Intravenous Colchicine for Treatment of Patients with Familial Mediterranean Fever Unresponsive to Oral Colchicine

MERAV LIDAR, RON KEDEM, PNINA LANGEVITZ, MORDECHAI PRAS, and AVI LIVNEH

ABSTRACT. Objective. To evaluate the efficacy and safety of weekly intravenous (IV) colchicine, in addition to oral colchicine therapy, in a subset of patients with familial Mediterranean fever (FMF) unresponsive to oral colchicine prophylaxis.

> Methods. Thirteen patients with frequent FMF attacks, despite oral doses of 2–3 mg/day colchicine, were treated with weekly IV injections of 1 mg colchicine for 12 weeks in an open-label pilot study. Patients were evaluated periodically for the number and severity of their attacks, use of analgesics, and erythrocyte sedimentation rate (ESR).

> Results. A 50% reduction in attack frequency and attack severity in at least one site was achieved by 10 and 6 of the 13 study patients, respectively (p < 0.001 and p < 0.01). Mean number of abdominal attacks declined significantly from 4.2 ± 3.0 per patient at baseline to 1.9 ± 2.6 attacks at the end of the third month of the study (p = 0.0002). The mean severity of abdominal attacks declined from a baseline of 6.1 ± 0.95 to 3.9 ± 2.8 after 3 months (p = 0.02). Comparable significant change was observed in chest attacks, ESR, and number of analgesic tablets used. Joint attacks were unrelieved during the study period. The treatment was safe and well tolerated, without side effects.

> Conclusion. Treatment with weekly IV colchicine injections in addition to oral colchicine therapy is effective and safe in patients with FMF refractory to oral colchicine. (J Rheumatol 2003;30:2620-3)

Key Indexing Terms: COLCHICINE

FAMILIAL MEDITERRANEAN FEVER COLCHICINE TREATMENT FAILURE

Familial Mediterranean fever (FMF) is an autosomal recessive disease, caused by mutations in the FMF gene (MEFV) and characterized by recurrent episodes of fever and sterile peritonitis, arthritis, and/or pleuritis¹⁻³. The disease prevails in the Mediterranean area, affecting most commonly North African and Iraqi Jews, Turks, Armenians, and Arabs³.

Colchicine in a dose of 1-2 mg is the mainstay of treatment of FMF, as it reduces attack frequency and duration in most patients⁴. Moreover, it has been proven effective in preventing, arresting, and reversing renal amyloidosis, which is the most dreaded manifestation of FMF^{5,6}.

Five to 10% of patients with FMF are colchicine nonresponders. With an estimated population of 100,000 FMF patients worldwide⁷, and despite colchicine daily doses of 2 mg or more, about 10,000 patients with FMF continue to experience debilitating attacks for which no alternative effective treatment is currently available^{8,9}.

From the Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, and Sackler School of Medicine, Tel-Aviv University, Tel-

M. Lidar, MD; R. Kedem, PhD; P. Langevitz, MD, Clinical Professor of Medicine; M. Pras, MD, Professor of Medicine; A. Livneh, MD, Associate Professor of Medicine.

Address reprint requests to Prof. A Livneh, Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer 52621, Israel. E-mail: alivneh@post.tau.ac.il

Submitted January 23, 2003; revision accepted May 28, 2003.

As the bioavailability of colchicine after oral intake is only 45% in healthy volunteers10, and lower colchicine concentration in nonresponder mononuclear cells (as compared to that of responders) has been observed¹¹, intravenous (IV) administration is a rational option for achievement of a better clinical response.

We report an encouraging pilot study of IV colchicine for the treatment of FMF patients with frequent attacks despite compliance with a full oral colchicine regimen.

MATERIALS AND METHODS

Patient selection. Thirteen patients participated in the study. All fulfilled the clinical criteria for FMF¹². They were selected from an original cohort of 59 patients unresponsive to colchicine therapy¹¹. Inclusion criteria required an attack frequency of at least twice a month at any typical site while compliant with an oral dose ≥ 2.0 (2-3) mg/day colchicine. Exclusion criteria were use of narcotics, chronic renal failure, liver disease, and intolerance to oral dose of 2 mg/day, usually manifested by diarrhea.

Study design. The study continued for 12 weeks. Clinical assessments were made at baseline and weekly thereafter, and included recording the number of the attacks at each site and their intensity, based on a 10 cm visual analog scale (VAS), use of analgesics and nonsteroidal antiinflammatory drugs (NSAID), and adverse events. Laboratory evaluation was made at 4-week intervals, and included determination of complete blood count, kidney function tests, serum electrolytes, albumin, globulin, uric acid, liver enzymes, bilirubin levels, urinalysis, and erythrocyte sedimentation rate

Colchicine (Bedford Laboratories, Bedford, OH, USA) was given intravenously at a dose of 1 mg, once a week. Caution was exercised to avoid extravasation of colchicine, which may cause phlebitis, cellulitis, or skin

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

necrosis. Oral colchicine treatment was continued throughout the study at the dose used at least 1 month before study entry. Analgesics and NSAID use was allowed at a dose no higher than at baseline.

Statistical analysis. Differences between treatment and prior to treatment categorical variables were analyzed using chi-square test or Fisher's exact test, according to the size of the cells examined. Student's t test was used for comparison of continuous variables between the 2 study groups. All tests of significance were 2-tailed; p-values < 0.05 were considered statistically significant.

RESULTS

Table 1 shows the baseline demographics and disease characteristics of the study patients. Their mean age was 35.8 ± 8.55 years. Mean age at FMF onset was 14.3 ± 7.94 and at diagnosis 18.5 ± 8.55 years. Most (8/13, 61.5%) patients were of North-African extraction, and had a positive family history for FMF. All patients received 12 weekly colchicine injections. Oral colchicine dose remained stable throughout the study period, at a mean dose of 2.3 ± 0.38 mg/day.

Efficacy. At the onset of the study, abdominal attacks were experienced by all patients, chest attacks by 11, and joint attacks by 13. After 3 months, 10 patients enjoyed $\geq 50\%$ improvement in attack frequency in at least one site, and in 6 patients, the intensity of the attacks dropped by $\geq 50\%$ (p < 0.001 and 0.01, respectively). Figure 1 illustrates the efficacy of the treatment for each site.

On evaluation of the 13 patients as a group, the mean number of abdominal attacks per patient declined significantly within the first 4 weeks of the study $(4.2 \pm 3.0 \text{ vs } 2.5 \pm 2.7 \text{ at baseline}$ and 4 weeks, respectively; p = 0.0006). Abdominal attacks continued to decline in number during the ensuing months to 2.1 ± 3.1 and 1.9 ± 2.6 at the end of Weeks 8 and 12, respectively (p = 0.0007 and p = 0.0002 vs baseline). Despite an insignificant rise in abdominal attack severity during the first 4 weeks of the study (from a base-

line mean patient score of 6.1 ± 0.95 to 6.7 ± 2.6 at Week 4; p = 0.42), the subsequent sharp decline to 4.3 ± 2.7 at Week 8 and 3.9 ± 2.8 at Week 12 was significant (p = 0.04 and p = 0.02, respectively). The composite outcome of abdominal attacks (the product of mean monthly frequency multiplied by mean severity) declined continuously from 25.6 at baseline to 16.75, 9.0, and 7.4 at 4, 8, and 12 weeks, respectively (p = 0.03, p = 0.009, and p = 0.008, respectively) (Figure 2A). A comparable course was observed in chest attacks (Figure 2B). In contrast, joint attacks were unrelieved during the study period (Figure 2C).

While blood count and chemistry were unaffected by the study medication (data not shown), a significant reduction in the mean ESR was observed, from a baseline of 31.1 ± 10.2 to 28.7 ± 11.9 , 20.15 ± 9.5 , and 18.15 ± 4.81 mm/h at Weeks 4, 8, and 12, respectively (p < 0.05). Similarly, the number of analgesic and NSAID pills used dropped steadily and significantly during the study period from a baseline of 24.9 \pm 20.9 tablets per patient per month to 16.6 ± 21.6 , 12.5 ± 21.2 , and 11.4 ± 21.4 at 4, 8, and 12 weeks, respectively (p < 0.05).

Adverse effects. Two patients (15.4%) experienced an episode of chemical phlebitis as a result of a colchicine injection during the study (0.011 from the injections given). However, with conservative care the local signs and symptoms resolved within 2 weeks.

DISCUSSION

Our results suggest a beneficial effect for weekly IV colchicine injections, in addition to oral colchicine therapy, in patients with FMF with frequent attacks while being compliant with a full-dose oral regimen. About 77% of the patients experienced > 50% reduction in abdominal attack frequency. Pleural attacks were relieved in half of the

Table 1. Baseline demographics and disease characteristics of the study patients.

Patient	Age/Sex	Ethnic Origin	MEFV Genotype	Age at Disease Onset, yrs	Family History of FMF	Abdominal/Chest/Joint Attacks per Month in 3 Months Prior to Study Entry, mean	ESR, mm/h	Current Colchicine Dose, mg/day
1	29F	Druze-Druze	V726A/E148Q	10	Yes	3/None/None	45	2.5
2	34F	Algeria-Algeria	M694V/M694V	0	Yes	5/4/1	40	2
3	40F	Algeria-Algeria	M694V/M694V	1	No	2/1/1	20	2
4	48F	Iraq-Iraq	V726A/E148Q	37	Yes	12/2/None	11	2
5	20F	Syria-Turkey	M694V/M694V	0.5	Yes	1/1/1	38	2
6	35F	Morocco-Morocco	M694V/?*	27	Yes	6/3/5	28	2
7	61M	Iraq-Iraq	V726A/M694V	44	Yes	4/None/1	35	2
8	27F	Arab-Arab	V726A/M680I	19	Yes	1/1/1	30	2
9	35M	Libya-Libya	M694V/M694V	10	No	2/2/1	40	3
10	29F	Libya-Libya	?/?	10	Yes	3/3/2	25	2.5
11	40M	Morocco-Morocco	M694V/?	5	Yes	3/4/2	40	3
12	30F	Morocco-Morocco	M694V/?	10	Yes	6/4/1	18	2.5
13	27F	Libya-Libya	?/?	0	Yes	7/7/2	35	2.5

^{* ?:} MEFV mutation is unknown (not one of the 4 common mutations studied).

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

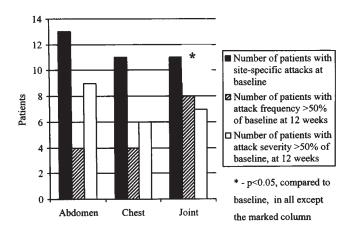


Figure 1. Reduction in site-specific attack frequency and severity after 12 weeks.

patients and joint attacks in a third. Improvement of joint attacks did not attain statistical significance in either analysis. This is not surprising given that arthritis is a manifestation, the least amenable to oral colchicine, that is also associated with more severe disease and an increased risk for amyloidosis.

These results were achieved without serious adverse

events. Two patients (15.4%) experienced an episode of chemical phlebitis, but the risk per given injection was only 1%. One patient, who continued to receive weekly IV colchicine after termination of the study period, developed a clinical and laboratory picture of myositis a few months later, while receiving a macrolide for the eradication of *Helicobacter pylori*. This adverse event serves as a reminder of the potential toxicity of colchicine, and the extreme caution required during its IV administration. Although our results support recent reports regarding the minor toxicity of properly administered IV colchicine^{13,14}, one should bear in mind that hundreds of patients may be required to elucidate even relatively common (1–2%) toxic adverse effects.

It is unclear how a weekly dose of as low an amount as 1 mg colchicine turns nonresponders, some of whom receive 20 mg of colchicine weekly, to responders. However, in a recent study, we found that in lymphocytes from nonresponders, colchicine concentration was very low (about 50% of the concentration in lymphocytes from responders)¹¹. One may therefore speculate that the bolus of colchicine created by IV administration overcomes the absorption defect in lymphocytes, at least partially, and increases colchicine concentration to the level required to produce its effect.

Interferon- α , recently found to be of possible merit in FMF prophylaxis¹⁵, is an expensive medication, potentially

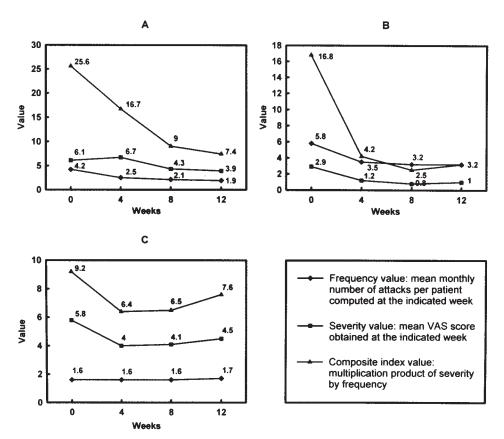


Figure 2. Treatment outcome of A: abdominal, B: chest, and C: joint attacks. A and B: p < 0.05 compared to baseline for all 12th week values. C: p > 0.05 compared to baseline for all 12th week values.

bearing numerous adverse effects and toxicity, and its longterm favorable effect in nonresponders to colchicine has yet to be shown. In contrast, oral colchicine is the only drug with a proven short term and longterm efficacy in FMF. Therefore, the beneficial effect achieved in this study favors colchicine use over interferon- α , and suggests that IV colchicine may be given judiciously to the colchicine nonresponder patient population.

REFERENCES

Lidar, et al: IV colchicine in FMF

- The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause FMF. Cell 1997;90:797-807.
- The French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997;17:25-31.
- Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967;43:227-53.
- Zemer D, Revach M, Pras M, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. N Engl J Med 1974;291:932-4.
- Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. New Engl J Med 1986;314:1001-5.
- Livneh A, Zemer D, Langevitz P, Laor A, Sohar E, Pras M. Colchicine treatment of AA amyloidosis of familial Mediterranean fever. An analysis of factors affecting outcome. Arthritis Rheum 1994;37:1804-11.

- 7. Pras M. FMF: past, present and future [abstract]. Clin Exp Rheumatol 2002;20 Suppl 26:66.
- Livneh A, Langevitz P, Zemer D, et al. The changing face of familial Mediterranean fever. Semin Arthritis Rheum 1996:26:612-27.
- Livneh A, Langevitz P. Diagnostic and treatment concerns in familial Mediterranean fever. Baillieres Best Pract Res Clin Rheumatol 2000;14:477-98.
- Rochdi M, Sabouraud A, Girre C, Venet R, Scherrmann JM. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. Eur J Clin Pharmacol 1994;46:351-4.
- Lidar M, Scherrmann JM, Chetrit A, Niel E, Gershoni R, Livneh A. Clinical, genetic, pharmacokinetic and socioeconomical characterization of colchicine nonresponsiveness in FMF [abstract]. Clin Exp Rheumatol 2002;20 Suppl 26:88.
- Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40:1884-90.
- Evans TI, Wheeler MT, Small RE, Breitbach SA, Sanders KM, Roberts WN. A comprehensive investigation of inpatient intravenous colchicine use shows more education is needed. J Rheumatol 1996;23:143-8.
- Maldonado MA, Salzman A, Varga J. Intravenous colchicine use in crystal induced arthropathies: A retrospective analysis of hospitalized patients. Clin Exp Rheumatol 1997;15:487-92.
- Tunca M, Tankurt E, Akbaylar Akpinar H, et al. The efficacy of interferon alpha on colchicines-resistant familial Mediterranean fever attacks: A pilot study. Br J Rheumatol 1997;36:1005-8.

Personal, non-commercial use only. The Journal of Rheumatology Copyright © 2003. All rights reserved.

2623