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Familial Mediterranean Fever: From Pathogenesis to Treatment

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Abstract

Familial Mediterranean Fever (FMF) is rare autosomal recessive autoinflammatory disorder characterized by periodic bouts of fever, serositis, synovitis, and/or cutaneous inflammation. Painful febrile attacks last 1 to 3 days and can vary in severity. FMF is almost exclusively affecting subjects with Mediterranean origin, especially Armenian, Arab, Jewish, Turkish, North Africans and Arabic descents. Cases have been reported in Italian population with a cluster of Italian patients living in Apulia and Basilicata. FMF results from the mutations in the *MEFV* (Mediterranean Fever) gene, consisting of 10 exons located on chromosome 16p13.3. *MEFV* encodes a 781 amino acid (86kDa) protein (pyrin or marenostrin) expressed in granulocytes, monocytes, serosal and synovial fibroblasts. In FMF, pyrin function is dysregulated with abnormal transcription of intranuclear peptides involved in inflammation. During acute attacks, a marked acute-phase response leads in leukocytosis, and elevated erythrocyte sedimentation rate, fibrinogen, C reactive protein, Serum Amyloid A protein. A worrisome manifestation of FMF is the evolution towards the secondary AA glomerular amyloidosis which puts a subgroup of patients at risk of end-stage kidney disease. Treatment of symptomatic FMF patients is aimed to prevent the acute attacks, and the development and progression of amyloidosis. Colchicine treatment given lifelong is the safe and effective in FMF patients at any age. In the few colchicine-resistant/ intolerant FMF patients, experimental off-label treatments include IL-1 β inhibitors (anakinra, riloncept, canakinumab), and anti-TNF- α agents (etanercept). This review describes pathophysiologic, diagnostic, and therapeutic aspects of FMF.

Keywords: Autosomal recessive autoinflammatory disorder; Colchicine; Chromosome 16p; Inflammasome; Periodic fever; Secondary amyloidosis

Introduction

Familial Mediterranean Fever (FMF, MIM249100) is a rare autosomal recessive an systemic autoinflammatory disorder characterized by recurrent bouts of fever, serositis, synovitis, and/or cutaneous inflammation [1-3]. Autoinflammatory diseases originate from inappropriate activation of antigen-independent inflammatory mechanisms, involving mediators and cells of the innate immune system. Typical autoinflammatory disorders are the periodic fever syndromes, in which fever is the predominant clinical feature (Table 1) [4].

FMF is described in several ethnic groups and accounts for about 150,000 patients worldwide [5,6]. Clinically, FMF consists of recurrent and self-limited attacks of fever and symptoms accompanied by a marked acute-phase response (leukocytosis, elevated erythrocyte sedimentation rate, fibrinogen, C reactive protein, serum amyloid A protein). The main clinical features during attacks are peritonitis (95%), arthritis (>50%) (mono-oligoarticular), pleuritis (40%) and less frequently pericarditis, scrotal swelling (inflammation of the tunica vaginalis testis), myalgia, and erysipeloid skin rash [7]. The first attack appears before the age of 20 in more than 85% of the patients.

The most worrisome manifestation of FMF is the progressive secondary AA amyloidosis which might put a subgroup of patients at risk of end-stage kidney disease [8].

FMF is common among ethnic groups originating in the Mediterranean littoral especially Armenian, Arab, Jewish, Turkish, North Africans and Arabic descendants. The prevalence of FMF in non-Ashkenazi Jews is estimated to be 1/250 to 1/1000 [3,9], in Ashkenazi Jews 1/73,000 [3,10], in Armenians 1/500 [3,11], in Turkish 1/1000 and

in Arabic people 1/2600. The carrier frequency is estimated to be 1/3 Armenians, 1/5–10 Sephardic Jews [3,12], 1/5 Ashkenazi Jews [3,12] and Turks [3,13]. Furthermore, FMF cases have been reported in Italian population [14] and we recently identified cluster of 60 Italian subjects with *MEFV* gene mutations (70% symptomatic FMF patients) living in Apulia and Basilicata Regions with likely Jewish-Armenian-Greek historical roots [15,16]. The disease is unusual in other populations, but other cases of FMF have been described in Greece, Cuba, Belgium, Sweden, Germany but also in Japan and Korea [17-23]. The prevalence of FMF is slightly higher in males than females (ratio M/F 1.5–2:1). A first case of FMF was the one of a Jewish girl with episodic fever and abdominal pain [24]. Cases were described as 'fever of unknown origin', Siegal depicted the symptom pattern of 'benign paroxysmal peritonitis'. Reimann used the term 'Periodic Disease', and Heller et al. the term 'FMF' [25-30].

Pathophysiology

The autoinflammatory syndromes or a disease (AIDs) comprises conditions with recurrent episodes of fever and systemic inflammation without microbial infection. In these conditions, there is no

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Syndrome	Abbreviation	Inheritance	Gene locus / chromosome / protein	Days of Fever	Clinical presentation	Secondary AA Amyloidosis
Familial Mediterranean Fever	FMF	Autosomal recessive	<i>MEFV</i> / 16p13.3 / pyrin (marenostrin)	1-3	Abdominal pain, erysipela-like rash, serositis, synovitis, arthralgias	++- (*)
Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis	PFAPA	Undefined	Undefined	3-4	Aphthous stomatitis, lymphadenopathy (cervical), abdominal pain (mild)	-
Hyperimmunoglobulin D syndrome	HIDS	Autosomal recessive	<i>MEVK</i> / 12p / mevalonate kinase	3-7	Lymphadenopathy (cervical), abdominal pain, arthralgias, arthritis, splenomegaly, rash	+--
Tumor necrosis factor alpha receptor 1 associated syndrome	TRAPS	Autosomal dominant	<i>TNFR1</i> / 12p / tumor necrosis factor alpha receptor-1	Longer than 5	Abdominal pain, conjunctivitis, arthralgias, arthritis, myalgia (local), rash	++-

(*) see text for details

Table 1: Periodic fever syndromes [4].

involvement of T or B cells. With FMF, there are at least 12 AIDs associated with genetic mutations affecting the innate immune system, which acts as primary defence against noxious agents and pathogens from outside of the body [31]. The periodic fever syndromes have been discussed earlier (Table 1). Mutation of different components of the multi protein inflammasome complex [32,33] accounts for AIDs in the group of Cryopyrin-Associated Periodic Syndromes (CAPS), where fever is usually an ancillary feature [2].

FMF is the result of mutations in the *MEFV* (Mediterranean Fever) gene, consisting of 10 exons located on chromosome 16p13.3. *MEFV* encodes a 781 amino acid (86kDa) protein (pyrin or marenostrin) which effectively regulates the transcription of intranuclear peptides involved in inflammation [34]. Pyrin has a key role in the innate immune system, and is expressed in the cytoplasm of neutrophils, eosinophils, dendritic cells, mature monocytes, serosal and synovial fibroblasts, and cells derived from the colon and prostate cancer [35]. Pyrin is also detected in spleen, lung and muscle, when leucocyte infiltration occurs [3]. Pyrin co-localizes with microtubules, suggesting a potential activity for microtubule-destabilizing agents such as colchicine [36]. Pyrin is a regulatory component of the inflammasome, an intracellular complex required for conversion of pro-interleukin (IL)-1 β to IL-1 β [37-40]. The activated inflammasome plays a fundamental role in fever, inflammation and apoptosis [33]. "Normal" pyrin negatively appears to inhibit the cleavage of pro-IL1 β by activated caspase-1 [39,41]. Dysregulation of the inflammasome due to mutated pyrin (a large percentage of FMF-associated pyrin mutations reside in the $\approx$ 200-residue C-terminal B30.2 domain), has been proposed as the main mechanism for FMF (Figures 1A and 1B). As pyrin is the inhibitor of the complement-derived mediator of inflammation C5a, FMF patients lack inhibition of neutrophil chemotaxis due to unregulated production of IL-1 β . Thus, as pyrin regulates the inflammatory response by blocking intracellular signal pathways via nuclear factor κ B (NF- κ B) or caspase 1, the absence of pyrin function due to mutated *MEFV* leads to the over secretion of inflammatory cytokines [42]. On the clinical ground, the acute FMF attacks develop because of neutrophil activation at the serosal and synovial surfaces. The key role of neutrophils in FMF is supported by their presence in the serosal fluid, by the expression of pyrin in neutrophils, and by the fast effect of colchicine in preventing the attacks [3].

Systemic reactive (secondary) or AA amyloid in FMF is the consequence of deposition in tissue of fibrils of fragment of Serum Amyloid A (SAA) protein, a major acute phase reactant [43]. Among the several forms identified, acute SAA1 and SAA2 are High-Density Lipoproteins (HDL)-associated apolipoproteins inducible by pro-inflammatory cytokines like interleukin 1 (IL-1), interleukin 6 (IL-

6), lipopolysaccharide (LPS) and Tumor Necrosis Factor (TNF) [44]. SAA1>SAA2 are precursors for tissue AA deposition during ongoing acute and chronic inflammation and AA amyloidosis is almost invariably related to increased levels of SAA in blood [45-47]. Beside the specific genetic background of FMF, other factors appear to play a role in governing the severity of AA amyloidosis, including frequency of attacks, the effect of therapy, individual susceptibility and amyloidogenic potential depending on both type and size of fragments [48-50].

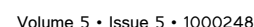
Diagnosis

Clinical presentation

In 90% of FMF patients, the first attack occurs before 20 years of age [51] and comprises recurrent sudden episodes of febrile severe pain (due to serositis at one or more sites with peritonitis, pleuritis, and synovitis), lasting 1-3 days and resolving spontaneously (Table 1).

Clinical manifestations

The event triggering FMF is difficult to establish and frequency of the attacks can be variable. Fever can be the only symptom, reaching also 38-40°C and can precede other symptoms [24]. Prodromic symptoms are discomfort, physical, emotional, neuropsychological complaints [52]. Abdominal painful attack is the most common symptom occurring in about 95% of patient [53-56]. Pain can be localized and afterwards becomes generalized. A dynamic ileus, tenderness, guarding, and rigidity may occur. The clinical picture resembling acute abdomen during attacks might erroneously lead to unnecessary laparotomy and appendectomy. In between the attacks, patients are completely symptom-free. During attacks, a recurrent peritoneal inflammation occurs, and visceral adhesions might develop later [57]. Constipation is typical, while late diarrhea occurs in 10-20% of FMF patients [54]. Arthritis is another common feature of FMF, usually presenting as monoarticular. The large joint of the lower extremities is most frequently affected. Although symptoms can last for more than one month, arthritis generally is not associated with joint destruction [54]. FMF patients with arthritis are usually younger when fever starts, and have more erysipelas-like rashes and myalgia. Vasculitis is more frequent in the presence of arthritis [55]. In one-third of patients, unilateral pleuritis occurs leading to acute febrile attacks of chest pain, either isolated or associated with abdominal and joint attacks [24,54,56]. Pericarditis occurs in less than 1% of patients [58]. Other clinical manifestations include pelvic inflammatory disease, inflammation of the tunica vaginalis with painful scrotal swelling mimicking testicular torsion and orchitis, Henoch-Schönlein purpura, Behçet disease and polyarteritis nodosa and protracted abdominal febrile myalgia [59-61].



AA amyloidosis

A severe complication of FMF is the AA (secondary) amyloidosis, which is dominating glomerular involvement and end-stage renal disease [8,62]. In western world, the overall autoptic prevalence of AA amyloidosis is 0.5-0.9%[63] but it is higher in FMF populations, ranging from 4% to 11% according to studies [63-66]. Prevalence is approaching 30% in Sephardic Jews (higher than Ashkenazi Jews) [67] and is more than 60% in Turkey [5,68]. After the introduction of colchicine, the incidence of amyloidosis has markedly decreased, but is still a major problem in Armenia and Turkey, with a prevalence of 13% in a large (2838 patients) survey[55].

In FMF, the sequence will involve increased SAA, AA secondary glomerular amyloidosis, or more rarely tubular or vascular level, heavy proteinuria, clinically apparent nephrotic syndrome with end-stage renal failure. Although clinical criteria and proteinuria (greater than 0.5 g of protein per 24 h) might suggest amyloidosis, the ultimate diagnosis of amyloidosis is established by biopsy of the bone marrow, periumbilical fat or rectum[69]. Phenotypically, fever and pain attacks can precede the development of amyloidosis. Rarely, renal amyloidosis can develop without preceding typical attacks of FMF[70]. Amyloidosis might affect gastrointestinal tract, vascular system, heart, thyroid, and testes. In FMF patients an additional complication is a subclinical cardiac autonomic dysfunction, similar to dysautonomia described in a variety of rheumatic disorders[71]. Country may represent the primary risk factor for renal amyloidosis in FMF pointing to possible environmental origin of amyloidosis susceptibility[72].

Other biomarkers and Imaging studies

There are no common biomarkers, but patients with FMF might display increased values of erythrocyte sedimentation rate and leukocytosis [56,73]. Decreased albumin levels and a significant increase of fibrinogen, C-reactive protein, the β_2 and α_2 globulin, haptoglobin and lipoproteins were detected during the different phases of FMF. These laboratory findings occurred especially during and immediately after the attacks, and even more markedly in the progression of amyloidosis [56]. Compared to the remission period, the concentration of serum amyloid A protein (SAA) during the attacks increases significantly [74]. Soluble phospholipase A2 type II (PLA2) increased by 50 times during attacks, while PLA2 is nearly undetectable during periods of remission [74]. PLA2 releases arachidonic acid, which is the precursor of prostaglandins and leukotrienes, a condition that might contribute to the inflammatory process. The immunoglobulins (Ig) were also measured in the serum of patients FMF [73]. The results show an increase of 23%, 13%, 17% and 13% of the IgA, IgM, IgD and IgG, respectively.

There is no specific imaging study for the diagnosis of FMF, although during the acute attack findings of peritoneal irritation are visible by computed tomography, and might include mesenteric pathology with engorged vessels and thickened mesenteric folds, mesenteric lymphadenopathy, ascites, and signs of focal peritonitis[75].

Diagnostic criteria

The diagnosis of FMF relies on clinical criteria, family history, historical, geographical, and ethnic considerations, response to colchicine treatment, and genetic analysis of known mutations [3,54,72]. A number of differential diagnoses must be taken into account to rule out other illnesses which include different hereditary periodic fever syndromes (i.e., hyper-IgD syndrome or Tumor Necrosis

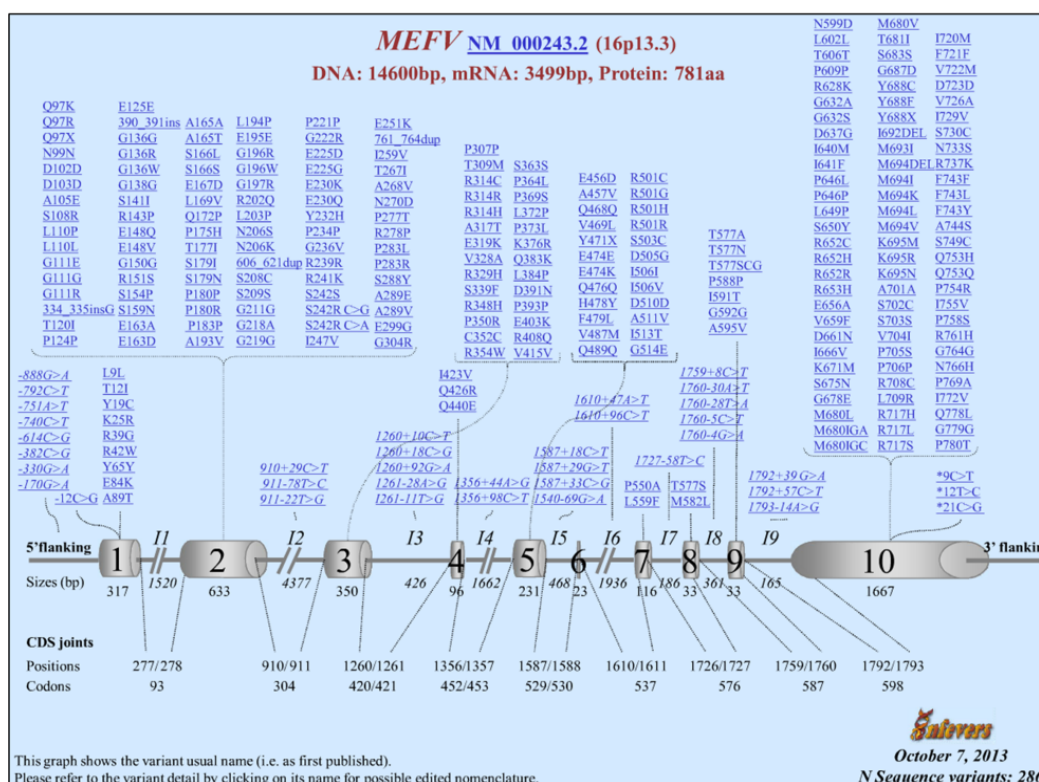
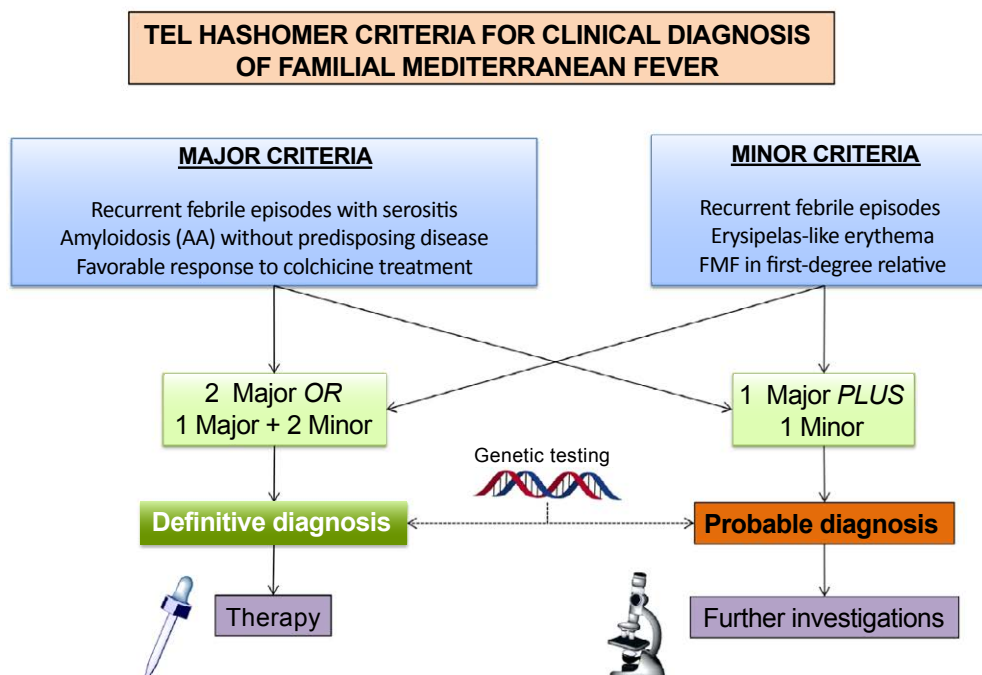
Factor Receptor-1-Associated Periodic Syndrome (TRAPS)) [24], surgical emergencies (i.e., pancreatitis, peritonitis due to perforated peptic ulcer, appendicitis) and a miscellanea of rheumatologic (i.e., systemic lupus erythematosus) and other conditions (i.e., vasculitis, acute intermittent porphyria etc.) [3].

Thus, the diagnosis of FMF which is mainly based on clinical ground an therapeutic efficacy of colchicine (see below: therapy). Genetic testing is available but some patients with clinical evidence of FMF have only one mutation or no MEFV mutation (see below: genetic testing). The presence of intermittent episodes of fever in otherwise healthy subjects, serositis, response to colchicine and absence of other plausible illnesses are suggestive of FMF. Although there are no strict Evidence Based Medicine (EBM) diagnostic criteria for FMF, "Tel Hashomer" criteria have been proposed since 1997 (Figure 2). The diagnosis is considered definitive if 2 major criteria or 1 major criterion plus 2 minor criteria exist. The diagnosis is considered probable in the presence of 1 major plus 1 minor criterion [76]. The same authors proposed an exhaustive list of detailed criteria (major, minor, and supportive) [3,76]. Although the detailed criteria provide a good yield in diagnosing FMF in adult subjects (up to 95-99% sensitivity and 99% specificity depending on symptom combination), the specificity is low (55%) in children [77], who have a poor ability to describe symptoms. A new sensitive and specific set of clinical criteria has been proposed for the diagnosis of FMF in childhood [77].

Genetic testing

Genetic testing of FMF is based on detection of MEFV mutations (Figure 3) and may also have a therapeutic value when integrated with clinical evaluation (Figure 2). As FMF is an inherited disease with an autosomal recessive trait, two mutations would be required for developing clinical manifestations. However, a large variability has been described and a subgroup of patients have only one identifiable mutations [78,79] while others have no identifiable mutations [78,80]. Modifier genes at new susceptibility loci might exist and research is active in this field. PCR-based double-stranded automated sequencing is used to perform a MEFV full sequence analysis [81,82]. According to the Hereditary Autoinflammatory Disorders Registry (Infevers database), more than 280 MEFV sequence variants have been identified nearly all are located on exon 10 between amino acids 680 and 761[83-86]. An abnormally small, nonfunctional pyrin may result from a few mutations deleting small amounts of DNA from the *MEFV* gene. Most *MEFV* gene mutations, however, cause the change of one of the protein building blocks (amino acids) in pyrin.

The first three mutations in MEFV were identified in 1997 [57,87]: M694V (A→G substitution at nucleotide 2080 with formation of valine instead of methionine), M680IGC (G→C substitution at nucleotide 2040 with formation of methionine instead of isoleucine), and V726A (T→C substitution at nucleotide 2177 with valine formation instead of alanine). Another mutation of MEFV gene is located on exon 1 at amino acid 148. The evaluation of the role of type of mutation on FMF phenotype is of great interest. Phenotypic expression can vary with MEFV mutation. For example, the M694V mutation in the presence of homozygosity leads to a more severe form of the disease and amyloidosis, which is more frequent in certain ethnic groups [88-91]. In a Israeli FMF pediatric population, the 3 most common MEFV mutations (M694V, V726A, and E148Q) was related to clinical presentation and disease severity by using the Tel Hashomer severity score [80]. M694V homozygotes has been shown to be associated with a more severe form of FMF if compared with compound M694V heterozygotes, V726A, M680I and E148Q [10]. Homozygous patients



are phenotypically more predisposed to arthritis, dermatological lesions, higher fever with more frequent attacks, and splenomegaly [92,93]. The E148Q mutation might be associated with the mildest and least penetrant form of FMF[94]. In our geographical area in Southern Italy, about 47% of identified subjects carried E148Q/R761H mutations in compound heterozygosity [16,95] (Portincasa et al, presentation at the 48th Annual Scientific Meeting of the European Society of Clinical Investigation, Utrecht, 2014). Some patients with symptoms highly suggestive for FMF exist without identifiable mutations in MEFV, a finding suggesting that other genes could be implicated in FMF phenotype.

MEFV mutations might be associated with the Inflammatory Bowel Disease (IBD) [96]. However, no sound evidences exists that MEFV mutations contribute to IBD susceptibility, despite one IBD locus exists in the pericentromeric region of the same chromosome [9].

Treatment

It is compulsory to treat symptomatic FMF patients for preventing the acute attacks and the development and progression of secondary (AA) amyloidosis. In 1972 Goldfinger at the Massachusetts General Hospital in Boston reported the consistent beneficial effect of 0.6-1.8 mg colchicine daily in five patients with FMF [97]. Colchicine is a tricyclic alkaloid, the main features of which include a trimethoxyphenyl ring, a seven membered ring with an acetamide at the seventh position, and a tropolonic ring (Figure 1B). Colchicine is an anti-gout and antimitotic agent that works to decrease leucocyte motility and phagocytosis in inflammatory responses [97,98]. In 2009 the drug has been approved by FDA for the treatment of FMF in USA. [99] (Table 2). Other (unlabeled) indications of colchicine (0.5-1.0 mg/day) include recurrent pericarditis due to previous autoimmune or idiopathic cause [100,101] and patients with primary biliary cirrhosis unresponsive to the hydrophilic bile acid ursodeoxycholic acid [102,103].

The biological target of colchicine is tubulin, a globular protein involved in the composition of microtubules[104]. Colchicine blocks tubulin polymerization interfering white blood cells migration and degranulation (Figure 1B). Also, colchicine interferes with activation of NALP3 (Nacht domain-, leucine-rich repeat-, and PYD-containing protein 3, also called cryopyrin) inflammasome [105]. Colchicine has an oral bioavailability of 50% and is absorbed in the jejunum and ileum into the enterohepatic circulation [106]. A second peak of serum concentration is generally observed 5-7 hours later [107]. After a single i.v. injection, colchicine plasma half-life is 20 min, while after oral administration is 60 min [108,109]. Colchicine is excreted mainly

by hepatic metabolism via oxidative demethylation by the cytochrome P450 system (isoform CYP 3A4). Metabolites of colchicine are 2- and 3-demethylcolchicine.

Colchicine has been recommended to prevent attacks in FMF patients, and this choice has EBM strength which is supported since 1974 by three double-blind, placebo-controlled trials using a crossover design [110-112]. Colchicine treatment should be started as soon as the FMF diagnosis is set, based on a clinical and genetic ground (Figure 2), and even in the presence of a single *MEFV* mutation associated with typical clinical manifestations [79]. As short-term therapy, administration of colchicine at 0.6-1.8 mg/day has been suggested in the USA [111]. In a long-term study, however, colchicine was given at 1.0-3.0 mg/day for 15 years and induced a good/partial response in severity, duration and frequency of attacks (87% of FMF patients treated) [113]. In patients older than 12 years the colchicine dose ranges from 1.0-2.4 mg/day in 1-2 oral daily doses. Patients receiving lower doses had significantly fewer adverse events in respect to patients treated with higher dose [2]. Colchicine, however, might not totally prevent febrile attacks [76].

Colchicine acts also as a preventive agent of amyloidosis and may reduce the renal damage by reversing the proteinuria when irreversible glomerular damage is absent [114-117]. Colchicine is also effective among FMF patients with nephrotic proteinuria, by preventing the progression of disease and reducing the proteinuria, although the dose should be higher (1.5-2.0 mg/day), and renal damage is not severe [116].

Colchicine administration (optimal dosage 1.5-2.0 mg/day) can also prevent the recurrence of renal injury after kidney transplant, while, in presence of severe hepatic or impairment the dose must be lowered (Table 2) [3]. According to our local experience in Apulia and available formulation of colchicine in Italy, total remission of symptomatic FMF patients was achieved with a dosage of 1.0-1.5 mg/day. Colchicine should be avoided in patients with severe hepatobiliary dysfunction [118].

During pregnancy, colchicine should be continued, even in patients with symptomatic remission. The use of this drug has not shown an increase in miscarriage, stillbirth or teratogenic effects in FMF patients[2]. Colchicine administration is safe also in FMF children [119], although dosing is lower (Table 2).

Potential adverse effects of colchicine (high dosing) include abdominal pain, nausea, vomiting, diarrhea, hematological toxicity (bone marrow suppression with transient leukopenia) and neuromyopathy in patients with renal impairment. Symptomatic treatment (e.g., loperamide in case of diarrhea) to maintain the effective dosage of colchicine or the dose reduction of colchicine should be considered in these patients [3]. Acute toxicity of colchicine is estimated to be 0.9 mg/kg [120]. Results about the possibility of gonadal toxicity in males are inconsistent [121,122].

Oral administration of colchicine interferes with vitamin B12 absorption via reduced intrinsic factor receptors on the intestinal mucosa; lactose intolerance has been described as well [2]. FMF patients are partially responsive to colchicine in 30-40% of cases [98,123], resistant to colchicine in 5-10% of cases [54] and are intolerant to colchicine in 5-10% of cases, especially due to gastrointestinal adverse effects [124]. It has been recently reported that FMF patients mainly carrying E148Q/R761H mutations in compound heterozygosity, the positive response rate to colchicine was 97% [15,95]. Mechanisms affecting colchicine unresponsiveness include decreased gastrointestinal

Patients	Dosing**
Adults	1.2-2.4 mg/day p.o. in 1-2 divided doses The dose can be increased or decreased in 0.3 mg/day amount based on efficacy or adverse effects
Children 4-6 years	0.3-1.8 mg/day in 1-2 divided doses
Children 7-12 years	0.9-1.8 mg/day in 1-2 divided doses
Children >12 years	Adult dosing

Table 2: Recommended dosing of colchicine* in symptomatic Familial Mediterranean Fever [4].

*approved by FDA in USA in october 2009 for use in FMF patients [99]; **dosing to be adjusted in case of renal impairment and in case of dialysis (colchicine is NOT removed). Contraindications exist during renal or hepatic impairment for combined colchicine and P-glycoprotein or strong CYP3A4 inhibitors. Dosing to be adjusted for concomitant therapy with P-glycoprotein inhibitors (eg, cyclosporine, ranolazine) or CYP3A4 inhibitors (strong: clarithromycin, ketoconazole, atazanavir, darunavir, indinavir, itraconazole, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranavir; moderate: erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, aprepitant, fosamprenavir).

absorption or decreased intraleucocyte concentration [125]. In a group of patients displaying a prodromic syndrome, intermittent therapy with colchicine is an option to improve compliance [126]. However, the persistent low-grade inflammatory status in FMF occurs also during the intercritical phases. During colchicine treatment it is advisable to monitor proteinuria and markers of inflammation, including SAA levels [127]. Furthermore, for the treatment of pain it is important to consider the administration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) because colchicine cannot block an established attack [24]. According to the consensus statement developed in Germany, Austria, and Turkey examining the use of colchicine in children and adolescents with symptomatic FMF, the therapy with colchicine is safe, effective, and should continue for life [119]. The available literature supports a recommendation based on grade of strength 1 (strong) and grade of evidence B (moderate) for the use of colchicine in symptomatic FMF patients starting from age of 4 years (International GRADE: Grading of Recommendation Assessment, Development, and Evaluation workgroup [128-130] (Table 2).

Other therapeutic agents such as IL-1 β inhibitors (anakinra, rilonacept, canakinumab) have been proposed in colchicine-resistant or colchicine-intolerant patients (Figure 1B). No EBM criteria are available in this therapeutic context, so far due to the scant number of reports and lack of controlled trials. Anakinra is a recombinant non-glycosylated homolog of the human IL-1 receptor antagonist (rhIL-1Ra) and acts as competitive inhibitor of IL-1 activation [2]. Anakinra inhibits the IL-1 proinflammatory pathway binding IL-1 α and IL-1 β to the IL-1 receptor type I [131]. A case of FMF patient with gastrointestinal toxicity and ongoing dialysis has been successfully treated with anakinra because not eligible for colchicine treatment [39]. Furthermore, anakinra has been given also in a child who had severe FMF attacks despite colchicine therapy [132]. As reported in several studies, anakinra has been administered to at least 30 FMF patients [39,132-146], and the majority of patients carried the M694V mutation in heterozygous state, presenting a severe FMF phenotype and a high risk of amyloidosis. Anakinra advised doses ranged from 100 to 200 mg/day three times /week in adults and 1 mg/kg/day in children. It has been found that anakinra displayed a time-dependent benefit [39,132,140], significantly improved abdominal pain and fever, with a consequent decrease of FMF attacks [133,136]. Anakinra is advisable in secondary amyloidosis, patients candidates for renal transplantation, patients unresponsive to colchicine [133,141,144,146], and patients experiencing major side effects with colchicine [133-135, 140]. Side effects include local pain and erythema due to subcutaneous injection, and the major complications are acute interstitial pneumonia [146], neutropenia [145], grade II acute rejection according to Banff classification and also hypertension requiring therapy [137,140].

Rilonacept, an IL-1 decoy receptor, is another alternative experimental treatment for colchicine-unresponsive or intolerant patients. This molecule is a dimeric fusion protein constituted by the extracellular domains of the IL-1 receptor I and the IL-1 adaptor protein. This means that the IL-1 receptor accessory protein is bound to the Fc portion of human IgG1, resulting in 'trapping' of IL-1. Rilonacept links to IL-1 β with 100 times greater affinity than that of the native receptor, while and to IL-1 α with lower affinity. Therefore, it blocks the interaction between IL-1 and endogenous cell surface receptors, resulting in the reduction of the IL-1-mediated signal transduction and thus the inflammation [147]. Rilonacept has a longer half-life (6.3-8.6 days) that allows its administration once a week. Administration of this agent begins with a subcutaneous loading dose, followed by a weekly injection of half the loading dose. It has been

reported a small randomized placebo-controlled trial in which 12 FMF patients colchicine-resistant or intolerant were treated subcutaneously with rilonacept at 2.2 mg/kg (maximum 160 mg) once weekly for 3 months. Rilonacept significantly reduced the fever episodes by 76%, improving the quality of life [148], but failed to reduce the duration of the attacks.

Canakinumab is a fully human selective anti-IL-1 β monoclonal antibody that binds human IL-1 β neutralizing its proinflammatory effects. It has been developed for immune disorders treatment and, it has been recently approved by FDA for the treatment of cryopyrin-associated periodic syndromes and for the treatment of systemic juvenile idiopathic arthritis, adult and juvenile rheumatoid arthritis, and gouty arthritis. Canakinumab differs by anakinra and rilonacept because of its high specificity for IL-1 β . It has 26 days half-life, and administration every two months inhibits IL-1 β action for a longer time [149]. A very limited clinical experience is available in FMF and further studies are required. In one case canakinumab was given as a first-line agent with a complete clinical remission [150]. Beneficial effects of canakinumab have been reported in a FMF patient with severe Henoch-Schönlein purpura [150] and in a patient unresponsive to colchicine and anakinra [151].

Several proinflammatory effects of TNF are mediated by TNF receptor type I (TNFR I). Therefore, it is believed that its blockade might be a valid treatment for these conditions. In FMF patients with atypical symptoms, anti-TNF- α agents have been initially used with partial benefits [152]. Furthermore, beneficial effects of TNF inhibitors were reported in 10 patients with FMF and chronic arthritis or sacroiliitis [153]. Etanercept, a recombinant human soluble fusion protein might be an option as an anti-TNF- α agent, but requires further studies and careful screening of selected patients.

Conclusion

FMF is common among subjects with Mediterranean origin. Advances about pathophysiology, clinical aspects, genetics and therapy have increased our knowledge of FMF disease. Historical geographical and ethnical factors are also key aspects that help to finalize the diagnosis. Although FMF is transmitted by autosomal recessive inheritance, genetic diagnosis is not reached in all patients with symptoms highly suggestive for FMF. After the discovery by Stephen Goldfinger in 1972, colchicine remains the mainstay treatment to prevent the acute febrile attacks, and the development and progression of secondary (AA) amyloidosis. In colchicine-resistant or colchicine-intolerant FMF patients, alternative treatments are being investigated.

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