The efficacy of continuous interferon alpha administration as an adjunctive agent to colchicine-resistant familial Mediterranean fever patients

M. Calguneri, S. Apras, Z. Ozbalkan, M.A. Ozturk, I. Ertenli, S. Kiraz

Section of Rheumatology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey.

Meral Calguneri, MD; Sule Apras, MD; Zeynep Ozbalkan, MD; M. Akif Ozturk, MD; Ihsan Ertenli, MD; Sedat Kiraz, MD.

The preliminary results of this study were presented at the FMF Congress 2002 Montpellier, France.

Please address correspondance to: Zeynep Ozbalkan, MD, Sehit Cetin Gorgu Sok., Ugur Apt. 17/3, 06570 Maltepe, Ankara, Turkey.
E-mail: zaslar@hotmail.com

Received on December 22, 2003; accepted in revised form on April 8, 2004.

Clin Exp Rheumatol 2004; 22 (Suppl. 34): S41-S44.

Key words: Familial Mediterranean fever, colchicine, resistance, interferon alpha.

ABSTRACT

Objective. *About 10-20% of familial Mediterranean fever (FMF) patients are resistant to regular colchicine treatment and have painful recurrent attacks due to polyserositis. In clinical practice there is no alternative drug for such patients. In a previous pilot study on a small number of colchicine-resistant patients, interferon-alpha (IFN-α) was administered when painful attacks were about to occur.*

Methods. *In this study we gave IFN-α continuously to 8 colchicine-resistant FMF patients in a schedule while the colchicine therapy had been continued. All those patients were complicated with vasculitis or arthritis or together during the FMF course. Those complications were treated with the other immunosuppressive drugs. While they were under intense immunosuppressive therapy, the abdominal and the other serosal attacks remained to continue.*

Results. *After the administration of IFN-α therapy only one out of eight patients had abdominal painful attacks in twice, and one patient had arthritis in knees and ankles, the others responded well. Observed side effects were generally mild and acceptable.*

Conclusion. *Continuous IFN administration in addition to the regular colchicine treatment may be useful for the colchicine-resistant attacks in FMF patients*.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by acute attacks of fever and localized inflammation, usually involving the peritoneum, pleura, joints, or skin. FMF primarily affects populations from the Mediterranean basin including Sephardic Jews, Armenians, Turks and Arabs. Regular colchicine is quite effective in the control of FMF attacks. About 65% of patients respond with complete remission, and 20-30% exhibit a partial response. However, 10-20% of patients remain resistant to colchicine therapy (1, 2).

Interferon alpha (IFN-α) is known to have pleiotropic effects, suppressing the symptoms in some diseases (3-5). FMF patients have some immune regulatory abnormalities (6-8). The combination of colchicine and IFN-α up-regulates the MEFV mRNA levels in neutrophils (8). Moreover IFN-α has recently been demonstrated to be efficacious when administered before the acute attack develops, preventing their occurrence in colchicine-resistant FMF patients in a pilot study (9). Therefore, in this prospective open study we investigated the effects of the continuous administration of IFN-α in FMF patients with a marked inflammatory response who failed to achieve remission with regular colchicine therapy.

Patients and methods

Eight adult patients (mean age: 24.7 ± 8 years, M/F: 4/4) with attacks of peritonitis and fever despite regular treatment with colchicine for more than one year were enrolled in this open prospective study. All patients fulfilled the Tel-Hashomer diagnostic criteria for FMF (10). They were treated with standard 1.5 – 2 mg/day colchicine therapy and the dose was increased up to 3 mg/day in patients who tolerated the treatment well. All patients had a severe FMF disease course with complications including: juvenile chronic arthritis together with non-differentiated vasculitides (n = 1), ankylosing spondilitis (n=v2), ankylosing spondilitis with non-differentiated vasculitides (n=2), ankylosing spondilitis and Henoch-Schoenlein purpura (n= 2), and polyarteritis nodosa

Table I. Clinical and laboratory features before and after IFN-α treatment in colchicine-resistant FMF patients.

Pt.	Sex Age	Disease duration (mos.)	Concomitant disease	Previous therapy	Clinical manifestations at initiation of INFα therapy	IFNα dosage (3 times/wk)	IFN duration	6-month status (outcome)	1-year status (outcome)
1	F/22 yr	84	JCA Vasculitides	Colchicine 3x0.5 mg OH-C 2x200mg SLZ 3x1g MTX 15mg/w CYP 3x50mg/d DC 20mg/eod	Fever and painful abdominal attacks Active peripheral arthritis (knee, hip and shoulder joints) ESR:120, CRP: 7.6 Fibrinogen: 950 Proteinuria 3759 mg/d Amyloid (-)	5 mIU	8	Good clinical condition ESR: 12 CRP: 1.2 Fibrinogen: 363 Proteinuria: 2774 mg/day	
2	M/24 yr	96	AS	Colchicine 3x0.5 mg SLZ: 3x1 g	Fever and pleuritic chest pain ESR 40, CRP: 9.3 Fibrinogen: 472 Proteinuria: 740 mg/dl Amyloid: (-)	3 mIU	15	Good clinical condition ESR: 9, CRP: 4.5 Fibrinogen: 396 Microproteinuria: 202 mg/day	Good clinical condition ESR: 5, CRP: 1.45 Fibrinogen: 365 Microproteinuria: 123 mg/day
3	M/38 yr	132	AS Vasculitides	Colchicine 3x0.5 mg OH-C 2x200 mg SLZ 3x1 g MTX 20 mg/w	Fever and painful abdominal attacks Total hip joint replacement ESR: 75, CRP: 8.9 Fibrinogen: 774 Proteinuria: 2836 mg/d Urine microscopy: Granular casts	5 mIU	20	Good clinical condition ESR: 34, CRP: 1.9 Fibrinogen: 453 Proteinuria: 1131 mg/day	ESR: 34, CRP: 1.27 Fibrinogen: 441 Proteinuria: 128
4	M/18 yr	252	AS HSP Amyloidosis	Colchicine 5x0.5 mg SLZ 2x1 g MTX 10 mg/w Alkeran 1x1 eod	Fever, painful abdominal attacks and myalgia ESR: 80, CRP: 12 Fibrinogen: 990 Proteinuria: 3279 mg/d	5 mIU	18	Ankle and knee arthritis ESR: 36, CRP: 1.19 Fibrinogen: 603 Proteinuria: 3428 mg/d	Good clinical condition ESR: 18, CRP: 0.75 Fibrinogen: 520 Proteinuria: 2571
5	M/18 yr	96	PAN	Colchicine 3x0.5 mg DC 25 mg/eod CYP 500 mg IV pulse/mo MP 1g pulse/mo	Fever and myalgia, purpuric skin rashes ESR: 60, CRP: 7.8 Fibrinogen: 584	5 mIU	24	Good clinical condition ESR: 9, CRP: 1.2 Fibrinogen: 380	Good clinical condition ESR: 12, CRP: 1.3 Fibrinogen: 331
6	F/19 yr	204	AS HSP	Colchicine 4x0.5 mg Quensyl 2x200 mg SLZ 3x1g MTX 15 mg/w	Febril attacks Peripheral arthritis (left knee) ESR: 84, CRP: 11.9 Fibrinogen: 741	5 mIU	12	Good clinical condition Remission in arthritis and fever ESR: 57, CRP: 1.7 Fibrinogen: 451	Good clinical condition ESR: 20, CRP: 0.5 Fibrinogen: 90
7	F/36 yr	144	AS	Colchicine 4-6 x 0.5 mg SLZ 2x1 g	Continuous febril and abdominal attacks Total hip joint replacement Fibrinogen: 780	3 mIU	24	Abdominal attack in twice at the beginning ESR: 18, CRP: 1.52 Fibrinogen: 461	No abdominal attack ESR: 10, CRP: 1.3 Fibrinogen: 299
8	F/24 yr	33	AS	Colchicine 4x0.5 mg OH-C 2x200 mg SLZ 3x1 g MTX 15 mg/w	Continuous pleuritic chest pain and febril abdominal attacks Bilateral ankle and left wrist arthritis ESR: 120, CRP: 12.6 Fibrinogen: 657	5mIU	12	Good clinical condition ESR: 28, CRP: 2.67 Fibrinogen: 430	Good clinical condition ESR: 16, CRP: 0.8 Fibrinogen: 364

Abbreviations: eod: every other day; AS: ankylosing spondilitis; JCA: juvenile rheumatoid arthritis; HSP: Henoch-Schonlein purpura; PAN: polyarteritis nodosa; IFN: Interferon-alpha; Attack dur.: attack duration; ESR: erythrocyte sedimentation rate (mm/h); CRP: C-reactive protein (mg/dl); Fibr.: fibrinogen (mg/dl); 1: Before interferon treatment; 2: After interferon treatment; DC: prednisolone; MTX: methotroxate; SLZ: sulphasalazine; OH-C: hyroxychloroquine; MP: methyl-prednisolone, CYP: cyclophosphamide.

Table II. Clinical and laboratory findings before and after IFN-α treatment in colchicine-resistant FMF patients (mean ± SD).

	Pre-treatment	Post-treatment (6th month)	Post-treatment (1st year)	P*
Mean attack frequency/year	34.7 ± 18.3	0.8 ± 1.5	-	< 0.01
Mean duration of attacks/days	2.9 ± 1.5	0.6 ± 0.8	-	< 0.01
CRP(g/dl)	11.2 ± 8.4	2.6 ± 1.9	1.4 ± 0.4	< 0.01
Fibrinogen (mg/dl)	726.7 ± 192	499.6 ± 139	410 ± 94.3	< 0.01
ESR (mm/h)	86.6 ± 25.8	44 ± 33.4	20.6 ± 15.8	< 0.01
24-hour proteinuria (mg/day)	1391.8 ± 48.1	-	726.7 ± 1249.3	< 0.05

*Wilcoxon test, $p < 0.05$ was considered significant.

(PAN) (n = 1). The mean disease duration was 146.5 ±58 months (mean ± SD) and the mean duration of medical care provided was 69.5 ± 48.1 months. Before receiving any medical therapy the patients had been suffering 34.7 ± 18.3 attacks/year and the duration of the attacks was 3.2 ± 1.5 days. After the administration of colchicine treatment, the number of attacks fell to 24 ± 9.1 per year, and their duration decreased to 2.9 ± 1.5/day ($p > 0.05$ for each). One patient remained completely unresponsive and suffered continual attacks. Her acute phase response in terms of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen values remained elevated despite the colchicine therapy. Patients with vasculitic complications (n = 6) had proteinuria in 24-hour urine and erythrocyte and granular casts in the urine analysis; they were treated with pulse cyclophosphamide and methylprednisolone therapy. The others, with the complications such as sacroiliitis and peripheral arthritis, were treated with methotrexate (7.5 – 15 mg/week, oral) and sulphasalazine (1.5 – 2 gr/day, oral) combination therapy. Despite intense immunosuppressive therapy, all 8 patients were experiencing polyserositis attacks. The patients' characteristics are given in Table I.

All 8 patients were diagnosed as being completely or incompletely resistant to regular colchicine therapy. IFN-α was given by self-administered dose of 3-5 million IU subcutaneous 3 times a week. All were informed regarding the possible benefits and side effects of the IFN-α therapy. Colchicine and immunosuppressive therapies including cyclophosphamide, methylprednisolone or methotrexate, and sulphasalazine were also continued in all patients while IFN-α was started. During the therapy all patients received IFN-α and none of them were excluded from the study.

Patients were regularly seen at 3-month intervals. The white blood cell count (WBC), ESR, CRP, fibrinogen and liver enzymes were measured at every visit. The data from these visits were analysed for 6-month periods. All were told to note the frequency and type of attacks. Seven patients completed the first year, while one patient reached the 8th month of the therapy.

Statistical analysis

All data were collected and analyzed by using SPSS 11.0 at the end of the first six months and the first year. The pre- and post-treatment laboratory values for the interferon group were compared by the paired sample t-test, and clinical and the laboratory values pre- and post-treatment were compared using the Wilcoxon and paired t-tests. A p value < 0.05 was considered statistically significant.

Results

All patients received IFN-α regularly. No patients dropped out due to toxicity or non-compliance. All patients experienced flu-like symptoms after injection of the drug. 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. The patients were encouraged to take paracetamol 500 mg q 4 h. All of them used it several times as needed. Slight elevations of liver enzymes (increased up the 2-fold of the normal range) were observed in 5 patients. Hepatitis markers determined in these patients and the results were negative. The intervals of interferon injections were prolonged or the injections were temporarily suspended till the enzymes recovered. No serious side effects such as opportunistic infections were observed. The mean follow-up time for the patients on IFN therapy was 16.6 ± 5.9 months (mean ± SD) (min. – max. 8-24 months). The mean attack frequency before IFN-α treatment was 24 ± 9.1 attacks/year. The mean duration of the attacks was 2.9 ± 1.5 day. After six months of IFN treatment, the mean attack frequency was 0.8 ± 1.5 attack/year, and the mean duration of the attacks decreased to 0.6 ± 0.8 days ($p < 0.05$, for each). One patient suffered abdominal attacks twice shortly after IFN-α therapy. Another developed arthritis bilaterally in the knees and ankles while he was on the therapy. At the end of the first year these findings also disappeared. The changes in CRP, ESR and fibrinogen levels at the end of the sixth months and the first year are given in Table II. The changes in the 24-hour daily proteinuria levels were not significant at the first 6 months of therapy, but after the given schedule was followed the proteinuria levels significantly regressed from 1391.8 ± 48.1 mg/day to 726.7 ± 1249.3 mg/day at the end of the first year ($p < 0.05$) (Table II).

Discussion

In this prospective open study we demonstrated that regular IFN administration was efficacious to control the symptoms and signs in colchicine-resistant FMF patients whose condition was complicated by chronic arthritis and/or vasculitides.

Colchicine has long been known to control the attacks in patients with FMF (11). Although the exact molecular events remain to be demonstrated, this drug is believed to suppress various neutrophil functions by inhibiting leukocyte migration and adhesion, and interfering with inflammatory signal-

ing (1, 2, 6, 7). The mechanisms behind the colchicine resistance in a subgroup of FMF patients remain unclear. Moreover, there is no alternative to colchine for the treatment of these cases. The cloning of the MEFV gene has greatly enhanced our understanding of the pathogenesis of FMF and provided new opportunities for the treatment of resistant cases. The MEFV gene is expressed in mature neutrophils, as well as in early leukocyte development. This gene is believed to function in controlling granulocyte-mediated inflammation. Recently it has been demonstrated that MEFV gene expression is induced by inflammatory cytokines including interferon gamma, tumour necrosis factor and lipopolysaccharide, and that it is inhibited by anti-inflammatory cytokines including interleukin (IL) 4, IL-10 and transforming growth factor beta. Hence, the MEFV gene has been suggested to mediate a Th1-responsive negative-feedback loop during pro-inflammatory activation of myeloid cells, and defects in this inhibitor activity could result in FMF (12, 13). The same authors also showed that the combination of colchicine and IFN-α induced MEFV gene expression in granulocytes. However, this induction was observed only with colchicine in conjunction with IFN stimulation. Therefore, IFN plus colchicine may cause overexpression of the functionally deficient MEFV gene product and help to control the symptoms in FMF patients who are resistant to colchicine alone. On the other hand, IFN has also been shown to reversibly block the release of neutrophils from the bone marrow. Therefore, IFN-α may add a synergistic effect to colchicine in suppressing the functions of polymorphonuclear leukocytes (8, 9, 14-16).

Clinical support for the beneficial effects of IFN in the treatment of FMF patients came from a previous study performed by Tunca and co-workers (9). They demonstrated that the self-administration of IFN at the earliest signs of FMF attack could halt the episode. However, later they added that in some cases control of the attacks could be difficult if interferon was administered before the attack was supposed to occur. Our results bring those observations one step forward, showing that the regular administration of IFN could prevent the occurrence of new attacks. Furthermore, the chronic arthritis or vasculitic syndromes associated with FMF in our patients also a showed good response to regular IFN treatment.

FMF patients with severe complications could be suggested to have an exacerbated inflammation. However, while FMF patients who had only abdominal serositis attacks could easily respond to colchicine treatment, rare patients with complications such as vasculitides or arthritis may not respond and the serositis attacks could continue. Therapeutic agents such as methotroxate, hydroxychloroquine, sulphasalasine for arthritis and cyclophosphamide for vasculitides also could be insufficient to prevent the serositis attacks. In these patients interferon alpha could be suggested for serositis attacks.

In conclusion IFN could be a good adjunct to prevent the attacks in FMF patients who are resistant to colchicine. Moreover IFN could also be efficacious in controlling the arthritic and/or vasculitic complications of FMF. Randomized controlled studies with a larger number of patients are needed to draw more definitive conclusions.

References

1. DRENTH J, VAN DER MEER J: Hereditary periodic fever. *N Engl J Med* 2001; 345: 1748-57.
2. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-63.
3. SHIOZAWA S, MORIMOTO I, TANAKA Y, SHIOZAWAK: A preliminary study on the interferon-alpha treatment for xerostomia of Sjögren's syndrome. *Br J Rheumatol* 1993, 32: 52-4.
4. KNOBLER RL, PANITCH HS, BRAHENY SL *et al.*: Systemic alpha-interferon therapy of multiple sclerosis. *Neurology* 1984; 34: 1273-9.
5. GEORGIOU S, MONASTIRLI A, PASMATZI E, GARTAGANIS S, GOERZ G, TSAMBAOS D: Efficacy and safety of systemic recombinant interferon-alpha in Behçet's disease. *J Intern Med* 1998; 243: 367-72.
6. MATZNER Y, AYESH SK, HOCHNER-CELNIKER D *et al.*: Proposed mechanism of the inflammatory attacks in familial Mediterranean fever. *Arch Intern Med* 1990; 150: 1289-91.
7. SCHATTNER A, HAHAN T: A proposed mechanism of the inflammatory attacks in familial Mediterranean fever. *Arch Intern Med* 1992; 152: 421-6.
8. CENTOLA M, WOOD G, FRUCHT DM *et al.*: The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to inflammatory mediators. *Blood* 2000; 95: 3223-31.
9. TUNCA M, TANKURT E, AKPINAR AH, AKAR S, HIZLI N, GÖNEN O: The efficacy of interferon alpha on colchicine-resistant familial Mediterranean fever attacks: a pilot study. *Br J Rheumatol* 1997; 36: 1005-8.
10. LIVNEH A, LANGEVITZ P, ZEMER D *et al.*: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1998; 41: 1516-7.
11. DINARELLO CA, WOLF SM, GOLDFINGER SE, DALE DC: Colchicine therapy for familial Mediterranean fever. A double-blind trial. *N Engl J Med* 1974; 291: 934-7.
12. CLARKE S, GORDON S: Myeloid-specific gene expression. *J Leukoc Biol* 1998; 63: 153-68.
13. GASPERINI S, MARCHI M, CALZETTI F *et al.*: Gene expression and production of the monokine induced by IFN-gamma (MIG), IFN-inducible T cell alpha chemoattractant (I-TAC), and IFN-gamma-inducible protein-10 (IP-10) chemokines by human neutrophils. *J Immunol* 1999; 162: 4928-37.
14. OZEN S, UCKAN D, BASKIN E *et al.*: Increased neutrophil appopitosis during attacks of familial Mediterranean fever. *Clin Exp Rheumatol* 2001; 19: 68-71.
15. ABEDAT S, URIELI-SHOVAL S, SHAPIRA E, CALKO S, BEN-CHETRIT E, MATZNER Y: Effects of colchicine and cytokines on MEFV expression and C5a inhibitor activity in human primary fibroblast cultures. *Isr Med Assoc* 2002; 4: 7-12.
16. TUNCA M, BEN-CHETRIT E: Familial Mediterranean fever in 2003. Pathogenesis and management. *Clin Exp Rheumatol* 2003; 21 (Suppl. 30): 49-52.