Review

Familial Mediterranean fever: a critical digest of the 2012-2013 literature

E.M. Eisenstein[1], Y. Berkun[1], E. Ben-Chetrit[2]

[1]*Department of Paediatrics, Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel;* [2]*Rheumatology Unit, Hadassah-Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel.*

Eli M. Eisenstein, MD
Yackov Berkun, MD
Eldad Ben-Chetrit, MD

Please address correspondence to:
Dr Eli M. Eisenstein,
Department of Paediatrics,
Hadassah-Hebrew University Medical Center,
POB 24035,
Mount Scopus,
Jerusalem 91240, Israel.
E-mail: eisenstein@hadassah.org.il

Received on July 29, 2013; accepted in revised form on August 2, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 77): S103-S107.

Key words: familial Mediterranean fever, colchicine, interleukin-1, spondyloarthropathy

Competing interests: none declared.

ABSTRACT

The year 2012–2013 has been a fertile one in the area of FMF inquiry. Recent studies have led to further insight into the possible mechanisms whereby pyrin mutations might cause the auto-inflammatory phenotype that is characteristic of FMF. Evidence-based guidelines for diagnosis of FMF, including the role of genetic testing, have become available. Risks for colchicine resistance have been partially defined, and a randomised, controlled trial showing efficacy of an interleukin-1 antagonist for treatment of colchicine-resistant or intolerant FMF patients was reported. In this review, we summarise these and other salient findings from the recent FMF literature, and discuss their significance for the clinician.

Introduction

Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory syndrome, characterised by recurrent bouts of fever, arthritis, and serositis (1). Although it is believed to be transmitted by autosomal recessive inheritance, FMF remains enigmatic in that homozygous or compound heterozygous *MEFV* mutations cannot be detected in many individuals with clear evidence of disease. Thus, clinical rather than genetic criteria have remained the basis for diagnosis of FMF (2), and the role of genetic testing for diagnosis of patients or for screening of clinically unaffected family members of patients with FMF is controversial.

In this review we discuss developments concerning FMF pathophysiology, clinical manifestations, diagnosis, and treatment that have appeared in the literature since our previous review (3). PubMed was searched using the terms familial Mediterranean fever in the topic field. An overview of major advances is presented.

Recent insights into the pathophysiology of FMF

It has been known for years that FMF occurs as a result of mutations in the *MEFV* gene, which results in an abnormally functioning gene product, termed pyrin (4, 5). However, the biochemical mechanism by which these mutations cause disease is uncertain. Depending on the experimental system chosen, pyrin has been shown to be either a positive or negative regulator of inflammation. Biochemical studies performed by two groups indicated that pyrin negatively regulates secretion of the pro-inflammatory cytokine by inhibiting cleavage of pro-IL1β by caspase-1 (6, 7). This interaction involves the c-terminal B30.2 domain of pyrin, where most FMF-associated human mutations are found. The concept of pyrin as a negative regulator of inflammation is consistent with the view of FMF as an autosomal recessive disease.

However, other lines of evidence support an alternative view that pathogenic gain-of-function pyrin mutations may result in an excessive inflammation. First, in cell line transfection studies, pyrin has been shown to associate with the intracellular molecules ASC (apoptosis associated speck like protein containing a CARD) and caspase 1 (8). Under certain circumstances, this "pyrin inflammasome" may have an activating role in promoting IL-1β secretion (9). Second, genetic "knock-in" mice carrying one or more copies of the human pyrin gene containing mutations in the B30.2 domain have been shown to develop hepato-splenomegaly and bone marrow-dependent inflammation. Two mutant pyrin alleles were necessary to produce the inflammatory phenotype, whereas pyrin knockout mice showed no signs of inflammation (10). These results suggest that pyrin mutations commonly associated with

human FMF produces inflammation by a gain-of-function, dose dependent mechanism in this model.

During the past year, a report appeared that supports the concept that gain-of-function pyrin mutations can result in inflammation. Yu *et al*. (11) presented further data supporting the pyrin inflammasome model. Cultured cell lines were transfected *in vitro* using the molecular components of the pyrin inflammasome. Upon ribotoxic cell stress, the inflammasome became activated, through a pathway involving p38 mitogen-activated protein kinase (MAPp38), and this MAPp38 mediated activation could be inhibited by colchicine. If confirmed, these findings suggest the MAPp38 kinase pathway as a potential target for drugs other than colchicine to inhibit pyrin inflammasome inactivation, thereby possibly controlling FMF.

Stoeffels *et al*. (12) reported a human autosomal dominant auto-inflammatory disease associated with pyrin mutations affecting amino acid 577 in three families, each of different ethnic background. Clinical symptoms in individuals affected by this illness differed from FMF in that attacks were prolonged, lasting up to weeks, but were colchicine responsive. Stimulation of peripheral blood mononuclear cells from these patients in cell culture resulted in over-secretion of IL-1β as compared to controls, supporting a possible gain-of-function role for this mutation in regulating inflammation. Aldea *et al*. previously reported a Spanish kindred with a colchicine-unresponsive, dominantly inherited auto-inflammatory syndrome associated with H478Y pyrin mutations (13). Febrile attacks in this family were also more prolonged than those typical of FMF. Additional reports of dominantly inherited FMF have been published (14, 15). Moreover, inflammatory presentations atypical for FMF have been described in the context of common pyrin mutations, leading to the hypothesis that the MEFV gene might be associated with conditions other than FMF (16). It remains open to question whether the dominant auto-inflammatory phenotypes seen in some families represents the severe end of the spectrum of conventional FMF, or alternatively, unique auto-inflammatory syndromes involving distinct molecular mechanisms.

Since FMF is a disease of the innate immune system, adaptive immunity is not directly affected. However, in the presence of high concentrations of pro-inflammatory cytokines such as IL-1β and IL-6, secondary changes may occur involving T cell mediated immunity (17). To test whether such changes might occur in FMF, Ovadia *et al*. (18) studied T cell subsets in the peripheral blood of patient with FMF, and found increased numbers of Th17 cells. This T cell subset has been associated with secretion of pro-inflammatory cytokines including IL-17A, and organ-specific inflammation involving joints and other tissues (19). Thus, secondary expansion of Th17 cells may contribute indirectly to some of the inflammatory symptoms observed in FMF patients.

In addition to genotype, it is well recognised that other factors including ethnicity and geography greatly influence FMF disease penetration (20). To gain further insight into the effects of environment on disease expression, Ozen *et al*. (21) used the Eurofever registry of auto-inflammatory diseases to identify and compare paediatric patients of Mediterranean origin living in Eastern Mediterranean countries, to children of the same ethnic origin but currently living in Europe. They found FMF symptoms were less severe among the patients living in Europe, pointing to a clear effect of the environment on disease expression.

FMF, spondyloarthropathy, and extremity pain

A possible relationship between FMF and spondyloarthopathy has been appreciated for several years. In a study from Israel, Langevitz *et al*. (22) originally noted that 11/160 FMF patients with chronic joint disease also had clinical findings consistent with ankylosing spondylitis, including sacroiliitis. Interestingly, all of the patients with ankylosing spondylitis in this study were negative for HLA-B27. Seronegative spondyloarthropathy was subsequently described in FMF patients from other ethnic backgrounds (23-25). In a very recent study from Turkey, Akar *et al*. studied 157 consecutive FMF patients for ankylosing spondylitis. Using modified New York criteria, a 7.5% prevalence of AS was found. All FMF patients with AS were negative for the HLAB27 antigen. The prevalence of the M694V mutation was higher among patients with AS, suggesting this mutation is a risk factor for AS in these patients. In addition, this study also found the prevalence of AS and spondyloarthropathy was increased among first degree relatives of FMF patients (relative risk 3.3 and 2.9, respectively) (26).

Recently, studies into the cause of extremity pain in FMF patients have also produced findings supporting a possible relationship between FMF and spondyloarthropathy. Extremity pain in FMF is quite common. During febrile attacks, joint pain results from acute arthritis, which is typically asymmetrically and involves large joints (1). Protracted febrile myalgia is another less common inflammatory manifestation of FMF, that often responds to treatment with glucocorticoids (27, 28). However, some FMF patients complain of extremity pain that is unrelated to disease exacerbations.

Eshel *et al*. (29) used magnetic resonance imaging (MRI) to examine 11 FMF with exertional leg pain, and found 10 to have findings compatible with enthesitis. Of them, nine also had evidence of sacroiliitis on pelvic radiographs. Interestingly, radiographic signs of inflammation were not present in baseline studies, but appeared only after exercise challenge. Ozkam (30) studied 50 FMF patients for enthesopathy using ultrasound. Madrid Sonographic Enthesitis Index scores were markedly higher in FMF patients as compared to controls. Among FMF patients, men had higher scores than women. Two additional ultrasound based studies also found an increased prevalence of enthesitis (31, 32); in one, enthesitis was associated with M694V mutations (32).

Taken together, these reports further strengthen the association between FMF and the spondyloarthropathies, and sug-

gest a possible role of the M694V pyrin mutation as a risk factor for spondyloarthropathy in this population.

Another MRI-based study suggested an additional possible mechanism for exertional leg pain in some FMF patients (33). MRI and 31P magnetic resonance spectroscopy (31PMRS) was used to evaluate calf muscles of eleven FMF patients with complaints of exertional leg pain, and six healthy controls individuals. 31PMRS is a non-invasive way of measuring energy metabolism in muscle tissue. The authors of this study found that following a 30 minute exercise challenge, FMF patients had significantly higher intra-cellular pH as compared to controls, indicating a possible metabolic defect. Based on similarity to findings in patients with glycogen storage diseases, they speculate that their findings may indicate impaired glycogen utilisation in muscle of FMF patients. However, this hypothesis remains to be confirmed.

Association between FMF and Behçet's disease

A possible link between FMF and Behçet's disease has long been suspected, based on certain shared clinical features, partial overlap in geographic distribution of disease, and colchicine responsiveness (34). Over the past 13 years, several relatively small studies have examining the prevalence of mutant *MEFV* alleles among patients with Behçet's disease from Behçet-endemic regions as compared to ethnically matched controls (35-39), with conflicting results. A genome-wide association study found no association between MEFV and Behçet's disease. However, this study was methodologically limited in that it was not designed to detect an association between relatively infrequent mutant *MEFV* alleles and disease. Recently, Kirono *et al*. reported using deep exonic re-sequencing to examine the possible association between polymorphisms in pre-selected innate immune genes with Behçet's disease. These investigators found that the MEFV M694V variant conferred increased risk for Behçet's disease, with a 2.6 odds ratio (40). Variants in additional innate immune genes, including IL23R and toll-like receptor 4, were also over-represented among Behçet patients as compared to ethnically-matched controls. The strength of this study is that it involved a very large sample size (2461 individuals with Behçet's disease and 2458 controls). However, it was limited to the Turkish population. Thus, while it may be difficult to replicate a study of this size, it will be important to confirm these findings in other ethnic groups.

Increased risk for mortality due to FMF

The availability of colchicine has markedly reduced the risk for early death due to renal amyloidosis among FMF patients. To evaluate the effects of FMF on longevity during the colchicine era, Twig *et al*. compared 1225 individuals found to have FMF by a rheumatologist during a screening medical examination prior to military conscription at age 16–20 years, with controls. National databases were used to identify patients who died before 50 years of age. The mean follow-up period was 24 years. This study found that the Hazard Ratio (HR) for early death due to FMF was increased in both men (1.71) and women (2.48). Renal amyloidosis accounted for 35 and 60% of deaths in men and women, respectively. The authors point our that survival curves for men during the period 1973–1986 and 1987–1997 were similar, arguing against the availability of colchicine as an important determinant of mortality. Rather, they attribute their findings to inadequate adherence to colchicine treatment, or colchicine unresponsiveness. These results emphasise the need for vigilance in following and effectively treating FMF patients, in particular those with evidence of persistent inflammation, in order to reduce their long-term risk for morbidity and mortality (41).

Advances in FMF treatment

Colchicine has been the mainstay of FMF treatment for over 40 years, having been convincingly shown to completely prevent attacks in 60–65% of patients, and induce a partial remission in an additional 30–35% (42, 43). In addition, regular use of colchicine greatly reduces the long-term risk for amyloidosis in affected individuals (44). Nevertheless, depending on the definition used, between 5–10% of patients may have inadequate symptom control despite good adherence to colchicine in maximally tolerated doses. Colchicine resistance occurs by several mechanisms including polymorphisms involved in transport of the drug to the intra-cellular compartment in some patients (45, 46). Recent studies have focused on defining how a specific homozygous *MEFV* mutation, already known to be associated with more severe FMF disease (47), might influence colchicine resistance. Lidar *et al*. (48) used a telephone survey to compare adult FMF patients who were homozygotic for M694V mutations, to patients with either M694V/V726A or V726A/V726A genotypes. All patients reported regular colchicine use, but M694V/M694V patients reported using higher doses, resulting in more side effects. Moreover, M694V/M694V patients reported experiencing a significant number of attacks, 0.7 per month on average. Ten percent of these patients reported no improvement at all in their symptoms while taking colchicine. These results are consistent with those reported in a previously study involving over 200 children with FMF from Turkey (49). Thus, the M694V/M694V genotype identifies a subgroup of FMF patients who may be clinically unresponsive to colchicine. The apparent lack or response of these patients to colchicine is likely to reflect the severe disease that is known to be associated with this pyrin mutation (50, 51). However, these patients may require supplemental treatment to prevent frequent attacks.

Based on the concept of FMF as an auto-inflammatory disease, and its association with hyper-secretion of the pro-inflammatory cytokine IL-1β, IL-1 antagonists have been proposed as a treatment for colchicine resistant FMF. To date, there have been published reports concerning the use of the recombinant IL-1 receptor antagonist anakinra to control symptoms in at least 30 FMF patients, with nearly all experiencing at least partial improvement (reviewed in ref. 52). There is also limited evidence

that IL-1 antagonists may retard progression of FMF-related amyloidosis resistant to colchicine (53). Recently, a controlled trial involving treatment of a small number of colchicine-resistant or intolerant patients was reported. Rilonacept, an IL-1 decoy receptor, was used to treat 14 patients in a study using a randomised, double-blind, single participant alternating treatment design (54). In this study, the number of FMF attacks during rilonacept treatment was reduced significantly as compared to the period during which patients received placebo. However, length of attacks, and acute phase reactant concentrations between attacks were not reduced significantly.

The availability of category 1B evidence of efficacy of an IL-1 antagonist to reduce the frequency of FMF attacks, albeit in only one small study, would appear to support more widespread use of IL-1 antagonists for colchicine-resistant FMF. However, in interpreting this result, several caveats should be kept in mind. First, despite persistence of clinical and laboratory evidence of ongoing inflammation in a significant number of FMF patients, FMF-related amyloidosis has diminished markedly in the colchicine era, suggesting that the capacity of colchicine to prevent amyloidosis is likely to occur independently of its ability prevent FMF symptoms. Thus, colchicine should always be continued in patients whenever supplemental treatment with IL-1 antagonists is given. Second, IL-1 antagonists are expensive, may have side effects. Therefore, potential risks and benefits including quality of life issues should be carefully considered when deciding whether to add biologic therapy for patients with FMF.

Evidence-based recommendations for management of FMF

From the perspective of the practicing rheumatologist, one of the most useful developments during the past year was publication of evidence-based guidelines for the practical management of FMF (55). A group of physician experts in FMF from France and Israel convened to develop guidelines for key issues, including colchicine dosing in children and adults, defining colchicine resistance, the use of IL-1 antagonists for colchicine-resistant patients. Based on a systematic literature review, level of evidence was provided for each recommendation.

Of particular interest, the role of genetic testing for asymptomatic screening of siblings of FMF patients was discussed. In retrospective reports from many years ago, clinically diagnosed patients are described who, despite reporting few symptoms, subsequently developed proteinuria due to amyloidosis (56, 57). These reports have been the source of continuing concern that some FMF patients might be "missed", only to be discovered later when they have irreversible complications of their disease. However, the existence of this putative "phenotype II FMF" was disputed by the panel. Moreover, based on accumulated experience at centres that have provided care for large numbers of FMF patients for over 10 years, it is believed that individuals with two or more MEFV mutations with no clinical FMF symptoms (phenotype III FMF, ref. 58) and normal acute phase reactants are at very low risk for developing secondary amyloidosis. In the absence of predictive value for identifying patients at long term risk for disease complications, the committee saw no advantage in genetic testing for MEFV mutations in asymptomatic individuals, and therefore recommended against routine genetic testing of asymptomatic siblings with normal acute phase reactants. The category of evidence that forms the basis for this recommendation is admittedly weak (Category 3 and 4). Furthermore, exceptions to this recommendation might be considered in families in which clinical follow-up might be poor, because in these families, individuals with clinical or laboratory evidence of persistent inflammation might go undetected.

Summary

During the past year there have been significant advances in understanding of FMF disease mechanisms. The association between FMF and Behçet's disease and an HLA-B27 negative form of spondyloarthropathy have been strengthened in patients of Turkish origin, but these associations need to be further confirmed in different ethnic groups. Colchicine treatment along with careful clinical and laboratory monitoring for ongoing inflammation remain the foundations of FMF diagnosis and management in 2013. For patients with uncontrolled disease despite excellent adherence to standard therapy, supplemental treatment using IL-1 antagonists seems to be an effective but expensive way to improve symptomatic control of disease.

References

1. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-64.
2. LIVNEH A, LANGEVITZ P, ZEMER D *et al*.: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.
3. BERKUN Y, EISENSTEIN E, BEN-CHETRIT E: FMF - clinical features, new treatments and the role of genetic modifiers: a critical digest of the 2010-2012 literature. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S90-5.
4. FRENCH FMF CONSORTIUM: A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; 17: 25-31.
5. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. *Cell* 1997; 90: 797-807.
6. 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-1beta production. *Proc Natl Acad Sci USA* 2006; 103: 9982-7.
7. PAPIN S, CUENIN S, AGOSTINI L *et al*.: The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1beta processing. *Cell Death Differ* 2007; 14: 1457-66.
8. YU JW, WU J, ZHANG Z *et al*.: Cryopyrin and pyrin activate caspase-1, but not NF-kappaB, via ASC oligomerization. *Cell Death Differ* 2006; 13: 236-49
9. GAVRILIN MA, ABDELAZIZ DH, MOSTAFA M *et al*.: Activation of the pyrin inflammasome by intracellular Burkholderia cenocepacia. *J Immunol* 2012;188: 3469-77.
10. CHAE JJ, CHO YH, LEE GS *et al*.: Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1β activation and severe autoinflammation in mice. *Immunity* 2011; 34: 755-68.
11. YU JW, FARIAS A, HWANG I, FERNANDES-ALNEMRI T, ALNEMRI ES: Ribotoxic stress through p38 mitogen-activated protein kinase activates in vitro the human pyrin inflammasome. *J Biol Chem* 2013; 288: 11378-83.
12. STOFFELS M, SZPERL A, SIMON A *et al*.: MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. *Ann Rheum Dis* 2013 Mar 16 [Epub ahead of print].
13. ALDEA A, CAMPISTOL JM, AROSTEGUI JI *et*

al.: A severe autosomal-dominant periodic inflammatory disorder with renal AA amyloidosis and colchicine resistance associated to the MEFV H478Y variant in a Spanish kindred: an unusual familial Mediterranean fever phenotype or another MEFV-associated periodic inflammatory disorder? *Am J Med Genet A* 2004; 124A: 67-73.
14. BOOTH DR, GILLMORE JD, LACHMANN HJ *et al*.: The genetic basis of autosomal dominant familial Mediterranean fever. *QJM* 2000; 93: 217-21.
15. CAGLAR MK, ALTUGAN FS, OZYURT H, ATASOY HI: Screening of family members of children with Familial Mediterranean Fever: true-autosomal and pseudo-autosomal inheritance. *Acta Reumatol Port* 2008; 33: 415-20.
16. BEN-CHETRIT E, PELEG H, AAMAR S, HEYMAN SN: The spectrum of MEFV clinical presentations--is it familial Mediterranean fever only? *Rheumatology* (Oxford) 2009; 48: 1455-9.
17. EISENSTEIN EM, WILLIAMS CB: The T(reg)/Th17 cell balance: a new paradigm for autoimmunity. *Pediatr Res* 2009; 65: 26R-31R.
18. OVADIA A, LIVNEH A, FELD O *et al*.: T helper 17 polarization in familial Mediterranean fever. *Genes Immun* 2013; 14: 212-6.
19. KORN T, BETTELLI E, OUKKA M, KUCHROO VK: IL-17 and Th17 Cells. *Annu Rev Immunol* 2009; 27: 485-517.
20. BEN-CHETRIT E, TOUITOU I: Familial mediterranean Fever in the world. *Arthritis Rheum* 2009; 61: 1447-53.
21. OZEN S, DEMIRKAYA E, AMARYAN G *et al*.; FOR THE PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO) AND THE EUROFEVER PROJECT: Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. *Ann Rheum Dis* 2013 Mar 5. [Epub ahead of print].
22. LANGEVITZ P, LIVNEH A, ZEMER D, SHEMER J, PRAS M: Seronegative spondyloarthropathy in familial Mediterranean fever. *Semin Arthritis Rheum* 1997; 27: 67-72.
23. KAŞIFOĞLU T, CALIŞIR C, CANSU DU, KORKMAZ C: The frequency of sacroiliitis in familial Mediterranean fever and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis. *Clin Rheumatol* 2009; 28: 41-6.
24. BALABAN B, YASAR E, OZGUL A, DINCER K, KALYON TA: Sacroiliitis in familial Mediterranean fever and seronegative spondyloarthropathy: importance of differential diagnosis. *Rheumatol Int* 2005; 25: 641-4.
25. BORMAN P, GÖKOĞLU F, TAŞBAŞ O, YILMAZ M, YORGANCIOĞLU ZR: Familial Mediterranean fever-related spondyloarthropathy. *Singapore Med J* 2009; 50: e116-9.
26. AKAR S, SOYSAL O, BALCI A *et al*.: High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence for the connection. *Arthritis Res Ther* 2013; 15: R21.
27. 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.
28. 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.
29. ESHED I, KUSHNIR T, LIVNEH A *et al*.: Exertional leg pain as a manifestation of occult spondyloarthropathy in familial Mediterranean fever: an MRI evaluation. *Scand J Rheumatol* 2012; 41: 482-6.
30. OZKAN F, CETIN GY, INCI MF *et al*.: Increased enthesopathy in patients with familial Mediterranean fever: evaluation with a new sonographic enthesitis index. *J Ultrasound Med* 2013; 32: 325-32.
31. YILMAZ O, KISACIK B, OZKAN F *et al*.: Does enthesopathy relate to M694V gene mutation in patients with Familial Mediterranean fever? *Clin Rheumatol* 2013 Jun 29 [Epub ahead of print].
32. TUFAN A, MERCAN R, TEZCAN ME *et al*.: Enthesopathy in patients with familial Mediterranean fever: increased prevalence in M694 V variant. *Rheumatol Int* 2013; 33: 1933-7.
33. KUSHNIR T, ESHED I, HELED Y *et al*.: Exertional muscle pain in familial Mediterranean fever patients evaluated by MRI and 31P magnetic resonance spectroscopy. *Clin Radiol* 2013; 68: 371-5.
34. BEN-CHETRIT E, YAZICI H: Thoughts on the proposed links between Behçet's disease and familial Mediterranean fever. *Clin Exp Rheumatol* 2002; 20 (Suppl. 26): S1-2.
35. TOUITOU I, MAGNE X, MOLINARI N *et al*.: MEFV mutations in Behçet's disease. *Hum Mutat* 2000; 16: 271-2.
36. RABINOVICH E, SHINAR Y, LEIBA M, EHRENFELD M, LANGEVITZ P, LIVNEH A: Common FMF alleles may predispose to development of Behçet's disease with increased risk for venous thrombosis. *Scand J Rheumatol* 2007; 36: 48-52.
37. BARUCH Y, DAGAN E, ROSNER I, FIORILLI M, GERSHONI-BARUCH R, ROZENBAUM M: MEFV, TNFRSF1A and CARD15 mutation analysis in Behçet's disease. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S24-S27.
38. YAZICI A, CEFLE A, SAVLI H: The frequency of MEFV gene mutations in Behçet's disease and their relation with clinical findings. *Rheumatol Int* 2012; 32: 3025-30.
39. ESMAEILI M, BONYADI M, KHABBAZI A *et al*.: Common MEFV mutations in Iranian Azeri Turkish patients with Behçet's disease. *Scand J Rheumatol* 2011; 40: 383-6.
40. KIRINO Y, ZHOU Q, ISHIGATSUBO Y *et al*.: Targeted resequencing implicates the familial Mediterranean fever gene MEFV and the toll-like receptor 4 gene TLR4 in Behçet disease. *Proc Natl Acad Sci USA* 2013; 110: 8134-9.
41. TWIG G, LIVNEH A, VIVANTE A *et al*.: Mortality risk factors associated with familial Mediterranean fever among a cohort of 1.25 million adolescents. *Ann Rheum Dis* 2013 Mar. 16 [Epub ahead of print].
42. ZEMER D, LIVNEH A, DANON YL, PRAS M, SOHAR E: Long-term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum* 1991; 34: 973-7.
43. BEN-CHETRIT E, AAMAR S: About colchicine compliance, resistance and virulence. *Clin Exp Rheumatol* 2009; 27 (Suppl. 53): S1-3.
44. ZEMER D, PRAS M, SOHAR E, MODAN M, CABILI S, GAFNI J: Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986; 314: 1001-5.
45. TUFAN A, BABAOGLU MO, AKDOGAN A *et al*.: Association of drug transporter gene ABCB1 (MDR1) 3435C to T polymorphism with colchicine response in familial Mediterranean fever. *J Rheumatol* 2007; 34: 1540-4.
46. OZTURK MA, KANBAY M, KASAPOGLU B *et al*.: Therepeutic approach to familial Mediterranean fever: a review update. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S77-S86.
47. BEN-CHETRIT E, TOUITOU I: The impact of MEFV gene identification on FMF: an appraisal after 15 years. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S3-S6.
48. LIDAR M, YONATH H, SHECHTER N *et al*.: Incomplete response to colchicine in M694V homozygote FMF patients. *Autoimmun Rev* 2012; 12: 72-6.
49. SOYLEMEZOGLU O, ARGA M, FIDAN K *et al*.: Unresponsiveness to colchicine therapy in patients with familial Mediterranean fever homozygous for the M694V mutation. *J Rheumatol* 2010; 37: 182-9.
50. MAJEED HA, EL-SHANTI H, AL-KHATEEB MS, RABAIHA ZA: Genotype/phenotype correlations in Arab patients with familial Mediterranean fever. *Semin Arthritis Rheum* 2002; 31: 371-6.
51. GERSHONI-BARUCH R, BRIK R, ZACKS N, SHINAWI M, LIDAR M, LIVNEH A: The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. *Arthritis Rheum* 2003; 48: 1149-55.
52. SORIANO A, VERECCHIA E, AFELTRA A, LANDOLFI R, MANNA R: IL-1β Biological Treatment of Familial Mediterranean Fever. *Clin Rev Allergy Immunol* 2013; 45: 117-30.
53. KORCMAZ C: Therapeutic approach to familial Mediterranean fever-related amyloidosis resistant to colchicine. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S104-7.
54. HASHKES PJ, SPALDING SJ, GIANNINI EH *et al*.: Rilonacept for colchicine-resistant or intolerant familial Mediterranean fever: a randomized trial. *Ann Intern Med* 2012; 157: 533-41.
55. HENTGEN V, GRATEAU G, KONE-PAUT I *et al*.: Evidence-based recommendations for the practical management of Familial Mediterranean Fever. *Semin Arthritis Rheum* 2013 Jun 3 [Epub ahead of print].
56. BLUM A, GAFNI J, SOHAR E, SHIBOLET S, HELLER H: Amyloidosis as the sole manifestation of familial Mediterranean fever (FMF). Further evidence of its genetic nature. *Ann Intern Med* 1962; 57: 795-9.
57. 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.
58. KOGAN A, SHINAR Y, LIDAR M *et al*.: Common MEFV mutations among Jewish ethnic groups in Israel: high frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the car-