Therapeutic approaches to familial Mediterranean fever. What do we know and where are we going to?

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Introduction
FMF (familial Mediterranean fever) is an autosomal recessive disease characterized by recurrent attacks of fever, serositis, arthritis, or erysipelas-like skin lesions (1-3). The disease is commonly distributed among Turks, Armenians, Middle-Eastern Muslims, and Sephardic Jews. The major complication of the disease is the development of secondary amyloidosis that may lead to renal failure. Amyloid fibrils may also accumulate in other organs, including the heart, intestines, and testes (3).

Over the years several therapeutic approaches have been tried, some of which have proved successful. Colchicine is the main drug used to control FMF in most cases. Nevertheless, therapeutic trials with interferon, thalidomide, anti-TNF agents and immunomodulatory medications have also been conducted among patients who are non-responsive to colchicine or who cannot endure its adverse effects.

Colchicine
Colchicine is the basis of all therapeutic approaches in FMF since 1972 (4). This drug, originally extracted from Colchicum autumnale, is an anti-inflammatory drug that has been in continuous use for more than 3000 years (5). In FMF colchicine prevents acute attacks and averts the development of amyloidosis (5-7).

The therapeutic action of colchicine has been ascribed to several mechanisms. Bessis and Breton-Gorius (8) discovered that colchicine disrupts the microtubules in a dose-dependent fashion. Colchicine does not enhance microtubule dissolution but abrogates the process of microtubule self-assembly by forming tubulin-colchicine complexes (9,10). Colchicine reduces the generation of TNF-α by macrophages and its receptors on endothelial cells (11,12). Colchicine also has been shown to interfere with the interaction of neutrophils and the vascular endothelium by abrogating their binding to adhesion molecules. Colchicine abrogates the E-selectin-mediated adhesiveness of the cytokine-stimulated vascular endothelium for neutrophils (13). At supra-therapeutic concentrations colchicine alters the surface expression of L-selectin on leukocytes, impeding their motion along the vascular endothelium (13). In addition, at such concentrations colchicine suppresses phospholipase A2 activation, lysosomal enzyme release, and phagocytosis (4, 14-16). On the other hand, colchicine does not exert its anti-inflammatory effect through the inhibition of cyclooxygenases (17).

The average dose of colchicine in adults is 1 mg daily, but it may be increased up to 2 mg if remission is not obtained or in patients who have already developed amyloidosis. In rare cases of severely active patients, the dose may be increased to 2.5-3.0 mg daily for a short period of time (2-3 months) and then reduced back to the original dosage. In these cases the kidney and liver functions should be closely monitored. 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 the patients do not respond to therapy; however, most of them are non-compliant. Abdominal pain and diarrhea are the main adverse effects of daily colchicine therapy, but many patients overcome these symptoms by reducing the dose or by dividing it during the day. Patients with either hepatic or renal impairment are predisposed to uncommon side effects such as myopathy, neuropathy, and leukopenia. However,
rare cases where patients presented with myopathy despite normal kidney and liver functions have also been reported (18). Patients should be encouraged to take colchicine daily, otherwise an acute attack may ensue within days (3).

Colchicine was not found to cause female infertility; it is highly recommended to continue the drug during all phases of pregnancy, since peritonitis resulting from an acute attack may induce premature contractions of the uterus and eventual abortions (19).

Solid data concerning the teratogenic potential of colchicine is lacking; Ravinnovitch et al. (20) reported four newborns with trisomy 21 out of 2000 (1:500) deliveries in FMF patients, which is twice the expected rate of a comparable normal population. It is not clear whether colchicine therapy itself plays a role with this increment; our policy is to perform an amniocentesis at 4-5 months of gestation (21). We do not find a substantial reason to recommend ceasing therapy with colchicine prior to conception as well. Regarding the outcome of offspring of FMF males who are on chronic treatment with colchicine, no differences were observed compared with a matching cohort of healthy males (22). Colchicine can be safely taken during lactation and can be safely given to children; the prevention of acute attacks is associated with a growth spurt following the commencement of therapy (22-23). In children the dose is adjusted according to their weight. The minimal dose is about 0.25 mg daily in 1-2 year old babies. From the age of 6-7, children can be treated with the full dose of 1.0 mg daily.

Although colchicine seems to be the mainstay therapy in FMF, as we previously mentioned not all patients with FMF enjoy a noteworthy clinical remission. Several clinical teams have been engaged in the development of new therapeutic approaches to the disease.

**Intravenous colchicine**

Lidar et al. (24) evaluated the efficacy and safety of weekly intravenous colchicine in addition to oral colchicine therapy among patients with FMF who were unresponsive to oral colchicine prophylaxis. In their study 13 patients with frequent FMF attacks, despite oral doses of 2-3 mg/day colchicine, were treated with a weekly intravenous injections of 1 mg colchicine for 12 weeks in an open-label pilot study. A 50% reduction in attack frequency and attack severity in at least one site was achieved by 10 and 6 of the 13 patients, respectively. The mean number of abdominal attacks declined from 4.2 ± 3.0 per patient at baseline to 1.9 ± 2.6 attacks at the end of the third month of the study, yet joint attacks were unrelied during the study period. Based on the 10 cm visual analog scale, the mean severity of abdominal attacks declined from a baseline of 6.1 ± 0.95 to 3.9 ± 2.8 after 3 months (p=0.02). Comparable significant changes were observed in chest attacks, the erythrocyte sedimentation rate, and the number of analgesic tablets used. The treatment was safe and well tolerated, without side effects. These results are in concordance with the finding that the concentration of colchicine in lymphocytes derived from non-responders reaches about 50% of the concentration in lymphocytes from responders (25). Therefore, the bolus intravenous administration of colchicine might have overcome the absorptive failure of non-responders. These results are in concordance with the finding that the concentration of colchicine in lymphocytes derived from non-responders reaches about 50% of the concentration in lymphocytes from responders (25). Therefore, the bolus intravenous administration of colchicine might have overcome the absorptive failure of non-responders.

Nevertheless, since no control group was elected, these results should be regarded in caution since they may merely reflect a placebo effect. Furthermore, the serum half-life of the drug given orally is about 9 hours and when given intravenously it is significantly shorter; the clinical impact that it confers after a week’s time is in a way ambiguous. In addition, since an intravenous bolus of colchicine is believed to raise the serum and tissue levels of the drug, it is conceivable that one can increase the oral dose of colchicine in order to achieve the same effect. Finally, the risk of colchicine intoxication is much higher when given intravenously compared to the oral route.

Regarding the concentration of colchicine in lymphocytes, it is worth noting that the colchicine level in lymphocytes was found to be significantly lower than that in neutrophils (26). This might reinforce the observation that the neutrophils are the main cells involved in the acute inflammatory process in FMF (27).

**Interferon alpha**

This approach has been adopted following the observation that acute FMF attacks ceased in a patient with a chronic hepatitis B infection who was being treated with interferon alpha, and reappeared after this regimen was discontinued (28). Tunca et al. treated 7 colchicine-unresponsive patients during 21 typical acute attacks of FMF with interferon-alpha at doses ranging from 3-10 million IU s.c (29). Eighteen of the 21 attacks could be halted in a mean time of 3.05 hours, and the intensity of abdominal pain remained very low. The side effects were mild and easily tolerated. Another experience with interferon treatment was reported by Calguneri et al. (30). However, in a recent double-blind controlled study by Tunca et al. there was no significant beneficial effect with interferon treatment (31).

**Thalidomide**

Seyahi et al. (32) reported on the successful results of thalidomide given to a patient with FMF who was resistant to 2mg daily colchicine. The patient had 3-6 attacks per month despite vigorous treatment with colchicine. Following the addition of 100 mg thalidomide daily, he experienced a single attack per month. Thalidomide has been shown to inhibit chemotaxis (33), and to decrease monocyte phagocytosis. This drug selectively inhibits TNF-alpha production without affecting IL-1 and IL-6. Nevertheless, it should be mentioned that the widespread use of this medication is hindered by its side effects. It has distinct teratogenicity and causes peripheral neuropathy at high rates.

**Anti-TNFAgents**

Several anti-TNF agents are used in various inflammatory diseases. Inflix-
imab (anti-TNF antibodies) and Etanercept (recombinant soluble TNF receptors) are given to many patients with rheumatologic diseases or inflammatory bowel diseases. There are some anecdotal reports (as yet unpublished) where these agents were used to alleviate acute FMF attacks and in cases of kidney amyloidosis. It seems that these therapeutic measures do have the potential to help FMF patients who are non-responsive to colchicine during abrupt episodes. However, their role in the long-term prevention of FMF attacks and amyloidosis remained to be elucidated.

**Immunosuppressive therapy**

Generally, immunosuppressive medications are not used in order to control FMF attacks. In the pre-colchicine era there were therapeutic trials with ACTH and steroids in FMF patients. Since steroids are potent anti-inflammatory agents, some FMF patients responded positively to this treatment. However, their role in FMF prophylaxis and amyloidosis prevention is not clear. Furthermore, their serious potential side effects in long-term treatment have averted their routine use in this disease. Regarding other immunosuppressive medications, there are some anecdotal reports (not published) where these agents were used to alleviate the acute inflammatory episodes, some FMF patients resistant to colchicine, mainly because of their ominous mechanism of action. In 3 patients with amyloidosis-induced nephrotic syndrome, colchicine was ineffective while treatment with prednisone and azathioprine significantly reduced their proteinuria (unpublished data). It seems that for the acute inflammatory episodes of FMF immunosuppressants are not an attractive alternative to colchicine, mainly because of their ominous side effects and low efficacy. However, in cases of amyloidosis their use may be justified.

**Allogenic bone marrow transplantation**

Bone marrow transplantation is a highly toxic mode of therapy with an extremely high mortality rate. We believe that the conception that bone marrow transplantation has no role in the therapeutical approach to patients with FMF is shared by all clinicians; however, an interesting case report underscoring the curative potential of this therapeutical modality has been reported by Millidge et al. (34). They reported on a 7-year-old girl with congenital dyserythropoietic anemia (CDA), who also had FMF. Repeated transfusions required since the age of 6 months to treat her CDA led to iron overload and a persistently high ferritin level. Her relapsing FMF made effective iron chelation therapy very difficult. Consequently, at the age of 4 years, she underwent allogeneic sibling bone marrow transplantation. During and following her conditioning for her bone marrow transplantation, symptoms of FMF, including splenomegaly, arthritis, and recurrent abdominal pain, began to resolve and she was gradually weaned off colchicine. Two years after the transplantation, she remains free from FMF symptoms and is off all immunosuppressants.

In a letter to the Editor by physicians dealing with FMF, an absolute reservation was expressed regarding this therapeutic approach in FMF, which is not a deadly disease and which may be well controlled by medical treatment (35).

In summary, colchicine remains the main and the best treatment for the prevention of FMF attacks and its complication—amyloidosis. The various modes of therapy mentioned above are of limited value since most of them may be effective only during the acute attack, but their role in FMF prophylaxis or amyloid prevention is still questionable.

**References**

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