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Efficacy and safety of long-term treatment with intravenous colchicine for familial Mediterranean fever (FMF) refractory to oral colchicine

Chagai Grossman[1,2,4] · Itzhak Farberov[1] · Olga Feld[1] · Avi Livneh[1,2,3,4] · Ilan Ben-Zvi[1,2,3,4]

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Abstract

Colchicine is the mainstay of treatment for familial Mediterranean fever (FMF). Intravenous (IV) colchicine, administered over several months, has been shown to be effective for FMF patients unresponsive to oral colchicine. The objective of this study was to evaluate the efficacy and safety of long-term IV colchicine treatment in oral colchicine-resistant FMF. We analyzed data of 15 patients with frequent FMF attacks, despite a maximal tolerated dose of oral colchicine (2–3 mg/day), who were treated with weekly IV injections of 1 mg of colchicine for at least 12 months. Treatment efficacy was determined by changes in frequency, duration and severity of FMF attacks. Safety was assessed according to adverse events. The mean duration of IV colchicine treatment was 5.16 ± 2.85 years. Decreases were observed from pre-treatment period in the monthly mean rates of abdominal attacks (from 5.6 ± 3.7 to 1.9 ± 3.3, $p = 0.0009$), joint attacks (from 6.5 ± 5.1 to 1.6 ± 1.6, $p = 0.01$) and overall attacks (from 22.3 ± 16.2 to 7.4 ± 5.7, $p = 0.002$) as well as in the mean duration (from 3.8 ± 1.5 to 2.4 ± 1.1 days per attack, $p = 0.008$) and severity of attacks (from 9.9 ± 0.3 to 5.7 ± 2.6, on a scale of 0–10, $p < 0.05$). The rate of adverse events was low, and they were mainly gastrointestinal. No severe or serious adverse events were recorded. Long-term treatment with IV colchicine in patients unresponsive to oral colchicine therapy is effective and safe.

Keywords FMF · Colchicine · Intravenous treatment · Adverse events · Oral colchicine-resistant FMF

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease with an autosomal recessive mode of inheritance. FMF is associated with mutations in the *MEFV* gene, located on the short arm of chromosome 16. The disease is most prevalent in individuals of Sephardi, Armenian, Turkish, and Arab descent [1, 2], and is characterized by sudden and irregular attacks of fever and serosal inflammation, as well as by the development of amyloidosis [3, 4].

Oral colchicine has been found to be very effective in reducing the frequency of attacks and preventing renal amyloidosis in FMF. Most patients require a dose of 1–2 mg of colchicine to control their attacks. Long-term oral colchicine therapy was established as quite safe, with only mild and infrequent side effects [5–8]. However, a subset of FMF patients is unresponsive to oral colchicine therapy [9]. Unresponsiveness has been defined as more than 6 classical FMF attacks in a year or 3 classical attacks in 3–4 months in patients fully compliant with their colchicine regimen [10].

The basis of colchicine non-responsiveness is not fully understood. Non-responders tended to have lower socioeconomic backgrounds, a lower level of education, and more severe disease. In addition, they had a significantly lower concentration of colchicine in mononuclear cells. Accordingly, it has been speculated that non-responders may be genetically predisposed to have a reduced mononuclear colchicine uptake or the inability to maintain a high mononuclear colchicine concentration [9]. The assumption that colchicine refractoriness may be due to poorer

Avi Livneh and Ilan Ben-Zvi contributed equally to this work.

✉ Ilan Ben-Zvi
Ilan.BenZvi@sheba.gov.il

1 Department of Internal Medicine F, The Chaim Sheba Medical Center, 52621 Tel-Hashomer, Israel

2 Rheumatology Unit, The Chaim Sheba Medical Center, 52621 Tel-Hashomer, Israel

3 Heller Institute of Medical Research, The Chaim Sheba Medical Center, 52621 Tel-Hashomer, Israel

4 Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

gastrointestinal absorption of the drug, in non-responders [11], or that the concentration of colchicine in polymorphonuclear cells in non-responders is low [12], is not compatible with the finding of similar plasma and polymorphonuclear colchicine concentrations in responders and non-responders [9]. Recent studies have demonstrated the efficacy of interleukin-1 (IL-1) blockers in ameliorating symptoms of colchicine refractory FMF. However, most data are still derived from uncontrolled trials [13–16], the benefit is limited to 60% of treated patients [17, 18], and safety concerns exist. In addition, the high cost of these agents constitutes a significant economic burden, and they are not available in certain countries. Therefore, an adjunctive treatment to oral colchicine in oral colchicine-resistant FMF patients is still needed.

One of the treatment strategies for colchicine unresponsive FMF is the administration of intravenous (IV) colchicine. This was reported to be effective and safe in 2 studies that assessed treatment periods of up to 6 months [19, 20]. In the present study, we aimed to investigate the long-term efficacy and safety of IV colchicine treatment in oral colchicine-resistant FMF.

Methods

Patients

Study inclusion criteria were: (1) Age $\geq$ 18 years. (2) Agreement with the clinical criteria for diagnosis of FMF [21]. (3) Compliance with the more stringent definition of colchicine resistance; namely, at least one attack per month in any site (including: abdomen, chest, joint or skin), despite treatment with oral colchicine at a dose of $\geq$ 2 mg/day as tolerated by the patient. (4) Treated with IV colchicine for at least 12 months.

This study comprised all the patients who were treated with IV colchicine in the FMF clinic of our medical center during the study period, January 2000–December 2015 and who met study inclusion criteria. None of the patients who met the inclusion criteria were excluded from the analysis. Genetic analysis for the detection of the 5 most common mutations (*M69V, M694I, V726A, E148Q, M680I*) was performed using PCR amplification and restriction enzyme digestion [21]. The study and its protocol were approved by the Sheba Medical Center institutional review board (2014, protocol number: RE8274-10, 2014). All patients included in the study received IV colchicine based on clinical decision, unrelated to the study. All, however, agreed to provide data concerning their experience with the treatment, by signing an informed consent.

Intravenous colchicine treatment

Colchicine 1 mg, pre-prepared in vials containing 2 ml solution, by pharmacy (pharmaceutical preparation, Superpharm Professional, Israel) under the authorization of the Israeli Ministry of Health, was diluted and administered in 100 ml saline, through an IV access (indwelling regular infusion catheter), after ensuring that the catheter sits well within the vein and no fluid extravasation occurs into tissues. The drug was infused during 10–20 min, on a weekly basis. IV colchicine was administrated in the rheumatology day-care center of the hospital under strict supervision. Comorbidities, additional drugs and periodic laboratory tests, particularly referring to liver and kidney function, were monitored frequently. All patients continued taking their oral colchicine dose, as well as all other medications they used prior to their inclusion in the IV colchicine treatment protocol. The treatment protocol, including possible adverse effects (particularly painful infusion site reactions) was explained to the patients, and they provided their consent to it. However, since colchicine is indicated for treatment of FMF in Israel, and consideration for treatment were purely clinical, patients were not required to provide a signed inform consent regarding the treatment itself.

Data collection

The study was retrospective, based both on patient recall and patient records. All patients included in the study completed a questionnaire regarding the efficacy and safety of treatment with IV colchicine. To ensure validity and understanding, completing the questionnaire was assisted by a physician. Patients were specifically questioned about the frequency, duration and severity of their FMF attacks, at each site, before and during treatment with IV colchicine. Patients were also asked about adverse events they experienced during the treatment. Additional data, including demographics, baseline disease manifestations and mutations in the *MEFV* gene, were derived from the computerized patient medical files.

Assessment of treatment efficacy

Treatment efficacy of IV colchicine was evaluated by the following clinical measures:

1. Overall monthly attacks. In the event of an overlap between attacks in different sites, each site was calculated as a separate attack.
2. Monthly attacks in each site, determined as above for each site.

3. Severity of attacks using visual analogue scale (VAS) (1–10), determined individually. The mean score was computed by dividing the sum of the scores by the number of patients.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS statistics) software version 21.0. Continuous variables were expressed as means ± standard deviations as well as medians and interquartile ranges. Categorical variables were expressed as frequencies (percentage). We used the Fisher exact test for comparison of categorical variables, and the Mann–Whitney *U* test for comparison of continuous variables. Means of continuous variables were compared. All tests were two-tailed. A p value < 0.05 was considered significant.

Results

Fifteen patients were included in the study. The mean age at which they received their first dose of IV colchicine was 44.2 ± 6.49 years. The mean age at onset of FMF symptoms was 13 ± 10.3 years, and the mean age at diagnosis was 22.3 ± 12.3 years. The mean oral colchicine dose was 2.13 ± 0.71 mg/day. The mean duration of IV colchicine treatment was 5.16 ± 2.85 (range 1.5–12) years (Table 1). At least 72 doses of IV colchicine were applied before response to treatment had been evaluated. Demographic and disease characteristics of study patients, including response to treatment and distribution of mutations in the *MEFV* gene are presented in Table 2. Eight (53%) of the patients were not carriers of any known mutation in the *MEFV* gene.

Efficacy of treatment

Table 3 presents assessments of the efficacy of IV colchicine during the treatment period. Improvement was seen in all the parameters examined, but was statistically significant only for the total number of attacks, abdominal and joint attacks (each separately), the duration of the attacks and their severity. The mean rate of abdominal attacks per patient per month decreased from 5.6 ± 3.7 before initiation of treatment to 1.7 ± 1.2 ($p = 0.009$). Similarly, mean rates of joint attacks per month were 6.5 ± 5.1 and 1.6 ± 1.6 ($p = 0.01$), pre-treatment and during treatment, respectively. Changes in mean rates of chest attacks, fever alone attacks and erysipelas-like erythema attacks, as well as in the mean number of sites with attacks, were not statistically significant. Overall,

Table 1 Demographic and clinical features of familial Mediterranean fever (FMF) patients treated with intravenous (IV) colchicine

Feature	
Age at study entry, years (mean ± SD), [median, IQR]	44.2 (± 6.5) [44, 39.5–48.5]
Male gender—no. (%)	5 (33)
Age at FMF first presentation, years (± SD), [median, IQR]	13.0 (± 10.3), [10, 4.75-17]
Age at FMF diagnosis and initiation of oral colchicine treatment, years (± SD), [median, IQR]	22.3 (± 12.38), [22, 15–28]
Duration of oral colchicine treatment, years (± SD), [median, IQR]	24.6 (± 12.1) [18, 15.5–28.5]
Age at initiation of IV colchicine treatment, years (± SD), [median, IQR]	37.3 (± 6.4) [40, 36.5–42]
Mean daily oral colchicine dose, mg (± SD), [median, IQR]	2.1 (± 0.7) [2, 1.5–2.5]
Proteinuria—no. (%)	5 (33)
Amyloidosis—no	0
Mean duration of IV colchicine treatment, years (± SD), [median, IQR]	5.2 (± 2.9) [5, 3–7]
Family history of FMF – no. (%)	12 (80)
Comorbidities	
Behcet Disease—no. (%)	4 (27)
Hypertension—no. (%)	3 (20)
Diabetes mellitus—no. (%)	2 (13)
Renal failure—no. (%)	1 (7)
Medications	
Corticosteroids—no. (%)	3 (20)
Azathioprine—no. (%)	2 (13)
Mycophenolate mofetil—no. (%)	1 (7)
Antihypertensive—no. (%)	3 (20)
Statins—no. (%)	1 (7)

FMF familial Mediterranean fever, *IV* intravenous, *SD* standard deviation, *IQR* interquartile range

Table 2 Individual characterization of colchicine response

Age (years)	Gender	MEVF mutations	Oral colchicine dose (mg)	Overall attacks per month prior to IV colchicine treatment	Overall attacks per month during IV colchicine treatment	Mean duration of attacks prior to IV colchicine treatment (days)	Mean duration of attacks during IV colchicine treatment (days)	Severity of attacks prior to IV colchicine treatment (VAS score)	Severity of attacks during IV colchicine treatment (VAS score)
49	F	0/0	2	41	4	3	1	9	3
35	M	M680I/V726A	2.5	15	8	4	3	10	7
54	F	M694V/M694V	1.5	52	6	2	1	10	1
34	M	V726A/0	1	15	7	3	3	10	6.5
53	F	0/0	2.5	10	1	4	2	10	5
44	M	M694V/E148Q	2.5	10	10	4	3	10	7
48	M	0/0	1.5	3	0	7	3	10	5
42	M	E148Q/V726A	1.5	16	12	4	3	10	3
53	M	0/0	2	18	16	4	3	10	3
39	F	0/0	3.5	4	2	7	4	10	4
40	F	0/0	3	26	12	3	1.5	10	1.5
48	F	M680I/0	1.5	56	4	3	3	10	3
38	F	0/0	3	15	11	3	3	10	3
41	F	M694V/M694V	1.5	30	18	2	2	10	2
45	F	0/0	2.5	32	0	4	0	10	0

VAS visual analogue score

Table 3 Efficacy of intravenous colchicine treatment

Parameter	Pre treatment	With treatment	*p* value *
Abdominal attack (per month) (mean ± SD), [median, IQR]	5.6 (± 3.7), [5, 3–8]	1.7 (± 1.2), [2, 1–2.5]	0.009
Joint attack (per month) (mean ± SD), [median, IQR]	6.5 (± 5.1), [5, 3.5–9]	1.6 (± 1.6), [1, 0–2.5]	0.01
Chest attack (per month) (mean ± SD), [median, IQR]	4.0 (± 3.6), [3, 1–4.5]	2.3 (± 3.8), [1, 0–3]	0.0536
Fever only attack (per month) (mean ± SD), [median, IQR]	4.7 (± 5.5), [3, 1–5]	1.3 (± 1.4), [1, 0–2.5]	0.07508
Erysipelas like erythema attack frequency (per month) (mean ± SD), [median, IQR]	1.9 (± 3.3), [0, 0–3.25]	0.5 (± 1.1), [0, 0–0]	0.3843
Overall attacks (per month) (mean ± SD), [median, IQR]	22.3 (± 16.2), [16, 12.5–28]	7.4 (± 5.7), [7, 3–11.5]	0.002
Mean attack duration (days) (mean ± SD), [median, IQR]	3.8 (± 1.5), [4, 3–4]	2.4 (± 1.1), [3, 1.75–3]	0.00804
Attack severity (VAS score 1–10) (mean ± SD), [median, IQR]	9.9 (± 0.3), [10, 10–10]	5.7 (± 2.6), [6.5, 5–7]	< 0.05
Mean number of sites involved in attacks over the course of the disease (mean ± SD), [median, IQR]	3.3 (± 0.8), [3, 3–4]	2.6 (± 1.2) [3, 2–4]	0.20408

SD standard deviation, *VAS* visual analogue score, *IQR* interquartile range

*p value refers to difference between means

the mean frequency of attacks decreased significantly, from 22.3 ± 16.2 per month to 7.4 ± 5.7 per month ($p = 0.002$), during treatment with IV colchicine. Significant improvement was also obtained by IV colchicine in the mean duration of attacks, with a reduction from 3.8 ± 1.5 to 2.4 ± 1.1 days per attack during treatment ($p = 0.00804$), and in the severity of the attacks, with a mean reduction of VAS score from 9.9 ± 0.3 to 5.7 ± 2.6 ($p < 0.05$). Five of 6 patients who discontinued treatment did so due to an unstable supply of

injectable colchicine. Only one patient discontinued the treatment due to inefficacy.

Adverse reactions

As expected, the adverse events spanned gastrointestinal, musculoskeletal, and allergic reactions (Table 4). Their rates were relatively low and mainly included gastrointestinal discomfort and myalgia. One patient developed urticaria following colchicine injection. Following desensitization to the drug, the patient continued treatment with no adverse events. No severe or serious adverse events were recorded.

Discussion

This study assessed the efficacy and safety of long-term treatment with IV colchicine in oral colchicine-resistant FMF. Treatment with IV colchicine showed significant reduction in the rate of abdominal attacks by 70%, and in joint attacks by 87%. Significant improvement was observed also in the duration and the severity of the attacks. The treatment was well tolerated. These results suggest that treatment with IV colchicine may retain its efficacy for a prolonged period and may benefit patients with colchicine refractory FMF. This study confirms 2 previous studies that demonstrated the efficacy of IV colchicine [19, 20]. The contribution of the current study is the longer duration of treatment.

Approximately 5–10% of FMF patients are unresponsive to oral colchicine at its maximal dose (2–3 mg/day) and another 5% are intolerant to the drug due to side effects [22]. These patients experience debilitating attacks, despite a maximal tolerable dose of colchicine. Adjunctive symptomatic treatment includes non-steroidal anti-inflammatory drugs, and for certain rare manifestations, corticosteroids are administered as well. The evolving experience with interleukin-1 (IL-1) blockers suggests an important role for these biological agents in ameliorating symptoms of colchicine refractory FMF. However, most data in this regard are still derived from uncontrolled trials [13–16], and the benefit is limited to 60% of treated patients [17, 18]. Moreover, safety concerns arise, particularly regarding infections, and their high cost constitutes a significant economic burden. Therefore, the consideration of treatment with IV colchicine as an adjunct to oral colchicine in oral colchicine resistant patients remains relevant.

In addition to the above, the pyrin inflammasome was recently revealed as a sensor of certain bacterial toxins; its activation is mediated indirectly by the Rho GTPases family member A, an inhibitor of the pyrin inflammasome assembly and function [23]. This RhoA pathway is specific to pyrin inflammasome. Therefore, colchicine, an activator of RhoA, specifically inhibits the pyrin inflammasome and the IL-1β production induced by it. Colchicine does not affect IL-1β from other sources [24]. Thus, IV colchicine has an advantage over Il-1 blockers by being more specific and better targeted at the biochemical error that leads to ill ILβ-1 production.

The mechanism of colchicine resistance is unclear. Lower than normal intestinal absorption of colchicine in non-responders was speculated to underlie colchicine unresponsiveness. However, both serum and leukocyte colchicine levels in patients who respond to colchicine and in those who fail to respond were found to be similar. The only particular feature in colchicine resistant patients was a lower colchicine concentration in their mononuclear cells [9]. Since responders and non-responders have similar *MEFV* genotype distributions, it was hypothesized that a genetic flaw unrelated to FMF determines colchicine failure. A search for such a flaw in the multiple drug resistance (MDR) system, responsible for the removal of drugs from cells, revealed that the rate of MDR1 3435 C to T polymorphism is higher in FMF that is unresponsive to oral colchicine. However, this finding was borderline and should have led to retention (higher concentration) and not disposal of colchicine.

The efficacy and safety of treatment with IV colchicine in patients unresponsive to oral colchicine was previously reported [19, 20]. Lidar et al. reported a beneficial effect of weekly IV colchicine treatment in 13 patients unresponsive to oral colchicine. The patients were treated for 12 weeks in an open-label study [19]. The treatment was safe and well tolerated. Rozenbaum et al. also demonstrated the favorable effect of IV colchicine in 5 patients unresponsive to oral colchicine over a period of 6 months [20]. Our study suggests that a much longer treatment duration, extending for a mean period of 5.16 ± 2.85 years, is feasible, with efficacy and safety comparable to that of short-term treatment. These results are encouraging, as they open another treatment route, complementary to biologics, for patients who fail oral colchicine.

Table 4 Adverse reactions following intravenous colchicine treatment

Adverse reaction	Number of patients (%)
Nausea	4 (27)
Vomiting	2 (13)
Diarrhea	3 (20)
Injection site reactions	3 (20)
Myalgia	4 (27)
Arthralgia	1 (7)
Allergic reaction	1 (7)
Any adverse events	11 (73)

The long-term safety of IV colchicine treatment was also explored in this study. Colchicine has narrow safety margins. Therefore, caution must be exercised when administrating IV colchicine [25–27]. Combined renal and hepatic disease, creatinine clearance below 10 cc/min and extrahepatic biliary obstruction are absolute contraindications to IV colchicine therapy [27]. In our study, IV colchicine was administrated in the rheumatology day-care center of the hospital under strict supervision. Comorbidities, additional drugs and periodic laboratory tests, particularly referring to liver and kidney function, were monitored frequently. There are no clear guidelines regarding the frequency of laboratory testing of patients treated with IV colchicine. Therefore, the employment of these tests should be based on clinical judgement. Based to the findings in the current study, appropriate administration of IV colchicine, according to indications, appears safe. No dropouts from the treatment occurred due to safety reasons. In light of the relatively long-term efficacy and safety of IV colchicine treatment demonstrated in our study, it would seem reasonable to continue this treatment for an extended period of time, given that there are no serious adverse events and the efficacy is maintained.

Since inappropriate and unapproved usage of injectable colchicine may pose health risks to patients, the drug was removed from the US market by the FDA. This action created a shortage of supply and led to a generation of compounded colchicine by pharmacies. Various circumstances often lead to the suspension of such production, and the maintenance of a steady treatment is often disrupted. Five of 6 patients who discontinued treatment did so due to an unstable supply of injectable colchicine. Only one patient discontinued the treatment due to inefficacy.

Contrary to our expectations for a higher presentation of the *M694V* mutation, surprisingly, only 20% of the patients carried the *M694V/M694V MEFV* genotype. Also, almost half had undetectable *MEFV* mutations. Contrasting with other genotypes, the *M694V/M694V* genotype has been shown to be associated with a more severe disease [28, 29], and higher rates of non-responders [30]. Also, absence of mutations is usually associated with a more benign phenotype [31]. Thus, our finding of a different genotype make-up is probably incidental. Another possibility is that some patients may carry rare mutations, not detected by assaying for only the 5 most common mutations in the FMF gene. It is also possible that some patients in our cohort may have another autoinflammatory disease, that might be elucidated using whole exome sequencing, which was not available at the time of the study. However, all the patients conformed with diagnostic criteria of FMF and none presented with manifestations specific for another autoinflammatory entity. *MEFV* mutation negative FMF is not an exceptional finding; it usually constitutes 20–40% of large cohorts of FMF patients [31]. Most importantly, all except 1 patient responded to IV colchicine.

This study has several limitations. First, the study is retrospective and based to a large extent on patients' recall. Being retrospective precludes engagement of a placebo control group. Another possible limitation is that in combined attacks (e.g. chest + abdomen + joints) we assessed the response to IV colchicine for each component of the attack separately, rather than assessing the effect of colchicine on the entire episode. This is due to the difficulty in determining whether the components are part of one attack or rather a sequence of separate attacks. An additional limitation is that the study population is relatively small. Nevertheless, to the best of our knowledge, this is the largest study on this subject and the first that assessed the long-term efficacy and safety of IV colchicine treatment.

In conclusion, we showed that among FMF patients unresponsive to oral colchicine treatment, IV colchicine administered for a relatively long period of time is highly effective in alleviating the symptoms of the disease, with no major adverse events.

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Compliance with ethical standards

Conflict of interest Chagai Grossman, Itzhak Farberov, Olga Feld, Avi Livneh and Ilan Ben-Zvi declare they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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