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
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 pleuritis. The disease prevails in the Mediterranean area, affecting most commonly North African and Iraqi Jews, Turks, Armenians, and Arabs.

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

Five to 10% of patients with FMF are colchicine nonresponders. With an estimated population of 100,000 FMF patients worldwide, 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.

As the bioavailability of colchicine after oral intake is only 45% in healthy volunteers, and lower colchicine concentration in nonresponder mononuclear cells (as compared to that of responders) has been observed, 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 FMF. They were selected from an original cohort of 59 patients unresponsive to colchicine therapy. 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 (ESR).

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 extravasation of colchicine, which may cause phlebitis, cellulitis, or skin

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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 ≥ 50% improvement in attack frequency in at least one site, and in 6 patients, the intensity of the attacks dropped by ≥ 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 ± 3.0 vs 2.5 ± 2.7 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 baseline 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).

**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

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<th>Age at Disease Onset, yrs</th>
<th>Family History of FMF</th>
<th>Abdominal/Chest/Joint Attacks per Month in 3 Months Prior to Study Entry, mean</th>
<th>ESR, mm/h</th>
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* ?: MEFV mutation is unknown (not one of the 4 common mutations studied).
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, 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). 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 prophylaxis, is an expensive medication, potentially
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
1. 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.