
Current trends in colchicine treatment in familial Mediterranean fever

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ABSTRACT

Objectives. Since the publication of the first reports on the efficiency of colchicine in familial Mediterranean fever (FMF), very few randomised studies have investigated issues related to its long-term use. Thus, different approaches taken by physicians involved in FMF care, are exclusively empiric, emulative, and based on case-reports or case-series. Problems such as colchicine intolerance and colchicine resistance have not been solved yet.

This paper aims to evaluate trends in colchicine therapy among physicians taking care of FMF patients around the world.

Methods. We conducted a survey by sending questionnaires to FMF research and treatment centres in Europe and Asia. Many issues (such as dosages, schedules, side effects, interactions, efficacy and toxicity monitoring, definition of colchicine intolerance, colchicine resistance and responsiveness, etc) have been investigated. When more than 70% of physicians responded giving similar answers to an item, the response was considered as a "trend". A comparison between answers of physicians from FMF-prevalent and non-prevalent countries was also made.

Results. Thirty-five physicians from 11 countries filled the questionnaires, taking care of a total of more than 15000 FMF patients (pts). Different approaches were evident among the various physicians. Statistically significant different approaches between physicians from FMF-prevalent countries with respect to those from non-prevalent countries were found in items like colchicine during pregnancy, severity score and blood tests for disease monitoring. No consensus was found regarding the definition of colchicine resistance.

Conclusion. The current study demonstrated significant variations in the strategy of colchicine therapy for FMF

around the world and re-emphasised the need for standardised definitions of colchicine resistance and colchicine intolerance.

Introduction

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disorder. It is characterised by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like erythema (1-2). Typical attack lasts between 24 to 96 hours. The disease is associated with mutations in the Mediterranean Fever (MEFV) gene, which encodes pyrin protein. Pyrin protein is predominantly expressed in neutrophils and involved in the modulation of inflammation. Modified pyrin, due to MEFV mutations, is thought to be responsible for uncontrolled inflammatory self-terminated attacks (3).

Colchicine is an alkaloid extracted from the plant *Colchicum autumnale* used for centuries for the treatment of gout (4). In 1972, colchicine was recommended to be the treatment of choice for FMF. It controls the acute attacks and prevents the development of amyloidosis (5, 6).

Since then, several well-designed trials have demonstrated the clinical efficacy of colchicine at 1-2 mg/daily dosage. Furthermore, chronic colchicine treatment was shown to be relatively safe and effective in pregnancy and during nursing (7-11). Studies suggested that colchicine efficacy in FMF is due to its suppressive action on nuclear factor (NF)- κ B-mediated cytokines induction and inhibition of chemotaxis of neutrophils, the main target cells in this disease (12).

Despite the high efficacy, safety profile and tolerability of colchicine, there are still FMF patients who cannot tolerate this medication or are resistant to its effect. This, of course, may put these patients at risk of developing amyloidosis.

Competing interests: none declared.

The exact portion of colchicine resistant is not known and in various studies the estimation ranges between 5 to 15% of FMF treated patients (5, 13). It also appeared that patients may not benefit from colchicine therapy, due to non-compliance or irregular intake of the drug. High colchicine compliance may explain the effective prevention of amyloidosis complicating FMF (and its low prevalence) in countries where regular colchicine therapy is practised for decades. Given the discrepancies in colchicine use and the existence of mechanisms hindering its efficiency in FMF, it is becoming increasingly urgent to examine trends in colchicine treatment and attitudes towards possible causes of colchicine resistance and intolerance (14-15). The aim of the current study is to examine current needs and uncertainties regarding colchicine use by surveying physicians involved in the management of FMF patients. In this survey, special emphasis was placed on obtaining opinions from experts working in countries where FMF is frequent and from physicians treating sporadic cases of FMF.

Materials and methods

We used a questionnaire which included 38-items covering the following issues of colchicine use: 1) physician's experience and number of patients followed by the physician, 2) colchicine dosages, routes of administration and treatment schedules, 3) side effects, toxicity, allergy and drug interactions, 4) colchicine monitoring of efficacy and toxicity, 5) proposals for definition of colchicine intolerance and colchicine resistance, 6) use of alternative treatments. The questionnaire was sent to 60 physicians around the world. When more than 70% of physicians responded with similar answers to an item, the response was considered as a "trend". A comparison between answers of physicians from FMF-prevalent and non-prevalent countries was made. Statistical significance was evaluated by Fisher's test (two-tailed).

Results

We received 35/60 (58%) questionnaires from 11 countries. According to

collected data, the responding physicians were following over 15000 FMF patients. The percentage of completion of the questionnaires was 89.5%. The data analysis included all the received questionnaires.

Physician's experience

The mean duration of experience with colchicine treatment of the physicians who responded to the questionnaire was 14.2 ± 7.76 years and the mean number of patients with FMF seen per month by each physician was 16.5 (± 17). Seven out of 35 physicians (20%) examined mainly paediatric patients, 20 out of 35 (57%) physicians saw mainly patients over the age of 20 years, and 14 out of 35 (40%) had experience with both paediatric and adult FMF patients.

Dosages, routes of administration and schedules

The overwhelming majority of the physicians (31/35; 88.6%) pointed out that they use colchicine therapy to ascertain diagnosis of FMF.

In adult FMF patients, 53.5% (15/28) of interviewed physicians used 1 mg/daily colchicine as an initial therapy, 68.6% (19/28) used 1–1.5 mg/daily as optimal dose and 51.4% (14/28) of them reached 2–2.5 mg/daily as the highest tolerated dosage.

In children younger than 5 years of age, 90.5% (20/22) of physicians said they used an initial therapeutic dose below 0.5 mg/day, 90% (18/20) of them used an optimal dose of 0.5–1 mg/day and only 35% (7/20) of them had to increase daily colchicine dose up to 1.5–2 mg.

In children over 5 years of age, the initial colchicine dose used by 59% (13/22) of interviewed physicians was 1 mg/day, 50% (11/22) of them experimented that 1 mg/day was the optimal dose, however 18.2% (4/22) of physicians needed to increase the dose up to 2.5 mg/day.

All the physicians prescribed colchicine for oral intake. None prescribed intravenous colchicine. None prescribed slow release colchicine (COL-CHRYN[®]). More than 80% of physicians (30/35) consider fractioned doses preferable (24/27, 88.8% of cases in

adults and 19/22, 86% in children). Only one physician calculated colchicine dose based on weight of patients. Seventy three percent of cases (19/26) reported a stepwise increase of colchicine dose by 0.25–0.5 mg increments, until either the attacks disappeared and a sufficient response to therapy was obtained or adverse effect(s) developed. Eighty two percent (28/34) of the physicians used more than 1 method to assess responsiveness to colchicine therapy. All physicians considered cessation of attacks as a response criterion; 70% of them (24/34) also considered the reduction of acute-phase reactants (APR), and 32% (11/34) diverse markers of FMF severity, colchicine side-effects (mainly gastrointestinal complaints), level of proteinuria, accompanied diseases, renal and liver function tests, as other criteria.

Not all the disease manifestations are equally controlled by colchicine according to the experience of half of the interviewed physicians. Among these protracted arthritis was mentioned by 78.6% (21/27), whereas leg pain by 55.5% (15/27) of the experts. About 67% (20/30) of the physicians used colchicine at doses over 2 mg/day in colchicine resistant patients. Seventy-eight percent (18/23) reached the level of 1.5 mg/daily in intolerant patients, and none of them calculated dose based on body mass in resistant and intolerant patients.

The majority of physicians (26/35; 74.3%) do not increase colchicine dose before menstruation, however, 88% (30/34) increase dose in patients with proteinuria. All of them continued to give colchicine during pregnancy.

The vast majority of the physicians do not increase dosage during attacks (91.4%; 32/35); 31/35, 88% used non-steroidal anti-inflammatory drugs as pain relievers during attacks and 8/35, 22.8% used steroids.

Side effects, toxicity, allergy and drug interactions

Eighteen out of 32 (56%) physicians never stopped colchicine because of its side effects. On average, the remaining physicians were obliged to stop colchicine in about 6% of their patients

(ranging from 0.1% to 30%). The most common causes of withdrawal were gastrointestinal symptoms (Table I).

Nineteen out of 33 physicians (57%) declared that they use other measures to increase colchicine tolerance such as lactose free diet, etc.

Only 2 physicians reported 4 cases of allergy to colchicine and proposed 2 different desensitisation protocols.

Only 10/32 (31%) of physicians reported drug interactions: 3/32, 9.4% with macrolides, 3/32, 9.4% with statins, 2/32, 6.25% with cyclosporine, 1/32, 3.1% with omeprazole and escitalopram.

Efficacy and toxicity monitoring

Eighteen out of 34 physicians (53%) suggested to evaluate patients' response and tolerance every 6 months, 28.1% (9/32) once a year, 15.6% (5/32) every 4 months.

All of them asked for urinalysis, 91.4% (3/34) for WBC, 80% (27/34) CRP, 77.1% (26/34) liver tests, 70.5% (24/34) ESR, 41% (14/34) muscle enzymes.

Twenty two out of 29 (75%) interviewed physicians do not adopt specific recommendations for patients with particular problems, such as esophageal reflux, atrophic gastritis, liver steatosis, endometriosis, metabolic syndrome and depression or in treatment with estrogen/progesterone agents or proton pump inhibitors (PPIs).

Criteria for a definition of colchicine intolerance

About 71% (24/34) of the interviewed physicians declared that they usually use more than one criterion to define colchicine intolerance. Among the most commonly used criteria is diarrhoea (28/34; 82.35%), followed by myopathy (23/34; 67.6%), neuropathy (20/34; 58.8%) and alopecia (14/34; 41.1%). Bone marrow suppression and signs of liver toxicity are rarely used.

When they were requested to suggest criteria to define colchicine intolerance, 82% (23/28) suggested more than 1 criterion. In a list of proposed criteria, 79% (22/28) indicated diarrhoea as a sign of colchicine intolerance, 42.8% (12/28) myopathy, 35.7% (10/28) neuropathy, 29% (8/28) altered liver function tests, 18% (6/28) leucopenia, 7% (2/28) cy-

Table I. Causes of dose reduction and withdrawal of colchicine therapy.

Causes	Dose reduction, %	Withdrawal, %
Gastrointestinal complaints	74.2% (26/35)	63% (21/33)
Altered liver function tests	22% (8/35)	7% (23/33)
Bone marrow suppression	11.4% (4/35)	45% (15/33)
Altered muscle enzymes	11.4% (4/35)	45% (15/33)
Neuropathy	–	18% (6/33)

topenia. Only 3 physicians referred to colchicine dose.

Criteria for a definition of colchicine resistance

Ninety percent (30/33) of the physicians use more than one criterion to define colchicine resistance. Twenty eight out of 33 (85%) of physicians define colchicine resistance on the basis of recurrence of attacks, attack frequency and duration, 60% (20/33) on the basis of colchicine dose (ranging from 1 mg/d to over 3 mg/d), 51.5% (17/33) of abnormal acute phase reactants during attack-free period, and 27.7% (9/33) also consider the persistence of chronic manifestations, mainly anaemia and splenomegaly or leg pain.

When they were requested to make a list of criteria to define colchicine resistance: 82% (23/28) of them reported more than one criterion (13/28, 46.4% two criteria and 9/28, 32% three criteria). About 93% (26/28) of physicians refer to attack frequency, 60.7% (17/28) to persistent high APR, 28.5% (8/28) to organ involvement mainly renal involvement, 25% (7/28) to colchicine dose, only 3.5% (1/28) to work limitations or absence from school or observation period.

Alternative treatments

Only 43% (13/30) of interviewed physicians tried at least an alternative treatment (10/30, 33.3% anti-TNF- α , 8/30, 26.6% anti-IL1, IFN or thalidomide) in case of colchicine resistance.

Comparison between the experience of physicians from FMF-prevalent and non-prevalent countries

The present survey included 18 physicians from FMF-prevalent countries (Turkey, Armenia, and Israel) and 17 from countries with low-prevalence FMF (*i.e.* Italy, Spain, France, Greece,

etc.). Table III summarises some differences in clinical practice between these two groups of physicians regarding their approach of colchicine dose increments and its use during pregnancy. However, statistical significance was reached only in 2 topics: "stepwise increase of colchicine dose after diagnosis" and the "use of serum amyloid A to monitor colchicine effect" ($p=0.0072$ and 0.023 , respectively). Both these behaviours are more common in physicians from low-prevalent countries. The differences in terms of use of severity score and of the same dose during pregnancy resulted not quite significant in the statistical analysis ($p=0.075$ and 0.087 , respectively).

No differences were found in terms of using colchicine as a diagnostic test or of increasing colchicine dose during attacks (the majority do not increase colchicine dose during attacks) and in terms of initial, mean and maximum tolerated dose in adults. However, 70% (12/17) of the interviewed physicians who use higher doses (mean and maximum tolerated) in children under 5 years of age were from FMF-prevalent.

There were no significant differences in terms of monitoring colchicine effect and adjusting dose, in terms of numbers of methods used (14/17, 82.3% among physicians from prevalent countries and 15/17, 88.2% among those from non-prevalent ones use more than one method). Nevertheless, physicians from countries where FMF is not prevalent tended to ask for more blood tests such as for acute phase reactants (APR) compared to physicians from FMF prevalent sites (14/17, 82.3% vs. 11/17, 64.7%).

The use of severity scores was also more common among physicians from countries with low frequency of FMF (even if there is no homogeneity of the utilised scores; 8/17, 47% vs. 3/17, 17.6%).

Table II. Comparison between the practice of physicians from FMF-prevalent and non-prevalent countries.

Topic	%, CACs (classically affected countries)	%, N-CACs (non-classically affected countries)	p-value
Stepwise increase of Co dose	50% (9/18)	94% (16/17)	0.0072
No increase of Co before menses	81% (13/16)	66.6% (8/12)	0.447
Same dose in pregnancy	93.3% (14/15)	69.2% (9/13)	0.087
<i>Monitoring of Co effects</i>			
Blood and urine tests every 6–12 months in responsive patients	77.7% (14/18)	94% (16/17)	0.337
Asking for all the proposed tests	44.4% (8/18)	53% (9/17)	0.73
Urinalysis	94.4% (17/18)	100% (17/17)	1.00
C-RP	77.7% (14/18)	88.2% (15/17)	0.65
Transaminases	66.6% (12/18)	88.2% (15/17)	0.228
White blood cells	83.3% (15/18)	82.3% (14/17)	1.00
ESR	66.6% (12/18)	76.4% (13/17)	0.711
Serum amyloid A	5.5% (1/18)	47% (8/17)	0.023
Creatinin-kinase	33.3% (6/18)	47% (8/17)	0.499
Fibrinogen	11% (2/18)	23.5% (4/17)	0.401
<i>Criteria of responsiveness</i>			
Use of more than 1 criterion	82.3% (14/17)	88.2% (15/17)	1.00
Attack cessation	100% (17/17)	100% (17/17)	1.00
Decrease in acute phase response	64.7% (11/17)	82.3% (14/17)	0.44
Severity score	17.6% (3/17)	47% (8/17)	0.075

Table III. List of trends.

1. Colchicine is only administered per os (in Tel hashomer in resistant – given IV)
2. Fractioned doses and stepwise increases are largely preferred (>80%; 73.5%)
3. Dosages: no real agreement observed
4. A diagnostic test with colchicine is often done (88.6%), although not on a regular basis
5. NSAIDs are prescribed as additional drugs during attacks (82%)
6. Colchicine dosage is not increased before menses (74.3%) and during attacks (91.4%) but is increased in microalbuminuric/proteinuric patients, if tolerated (88%)
7. During pregnancy, it is not stopped (100%) and the same dosage is maintained (85%)
8. Colchicine responsiveness is evaluated on more than 1 criterion (82%): attack disappearance (100%) and reduction of APR (70%) are the most commonly used
9. Efficacy and toxicity are evaluated every 6–12 months in responsive patients 81%). Urinalysis is the universal test of choice (100%), followed by WBC (91.4%), CRP (80%), transaminases (77%) and ESR (71%)
10. 1.5 mg/d is the dose more frequently reached in intolerant patients (78.2%)
11. More than one criterion is used and suggested to define colchicine resistance (90% and 82%, respectively). A variable time of observation and the post-colchicine number and frequency of attacks are largely applied as criteria (85% and 93%)
12. More than one criterion is used and suggested to define colchicine intolerance (71% and 83%, respectively). The main criterion used and suggested is diarrhea (82.2%; 79%)

Discussion

Apart from the 3 double-blind and randomised studies (7-9) that proved colchicine efficacy immediately after its introduction in 1972, very few randomised studies on large scale, aimed to investigate problems related to its long-term use have been conducted (16-19). Many different approaches taken by physicians involved in FMF care, such as stepwise dosage increase, dosage increase in case of exposure to

trigger factors, lactose-free diet and/or gastro-protective agents to increase tolerance, avoiding pharmacological interactions, dosage adjustments in case of associated diseases, are exclusively empiric and emulative, based on isolated case reports or case-series. Due to the lack of standardised definitions of colchicine intolerance and resistance, randomised studies are also lacking. However, today, the demonstrated efficacy of biologic agents, such as an-

ti-TNF and anti-IL-1 agents (20-25), along with their high costs and potential serious side-effects, raise the importance of the comprehensive assessment of factors implicated in effective colchicine therapy and its safety profile. In this scenario, a sort of census of the commonest approaches related to colchicine therapy in order to identify similar or different practices and areas of uncertainties appears essential.

The purpose of this first multinational assessment of colchicine use in FMF was to elucidate trends in colchicine use in 35 FMF centres from 11 countries, covering more than 15000 patients. As already mentioned, when similar answers were given by more than 70% of the responders, the answers were considered as “trends” in colchicine therapy (Table III).

A well-established trend is the oral administration of colchicine, mainly in fractioned doses (none prescribe intravenous colchicine during attacks), in children and adults. Nevertheless, none of the physicians calculated the dose according to weight or body surface.

Regarding colchicine dosages, the maximum agreement was found on doses used in children less than 5 years of age, where up to 90% of physicians use the same initial and optimal dose and only 1/3 of them reach higher doses. The relatively high doses used in children by physicians from FMF-prevalent countries may reflect the frequency of more aggressive phenotypes in these regions.

From the answers collected, it was clear that more than one method is utilised to monitor colchicine efficacy or for adjusting its dose by physicians from FMF-prevalent and non-prevalent countries. About tests for monitoring efficacy and toxicity, it is worth noting that urinalysis or blood count is widely used in non-prevalent countries; however, only one cautioned the patients against using CY3A4 inhibitor. Few centres monitored muscular enzymes after the first month of therapy or in case of renal failing function.

Very few of the issues compared between physician from FMF-prevalent and non-prevalent countries reached statistical significance: 1) the stepwise

increase of colchicine dose after the diagnosis ($p=0.0072$), 2) the use of serum amyloid A to monitor colchicine efficacy ($p=0.023$), 3) the use of severity score ($p=0.075$), 4) the use of the same dose during pregnancy ($p=0.087$).

These findings confirmed a stronger awareness of colchicine use in FMF-prevalent countries, due to longer and wider experience. In non-prevalent countries, instead, there is a consistent group of physicians that still increase colchicine dose during attacks (11.5%) or mainly reduce/stop colchicine dose during pregnancy (52.8%). These findings could reflect lack of experience and update in the current literature pertaining colchicine use. On the other hand, in non-prevalent affected countries a tendency to use more often blood tests and severity score appeared, probably because of less clear phenotypes and/or more cases of FMF-like syndrome and wider availability of tests.

Allergy, drug interactions and side effects were confirmed not to be a frequent problem with colchicine (<0.1% of patients). In the experience of interviewed physicians, up to 11% of patients had to reduce colchicine dose because of side effects and a mean of 6% had to stop it for the same reason, because of serious ADR.

Approaches aimed to increase colchicine tolerance appeared really under-utilised, apart from lactose-free diet, mainly because of lack of well-designed studies on this topic.

The most important section of the survey was about the definition of colchicine intolerance and resistance, as it opens the way to emerging alternative treatments.

Each of these two issues was examined from 2 different points of view. The proposed questions were “When do you consider a patient intolerant to colchicine? When he complains of...” and “Would you make a list of criteria for colchicine intolerance?”, “Do you consider a patient not responsive to colchicine on the basis of...” and “Would you make a list of criteria for colchicine resistance?”, in order to distinguish between what physicians do and what they would do. The majority of the physicians uses and proposes

more than a single criterion in order to define intolerance or resistance.

According to general accepted definitions of “drug intolerance”, from answers it appears clear that most physicians refer only to side-effects according to their frequency (so, gastrointestinal complaints are the most suggested and used criterion). Nevertheless, still a minority of them refer also to the dose administered.

Regarding colchicine resistance, answers reflect the same uncertainty present in the literature. Recent papers and experimental studies have reported different definitions for colchicine non-response (13, 14, 26, 27). None of the current definitions is comprehensive enough: only one includes laboratory parameters, only two refer to colchicine dose, none considers age or body weight of patients, plasma levels of colchicine, exclusion of malabsorption, exposure to known triggers or non-compliance that, as it was demonstrated by Ben-Chetrit and Amar (15), is surprisingly frequent and can overestimate the real rates of non-responders.

In our survey, actually over a half of the physicians refer and propose to refer to attack frequency, APR control and colchicine dose in defining colchicine resistance. However, the definition of colchicine resistance by different physicians with regard to the change observed after administration of colchicine in the characteristics of the attacks are so variable in terms of definition, number, severity and frequency of attacks, etc. A quarter of them considered also chronic manifestations or particular organ involvement, like the renal amyloidosis, proteinuria, etc. Only one physician suggested as criterion the measurement of plasma levels of colchicine. The practical consequence of this is early seen: alternative treatments are sporadic (reported by 43% of physicians).

Conclusion

In conclusion, despite the fact that colchicine has been used for approximately 40 years in the treatment of FMF, there is a large variability in its worldwide practice, which is based mainly on eminence and experience.

This observation confirms the need of standardised guidelines and definition of difficult issues, such as colchicine intolerance and resistance, stratification of disease severity and response to treatment and eventually randomised trials for comparison with new slow-release colchicine formulation.

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