Therapeutic approach to familial Mediterranean fever: a review update

M.A. Ozturk[1], M. Kanbay[2], B. Kasapoglu[3], A.M. Onat[1], G. Guz[4], D.E. Furst[5], E. Ben-Chetrit[6]

[1]Department of Medicine, Division of Rheumatology, Gazi University School of Medicine, Turkey;
[2]Department of Medicine, Division of Nephrology, Kayseri Training and Research Hospital, Turkey;
[3]Department of Medicine, Fatih University School of Medicine, Turkey;
[4]Department of Medicine, Division of Nephrology, Gazi University School of Medicine, Turkey;
[5]Department of Medicine, Division of Rheumatology, David Geffen School of Medicine at University of California, USA;
[6]Department of Medicine, Division of Rheumatology, Hadassah- Hebrew University Medical Center, Jerusalem, Israel.

Mehmet Akif Ozturk, MD, Professor
Mehmet Kanbay, MD, Assoc. Professor
Benan Kasapoglu, MD,
Ahmet Mesut Onat, MD, Assoc. Professor
Galip Guz, MD, Professor
Daniel E. Furst, MD, Professor
Eldad Ben-Chetrit, MD, Professor

Please address correspondence to:
Prof. Dr. Mehmet Akif Ozturk,
Gazi Universitesi Tip Fakultesi,
I˙c Hastaliklari Romatoloji,
TR 06500, Besevler,
Ankara, Turkey.
E-mail: makifozturk@yahoo.com

Received on June 4, 2011; accepted in revised form on August 30, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 67): S77-S86.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2011.

Key words: familial Mediterranean fever, treatment, colchicine

Competing interests: D.E. Furst has received research grants, consultancy fees and honoraria from Abbott, Actelion, Amgen, BMS, Biogen Idec,Centocor, Corrona, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, and UCB. The other co-authors have declared no competing interests.

ABSTRACT

Familial Mediterranean fever (FMF) is a hereditary disorder characterised by recurrent attacks of fever with peritonitis or pleuritis, arthritis, myalgia or erysipelas-like skin lesions. The continuous inflammation in FMF is associated with increased serum amyloid A (SAA) protein which may lead to secondary amyloidosis and deposition of this insoluble protein in the kidney, gut, spleen, liver, heart etc. Therefore, treatment of patients with FMF is beneficial not only for the prevention of the acute attacks but also for improving their prognosis. In the present review we summarise the medical literature concerning FMF treatment, including new therapeutic agents and management of colchicine-resistant patients. Three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched from 1 January 1960 to 28 February 2010 for any therapeutic approach to FMF, with MeSH headings and text words (Familial Mediterrenean Fever, FMF treatment, colchicine, infliximab, anakinra, SSRI). In conclusion, colchicine remains the mainstay therapeutic option in FMF. It is effective in various manifestations of the disease such as fever, peritonitis and pleuritis. It prevents the development of amyloidosis. It is safe in humans regarding fertility, and can be used during pregnancy and nursing. Dose adjustment should be made in patients with renal or hepatic failure. It is less effective in arthritis or myalgia, requiring additional treatment with NSAIDs and steroids. In the few cases where FMF is resistant to colchicine other measures, including corticosteroids, non-biological and biological DMARDs, interferon alpha and SSRIs should be employed.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterised by recurrent febrile attacks with peritonitis, pleuritis, arthritis, myalgia or erysipelas-like skin lesions (1). It is one of the most common periodic fever syndromes (also known as the autoinflammatory diseases) (2). Although it generally affects eastern Mediterranean people (*i.e.* non-Ashkenazi Jews, Armenians, Arabs and Turks), it has been reported throughout the world (3). A major devastating complication of FMF is amyloidosis, where serum amyloid A (SAA) protein is deposited in the kidneys, gastrointestinal tract, spleen, liver and bone marrow. Colchicine is the drug of choice for FMF since 1972 (4, 5). It is an alkaloid extracted from bulbs of a plant called *Colchicum autumnale* (meadow saffron). It was first recommended for the treatment of gout by the Byzantine physician Alexander of Tralles in the 6th century AD (6). Later it was employed for an increasing number of indications including primary biliary cirrhosis (PBC), Behçet's disease, Sweet's syndrome, scleroderma, and amyloidosis. Perhaps the most effective results have been obtained in familial Mediterranean fever (FMF). It may prevent the acute febrile attacks and inhibit the development of amyloidosis. Before the era of colchicine therapy, many patients with FMF developed chronic renal failure due to amyloidosis by the age of 40 years (7). In the present review we wish to summarise the recent medical literature concerning FMF treatment, including new therapeutic agents and management of colchicine resistant patients. We believe it will be of help for physicians caring for FMF patients worldwide.

Methods

Three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched from 1 January 1960 to 28 February 2010 for randomised controlled trials investigating any therapeutic approach to FMF, with MeSH headings and text words (Familial Mediterranean Fever, FMF treatment, colchicine, infliximab, anakinra, SSRI). Since there were very few randomised controlled trials, case reports, case series and letters were also reviewed and included. The grades of evidence of all studies are shown before the reference number of all cited publications (Table I). The grade of evidence seeks to assess the strength of evidence of the risks and benefits of treatments (including lack of treatment) and diagnostic tests. Evidence quality can range from meta-analyses and systematic reviews of double-blind, placebo-controlled clinical trials at the top end, down to conventional wisdom at the bottom.

Table I. Quality of evidence.

I.	One or more properly randomised, controlled trial
II.	- Well-designed controlled trial without randomisation - Well-designed cohort or case-control analytic study, preferably from 1 centre or research group - Comparisons between times or places with or without the intervention - Dramatic results in uncontrolled experiments
III.	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
IV.	Expert opinion

Results

Colchicine: the oldest but still the best prophylactic medication

Colchicine is the principal therapy in FMF. Based on numerous case series, letters and controlled trials it appears that colchicine reduces attack frequency, decreases severity and shortens duration of the acute attacks in most FMF patients (Grade I) (8, 9). Furthermore, colchicine can prevent, arrest or even reverse renal amyloidosis in patients who have already developed this complication (Grade II) (10). However, the most appropriate dosing regimens and time of introduction remain less clear. Most FMF patients (>18 years) are treated with at least 1.0 mg colchicine daily. If the patients still have frequent attacks the dose is increased to 1.5 and than 2.0 mg daily. Patients should take the medication continuously since missing even a single dose may lead to an acute attack within a few days. We recommend taking the whole dose at once, unless the patient complains about diarrhoea; if that is the case the dose should be divided to twice a day (Grade III). As a matter of fact, in Japan several case reports showed that their adult patients with FMF are controlled by low-dose colchicine (0.5 mg daily). This suggests that in Japan there may be genetic or environmental modifiers leading to a milder disease (11, 12).

Recently, a consensus statement on the use of colchicine in children and adolescents with FMF was also developed on the basis of expert opinion and literature analysis (13). It should be emphasised that there are no pharmacokinetic or pharmacodynamic studies on colchicine in children, raising some questions with respect to these "consensus" recommendations. Currently, there is a trial investigating the pharmacodynamics and kinetics of colchicine in children and its results are expected in two years.

Based upon the current available literature (13) and our experience we recommend the following:

1. Colchicine should be introduced in children with FMF as soon as the diagnosis has been established and should be continued for life (Grade III).
2. Suggested dosages according to the ages of the children are as follows:

The oral starting doses should be: ≤0.5 mg/day (for children <5 years of age); 1.0 mg/day (for children 5-10 years of age); above the age of 10 years, patients can take more than 1.0 mg colchicine daily (Grade III). Colchicine dosage should be increased in a stepwise fashion (*e.g.* 0.25 mg/step) up to a maximum of 2.0 mg/day in order to control the disease in patients who do not clinically respond to the standard dosage (Grade III).

3. In high-risk patients (*e.g.* after kidney transplantation, patients with amyloidosis), higher colchicine doses (up to 2 mg/day) should be given independent of the dose needed for controlling the clinical symptoms (Grade II). However, creatinine should be normal otherwise the dose should be reduced and adjusted.
4. Monitoring should be done in the presence of impaired renal or liver function. For patients with severe renal failure (GFR of < 10 mL/min), the dosage should be reduced by 50% (*e.g.* ≤1 mg/day) (Grade III).

Colchicine overdose can cause many side effects.

Side effects of colchicine

The most common side effects of colchicine is gastrointestinal. Therapeutic oral doses of colchicine may cause cramping, abdominal pain, hyperperistalsis, diarrhea, and vomiting. Rarer side effects of colchicine include bone marrow suppression and neuromyopathy, which is most commonly seen in elderly patients with renal insufficiency. Colchicine overdose may lead to a cholera-like syndrome associated with dehydration, shock, and acute renal failure, alopecia, bone marrow failure, hepatocellular failure, disseminated intravascular coagulation (DIC), epileptic seizures, coma, and death (14, 15) (Table II).

Most side effects of colchicine are dose-related. However, colchicine toxicity can develop on standard dose of the drug in patients taking concomitant medications that can affect colchicine metabolism either by inhibiting cytochrome CYP 3A4 or deranging the ATP-binding cassette subfamily B member 1 (ABCB1) (Table III, Fig. 1).

Management of acute FMF attack

Colchicine is an excellent drug to prevent the acute FMF attack. However, in contrast to gouty arthritis where colchicine may serve as an immedi-

Table II. Adverse effects of colchicine.

• Diarrhoea	• Severe abdominal pain
• Nausea	• Vomiting
• Thrombocytopenia	• Leukopenia
• Stomatitis	• Alopecia
• Liver damage	• Renal failure
• Respiratory failure	• Fatigue
• Coagulopathy	• Shock
• Neuromyopathy	• Paralysis
• ST elevation	

Table III. Drug-drug interaction: representative substrates and inhibitors of CYP 3A4.

Substrates	Inhibitors
Colchicine Erythromycin	Diltiazem
Lovastatin	Gestodene
Estrogen Midazolam	Ketoconazole
Steroids Quinidine	Toleandomycin
Dapsone Terfenadine	Erythromycin
Diltiazem Nifedipine	FK-506
Lidocaine	Grapefruit Juice

Fig. 1. PGP (ABCB1) inhibitors.

ate medication for the acute event, in FMF it should not be used during the acute attack because it is not beneficial (Grade III). Since currently there is no effective medication for the acute attack, the therapeutic approach is mostly supportive, such as intravenous saline hydration, and NSAIDs, paracetamol or dipyrone for pain relief.

For treating acute attacks, a potential agent is anti IL-1 receptor antagonist (Anakinra). This medication should be given as the event starts. It is a short-acting agent with a quick action so that a daily subcutaneous injection of 100 mg for one or two days may restrain or suppress FMF attack (16). Official clinical trials addressing this approach are on the way and this medication will hopefully be in use in the near future.

Management of FMF patients non-responsive to colchicine

Colchicine prevents febrile attacks in more than 60% of patients and significantly reduces the number of attacks in another 20–30%. Five to ten percent of patients do not respond to therapy, but most of them are non-compliant (1). The problems regarding the definition of colchicine non-response and the possible reasons for it are dealt with in 2 recent editorials (17, 18). Theoretically, problems with its absorption in the intestine, problems with the functioning of the MDR1 gene in white blood cells or serous membrane cells, and modulation of colchicine metabolism by different factors at the level of cytochrome 3A4 can influence the effect of colchicine (17, 18). Whatever the cause might be in FMF patients with no response to colchicine, there are several therapeutic options as follows:

– Corticosteroids

Although it is generally felt that steroids have no role in the treatment of FMF attacks, a recent non-randomised, single-blind, placebo-controlled study in 31 FMF patients – who were in the first 24 h of the attacks – suggested that 40 mg of methylprednisolone infusion significantly relieved abdominal pain and tenderness, without any effect on the CRP or SAA levels compared to placebo (Grade II) (19). The effect of repeated methylprednisolone infusions throughout the attack period should be confirmed in further controlled trials.

Steroid infusions might be tried in colchicine-resistant cases since it is an inexpensive treatment. However, in patients with frequent attacks, the side effects of steroids can cause problems in the long term. Theoretically, in such cases one should consider steroid spar-

ing immunosuppressive agents, such as azathioprine, in order to reduce steroid side effects.
In summary, steroids are a potential measure to treat colchicine-resistant patients. However, their long term adverse effects should be seriously considered.

– Interferon alpha
Interferon is an antiviral agent with immunomodulatory properties. Interferon alpha (IFN-α) injection at the earliest signs of an attack provided some benefit in recent studies (Grade II) (20). In a double-blind, placebo-controlled trial, Tunca *et al*. treated 34 acute abdominal attacks with interferon 5 million IU or placebo sc IFN-α in the early phase of the attack. They found that CRP and SAA were extremely elevated and peaked at 24 hours, remaining numerically less marked in the interferon-treated patients (not statistically significant). Although they could not demonstrate a definitive effect of interferon alpha, they found some evidence indicating a depressed inflammatory response with this agent especially if administered at the earliest phase (Grade II) (20). Likewise, Tweezer-Zaks *et al*. demonstrated an association between early intervention with interferon-alpha injections and reduced attack duration and/or severity in 10 patients with a total of 80 attacks (21). Compared to 22 untreated attacks, a >20% reduction in the duration of the attacks was noted in 100% of the patients and >50% reduction in 90% of the 58 interferon-alpha-treated attacks. The most common drug-related adverse events were chills and fatigue, a common side effect of IFN-α in this study (Grade II). Calguneri *et al*. also showed that continuous interferon-α administration, in addition to the regular colchicine treatment, was effective in the treatment of attacks in eight colchicine-resistant FMF patients, 6 of whom responded well. It was also effective in another patient with resistant FMF complicated by polyarteritis nodosa (Grade III) (22). Observed side effects were generally mild and acceptable in the study of Calguneri *et al*. Despite these favorable results, the efficacy of this agent should also be tested in larger well-controlled trials.
In summary, interferon-α is a relatively safe drug and may be tried in the treatment of colchicine-resistant FMF patients. Nevertheless, since FMF attacks start unexpectedly, it is very difficult to use this drug in the earliest phases of the attack. Furthermore, since FMF starts at a young age and is a lifelong disease, continuous interferon administration is not a cost-effective or feasible treatment modality. Therefore, interferon should be kept as a last resort in treating FMF patients resistant to other drugs.

– TNF blocking agents (Thalidomide, Etanercept, Infliximab)
Seyahi *et al*. treated five FMF patients - who were experiencing at least two attacks per month despite regular colchicine treatment – with thalidomide 100 mg/day or etanercept 25 mg twice a week (23). Median follow-up period was eight months. The authors demonstrated that both thalidomide and etanercept lowered the number of the abdominal attacks (Grade III). Similarly, in a 35-year-old FMF patient in whom diarrhoea prevented optimal treatment with colchicine, Mor *et al*. demonstrated resolution of FMF manifestations with etanercept (25 mg twice a week) during three years of follow-up (24). Likewise, Sakallioglu *et al*. reported a 15-year-old patient with polyarthritis while on colchicine treatment for FMF who was also resistant to treatment with prednisolone and methotrexate. The patient responded dramatically to etanercept (0.8 mg/kg/week) and remained in full remission for four months (Grade III) (25). Metyas *et al*. also reported that treatment with infliximab resulted in a rapid suppression of FMF-associated recurrent attacks of arthritis, abdominal pain and high sedimentation rate, and a remarkable improvement of the proteinuria (Grade III) (26). Moreover, a combination of infliximab (3 mg/kg) and low-dose methotrexate (6 mg/week) was effective in controlling the attacks in another colchicine-resistant FMF patient (Grade III) (27).
Treatment with TNF blocking agents is associated with an increased risk of infections (especially tuberculosis) as well as rare instances of leucopenia, thrombocytopenia or exacerbation of hepatitis B, demyelinating disorders, and neoplastic diseases (28).
Therefore, using these agents in FMF needs to be balanced against their numerous side effects and their high cost.

– Anakinra (IL-1ra)
Anakinra, a recombinant nonglycosylated homologue of human interleukin (IL)-1 receptor (IL-1Ra), competitively inhibits binding of IL-1α and IL-1β to IL-1 receptor type I. Since pyrin has a role in activating the proinflammatory cytokine IL-1β, and IL-1β may have a role in the pathogenesis of FMF, anakinra has been suggested as a new therapeutic option in colchicine-resistant FMF patients (29). Immediate and sustained resolution of symptoms and laboratory markers of inflammation have been reported with anakinra in colchicine-resistant FMF patients (Grade III) (30-35). However, anakinra can be associated with frequent injection site reactions, and there is a slightly increased risk of infection. In summary, anakinra should be considered seriously in colchicine-resistant patients since it is an effective and short-acting agent. However, its high cost may postpone its widespread use in these cases.

– Selective serotonin reuptake inhibitors
In clinical practice, it is a common observation that FMF patients may have more attacks when they are under great stress (Grade III). Furthermore, depression may be an important component of the overall illness for FMF patients. In an observational study, plasma and platelet serotonin levels were found to be different in colchicine-resistant FMF patients during and after an attack in 13 colchicine non-responders compared with 11 responder FMF patients and 32 healthy controls (Grade II) (36). This suggested that serotonin may play a role in the pathogenesis of FMF, and those disturbances in serotonin transport mechanisms may modulate colchicine resistance. Initially, one patient noted apparent remission when an SSRI, paroxetine, was used (Grade III) (37). Sub-

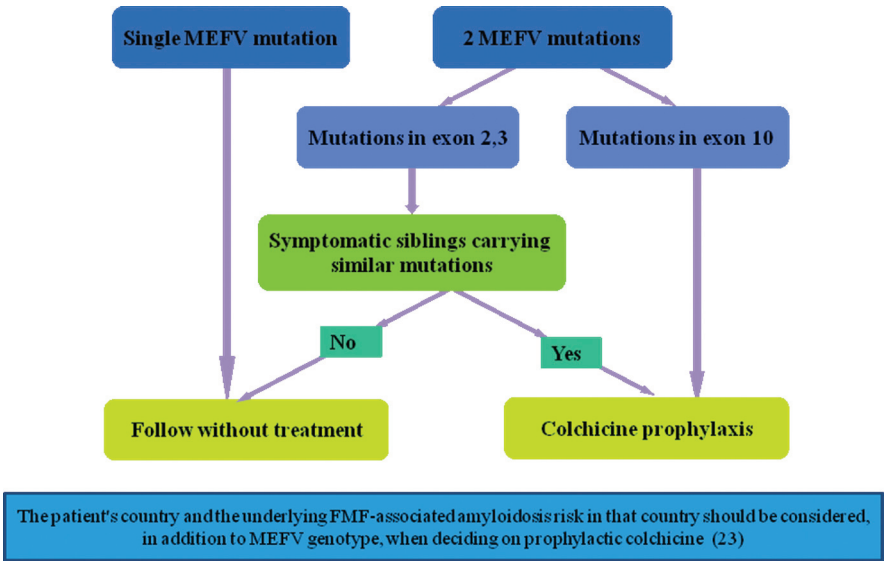

Fig. 2. Management of asymptomatic individuals carrying MEFV mutations.

sequent retrospective analysis of 11 colchicine-resistant FMF patients who had been treated with SSRI revealed a great decline in attack frequency after adding SSRI to colchicine. Moreover, acute phase response significantly improved after SSRI treatment (Grade III) (38). However, since these studies included FMF patients who had depression or fibromyalgia, further studies with SSRIs are needed to determine whether those agents are effective in colchicine-resistant FMF patients without symptoms of depression.

Management of FMF patients in whom the attacks are controlled but still having elevated acute phase reactants

Whether the colchicine dose should be increased in patients with elevated acute phase reactants, despite the absence of any clinical symptom, is another clinical problem. Regardless of the conflicting data, there is some evidence that ongoing subclinical inflammation of FMF could be associated with increased intima-media thickness of the carotid arteries, an early predictor of atherosclerosis (Grade II) (39, 40). However, it is not yet clear whether elevated acute phase reactants reflect subclinical inflammation or if they are surrogate predictors of amyloid development (Grade II) (41). Although elevated acute phase response during attack-free periods may be controlled by increasing the colchicine dosage (Grade II) (42), prospective studies should be performed to determine whether such dose adjustment is necessary for better long term prognoses in FMF. Until this issue is settled in future studies, our policy is to treat patients according to their clinical symptoms rather than their acute phase reactant levels.

Management of asymptomatic individuals carrying 2 MEFV mutations

The *MEFV* gene associated with FMF has been mapped to chromosome 16p13.3 and encodes a protein called Pyrin. This peptide is thought to be a negative regulator of inflammation. Up until now, about 198 MEFV mutations have been reported most of which are not associated with clinical manifestations. Five founding mutations M694V, V726A, M680I, M694I (in exon 10) and E148Q (in exon 2) are the most frequently encountered mutations, accounting for 74–85% of FMF mutations in typical patients (43,44). Incidental family screenings for MEFV mutations may identify asymptomatic subjects carrying 2 mutations. The question has been raised regarding the justification of colchicine treatment in these cases. There are no studies addressing this interesting issue and our recommendations are based on logical assessments rather than on firm evidence. First of all it should be emphasised that asymptomatic subjects found incidentally to carry a single mutation should not be treated. In patients carrying 2 mutations, either homozygotes or combined heterozygotes, it seems that our approach depends on the kinds of mutations. In individuals homozygous for mutations in exon 10 such as M694V, M680V V726A etc., we suggest full treatment with colchicine. The first reason is that these patients may develop FMF symptoms later in life. Secondly, they may still have risks for amyloidosis since development of this complication does not necessarily correlate with the frequency of the acute attacks as the case with phenotype II (FMF patients presenting with amyloidosis without any history of typical attack). In asymptomatic subjects carrying 2 mutations in exon 2 or 3 (*e.g.* E148Q) we recommend following their urine for proteinuria once every 4–6 months without colchicine treatment. If their siblings carrying similar mutations are symptomatic, treatment with colchicine should be considered (Grade III) (45). However, in a recent multicenter study of 2482 patients homozygous for M694V from 14 countries, the country of origin, rather than *MEFV* genotype, was the definitive risk factor for renal amyloidosis in FMF (odds ratio 3.2 [95% confidence interval 1.8–5.9]). The authors suggested that the patient's country and the underlying FMF-associated amyloidosis risk in that country should be considered, in addition to *MEFV* genotype, when deciding on prophylactic colchicine (Grade II) (46) (Fig. 2).

Management of special FMF manifestations

Arthritis

Arthritis in FMF has some characteristic features which are different from other inflammatory rheumatic diseases. The monoarticular pattern, especially involving the knee, is the prominent type. The acute attack usually subsides spontaneously within 4-7 days without sequela (47). However, protracted arthritis can occur in up to 5% of the patients and may cause disability, especially when the hip is involved (48, 49). Bakkaloglu *et al*. suggested sulphasala-

zine for protracted arthritis (Grade III) (50). Intramuscular gold was effective, anecdotally, in one patient (Grade III) (51). One of our patients with protracted knee arthritis had excellent results with continuous interferon alpha (4.5 million units, three times a week) (20, 52). Lastly, in resistant cases, etanercept and infliximab seems to be beneficial but there are neither long term data nor a large number of cases (Grade III) (53, 25). In mild cases, the addition of NSAIDs to colchicine may alleviate the joint pains.

Vasculitis

Polyarteritis nodosa (PAN) and Henoch-Schönlein purpura (HSP) are associated with FMF in approximately 1% and 3% of patients, respectively (48). Colchicine does not prevent the development of vasculitis, and thus additional therapies are required (54). Corticosteroids and immunsuppressives are the principal drugs used to treat FMF-associated vasculitis, and the outcome is satisfactory for most patients (55). However, there is an important group which does not respond to steroids and immunsuppressives. Calguneri *et al*. used interferon alpha three times a week and concluded that 6 of their 8 patients who were resistant to steroids and cyclophosphamide, benefited from the addition of interferon alpha with further improvement during 1 year of continued use (Grade III) (22, 56). In summary, in vasculitic diseases accompanying FMF, steroids and immunsuppressives should be added to colchicine treatment. Since interferon has been used as an alternative treatment in such cases, it should be tried only in FMF patients non responsive to immunosuppressive agents.

Protracted febrile myalgia

Protracted febrile myalgia (PFM) is an uncommon dramatic manifestation of FMF that may occur despite colchicine therapy (57). It is characterised by severe disabling myalgia accompanied by fever, high erythrocyte sedimentation rate, and hyperglobulinemia. Sometimes PFM may be accompanied by abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic rashes mimicking Henoch-Schönlein purpura (58). In contrast to typical FMF attacks, PFM may last up to 6 weeks. It can affect adults as well as children (59). The treatment of choice is high dose steroids (about 1 mg/kg daily) given for a few weeks. In rare cases, azathioprine as a steroid sparing medication can be used.

Management of amyloidosis due to FMF

Unfortunately, there is no proven effective treatment for established amyloidosis in FMF. Several case reports demonstrated some benefit of azathioprine (3 patients), and infliximab (2 cases) in FMF patients with amyloidosis (Grade III) (26, 60, 61).

Recently, eprodisate disodium, an inhibitor of amyloid fibril formation, has been tested in patients with AA amyloidosis and kidney involvement in a multicenter, randomised, double-blind, placebo-controlled trial (Grade I) (62). The study groups included patients with various chronic inflammatory disorders, predominantly rheumatoid arthritis (49% of patients) and FMF (19%). One hundred and eighty-three patients were randomly assigned to treatment with eprodisate or placebo. Improvement of renal disease occurred in only one patient in the eprodisate group and in two patients in the placebo group. On the other hand, as compared with placebo, eprodisate significantly reduced the risk of serum creatinine doubling, the risk of 50% reduction in creatinine clearance, and the slope of decline in creatinine clearance. Accordingly, the authors reported that eprodisate reduced the progression of AA amyloidosis–associated renal disease. Eprodisate had no significant effect on progression to end-stage renal disease or risk of death (perhaps because the study was only 2 years in length), and did not affect proteinuria. Moreover, there were some differences in the baseline characteristics of the groups. At baseline, patients in the eprodisate group had lower serum creatinine levels and lower diastolic pressure, and more frequent underlying chronic infection. The results might have also been confounded by accompanying medications which can modify renal damage (angiotensin converting enzyme inhibitors, cytotoxic agents, tumor necrosis factor (TNF) antagonists, and colchicine) (62). This study provided some evidence regarding the efficacy of eprodisate for the treatment of FMF amyloidosis but the results should be interpreted cautiously. Further studies are needed in more homogenous populations, and preferably in earlier stages of FMF amyloidosis.

In summary, in FMF patients with amyloidosis, colchicine should be continued at a maximal tolerated dosage. Beyond colchicine, little data are available to guide therapy. A few anecdotal reports support the use of azathioprine, infliximab or anti IL-1 agents. Based on simplicity of use and cost, azathioprine should be tried for up to 6 months (60). However, anti TNF and anti IL-1 agents should be the next therapeutic trials (Grade III) (26, 61, 63).

Management of FMF in males – effect on fertility

Colchicine is a drug which may affect cellular microtubules in various cells. In high concentrations it may inhibit mitosis within the process of cell division (64). Therefore, concern was raised as to the effect of colchicine on sperm proliferation and motility in patients taking this medication.

Merlin reported a patient with gout who developed azoospermia following treatment with colchicine (65). In this case, rechallenge with the drug resulted in reappearance of azoospermia. Because most FMF patients who receive colchicine – unlike patients with gout – are of child bearing age, the concern about fertility is more relevant. Indeed, rabbits treated with a relatively high dose of colchicine showed various degenerative changes of the testes, including loss of differentiation from spermatogonia to spermatozoa (66). In a study by Levy *et al*., no effect on fertility was noted in six patients receiving long-term colchicine therapy, and levels of spermatocytes, testosterone stimulating hormone, luteinizing hormone and prolactin were all within normal limits (67). Bremner and Paulson failed to show any effect on spermatogenesis in six healthy volunteers who

received commonly used doses of colchicine for 4–6 months (68). Conversely, in a study of 62 Turkish men with Behçet's disease on chronic colchicine treatment, oligospermia was evident in 23 patients (37%) and azoospermia in two patients (69). These findings suggest that other factors such as a genetic background or an underlying disease could affect the development of infertility and disturbed spermatogenesis after the use of colchicine. Local ischaemia in patients with Behçet's disease may also potentiate the colchicine-induced oligospermia.

Based on the above observations and studies, it is tempting to ascribe the development of azoospermia in FMF patients to colchicine. However, in three FMF patients with infertility, testicular biopsy was obtained and demonstrated amyloidois of the testes (70). Thus, it seems that one should be cautious in relating azoozpermia in FMF to colchicine and exclusion of amyloidosis is warranted.

Since sperm motility and hence ovum penetration depend upon microtubular function, a question was raised as to whether colchicine may affect sperm motility. The effect of colchicine on sperm motility in an *in vitro* system was studied exposing them to different colchicine concentrations and different durations (71). Sperm motility was inhibited significantly only after an incubation period of at least 18 hours with a minimum concentration of 10 mcg per ml. Because plasma colchicine concentration under therapeutic dose is about 3–9 ng/ml, the amount of colchicine needed for affecting sperm motility *in vitro* is 3,000-fold higher. Thus it seems unlikely that standard colchicine treatment would inhibit sperm motility unless the drug has a very high and special affinity to spermatozoa.

Another concern related to male fertility is the question of pregnancy outcome in wives of men with FMF. Owing to our poor data regarding the effect of FMF or colchicine taken by male patients on the pregnancy of their wives and the outcome of their newborns, some physicians used to advise them to discontinue the drug 3 months before attempting to conceive. A semi-prospective study followed the outcome of pregnancies and deliveries in 60 wives of FMF patients, 53 of whom were taking colchicine at the time of conception (72). As a control, the outcome of pregnancies and deliveries in 230 healthy women married to healthy men was also screened. No difference regarding the rates of abortions – early or late – or congenital malformations was found. Therefore, it seems that there is no need for FMF men to discontinue colchicine prior to their wives conceiving (Grade II) (72). Colchicine is safe in men and the occurrence of azo or olygospermia is extremly rare in FMF patients.

The management of FMF during menstruation

In some FMF female patients, the acute attacks may be preceded by their menstrual period. Several case reports of such patients have been described previously (73-75). Ten women in whom the acute FMF attacks occurred only in association with menstruation were studied (76). No specific epidemiological or clinical characteristics were found with respect to age of onset of the disease, disease duration or colchicine dosage. There was no correlation with any of the common *MEFV* mutations tested. Nevertheless, the association with menstruation raised the possibility of a hormonal connection. Previously it was shown that oestrogen significantly decreased intercellular adhesion molecules (77). Furthermore, in another study it was demonstrated that estrogens inhibits tubulin assembly interacting directly with tubulin 6S sites analogous to colchicine sites (78). Moreover, oestrogen is metabolised by the 3A4 liver Cytochrome 450 which also degrades colchicine. Thus, it is tempting to speculate that the estrogens mimic the effect of colchicine on tubules and adhesion molecules thereby enhancing colchicine effect. In menstruation there is a sharp decrease in oestrogens so that their accumulative suppressive effect on inflammation is diminished. In addition, the lack of oestrogen allows for more effective metabolism of colchicine by the 3A4 cytochrome (less inhibitory competition) so that the effective level of colchicine is further reduced. Therefore, in order to control menstruation-associated attacks, it is recommended that colchicine dosage should be increased for two or three days prior to the onset of the menstrual period and 2 days after its start. During this finite time interval it is necessary to administer a higher dose of colchcine – up to 2.5 mg daily (Grage III) (76). If this fails and the patient does not have medical or religious restrictions, it is suggested to take contraceptive medication.

Management of FMF during pregnancy

Serious concern was raised regarding a teratogenic effect of colchicine. Therefore, in the 1970s we advised our patients to discontinue the drug 3 months before planned conception and during pregnancy. Nevertheless, sporadic reports claimed that colchicine was safe during pregnancy (79).

Out of 500 pregnancies in FMF patients treated with colchicine, Down syndrome was found in 4 instances (80). Three were diagnosed by karyotyping in amniocentesis and one was born alive. In an updated series there were 2 cases out of 1124 pregnancies (81). The calculating rate of 1:600 is slightly higher than that expected in the FMF patient group (1:900). It was not clear whether colchicine or the disease itself increases the risk for 21 trisomy (if at all). Therefore, we used to recommend amniocenthesis in FMF patients taking colchicine during pregnancy. A recent study evaluated the outcome of pregnancies in FMF patients taking colchicine in order to reconsider the justification for amniocentesis in these women (82). Two hundred and thirty-two pregnancies in a group of FMF patients taking colchicine were compared with the outcome of 248 pregnancies in FMF women who did not take colchicine during pregnancy and with 337 pregnancies in another cohort of healthy pregnant women of similar age and ethnicity. There was no difference between the three groups regarding early abortions, late abortions or congenital malformations. There was a mild trend towards a better outcome for

the colchicine-treated group but these results did not reach a statistical significance. Since treatment with colchicine during pregnancy in FMF patients is beneficial in controlling the disease while not affecting its outcome, there is no justification for recommending amniocentesis (Grade II) (82) .

Management of FMF during nursing

Pharmaceutical company leaflets and textbooks of pharmacology warn women not to nurse their babies while on colchicine treatment (83). Milunsky and Milunsky found colchicine in the breast milk of patients taking the drug (84). In an additional study, the levels of colchicine were determined in sera and milk of 4 FMF patients at various time points after drug ingestion (85). Colchicine was detected in all samples of sera and milk, and its concentrations were similar. However, the estimated daily amount of colchicine ingested by the nursing babies is less than one-tenth the therapeutic dose (per kilogram) given to the adult. Therefore, it is recommended to continue breast feeding while on colchicine (Grade II) (85).

Management of FMF in patients with renal or hepatic failure

Colchicine is metabolised in the liver by the cytochrome (CYP) p450-3A4 isotype. The major two metabolisers are 3 methylcolchicine and 2 methylcolchicine (86). The parent drug and its metabolites are present in the intestine as well as in the bile secretion, suggesting that there is an entero-hepatic circulation. About 40% of the drug and its metabolites are secreted by the biliary system whereas the remaining 60% are secreted by the kidneys. Therefore it is expected that compromised function of these two organs may lead to an accumulation of the drug and a severe risk of intoxication. In rats, experimentally-induced liver damage was associated with a marked decrease in colchicine clearance and significant prolongation of its T1/2 (87). The evaluation of the pharmacokinetics of colchicine in FMF patients with and without renal or liver damage revealed that colchicine clearance was impaired in those with kidney or liver failure (88). The T1/2 of colchicine in patients with severe renal failure was two- to three-fold longer, and in a patient with renal failure and liver cirrhosis even 10-fold longer than that of patients without these diseases. Leighton *et al*. reported similar results in patients with liver cirrhosis (89). These findings suggest that patients with either liver or renal disease should be closely monitored and their colchicine dose should be reduced. Furthermore, in patients with kidney or liver impairment caution should be exercised when giving concomitant medications potentially capable of affecting colchicine metabolism either by inhibiting cytochrome CYP 3A4 or deranging the ATP-binding cassette subfamily B member 1 (ABCB1) (Table III, Fig. 1).

Conclusion

In conclusion, colchicine remains the leading therapeutic option in FMF. It reduces attack frequency, decreases severity and shortens duration of the acute attacks in most FMF patients. It also prevents the development of amyloidosis. However, it is less effective in arthritis or myalgia which requires additional treatment with NSAIDs and steroids. In a few cases where FMF is resistant to colchicine, other measures should be employed. Case reports, case series and small controlled trials have supported the use of corticosteroids, SSRIs, non-biological DMARDs, and interferon alpha. However, it seems that a breakthrough is expected with TNF blocking agents and especially with inhibitors of IL-1 and other possible interleukin pathways.

References

1. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-64.
2. GRATEAU G: Clinical and genetic aspects of the hereditary periodic fever syndromes. *Rheumatology* (Oxford) 2004; 43: 410-5.
3. BEN-CHETRIT E, TOUITOU I: Familial Mediterranean fever in the world. *Arthritis Rheum* 2009; 63: 1447-53.
4. GOLDFINGER SE: Colchicine for familial Mediterranean fever. *N Eng J Med* 1972; 287: 1302.
5. OZKAN E, OKUR O, EKMEKCI A *et al*.: A new approach to the treatment of periodic fever. *Med Bull Istanbul Med Fac* 1972; 5: 44-9.
6. COPEMAN WSC: *A Short History of the Gout and the Rheumatic Diseases*. Los Angeles, CA: University of California Press; 1964.
7. EL-SHANTI HI: Familial mediterranean fever and renal disease. *Saudi J Kidney Dis Transpl* 2003; 14: 378-5.
8. ZEMER D, REVACH M, PRAS MA *et al*.: A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med* 1974; 291: 932-4.
9. DINARELLO CA, WOLFF SM, GOLDFINGER SE *et al*.: Colchicine therapy for familial Mediterranean fever: a double-blind trial. *N Engl J Med* 1974; 291: 934-7.
10. ŞIMŞEK B, ISLEK I, ŞIMŞEK T, KÜÇÜKÖDÜK S, CENGIZ K: Regression of nephrotic syndrome due to amyloidosis secondary to familial Mediterranean fever following colchicine treatment. *Nephrol Dial Transplant* 2000; 15: 281-2 .
11. KIM S, IKUSAKA M, MIKASA G *et al*.: Clinical study of 7 cases of familial Mediterranean fever with MEFV gene mutation. *Intern Med* 2007; 46: 221-5.
12. TSUCHIYA-SUZUKI A, YAZAKI M, NAKAMURA A *et al*.: Clinical and genetic features of familial Mediterranean fever in Japan. J *Rheumatol* 2009; 36: 1671-6.
13. KALLINICH T, HAFFNER D, NIEHUES T *et al*.: Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; 119: e474-e483.
14. BEN-CHETRIT E, LEVY N: Colchicine: 1998 *Update Semin Arthritis Rheum* 28: 48-59.
15. KUNCL RW, DUNCAN G, WATSON D *et al*.: Colchicine myopathy and neuropathy. *N Engl J Med* 1987; 316: 1562-8.
16. OZEN S, BILGINER Y, AKTAY AYAZ N, CALGUNERI M: Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine. *J Rheumatol* 2011 Mar; 38: 516-8.
17. BEN-CHETRIT E, AAMAR S: About colchicine compliance, resistance and virulence. *Clin Exp Rheumatol* 2009; 27 (Suppl. 53): S1-S3.
18. BEN-CHETRIT E, OZDOGAN H: Non-response to colchicine in FMF--definition, causes and suggested solutions. *Clin Exp Rheumatol* 2008; 26 (4 Suppl. 50): S49-S51.
19. ERKEN E, OZER HT, BOZKURT B et al.: Early suppression of familial Mediterranean fever attacks by single medium dose methyl-prednisolone infusion. *Joint Bone Spine* 2008; 75: 370-2.
20. TUNCA M, AKAR S, SOYTÜRK M et al.: The effect of interferon alpha administration on acute attacks of familial Mediterranean fever: A double-blind, placebo-controlled trial. *Clin Exp Rheumatol* 2004; 22 (4 Suppl. 34): S37-S40.
21. TWEEZER-ZAKS N, RABINOVICH E, LIDAR M et al.: Interferon-alpha as a treatment modality for colchicine- resistant familial Mediterranean fever. *J Rheumatol* 2008; 35: 1362-5.
22. CALGUNERI M, APRAS S, OZBALKAN Z *et al*.: The efficacy of continuous interferon alpha administration as an adjunctive agent to colchicine-resistant familial Mediterranean fever patients. *Clin Exp Rheumatol* 2004; 22 (4 Suppl. 34): S41-S44.
23. SEYAHI E, OZDOGAN H, CELIK S *et al*.: Treatment options in colchicine resistant familial Mediterranean fever patients: thalidomide

and etanercept as adjunctive agents. *Clin Exp Rheumatol* 2006; 24 (Suppl. 42): S99-S103.
24. MOR A, PILLINGER MH, KISHIMOTO M *et al*.: Familial Mediterranean fever successfully treated with etanercept. *J Clin Rheumatol* 2007; 13: 38-40.
25. SAKALLIOGLU O, DUZOVA A, OZEN S: Etanercept in the treatment of arthritis in a patient with familial Mediterranean fever. *Clin Exp Rheumatol* 2006; 24: 435-7.
26. METYAS S, ARKFELD DG, FORRESTER DM *et al*.: Infliximab treatment of familial Mediterranean fever and its effect on secondary AA amyloidosis. *J Clin Rheumatol* 2004; 10: 134-7.
27. NAKAMURA A, MATSUDA M, TAZAWA K *et al*.: Successful treatment with infliximab and low-dose methotrexate in a Japanese patient with familial Mediterranean fever. *Intern Med* 2007; 46: 1247-9.
28. CAPORALI R, PALLAVICINI FB, FILIPPINI M *et al*.:Treatment of rheumatoid arthritis with anti-TNF-alpha agents: a reappraisal. *Autoimmun Rev* 2009; 8: 274-80.
29. CHAE JJ, WOOD G, MASTERS SL *et al*.: The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1B production. *Proc Natl Acad Sci USA* 2006; 103: 9982-7.
30. ROLDAN R, RUIZ AM, MIRANDA MD *et al*.: Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine* 2008; 75: 504-5.
31. GATTRINGER R, LAGLER H, GATTRINGER KB *et al*.: Anakinra in two adolescent female patients suffering from colchicine-resistant familial Mediterranean fever: effective but risky. *Eur J Clin Invest* 2007; 37: 912-4.
32. KUIJK LM, GOVERS AM, FRENKEL J *et al*.: Effective treatment of a colchicine-resistant familial Mediterranean fever patient with anakinra. *Ann Rheum Dis* 2007; 66: 1545-6.
33. CALLIGARIS L, MARCHETTI F, TOMMASINI A *et al*.: The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever. *Eur J Pediatr* 2008; 167: 695-6.
34. BELKHIR R, MOULONGUET-DOLERIS L, HACHULLA E *et al*.: Treatment of familial Mediterranean fever with anakinra. *Ann Intern Med* 2007; 146: 825-6.
35. OZEN S, BILGINER Y, AYAZ NA, CALGUNERI M: Anti-Interleukin 1 treatment for patients with Familial Mediterranean Fever Resistant to Colchicine. *J Rheumatol* 2011; 38: 516-8.
36. ONAT AM, OZÇAKAR L, OZTÜRK MA *et al*.: Plasma and platelet serotonin levels in familial Mediterranean fever. *Clin Exp Rheumatol* 2007; 25 (Suppl. 45): S16-S20
37. OZCAKAR L, ONAT AM, KAYMAK SU *et al*.: Selective serotonin reuptake inhibitors in familial Mediterranean fever: Are we treating depression or inflammation? *Rheumatol Int* 2005; 25: 319-0.
38. ONAT AM, OZTÜRK MA, OZÇAKAR L *et al*.: Selective serotonin reuptake inhibitors reduce the attack frequency in familial Mediterranean Fever. *Tohoku J Exp Med* 2007; 211: 9-14.
39. PERU H, ALTUN B, DOĞAN M *et al*.: The evaluation of carotid intima-media thickness in children with familial Mediterranean fever. *Clin Rheumatol* 2008; 27: 689-94.
40. SARI I, KARAOGLU O, CAN G *et al*.: Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. *Clin Rheumatol* 2007; 26: 1467-73.
41. YALCINKAYA F, CAKAR N, ACAR B *et al*.: The value of the levels of acute phase reactants for the prediction of familial Mediterranean fever associated amyloidosis: a case control study. *Rheumatol Int* 2007; 27: 517-22.
42. DUZOVA A, BAKKALOGLU A, BESBAS N *et al*.: Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. *Clin Exp Rheumatol* 2003; 21: 509-14.
43. INFEVERS The registry of Familial Mediterranean Fever (FMF) and hereditary Autoinflammatory Disorders Mutations. http://fmf.igh.cnrs.fr/ISSAID/infevers/. Accessed 11 Mar 2008
44. TOUITOU I: Standardized testing for mutations in familial Mediterranean fever. *Clin Chem* 2003; 49: 1781-2.
45. LIVNEH A, LANGEVITZ P, SHINAR Y *et al*.: MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. *Amyloid* 1999; 6: 1-6.
46. TOUITOU I, SARKISIAN T, MEDLEJ-HASHIM M *et al*.; INTERNATIONAL STUDY GROUP FOR PHENOTYPE-GENOTYPE CORRELATION IN FAMILIAL MEDITERRANEAN FEVER: Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum* 2007; 56: 1706-12.
47. INCE E, CAKAR N, TEKIN M *et al*.: Arthritis in children with familial Mediterranean fever. *Rheumatol Int* 2002; 21: 213-7.
48. TUNCA M, AKAR S, ONEN F *et al*.; TURKISH FMF STUDY GROUP: Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine* (Baltimore) 2005; 84: 1-11.
49. OZCAKAR L, ONAT AM, URETEN K *et al*.: Sonographic evaluation of the tendons in familial Mediterranean fever and Behçet's disease. *Joint Bone Spine* 2006; 73: 514-7.
50. BAKKALOGLU SA, AKSU T, GOKER B *et al*.: Sulphasalazine treatment in protracted familial Mediterranean fever arthritis. *Eur J Pediatr* 2009; 168: 1017-9.
51. DEMIRAG MD, OZTURK MA, GOKER B *et al*.: Intramuscular gold for the treatment of seronegative spondyloarthropathy associated with familial Mediterranean fever. *Rheumatol Int* 2008; 29: 77-9.
52. URETEN K, CALGÜNERI M, ONAT AM *et al*.: Interferon alfa in protracted arthritis of familial Mediterranean fever: a robust alternative for synovectomy. *Ann Rheum Dis* 2004; 63: 1527.
53. DAYSAL S, AKCIL G, GOKER B *et al*.: Infliximab therapy in a patient with familial Mediterranean fever and chronic hip arthritis. *Arthritis Rheum* 2005; 53: 146-7.
54. TEKIN M, YALCINKAYA F, TÜMER N *et al*.: Familial Mediterranean fever – renal involvement by diseases other than amyloid. *Nephrol Dial Transplant* 1999; 14: 475-9.
55. OZEN S, BEN-CHETRIT E, BAKKALOGLU A *et al*.: Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF? *Semin Arthritis Rheum* 2001; 30: 281-7.
56. CALGUNERI M, APRAS S, OZBALKAN Z, OZTURK MA: The efficacy of interferon-alpha in a patient with resistant familial Mediterranean fever complicated by polyarteritis nodosa. *Intern Med* 2004; 43: 612-4.
57. LANGEVITZ P, ZEMER D, LIVNEH A, SHEMER J, PRAS M: Protracted febrile myalgia in patients with familial Mediterranean fever. *J Rheumatol* 1994; 21: 1708-9.
58. KAPLAN E, MUKAMEL M, BARASH J *et al*.: Protracted febrile myalgia in children and young adults with familial Mediterranean fever: analysis of 15 patients and suggested criteria for working diagnosis. *Clin Exp Rheumatol* 2007; 25 (Suppl. 45): S114-7.
59. TUFAN G, DEMIR S: Uncommon clinical pattern of FMF: protracted febrile myalgia syndrome. *Rheumatol Int* 2010; 30: 1089-90.
60. SAYARLIOGLU H, ERKOC R, SAYARLIOGLU M *et al*.: Successful treatment of nephrotic syndrome due to FMF amyloidosis with azathioprine: report of three Turkish cases. *Rheumatol Int* 2006; 27: 197-9.
61. YUKSEL S, YALCINKAYA F, ACAR B *et al*.: Clinical improvement with infliximab in a child with amyloidosis secondary to familial Mediterranean fever. *Rheumatology* (Oxford) 2006; 45: 1307-8.
62. DEMBER LM, HAWKINS PN, HAZENBERG BP *et al*.; EPRODISATE FOR AA AMYLOIDOSIS TRIAL GROUP: Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; 356: 2349-60.
63. BILGINER Y, AYAZ NA, OZEN S: Anti-IL-1 treatment for secondary amyloidosis in an adolescent with FMF and Behçet's disease. *Clin Rheumatol* 2010; 29: 209-10.
64. BAKER ME: Colchicine inhibits mitogenesis in C1300 neuroblastoma cells that have been arrested in G0. *Nature* 1976; 262: 785-6.
65. MERLIN HE: Azoospermia caused by colchicine – a case report. *Fertil Steril* 1972: 23, 180-1.
66. BARSOU IS: The effect of colchicine on the spermatogenesis of rabbits. *J Pharmacol Exp Ther* 1955; 113: 319-22.
67. LEVY M, YAFFE C: Testicular function in patients with familial Mediterranean fever, on long-term colchicine treatment. *Fertil Steril* 1978; 29: 667-8.
68. BREMNER WJ, PANLSON CA: Colchicine and testicular function in man. *N Engl J Med* 1976; 294: 1384-5.
69. SARICA K, SUZER O, GURLER A, BALTACI S, OZDILER E, DINCEL C: Urological evaluation of Behcet patients and the effect of colchicine on fertility. *Eur J Mol* 1995; 22: 39-42.
70. HAIMOV-KOCHMAN R, PRUS D, BENCHETRIT E: Azoospermia due to testicular amyloidosis in a patient with familial Mediterranean fever. *Hum Reprod* 2001; 16: 1218-20.
71. BEN-CHETRIT A, BEN-CHETRIT E, NITZAN R, RON M: Colchicine inhibits spermatozoal motility *in vitro*. *Int J Fertil Menopausal Stud* 1993; 38: 301-4.
72. BEN-CHETRIT E, BERKUN Y, BEN-CHETRIT E, BEN-CHETRIT A: The outcome of pregnancy in the wives of men with familial mediterranean fever treated with colchicine. *Semin*

Arthritis Rheum 2004; 34: 549-52.
73. SCHWARTZ J: Periodic peritonitis, onset simultaneously with menstruation. *Ann Intern Med* 1960; 53: 407-11.
74. GOLDEN RL, WEIGERS EW, MEAGHER JG: Periodic fever and menses. *Am J Obstet Gynecol* 1973; 855-6.
75. MILANO AM: Familial Mediterranean fever associated with menstruation. *Am J Gastroenterol* 1981; 76: 363-4.
76. BEN-CHETRIT E, BEN-CHETRIT A: Familial Mediterranean fever and menstruation. *BJOG* 2001,108: 403-7.
77. KOH KK, BUI MN, MINCEMOYER R, CANNON RO 3RD: Effects of hormone therapy on inflammatory cell adhesion molecules in postmenopausal healthy women. *Am J Cardiol* 1997; 80: 1505-7.
78. CHAUDOREILLE MM, PEYROT V, BRAGUER D, CODACCIONI F, CREVAT A: Qualitative study of the interaction mechanism of estrogenic drugs with tubulin. *Bichem Pharmacol* 1991; 41: 685-93.
79. BEN-CHETRIT E, LEVY M: Colchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years. *Semin Arthritis Rheum* 1991; 20: 241-6.
80. RABINOVITCH O, ZEMER D, KUKIA E *et al*.: Colchicine treatment in conception and pregnancy: two hundred and thirty one pregnancies in patients with familial Mediterranean fever. *Am J Reprod Immunol* 1992; 22: 145-6.
81. BARKAI G, MEITAL Y, CHETRIT A, BARELL V, AVIRAM A, ZEMER D: Evaluation of pregnancy outcome among FMF colchicine treated women. 1st International Conference on FME September 1997, Jerusalem, Israel (abstract).
82. BEN-CHETRIT E, BEN-CHETRIT A, BERKUN Y, BEN-CHETRIT E: Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified? *Arthritis Care Res* 2010; 62: 143-8.
83. BRIGGS GG, FREEMAN RK, YAFFE RS: Drugs in pregnancy and lactation. 4th ed. Baltimore: Williams & Wilkins, 1994.
84. MILUNSKY JM, MILUNSKY A: Breast feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr* 1991; 119: 163.
85. BEN-CHETRIT E, SCHERRMANN J-M, LEVY M: Colchicine in breast-milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; 39: 1213-7.
86. SCHONHASTING M, MENDE G, SIEBERT G: The metabolism of colchicine by mammalian liver microsomes. *J Physiol Chem Biol* 1974; 355: 1391-9.
87. LEIGHTON SA, BAY MK, MALDONADO AL, JOHNSON RF, SCHENKER S, SPEEG KV: The effect of liver dysfunction on colchicine pharmacokinetics in the rat. *Hepatology* 1990; 11: 21-5.
88. BEN-CHETRIT E, SCHERRMANN J-M, ZILBER-KATZ E, LEVY M: Colchicine disposition in FMF patients with renal diseases. *J Rheumatol* 1994; 21: 710-3.
89. LEIGHTON JA, BAY MK, MALDONADO AL, SCHENKER S, SPEEG KV: Colchicine clearance is impaired in alcoholic cirrhosis. *Hepatology* 1991; 14: 1013-5.