Original Article

Comparison of Different Pharmaceutical Preparations of Colchicine in Children with FMF: Is Colchicine Opocalcium a Good Alternative?

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Background: Colchicine is an anti-inflammatory agent used for preventing FMF attacks and amyloidosis. Remarkable numbers of patients are non-responsive or intolerant to domestic drug colchicum dispert.
Aim: This study aimed to compare the efficacy and side effects of colchicum dispert and colchicine opocalcium in children with FMF.
Study Design and Methods: Twenty-nine children with FMF, who used colchicum dispert (CD) at least six months initially, and another consecutive 6 months of colchicine opocalcium (CO) were included. Sex and gender equity in research (SAGER) was considered. Clinical features, visual analog scale (VAS) for pain scores, exercise induced leg pain (EILP), and FMF severity scores with laboratory parameters were evaluated for both treatment periods. Bristol stool chart and number of stools per 24 hours were recorded for comparing gastrointestinal side effects.
Results: Major indication was non-responsiveness in 18 patients (62 %), and intolerance in 11 patients (38 %). Usage of CO (significantly higher dosage than CD) showed beneficial effects on number and duration of attacks, VAS for pain and EILP scores, also on FMF severity scores, statistically significantly ($p<0.05$ for each parameters). Bristol stool chart questionnaire scores decreased from 5.62 ± 1.56 to 4.15 ± 1.73 points, and scores of daily stool number decreased from 0.46 ± 0.894 points to 0.03 ± 0.118 ($p<0.05$). There were 12 patients who benefited from the switch without a change in dosage and the clinical features were better under CO treatment significantly.
Conclusion: Pediatric FMF patients, who have active disease and/or gastrointestinal complaints during the use of CD, may benefit from CO.
Keywords: Familial Mediterranean fever, colchicine, intolerance, non-responsiveness.

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease among Mediterranean populations that can cause serious complications such as amyloidosis, without proper treatment (1). Colchicine is an herbal anti-inflammatory agent that is used for FMF treatment, obtained from the flower named colchicine autumnale (2). After the first description of its efficacy in this disease by Ozkan and Goldfinger et al, it has been the cornerstone agent in FMF treatment (3, 4). It is shown that colchicine is very effective and safe for preventing FMF attacks and amyloidosis (5). On the other hand, there are remarkable number of patients who can not tolerate the therapeutic doses of colchicine due to side effects, especially diarrhea. In addition, nearly 5% of patients are non-responsive to colchicine treatment despite the maximum effective dose (6). Having M694V mutation, and poor bioavailability due to low intestinal absorption are the main reasons (7, 8, 9).

There are different pharmaceutical forms of colchicine in the market throughout the world. Despite the contents of the same active ingredient in different doses, these preparations have different methods of production and excipients. In Turkey, pediatric rheumatologists initially use the domestic preparation, brand name is Colchicum Dispert® 0.5 mg (Recordati Turkey) (CD). This film-coated tablet form of colchicine preparation has 0.5 mg active ingredient and excipients such as lactose, cornstarch, talc, Kollidon® VA64, magnesium stearate and others. They prefer to use Colchicine Opocalcium® (Mayoly Spindler, France) (CO) that has 1 mg active ingredient, when the child is intolerant or non-responsive to the domestic product. It is in the form of a compressed tablet including several excipients such as lactose, sucrose, povidone, magnesium stearate and erythrosine Aluminum Lake.

The aim of this study is to compare the efficacy and side effects of Colchicum Dispert® (CD) and Colchicum Opocalcium® (CO) in pediatric FMF patients: is CO safer and more effective than CD?

MATERIALS AND METHOD

Patients

The charts of twenty-nine pediatric patients with FMF in two main pediatric rheumatology centers were reviewed retrospectively. Sex and gender equity in research (SAGER) was considered (10). The patients were diagnosed as FMF based on Ankara criteria (11). Demographic features such as age and gender with clinical features such as age at the first attack, age at the time of diagnosis and MEFV mutations were noted. Also, the indication of switching the two preparations were noted as "intolerance" or "non-responsiveness". Non-responders defined by using FMF-50 criteria, who did not have at least 50% improvement in five of the six criteria by 3–6 months or worsening at least one criterion (12). Informed consent forms were taken from parents of all patients.

Clinical and Laboratory Assessment:

Patients who used CD at least six months initially, and another 6 months of CO, after switching from CD, were included in the study. Patients were asked if they regularly used colchicine as prescribed and defined as "compliant" if they took the recommended doses. The patients who missed drug doses were defined as "non-compliant". All the patients were compliant by their statements. Colchicine Opocalcium® was given to patients who were intolerant or unresponsive despite using colchicine dispert at the maximum dose according to their weight and age. Drug doses, duration of treatments, number of attacks at the last six months, median duration of FMF attacks, visual analog scale (VAS) for pain scores, exercise induced leg pain (EILP), and FMF severity score (Pras et al, 13) were noted for both treatment periods separately. All of the clinical features either during attacks or attack-free periods (such as presence of fever, peritonitis, pleuritis, pericarditis, arthritis and orchitis in attacks and erysipelas-like erythema, arthralgia and myalgia in attack-free period) were recorded for both treatment periods. Also, laboratory data indicating either inflammation or drug side effects (such as hemoglobin (Hb), white blood cell count (WBC), platelet count (Plt), neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which the most recent attack-free period values) were recorded.

Questionnaire for gastrointestinal side effects:

Bristol stool scale was applied to all patients to investigate gastrointestinal side effects for both treatment periods separately. The Bristol stool scale is a diagnostic tool designed to classify the form of human feces into seven categories (14). Stool consistency decreases from type 1 to 7. Type 6 stool is defined as mild diarrhea, also type 7 as severe diarrhea (Picture 1) (15). In addition, number of stools per 24 hours was recorded with using PUKAI (pediatric ulcerative colitis activity index), which is a useful for assessing the frequency of daily defecation and disease activity in pediatric ulcerative colitis patients (16). Number of stools per day was scored between 0 and 3 (number of stool 0-2: 0 point, 3-5: 1 point, 5-8: 2 point, >8: 3 point) based on PUKAI.

The patients, who filled out the Bristol stool chart questionnaire as type 6 and 7, also answered the question about number of stools per 24 hours as 2 or 3 points were included in the "intolerance group". Patients and/or their parents answered the questionnaire together.

Uncommon Side Effects:

The less frequent side effects of colchicine such as nausea-vomiting, neuropathy and myopathy for both drugs were noted based on medical history and records, separately.

Statistical Analysis:

Statistical analysis was performed using SPSS 22 software. Shapiro-Wilk test was performed to evaluate the distributions of the values. Normally distributed values were presented as mean ± SD and non-normal values were presented as median and interquartile ranges (25%-75%). The numerical consecutive parameters of both treatment periods were evaluated with paired-sample t-test when normally distributed. If they distributed non-normally, the Wilcoxon paired rank test was performed. Clinical data of attacks were compared before and after switching preparation evaluated with using McNemar test. $p<0.05$ was considered as statistically significant.

RESULTS

Demographic and clinical results:

There were 13 female (43.4%) and 16 male (56.6%) patients and the mean age was 14 ± 3.8 years. Non-responsiveness to CD was the major indication for switching preparation in 18 patients (62 %), and also intolerance was noted in 11 patients (38 %) due to gastrointestinal symptoms, i.e. diarrhea. 19 patients had homozygous M694V mutation (62 %) and 27 patients had exon-10 mutation in at least one allele of MEFV gene (93 %). Only two patients had solely exon-2 mutations (one patient had E148Q/R202Q and the other had R202Q variants). These patients were further searched for mutations on MVK, TNFRF1A and NLRP3 genes, and showed no mutations (Table 1), and they were diagnosed as FMF due to typical clinical findings as defined in Ankara criteria.

Clinical and laboratory results for both treatment periods:

The median duration for CD treatment was higher than that for CO. The mean dosage of CO was higher (1.71 ± 0.44 mg/day) than CD (1.49 ± 0.41 mg/day), and the difference was statistically significant ($p<0.001$).

Regarding the comparative efficacy of the preparations, there was a substantial decrease in the number of attacks; from 4.83 ± 2.1 to 1.89 ± 1.50, at the end of 6 months of CO usage. Also, the average duration of FMF attacks decreased from 63.98 ± 25.84 hours to 44.41 ± 21.81 hours, in parallel with FMF severity scores (from 8.88 ± 2.08 points to 6.52 ± 1.83) during the same period. The musculoskeletal complaints also decreased from 7.36 ± 1.43 points to 2.84 ± 1.77 in terms of VAS scores of exercises induced leg pain. All mentioned clinical improvements were statistically significant ($p<0.05$)

Usage of Colchicine Opocalcium® was successful also in terms of controlling gastrointestinal symptoms. Bristol stool chart questionnaire scores decreased from 5.62 ± 1.56 to 4.15 ± 1.73 points, and scores of daily stool number decreased from 0.46 ± 0.894 points to 0.03 ± 0.118. Decrease in gastrointestinal complaints were statistically significant ($p<0.05$).

Laboratory markers of inflammation, such as NLR, ESR and CRP values decreased significantly on CO usage. Especially NLR, the useful biomarker of subclinical inflammation, decreased from 2.43 ± 1.72 to 1.67 ± 0.85. Acute phase reactants (CRP and ESR) were in normal limits for both drugs, so comparison was insignificant (Table 2).

Results of patients treated with equivalent doses following switch

There were 12 patients in which colchicine dose remained the same. We further analyzed this group separately to see if there was a bias in terms of change of dosage. The results were similar to the whole group analysis. There was a significant decrease of the clinical findings such as number of attacks at the last six months, average duration of attacks, FMF severity score and VAS scores of EILP ($p<0.05$). Also, the laboratory findings such as NLR, ESR and CRP values were decreased following switch. (Table 3).

Results of clinical findings during attacks and attack-free periods:

Switching colchicine preparation influenced the presence of FMF symptoms during attacks, such as fever, peritonitis, pericarditis, pleuritis, arthritis and orchitis. Existence of these clinical symptoms decreased significantly (Graphic 1).

Also, presence of musculoskeletal complaints in attack-free period, such as arthralgia, myalgia and erysipelas-like erythema decreased after switching. The improvement in arthralgia and myalgia complaints were statistically significant ($p<0.05$).

DISCUSSION

Colchicine is still the mainstay treatment option in FMF, since its efficacy was determined in 1970s (3, 4). However, today, approximately 5% of patients need biological treatment, particularly anti-IL-1 (anakinra, canakinumab), due to intolerance or non-responsiveness to colchicine (5, 17, 18). On the other hand, the efficacy and side effects of different colchicine preparations can vary due to their different production properties and distinct excipients. Therefore, switching colchicine preparations might be helpful in controlling the disease, before labeling the patient as “non-responsive” or “intolerant” (19). In current study, we found that switching from CD to CO preparation had beneficial effects in diminishing gastrointestinal complaints and reducing disease activity.

Clinical characteristics of disease such as FMF severity score, duration and frequency of attacks, as well as severity of joint complaints in attack-free period benefited significantly following switch from CD to CO. There is only one study in the literature evaluating the efficacy of a different pharmaceutical preparation of colchicine, in case of non-responsiveness to one. Emmungil et al recently reported that, there was a significant decrease in the severity and activity scores of the disease and the number of annual attacks after switching domestic colchicine preparations to CO (19). They attributed the effect of CO to its different pharmacokinetic properties. However; they did not evaluate “intolerance”, which in fact is another major concern. Gastrointestinal side effects, especially diarrhea is a very common restrictive cause for using optimal dosage of colchicine, especially in pediatric FMF patients. In another recent study by Baglan et al reported that compressed film-tablet (CO) was able to reduce the mean FMF attack duration and acute phase reactant levels during attack-free period, in their 35 pediatric FMF patients (20). A meta-analysis by Stewart et al reported that the estimated relative risk of experiencing diarrheal symptoms in colchicine group was 2.44 (95% CI: 1.69-3.62) compared to control group (21). In our study there were 11 patients (38%) with gastrointestinal side effects who benefited from the switch.

The frequency of diarrhea decreased, and this enabled us to increase the dose for the disease control. On the other hand, there were 12 patients who benefited from the switch without a change in dosage. They had decreased FMF severity score, duration and frequency of attacks and joint complaints as significant as the "dose increased" group. Our results showed that, despite no dosage change, the clinical features were better under CO treatment.

There are some limitations of this study. This is a retrospective study with limited number of patients. A randomized controlled trial would yield more reliable results. Also, there was a difference in dosage of CO after switching from CD between the centers. In fact, this difference cannot be considered as a bias, but an ability to increase the dose in order to control the disease activity.

In conclusion, the patients with FMF in pediatric age group who have active disease and/or gastrointestinal complaints during the use of Colchicum Dispert®, may benefit from Colchicine Opocalcium®. It might be a valuable treatment option before considering biological agents.

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Table 1. Demographic and clinical data of patients (n=29)	
Gender	16 males (56.6%) 13 females (43.4%)
Age (year)	14 ± 3.8
Age at first attack (year)	6.7 ± 4.11
Age at the time of diagnosis (year)	8.2 ± 4.31
Diagnosis lag time (year)	1 (0-9)
Indication for switch from CD to CO	Intolerance: 11 (37.93%) Non-responsiveness: 18 (62.07%)
Genetically assessment	**M694V (+/+): n=19 (% 62)**
	M694V (+/-): n= 3 (% 10.3)
	M694V/M680I/R202Q: n=1 (3.4%)
	M680I/V726A: n=1 (3.4%)
	M694V/R202Q: n=1 (3.4%)
	M680I/R202Q: n=1 (3.4%)
	V726A/E167D/F479L: n=1 (3.4%)
	E148Q/R202Q: n=1 (3.4%) *
	R202Q (+/-): n=1 (3.4%) *
* These patients were further searched for mutations on MVK, TNFRF1A and NLRP3 genes, and showed no mutations and they were diagnosed as FMF due to typical clinical findings as defined in Ankara criteria	

Table 2. Comparison of clinical and laboratory results for both preparations (n=29)			
	Colchicum Dispert®	*Colchicine Opocalcium®*	*p value*
Duration of treatment (months)	**59.54 ± 36.43**	**26.39 ± 16.64**	**<0.001**
Dosage (mg/day)	**1.49 ± 0.41**	**1.71 ± 0.44**	**<0.001**
Number of attacks at the last 6 months	**4.83 ± 2.1**	**1.89 ± 1.50**	**<0.001**
Average duration of FMF attacks (hours)	**63.98 ± 25.84**	**44.41 ± 21.81**	**<0.001**
EILP (attack-free period)	**7.36 ± 1.43**	**2.84 ± 1.77**	**<0.001**
FMF severity score	**8.88 ± 2.08**	**6.52 ± 1.83**	**<0.001**
Bristol stool scale	**5.62 ± 1.56**	**4.15 ± 1.73**	**0.044**
Number of stools/24 h	**0.46 ± 0.894**	**0.03 ± 0.118**	**<0.001**
Hb (gr/dL)	12.40 ± 0.26	12.75 ± 0.76	0.062
WBC (/mm^3)	7654 ± 2290	7672 ± 2207	0.958
Plt (10^3/mm^3)	287 ± 74	293 ± 46	0.385
NLR (Neu/Lym)	**2.43 ± 1.72**	**1.67 ± 0.85**	**0.01**
MPV (fL)	7.99 ± 1.56	8.19 ± 1.06	0.224
ALT (U/L)	**19.94 ± 11.82**	**24.61 ± 12.83**	**<0.001**
CRP (mg/L)	**0.95 (0.65-3.00) ***	**0.66 (0.03-2.10) ***	**0.044**
ESR (mm/h)	**27.07 ± 13.03**	**19.11 ± 9.20**	**<0.001**

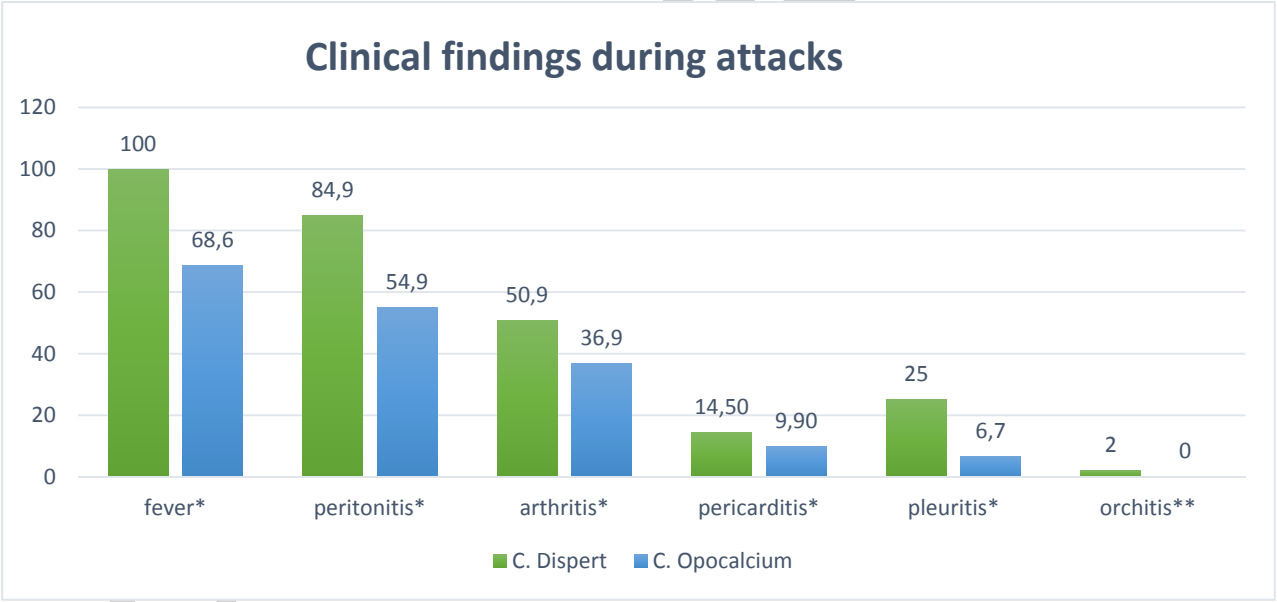
*Mean ± SD
**Median (25-75 percentile)
FMF: familial Mediterranean fever
EILP: Exercise induced leg pain (visual analog scale score)
Hb: hemoglobin, WBC: White blood cell count, Plt: platelet count, NLR: neutrophil/lymphocyte ratio, MPV: mean platelet volume, ALT: alanine aminotransferase, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.
number of stool/24 hours: 0-2: 0 point, 3-5: 1 point, 5-8: 2 point, >8: 3 point.

Table 3. Clinical and laboratory data of the patients without dose change after preparation switch (n=12)			
	Colchicum Dispert®	*Colchicine Opocalcium®*	*p value*
Duration of treatment (months)	**61.51 ± 37.74***	**19.76 ± 15.34***	**<0.001**
Dosage (mg/day)	**1.71 ± 0.45***	**1.71 ± 0.45***	
Number of attacks at the last 6 months	**5.22 ± 2.09***	**1.17 ± 1.66***	**<0.001**
Average duration of FMF attacks (hours)	**48 (48-51)****	**24 (24-30)****	**<0.001**
EILP (attack-free period)	**7.04 ± 1.35***	**2.29 ± 1.90***	**<0.001**
FMF severity score	**9.26 ± 1.88***	**5.92 ± 2.08***	**<0.001**
Hb (gr/dL)	**12.26 (12.27-12.33)****	**12.1 (12.10-12.11)****	**0.045**
WBC (/mm^3)	6560 (6560-6590**)	6510 (6510-6583)**	0.798
Plt (10^3/mm^3)	249 (249-249.37)	284 (287.75)	0.540
NLR (Neu/Lym)	**1.07 (1.07-1.09)****	**1.07 (1.04-1.07)****	**<0.001**
MPV (fL)	**8.10 (8.10-8.11)****	**6.70 (6.70-6.74)****	**0.046**
ALT (U/L)	**43 (42-43)****	**45 (41.37-45)****	**<0.001**
CRP (mg/L)	**1.54 (1.54-1.64)****	**0.03 (0.03-0.17)****	**0.01**
ESR (mm/h)	**44 (41.75-44.00)****	**23 (21.25-23.00)****	**<0.001**

*Mean ± SD
** Median (25-75 percentile)
FMF: familial Mediterranean fever
EILP: Exercise induced leg pain (visual analog scale score)
Hb: hemoglobin, WBC: White blood cell count, Plt: platelet count, NLR: neutrophil/lymphocyte ratio, MPV: mean platelet volume, ALT: alanine aminotransferase, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

Type 1		Separate hard lumps	Severe constipation
Type 2		Lumpy and sausage like	Mild constipation
Type 3		A sausage shape with cracks in the surface	Normal
Type 4		Like a smooth, soft sausage or snake	Normal
Type 5		Soft blobs with clear cut-edges	Lacking fiber
Type 6		Mushy consistency with ragged edges	Mild diarrhea
Type 7		Liquid consistency with no solid pieces	Severe diarrhea

FIG. 1. Bristol stool chart.



Graphic 1. Comparison of both colchicine treatment periods regarding clinical findings in FMF attacks.
* statistically significant ($p<0.05$), ** not statistically significant ($p>0.05$)