

**Intravenous colchicine treatment for six months: adjunctive therapy in familial Mediterranean fever unresponsive to oral colchicine**

Sirs,

We wish to present our experience as to the efficacy and safety of weekly intravenous (IV) colchicine, in addition to oral therapy, for six months, in colchicine-resistant patients suffering from familial Mediterranean fever (FMF).

In a cohort of 295 FMF patients at our institution's FMF clinic, we recently evaluated five patients who had frequent FMF attacks despite maximal oral colchicine therapy (2 mg to 3 mg/day) and were treated with supplemental weekly IV infusions of 1 mg colchicine for 6 months. All the patients fulfilled diagnostic criteria for FMF as previously described (1). Inclusion criteria required an attack frequency of at least once a month at any typical site while compliant with an oral dose  $\geq 2.0$  mg/day colchicine. Exclusion criteria were chronic renal failure and liver disease.

Clinical assessments were made over a 6 month baseline and weekly thereafter for another 6 months and included the number of abdominal and pleuritic febrile attacks, joint flares and erysipelas-like skin lesions. Laboratory evaluations, including determination of complete blood count, kidney function tests, serum electrolytes, CPK, albumin, globulin, uric acid, liver enzymes, bilirubin levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and urinalysis were checked monthly.

Table I shows the baseline demographics and disease characteristics of the study patients. Their mean age was  $28.8 \pm 7.8$  years, range 20-39. Two male patients were Sephardic Jews of North African origin (Morocco); two other males were Israeli Arabs; and the female patient was an Israeli Druze. All had a positive family history for FMF.

A 50% reduction in frequency of febrile abdominal and chest attacks was achieved in 6 months. Statistically significant (paired *t*-test) reductions were observed in WBC, ESR, and CRP ( $p < 0.05$ ). Joint attacks and erysipelas like skin lesions were unrelieved during the study period ( $p = 0.28$ ). The treatment was safe and well tolerated, without side effects.

**Table I.** Baseline demographics and disease characteristics of the study patients.

Patients age/sex	FMF patients before / under colchicine IV therapy, 6 months.					
	MEFV mutations	Abdominal/thoracic febrile attacks	Joints/erysipelas-like attacks	WBC /cc	ESR mm /hour	CRP mg/L
39/F	V726A E148Q	7/0	2/2	12,700/8810	35/14	149/18
28/M	M694V M694V	12/8	6/5	16,200/7120	60/30	104.3/22.5
23/M	M694V M694V	6/1	0/0	17,900/7520	80/25	45/25.4
34/M	M680I M680I	11/7	3/3	13,000/8500	65/44	25/0.3
20/M	not done	5/0	5/0	17,000/9460	55/20	200/3.7
Paired <i>t</i> -test difference		$p < 0.0008$	$p = 0.28$	$p < 0.005$	$p < 0.007$	$p < 0.053$

To prevent chemical phlebitis or avoid extravasation, which may cause well known skin necrosis, caution was exercised and the colchicine, diluted in 500 ml normal saline, was administered over a two-hour period.

After more than thirty years, colchicine remains the cornerstone of FMF therapy, with very few options for treating colchicine-resistant patients. The safety and efficacy of a short course of IV colchicine therapy in FMF patients unresponsive to oral colchicine had been previously reported (2). The use of colchicine is limited, however, by its toxicity, overdose being associated with a high mortality rate (3). In March 2007, the death of two persons receiving IV colchicine for back pain, in an alternative medicine clinic in Oregon, was reported (4).

The clinical effect of colchicine is principally mediated by its action on neutrophils, it being unclear how a weekly IV dose as low as 1 mg turns non-responders to responders. One hypothesis is that the bolus of colchicine created by IV administration overcomes intestinal CYP3A4 and P-glycoprotein regulation, increasing colchicine concentration in tissue, mainly in neutrophils, to a therapeutically effective level.

Therapeutic guidelines for the safe use of IV colchicine in addition to oral colchicine must be applied strictly: the IV dose being no more than half the daily oral dose, administered no more than once weekly. Absolute contraindications to intravenous colchicine therapy should include combined renal and hepatic disease, creatinine clearance below 10 cc/min and extrahepatic biliary obstruction. It may be best left for

treatment of young adult patients without comorbid conditions and then in a medical center with experience in colchicine infusions. Local chemical phlebitis may be prevented by a protocol of slow infusion of highly diluted colchicine.

M. ROZENBAUM  
N. BOULMAN  
J. FELD  
N. AVSHOVICH  
S. PETROVICH  
M. ELIAS  
G. SLOBODIN  
I. ROSNER

*Department of Rheumatology, Bnai Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel.*

*Address correspondence and reprint requests to: Itzhak Rosner MD, Department of Rheumatology, Bnai Zion Medical Center, 47 Golomb St, POB 4940, Haifa 31048, Israel. E-mail: rosneri@tx.technion.ac.il*

*Competing interests: none declared.*

**References**

- LIVNEH A, LANGEVITZ P, ZEMER D *et al.*: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.
- LIDAR M, KEDEM R, LANGEVITZ P, PRAS M, LIVNEH A: Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. *J Rheumatol* 2003; 30:2620-3.
- BONNEL RA, VILLALBA ML, KARWOSKY CB, BEITZ J: Deaths associated with inappropriate intravenous colchicine administration. *J Emerg Med* 2002; 22: 385-7.
- CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC): Deaths from intravenous colchicine resulting from a compounding pharmacy error Oregon and Washington, 2007. *MMWR* 2007; 40: 1050-2.