leukemia, and melanoma). It was first noted as a possibly effective drug for prophylaxis of FMF by Tankurt, *et al* in a patient with uncontrolled FMF attacks, who had hepatitis C infection as well, for which he received IFN-α[5]. Encouraged by this observation, Tunca, *et al* noted in 7 patients with FMF treated with IFN-α that 18/21 attacks were halted within a mean of 3 hours with attenuation of pain intensity[6]. Yet another report, published by the same group in 2004, failed to elicit favorable response, possibly related to the late administration of the drug[7]. Since then, additional results favoring IFN-α treatment were published

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by 2 other groups, consolidating the possible positive role for IFN-α in this scenario[8-10].

In view of these conflicting reports and shortage of treatment modalities for colchicine-resistant FMF, and because we wanted to determine the appropriateness of IFN-α use under these circumstances in our patient population, we conducted an open-label, prospective, patient self-controlled study, in a group of 10 patients with FMF experiencing severe and frequent FMF attacks, not amended by oral or oral plus IV colchicine.

MATERIALS AND METHODS

Patients. Over the course of 18 months, from April 2003 to December 2004, 10 patients with FMF, diagnosed based on our published criteria[11], who had FMF attacks resistant to both oral (≥ 2 mg/day) and IV colchicine therapy (1 mg/week), were recruited for the study, while coming to their regular followup visit at the FMF outpatient clinic. Clinical, demographic, genetic, and management data were abstracted from the outpatient clinic files and completed at the time of recruitment and medical interview. The patients discontinued IV colchicine prior to the study for lack of efficacy, but were allowed to continue treatment with oral colchicine at the most recent dose. Global severity score of the disease was determined using a published score[12]. The institutional review board of Sheba Medical Center approved the study. All patients signed an informed consent for participation.

Study design. Our study was aimed at evaluation of the efficacy and safety of IFN-α for the treatment of colchicine-resistant FMF, using an open-label, prospective, patient self-controlled approach. Participating patients were asked to record all their FMF attacks, over a 6-month period, most of which had to be treated by IFN-α injections. Attacks with similar distribution or location not treated with IFN-α were matched to those treated in the same individual, thus serving as the patient's own negative control. The course of IFN-α-treated and untreated attacks was recorded for each attack in a patient diary, which included a questionnaire designed specifically to answer the study aims. At the study conclusion, one of us (NTZ) evaluated the efficacy (reduction of the duration and severity of the attacks) and the safety of IFN-α treatment.

Recording of the attack. For each attack, during the attack and/or immediately after the attack was completed, the patients fulfilled a detailed questionnaire, which included items on the exact time of the initial manifestation of the attack, the sites of pain, the presence and degree of fever, the maximal intensity of pain, using a 10 cm visual analog scale (VAS), the time of IFN-α injection, the time at entire symptom resolution, the side effects and other medications used, as well as any other relevant important information.

Attacks treated with IFN-α. All patients received 1 or more, as needed (one patient received 4), IFN-α automatic injecting pens (Intron A®, Shering-Plough, distributed by Trading Pharma, Petah Tikva, Israel), and were taught by the investigators how to use them when needed. Patients were instructed to inject the IFN-α preparation subcutaneously, 3 million international units (MIU) per attack, immediately at the first signs and symptoms of the attack. Additional oral paracetamol (1 g), immediately following the injection, was also advised in order to minimize potential side effects (fever, headache, and generalized myalgia).

Control attacks. Patients were asked to also record all the attacks not treated with IFN-α during the study period. For these attacks, similar measures were documented in the questionnaire. Untreated attacks served as the basis for a comparison with the IFN-α-treated attacks in a given patient.

Evaluation and statistical analysis. Each IFN-α-treated attack was compared to the untreated attacks of the same patient and in the same site, with respect to duration (in hours from the first manifestation to the complete resolution of all signs and symptoms) and severity (intensity of pain as determined by VAS). Then each IFN-α-treated attack was assigned to one of 3 duration and one of 3 severity categories: resulting in < 20%, 20–50%, or > 50% reduction in each of the respective measures (duration and severity of attack). Statistical evaluations of the change induced by IFN-α treatment in the duration and severity of the attacks, and determination of drug-related adverse events, were performed using the 2-tailed chi-square test and Yates' correction, or Fisher exact test as appropriate, with a p value < 0.05 considered significant.

RESULTS

The clinical, demographic, and genetic characteristics of the 10 colchicine-nonresponsive patients with FMF are shown in Table 1. Most patients were in their third to fifth decade of life (average 35 yrs). They have had FMF attacks since early childhood (data not shown) and experienced very frequent and prolonged attacks (lasting around a mean of 2 days, data not shown), despite maximal colchicine therapy (≥ 2 mg/day orally plus IV 1 mg/week). Some attacks affected 2–3 sites. In all patients, global disease severity was high (≥ 9). Most of them were either homozygous to the M694V or compound heterozygous, with the M694V and the E148Q mutations in the MEditerranean FeVer gene (*MEFV*).

A total of 58 attacks treated with IFN-α injections were compared to 22 site-matched control attacks of the same patient. Figure 1 illustrates a major improvement with IFN-α therapy as compared to untreated attacks with regard to the attack duration. Over 50% decrease in attack duration was noted in 90% of the attacks treated with IFN-α ($p < 0.001$). None of the attacks had less than 20% reduction in duration following IFN-α administration ($p < 0.001$). Attenuation in the severity score (by VAS) of the attacks treated with IFN-α, as compared to control attacks, was also statistically significant, although less impressive. In 88% of the attacks, > 20% reduction in attack severity was noted ($p < 0.001$). Yet a major (> 50%) attenuation in pain intensity was observed in only about half of the patients (49% of the attacks; $p < 0.001$).

From the patients' perspective, there were only 2 patients with a very good response to IFN-α (in both attack duration and severity), regardless of the attack site. In the remaining patients, a mix of responses was noted. Site-specific analysis and factor evaluation to determine features predicting the very good response to IFN-α could not be carried out due to the diversity of attack sites (peritoneum, pleura, joints) and the small number of patients.

Side effects were reported in all IFN-α-treated attacks, and ranged from mild to moderate in severity. Of note, even though the patients stated they were able to identify IFN-α-induced symptoms, we could not distinguish safely between some manifestations of FMF and IFN-α adverse events. Common side effects included fever, reported in 24 of the 58 attacks (41%) treated by IFN-α versus 8 in untreated attacks ($p = 0.89$); fatigue and malaise, reported in 37 of the 58 treated attacks (63%) versus only 4 (18%) in untreated

Table 1. Disease characteristics of patients with FMF.

Patient	Age, yrs	Attack Frequency (no. per mo)	*MEFV* Genotype	Daily Oral Colchicine dose*, mg	Severity Score**
1	47	1	ND	3	13
2	44	4	ND	2.5	13
3	25	2	M694V/M694V	3	13
4	45	2	M694V/E148Q	3	12
5	23	1	M694V/M694V	2	13
6	32	2	M694V/M694V	2.5	12
7	26	2	M694V/M694V	3	13
8	33	1	M694V/E148Q	2.5	11
9	26	4	M694V/M694V	2.5	13
10	55	2	V726A/V726A	2	11

* All patients were also taking intravenous colchicine 1 mg weekly, prior to the study. ** Determined by published severity score[12]. *MEFV:* MEditerranean FeVer gene. ND: not done.

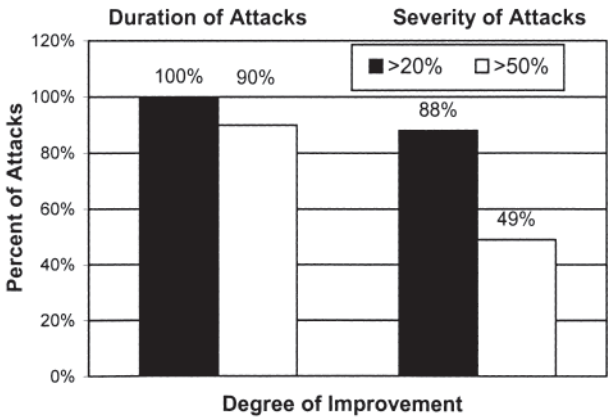

Figure 1. Reduction of duration and severity in 58 attacks of 10 colchicine-resistant FMF patients induced by IFN-α injections at the onset of the attacks. Twenty-two control attacks served as a reference for the expected duration and severity (by VAS). The milder, > 20% reduction in duration/severity and the more important, > 50% reduction were highly significant ($p < 0.001$) for both duration and severity.

attacks ($p = 0.001$); chills, reported in 21 (36%) IFN-α attacks versus none in the noninjected attacks ($p = 0.003$); and headache in 10 treated attacks versus 1 untreated attack ($p = 0.27$). Arthralgias, myalgias, nausea, dizziness, and somnolence were reported in several cases. Two patients discontinued IFN-α after several trials due to intolerable adverse effects. Particular combinations of side effects tended to cluster in the same individuals and persisted throughout the study period, with no change in type and severity over time.

DISCUSSION

IFN-α injected early, upon the first symptoms of the FMF attack, exerts a beneficial effect in reducing the duration of the attack by more than 50% in about 90% of the attacks. The intensity of pain is attenuated in most of the attacks, but a significant improvement (> 50% decrease in VAS) was observed in only 49% of the attacks. Viewing the results from the patients' side, it appears that only 2 responded excellently to IFN-α injections, with respect to reduction of both duration and severity of the attacks. IFN-α injections were not associated with serious adverse events. Yet moderately severe side effects, some resembling symptoms associated with FMF attacks, were frequently observed and led to early study cessation in 2 patients.

It is not known how IFN-α exerts its effect in FMF. IFN-α is a cellular glycoprotein produced by many cell types, some of which are involved in the inflammatory reaction at the FMF attack target sites. Its immunomodulatory functions include increasing macrophage phagocytic activity and natural killer cell and lymphocyte cytotoxicity. An examination of cytokine modulation of *MEFV* demonstrated that IFN-γ and IFN-α cause upregulation of *MEFV* gene expression in the system studied[13], suggesting that IFN-α may enhance pyrin (protein encoded by *MEFV*) production under the circumstances of pyrin shortage characterizing the FMF attacks[14,15]. It has also been shown by Shiohara, *et al* that the apoptosis-associated speck-like protein (ASC), a protein identified as a binding partner of pyrin in the inflammation pathway they share, is also upregulated by IFN-α[16]. Of note, we are not aware of a study in which IFN-α levels were determined during the FMF attack or remission. A recent study, however, found increased IFN-γ levels during both attacks and remissions (more so during the attacks), suggesting a possible natural role, either stimulatory or compensatory, for this protein during FMF attacks[17].

Our results, showing that early treatment with IFN-α offers a significant improvement in the duration and severity of FMF attacks, support previous studies on this matter[5,6,8-10]. The disparity in IFN-α effect on attack duration and attack severity offers insight to the role of IFN-α in suppressing the FMF attacks and suggests that it probably better interferes with the recruitment of more inflammatory cells (hence shortening the attack) than with inactivating

already primed cells, and thus is less effective in preventing the painful stimuli from reaching their predetermined peak.

The inconsistency in IFN-α efficacy, previously reported[7], prompted us to reassess its value for attack control, with an emphasis on the time of the injection during the window of opportunity early in the attack. Since the drug is being kept at 4°C, the most pertinent users of this medication are patients who experience a prodrome[18], a set of manifestations preceding the attack, allowing IFN-α administration before the attack commences or at its very onset. However, since this therapy is both effective and scientifically logical, but only 50% of the patients experience a prodrome[18], it may be of value to treat patients with colchicine-resistant FMF who do not experience a prodrome with weekly regular or pegylated IFN-α injections. Such a regimen, already proven to be very effective[8], may allow the patients not to be dependent on the recognition of early signs of the attack.

Our results show a positive role for IFN-α administered at the onset of the attack in patients with FMF not responding to intensified colchicine treatment. This is in agreement with most previous studies. Encouraged by these results and acceptable adverse events, and because of the suffering, poor quality, nonproductive life, and high risk of AA amyloidosis affecting these patients, we recommend that colchicine-resistant patients with FMF receive a trial with IFN-α, or its pegylated form.

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