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# THE EFFICACY OF INTERFERON ALPHA ON COLCHICINE-RESISTANT FAMILIAL MEDITERRANEAN FEVER ATTACKS: A PILOT STUDY

**M. TUNCA, E. TANKURT,* H. AKBAYLAR AKPINAR,* S. AKAR, N. HIZLI† and Ö. GÖNEN***

*Departments of Internal Medicine, *Gastroenterology and †Rheumatology, Balçova, 35340, Dokuz Eylül University School of Medicine, Izmir, Turkey*

SUMMARY

About a quarter of familial Mediterranean fever (FMF) patients have recurrent painful attacks of polyserositis despite regular colchicine treatment. There is no known alternative drug for colchicine-resistant cases. We had previously observed a patient with FMF whose painful attacks disappeared during the 6 month period of interferon alpha (IFN) treatment for his chronic hepatitis B. The objective of the present study was to investigate the possible beneficial effect of IFN on these episodes. Twenty-one consecutive attacks in seven adult patients with FMF were treated at early onset with IFN, the dosage being 3–10 million IU s.c. Eighteen of the 21 attacks could be halted in a mean time of 3.05 h, while the intensity of abdominal pain remained very low. Observed side-effects were generally mild and acceptable. IFN may be a useful adjunct for the treatment of colchicine-resistant attacks in FMF patients.

KEY WORDS: Familial Mediterranean fever, Interferon alpha.

FAMILIAL Mediterranean fever (FMF) is a genetic disease characterized by recurrent painful attacks of fever, polyserositis (usually peritonitis and/or pleuritis) and arthritis. A typical attack continues for 24–72 h and remits spontaneously, and can be prevented with regular daily administration of colchicine in the majority of patients [1]. However, about a quarter of them suffer occasional attacks despite colchicine or are completely resistant to the drug. There is no known alternative or adjunct to colchicine therapy, although non-steroidal anti-inflammatory drugs (NSAIDs) may have some benefit for synovial symptoms.

We had previously observed a patient with colchicine-resistant FMF whose attacks disappeared during the 6 months of interferon alpha (IFN) treatment (10 million IU, 3 days/week) for his chronic hepatitis B [2]. The FMF attacks of this patient recurred at their previous frequency and severity 1 month after cessation of his IFN treatment. This observation led us to try IFN as an adjunct to treatment at early onset since virtually all FMF patients can reliably predict and recognize their oncoming attacks [3].

## MATERIALS AND METHODS

We identified 10 adult cases, among our registered FMF patients, with frequent or occasional attacks of peritonitis and fever despite regular treatment with colchicine 1.5–2 mg/day. All of the patients fulfilled the Tel-Hashomer diagnostic criteria for 'definite FMF' [1]. The patients had been having acute attacks at a frequency of 1–4/month (mean 2/month) since the age of 8–16 yr and the duration of the attacks was 1–5 days (mean 3.1 days). They were all on regular colchicine treatment and their attacks had thus become occasional, except for one patient who was completely unresponsive. All of the patients declared that they could recognize the prodromal stage of an oncoming attack. They were informed about our coincidental observation and the possible benefits and potential side-effects of INF administration. Eight patients agreed to participate. Informed consent approved by the ethical committee of our institute was obtained from each patient. Seven of the eight patients have used IFN in 21 consecutive FMF attacks. The patient characteristics and results of treatment are summarized in Table I.

The patients were taught to self-administer the drug s.c. and were told to use it at the earliest signs of attack. They were given a list of possible side-effects and were told to score their intensity as: 0 (none), 1 (mild—no interference was required), 2 (moderate—additional treatment was required) and 3 (severe—requiring hospitalization). The patients were also asked to rate their pain on a scale from 0 to 10 and score the response to treatment (10: extremely painful attack; 5: tolerable pain not interfering with daily activity; 0: no pain) and note the duration of pain in hours. Resolution of an attack was defined as a pain score of 5 or less (the patient was expected to be able to perform daily activities comfortably and be able to go to work or sleep). The visual analogue scale for pain scoring was utilized, but the results were not analysed statistically since the study design was open and uncontrolled. Patients made a telephone call to one of us immediately after administering the drug; they were told to come to the hospital as soon as possible for the medical examination and interview, with the aim of continuing contact until resolution of the attack. Next day, every patient was re-examined and interviewed by two members of our group for the efficacy and side-effects of treatment.

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Correspondence to: M. Tunca, Department of Internal Medicine, Dokuz Eylül University School of Medicine, Balçova, 35340, Izmir, Turkey.

For closer observation and blood analyses, IFN was administered to the patients by our team at the hospital in the last six attacks. A general medical examination was performed and their vital signs were followed every hour. Serum samples were obtained before administering IFN, at the time when the patient reported that his pain had subsided and 24 h later.

*Laboratory examinations*

The following acute-phase reactants were measured: leucocyte count, thrombocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and haptoglobin. Serum CRP and haptoglobin levels were determined immediately (or from serum samples stored at $+2^{\circ}$C overnight) by the rate nephelometric method utilizing the Array Protein 360 System of Beckman Instruments Inc., Ireland.

*Statistics*

The test results were analysed statistically with the use of the SPSS statistical software package, version 6.1 (Friedman two-way ANOVA) and $P$ values $<0.05$ were considered to indicate statistical significance (Table II).

TABLE I
Patients treated with interferon alpha (IFN) at an early phase of a FMF attack

| Patient no. | Age/ sex | Attacks treated | IFN dose ($10^6$ IU) | Resolution of attack | Side-effects attributable to IFN |
|---|---|---|---|---|---|
| 1 | 25 M | 1 | 10 | 2 h | Severe nausea, vomiting, headache, fever |
| 2 | 20 M | 1 | 3 | 3 h | Mild nausea, headache, fever, diarrhoea |
| 3 | 28 M | 1 | 3 | 3 h | Moderate fever and fatigue, mild somnolence |
| 4 | 31 F | 1 | 3 | No response | Moderate fever, vomiting, arthralgia |
| 5 | 31 M | 3 | 3 | 3 h | Moderate fever |
| | | | 3 | 2 h | Same as above |
| | | | 3 | 6 h | Same as above |
| 6 | 22 F | 6 | 3 | 3 h | Moderate fever, fatigue |
| | | | 3 | 1 h | Same as above |
| | | | 3 | 4 h | Moderate nausea, vomiting, fever |
| | | | 3 | 12 h | Same as above |
| | | | 5 | 1 h | Moderate fever, headache |
| | | | 5 | 4 h | Same as above |
| 7 | 41 M | 8 | 3 | 5 h | Mild influenza-like |
| | | | 3 | 6 h | Same as above |
| | | | 3 | 12 h | Same as above |
| | | | 6 | 2 h | Same as above |
| | | | 5 | 2 h | Moderate fever, mental slowness |
| | | | 5 | 2 h | Same as above |
| | | | 5 | 4 h | Moderate fever |
| | | | 5 | 2 h | Mild nausea, moderate fever and fatigue |

TABLE II
The results of acute-phase reactants measured during six attacks treated with IFN

| Acute-phase reactant | Attack | Before IFN | End of attack | 24 h later | $P$ |
|---|---|---|---|---|---|
| Leucocyte count ($10^9$/l) | 1 | 12.6 | 12.0 | 5.5 | |
| | 2 | 9.2 | 8.3 | 4.3 | |
| | 3 | 12.0 | 11.5 | 6.1 | |
| | 4 | 13.9 | 7.1 | 4.6 | |
| | 5 | 12.4 | 11.0 | 5.3 | |
| | 6 | 14.0 | 7.0 | 7.2 | 0.0057 |
| Thrombocyte count ($10^9$/l) | 1 | 215 | 185 | 238 | |
| | 2 | 228 | 107 | 104 | |
| | 3 | 197 | 188 | 184 | |
| | 4 | 233 | 188 | 208 | |
| | 5 | 234 | 204 | 243 | |
| | 6 | 310 | 262 | 80 | 0.1146 |
| ESR (mm/h) | 1 | 15 | 23 | 37 | |
| | 2 | 14 | 17 | 22 | |
| | 3 | 5 | 4 | 19 | |
| | 4 | 32 | 32 | 40 | |
| | 5 | 18 | 19 | 30 | |
| | 6 | 22 | 24 | 35 | 0.0076 |
| CRP (mg/l) | 1 | 32.5 | 31.4 | 182.0 | |
| | 2 | 2.4 | 3.9 | 50.7 | |
| | 3 | 10.6 | 34.5 | 225.0 | |
| | 4 | 15.2 | 74.0 | 90.7 | |
| | 5 | 30.3 | 39.6 | 108.0 | |
| | 6 | 7.2 | 37.4 | 185.0 | 0.0057 |
| Haptoglobin* (g/l) | 1 | 1.2 | 1.7 | 2.6 | |
| | 2 | 1.4 | 1.5 | 2.5 | |
| | 3 | 1.0 | 0.7 | 2.0 | |
| | 4 | 1.5 | 1.7 | 2.1 | |
| | 5 | 1.4 | 1.1 | 2.1 | |
| | 6 | 1.9 | 1.8 | 2.3 | 0.0111 |

*Normal: 0.3–2.15 g/l.

## RESULTS

Seven patients have used IFN in 21 consecutive FMF attacks. The first patient received IFN at the dosage given to the index patient (10 million IU s.c.), but severe side-effects were observed and 3 million IU was decided as the starting dose. Abdominal pain resolved in a mean time of 3.05 h in 18 attacks (range 1–6 h, median 3 h). Two patients have observed progress and resolution of their attacks in 12 h, and one patient's abdominal pain continued for 36 h. Since FMF attacks may sometimes resolve spontaneously in $<24$ h, these three treatment episodes were considered as non-response (14.3%). Two patients proposed to increase their IFN doses when the drug was less effective than the previous administration at 3 million IU, and their next attacks were better controlled. Side-effects were tolerable and generally mild or moderate (see Table I for details). Fever was observed in every patient receiving IFN, but it was not possible to clarify whether it was due to the drug or to the disease itself. Although the patients were encouraged to take paracetamol 500–750 mg q 4 h, only five of them used it or NSAIDs in 11 attacks. All of the patients demanded to re-use IFN in their future attacks.

The acute-phase reactants were measured in the last six attacks treated. There was a significant decline in leucocytes and a rise in ESR, haptoglobin and CRP during the 24 h of observation, confirming the

capability of the patients to predict correctly the oncoming attacks. The changes observed in thrombocytes were not statistically significant.

## DISCUSSION

An acute serositis attack of FMF resistant to regular colchicine treatment is worrisome both for the patient and his physician as there is no known remedy for it. Some patients take extra doses of colchicine, but usually gastrointestinal toxicity of the drug and little, if any, additional potency at that setting preclude its utilization. NSAIDs may be only marginally effective, except for the arthritis. Patients may even discontinue colchicine as it is seemingly useless, although it is critically necessary for preventing amyloidosis [4, 5]. INF may be an effective adjunct to colchicine. We have observed efficacy of IFN in 18/21 consecutive attacks. The drug has also been repeatedly effective in 15/17 attacks in the three patients who used it more than once. The significant change in acute-phase reactants, particularly very high CRP values, that were measured during the attacks lessen the probability of a 'false alarm'. All of our patients demanded to have IFN at their disposal for possible future attacks. However, two of our patients proposed dose escalations, and chronic administration of IFN may necessitate higher doses which may be a sign of antibodies being formed against it. Patients were generally reluctant to take paracetamol for fever since this was not an annoying symptom as long as the peritonitis was resolving. In the three episodes which were considered as a non-response, patients had utilized IFN 4–6 h after the start of abdominal pain. Probably, the drug has to be administered at the prodromal phase in order to obtain full benefit.

IFN has no analgesic properties and many of its side-effects, such as fever, nausea, vomiting, myalgias and fatigue, overlap with the features of a FMF attack; the drug may thus be expected to aggravate the picture with no benefit. Our results are both unexpected and optimistic. However, FMF is a disease with unpredictable features and there are many treatment reports in the literature claiming success which could not withstand the test of time. Although we had followed the physical signs of resolution of acute abdomen in the last six attacks, our results rest mainly on subjective responses of the patients who may be more than ready to find an effective remedy for their pain. Moreover, taking 'pain', which itself is highly subjective and open to suggestion, as the main criterion is somewhat inevitable but a weak point of this study. Our observations have to be tested further in placebo-controlled trials. In a classic study which investigated the abortive potential of colchicine on FMF attacks, the placebo effect was observed in $\sim$10% of the patients [3]. In another double-blind trial, 23% of the patients on placebo guessed their courses as colchicine and 13% on the colchicine courses as placebo [6]. We assume that attaining positive results in 85.7% of the attacks in our patients would be difficult to ascribe to a placebo effect only.

How would IFN be effective? The drug reversibly blocks the release of neutrophils from the bone marrow [7]. This action of IFN is of short duration and seems to fit well to the pathological sequence of the FMF attack. It has been shown that FMF patients may have reduced levels of inhibitor of complement 5a (C5a) in their serosal and synovial surfaces [8, 9], which is necessary to inhibit 'accidentally started or inappropriate' neutrophil chemotaxis. Colchicine inhibits chemotaxis of the neutrophils and IFN may be synergistic by inhibiting their release from the bone marrow. As proposed by Dinarello *et al*. [6] for colchicine action, the initiating event remains intact, but the attack is halted in an early phase. This may also help to explain the failure of both drugs in full-blown attacks. The role of tumour necrosis factor (TNF) and its possible additive effect on deficiency of C5a inhibitor in FMF is not yet resolved [10–12], but it would be interesting to note that IFN may increase TNF and its receptors [13].

There are several questions to be answered. Will IFN remain significantly effective in larger groups of patients? What is its optimum dose? Will patients develop resistance to it as IFN antibodies are formed? Could those patients who are completely resistant to colchicine benefit from IFN by regular injections? Would IFN delay or hasten the next FMF attack? Our initial observations are encouraging and a placebo-controlled study is planned.

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