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Review

REVIEW

Familial Mediterranean fever: clinical state of the art

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Abstract

As the inflammation research improves year-by-year, so does our understanding of the autoinflammatory conditions. Over the past years, the number of monogenic autoinflammatory conditions snowballed thanks to our understanding of basic immunology and genetics. Familial Mediterranean fever (FMF), being the entrance to this fascinating world, still has clinical relevance as it enables us to understand our approach to these patients, treatment modalities and pathological mechanisms. This review can be used as a tool for clinicians already working with FMF patients to update themselves on recent scientific literature.

Introduction

Familial Mediterranean fever (FMF) is the most common disease characterized by self-remitting periodic fevers. It is the disease of the innate immune system also identified as a systemic autoinflammatory disease. The genetic component and the autosomal recessive inheritance can be quite striking, yet the diagnosis is mostly based on the signs and the symptoms.

Over the years, FMF earned its place by not only its unique clinical features but also thanks to its pathogenesis of autoinflammation. The transition from a section of the autoimmune diseases to a separate clinical entity, the disease has paved the way for numerous novelties in basic science studies, clinical diagnostic features and treatment modalities. This review aims to give an update on the recent studies related to this disease.

Epidemiology

FMF has a geographical predilection towards middle eastern nations such as Turks, Arabs, Sephardic Jews and Armenians[1] with an average carrier rate of one-fifth.[2] The recent epidemiologic studies were mostly from this region. There is additional data on the early and late-onset of the disease.

Even though it has been known that the disease is common in the Middle East, the role of the environment has not been studied. Touitou *et al.*[3] published their study of 14 endemic countries showing that the country of origin signals towards worse prognosis. This was further studied by Ozen *et al.*[4] showing that patients living in Turkey had a more severe disease outcome in comparison with the Turkish patients living in Germany. Another factor shown to be affecting the disease severity is age. Aydin *et al.*[5] evaluated 180 patients who were over 40 years of age, and they have shown that both attack frequency and daily colchicine dose decreased significantly.

Koshy *et al.*[6] analyzed the unison of 5 whole-genome and whole-exome datasets for 2115 individuals showing different subpopulations in the Middle East and North Africa. The analysis showed us that there is indeed a higher frequency of different alleles in these subpopulations and the MEFV genetic variant carrier frequency to be about 8%. Whereas a similar study from Turkey has shown that nearly half of the patients were carrying at least one M696V.[7]

Another different aspect of epidemiology was related to the onset of the disease. Çelikel *et al.*[8] described the features of patients with neonatal-onset. They concluded that M694V

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mutation was the most prominent in this group, showing a rather poor prognosis. The significant delay of diagnosis and treatment also hints towards poor prognosis (range 7 months to 17 years). Besides, two studies were published focused on comparing early and late-onset of the disease. Early onset is defined as the age of onset is <20, and late-onset being more than 20. The Turkish national FMF registry of 2246 patients from 14 adult rheumatology clinics has shown that early onset disease is associated with more severe symptoms, and M694V mutation can be responsible for the early expression of the disease.[9] Another single-center study of 2180 FMF patients had similar findings with additional data on the rarity of the late-onset disease.[10] Their results had shown that the frequency of the late-onset disease was <3%.

Genetics and epigenetics

There were interesting approaches to FMF regarding the studies based on genetics and epigenetics. These studies mostly focused on the information for facilitating the diagnosis and understanding the nature of the disease.

Even though FMF is known to have an autosomal recessive mode of inheritance, recent studies aimed to search for the role of epigenetics, specifically microRNAs (miRNA). Amarilyo *et al.*[11] probed 798 mature miRNAs and identified four upregulated and three downregulated miRNAs. Another study demonstrating the role of miRNAs was published by Hotu *et al.*[12]

Most of the disease-related mutations are located in the Exon 10, yet Exon 2 variants are quite common, and the exon was one of the focal points of the recent studies. The pathogenic MEFV mutations are shown in Table 1.[13] The observational study including 2246 patients from 14 rheumatology clinics reported that patients with an Exon 2 mutation had an older age of onset and with less severe symptoms.[14] Similar findings were observed from three studies of patients with homozygous E148Q mutation.[15–17] Despite, these results associate the exon with a milder presentation, the authors collectively still recommend prophylactic colchicine treatment.

So far, numerous variants have been found in FMF patients and this high number hinders the diagnosis of the clinician. Accetturo *et al.*[18] aimed to reduce the number of these variants by analyzing their clinical correlation with expert opinions. Following the analysis of 216 MEFV missense variants, and the reclassification of the 96 MEFV gene variants, they managed to reduce the uncertain variant ratio from 61.6% to 17.6%.

Pathogenesis

Recent studies tried to explain the disease manifestation, link of pyrin to inflammation and other molecules causing cytokine surge.

Table 1. Major pathogenic variants for screening on Exons 10 and 2

Exon 10	M694V
	V726A
	M680I
	M694I
	R761H
	A744S
	I692 deletion
Exon 2	E167D
	T267I

There is an increasing amount of evidence in a potential link between gut microbiota and the disease manifestation. The review by Di Ciaula *et al.*[19] summarized the abundance of microbial species in the digestive tract. Due to the increased inflammation in FMF, the systemic response against the gut microbiota may cause the alteration of the flora. In different mutations, ethnicities, and genders these alterations are sometimes more pronounced.

To date, FMF has a well-established explanation for pyrin-related amplified innate immune response. There is ongoing research on answering questions about how pyrin dysregulation affects different cascades and produces a multisystemic condition. The examination of pyrin during inflammatory cell migration explains how it is linked to the polymerization of actin.[20] Another study by Sharma *et al.*[21] showed that TNFR1 blockade or TNFR2 activation can protect against FMF-related inflammatory responses in mice. These results essentially portray tumor necrosis factor (TNF) as a modulating factor of pyrin expression. Unlike these results, Magnotti *et al.*[22] claim that the sole source of pyrin activation is via pyrin (de)phosphorylation.

Cytokine surge has even influenced our treatment approach. The mechanism behind interleukin (IL)-1β-associated autoinflammation and its link to the pyrin pathway is a hot topic of discussion. Kanneganti *et al.*[23] showed how the FMF knock-in macrophages expressed pyrin elicited pyroptosis and gasdermin D-mediated IL-1β secretion. The authors identified pyroptosis as a crucial part of the autoinflammatory response. Another study on the cytokine surge in FMF was published by Ibrahim *et al.*[24] Their results highlighted the role of RAC1 protein in the Caspase-1-associated IL-1β production.

Clinical manifestations

Primarily FMF clinical manifestations are fever and serositis (chest, abdominal or joint pain; Figure 1). Typical attacks are self-remitting (lasting less than 3 days) with rectal temperature reaching over 38°C. In addition to self-remission, attack-free intervals with no sequela is characteristic. This section is for recent research identifying unusual clinical manifestations associated with the disease.

Protracted febrile myalgia syndrome is characterized by extended episodes (usually 4–6 weeks) of myalgia and other typical FMF symptoms. The review published by Yildirim *et al.*[25] summarizes five patients with this syndrome. The striking use of corticosteroids in all of the patients with NSAIDs and either partial or complete response should be highlighted. The authors also state the benefit of anti-IL-1 treatment in cases of inadequate response to steroids and NSAIDs. Overall, musculoskeletal symptoms are more common in late-onset FMF patients (Figure 2).[26]

Another common yet ignored symptom of FMF is fatigue. The case-control study by Duruoz *et al.*[27] summarized 61 patients diagnosed with FMF. The patients had significantly more fatigue in comparison with healthy individuals.

Last, FMF prodromal symptoms are not studied as much as the attacks. The recent cross-sectional study by Babaoglu *et al.*[28] showed that of 401 enrolled patients with FMF, 141 (35.2%) had a prodrome.

Diagnosis and follow-up

As the symptoms of FMF are often non-specific, diagnosis, and identifying the attacks are challenging. Erdogan *et al.*[29] found that 84% of their cohort (197 FMF patients) were

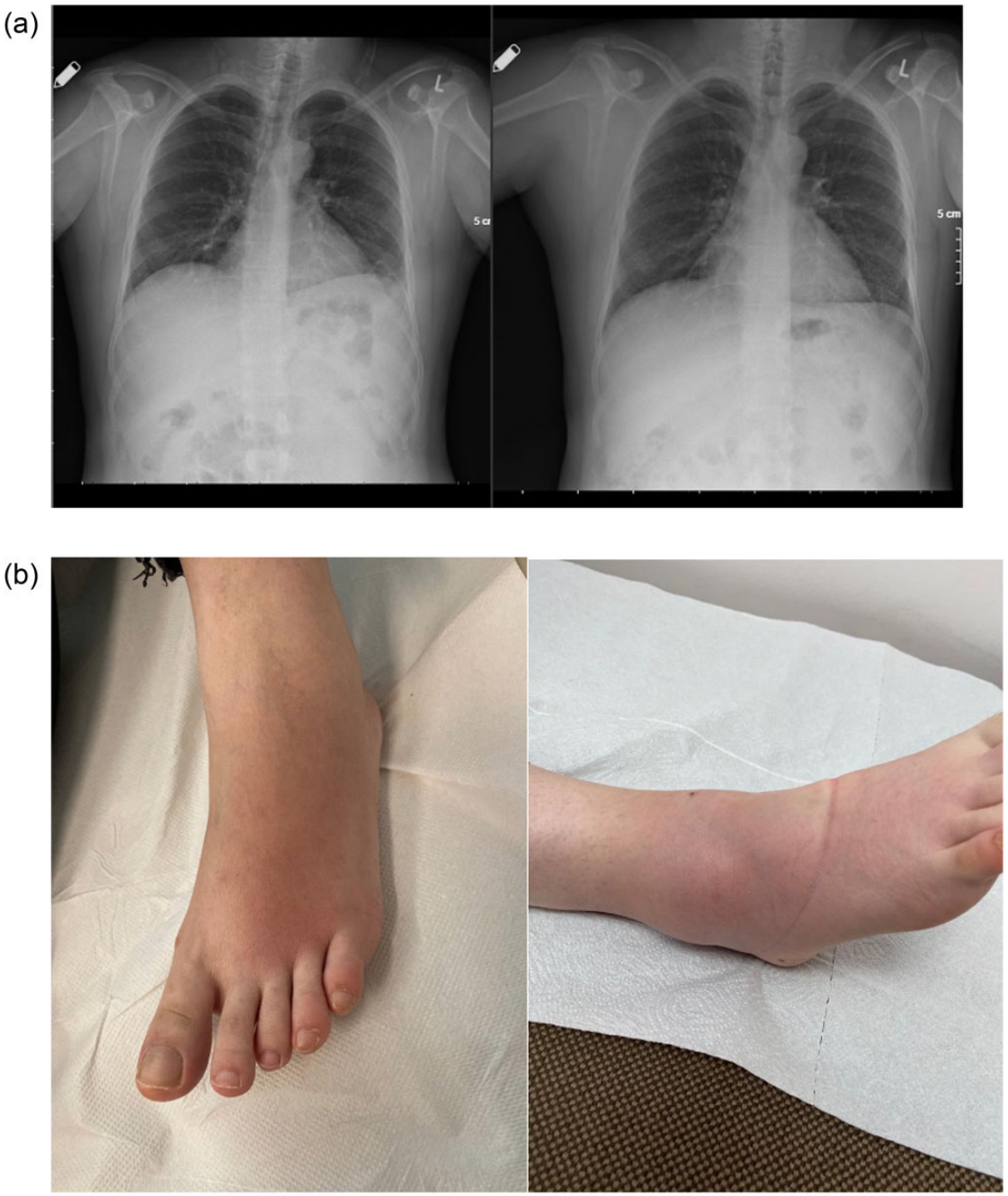

Figure 1. (a) FMF pleuritis before and after treatment. (b) FMF arthritis. Color figure is available in online version.

misdiagnosed and the median diagnostic delay was 11 years. Especially patients with an atypical presentation such as arthritis attacks are associated with the diagnostic delay. Hence, newer studies aim to facilitate this process by identifying new biomarkers with high specificity and designing new guidelines (Table 2).

The most studied biomarker was calprotectin. Calprotectin is a cytokine showing trauma or infection. A recent case-control study on 60 patients, studied the role of calprotectin and its sensitivity and specificity. There was a statistically significant difference between the FMF group and the control ($P < 0.001$).[30] At levels above 238 pg/ml, the sensitivity was 96.7% and the specificity was 100%. The same statistical difference was reached in two similarly designed studies.[31,32]

Another important aspect of the disease is distinguishing the attacks from febrile infections. Çakan *et al.*[33] compared FMF patients who were having an attack on healthy controls with an acute febrile infection by measuring serum amyloid A (SAA) SAA was found significantly higher than the control (497.5–131.5 mg/l) ($P < 0.001$). According to their results, the best cut-off value was 115.mg/l with a sensitivity of 100% and specificity of 65.1% (area under curve = 0.78, CI 0.66–0.90, $P < 0.001$).

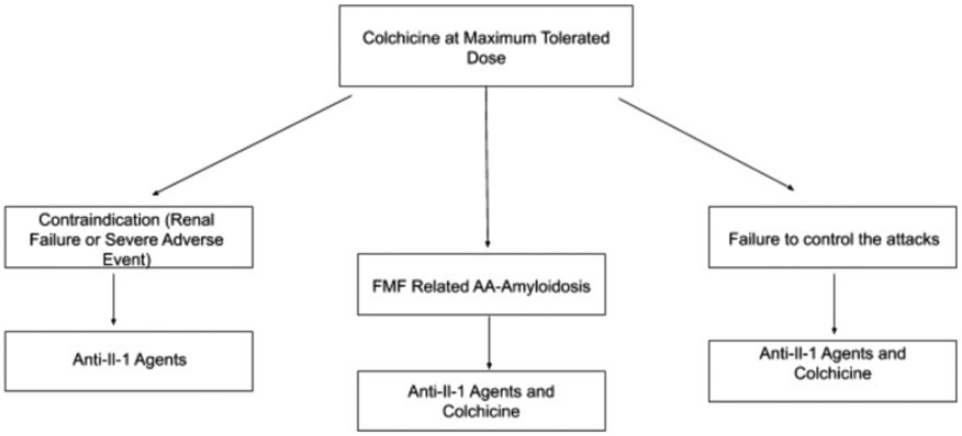

Figure 2. Algorithm for the anti-IL-1 treatment in FMF patients with inadequate colchicine response.

Table 2. Eurofever/PRINTO and Tel-Hashomer diagnostic criteria

Eurofever/PRINTO[33]	Tel-Hashomer[34],a
Confirmatory MEFV genotype-one of the following	Major criteria
Duration of episodes (1–3 days)	Recurrent febrile attacks with serositis
Arthritis	Idiopathic AA amyloidosis
Chest pain	Colchicine response
Abdominal pain	Minor criteria
Non-confirmatory MEFV genotype+at least two of the following	Recurrent febrile attacks
Duration of episodes (1–3 days)	FMF in first degree relative
Arthritis	Erysipelas-like erythema
Chest pain	
Abdominal pain	

[a]For diagnosis >2 Major or 1 Major + 2 Minor criteria are required.

The new Eurofever/PRINTO diagnostic guidelines included two sets of criteria for all of the diseases: genetic and clinical.[34] For FMF, the addition of genetic tests is new unlike the previous Tel-Hashomer criteria.[35] The addition of the genetic screening is questioned by three studies. The International Delphi Survey ranked the genetic test on top of its disease-related variable list.[36] Tanatar *et al.*[37] compared the performance of the two diagnostic tools specifically for FMF. They divided 1291 patients into three groups according to their genetic information: Group 1 included 447 patients with homozygous mutations, Group 2 included 429 patients with compound heterozygous mutations and Group 3 included 415 patients with the heterozygous mutation. Of these patients 98.2% of the first group, 94.2% of the second group and 80.2% of the third group had an FMF diagnosis according to Eurofever/PRINTO criteria, also none of the healthy controls had an FMF diagnosis according to the same criteria. Both Tel-Hashomer and Eurofever/PRINTO failed to diagnose a high percentage of patients in Group 3. A similar analysis was made in a Turkish cohort of 151 patients.[38]

Overall, in terms of disease diagnosis and follow-up, the exciting findings from the last few years hint towards a near future resolution of this diagnostic mystery,

Associated diseases

FMF is associated with many different types of clinical entities. However, in very few, the reasons for the association have been identified. The most frequently suggested associations in the literature are cardiovascular problems, malignancies, other rheumatologic conditions, and infertility. Here, we discussed their clinical significance and recent findings.

Cardiovascular associations

As the nature of FMF is characterized by chronic and recurrent inflammatory presentation, cardiovascular morbidity and mortality due to this inflammation is expected. Besides the known complication of amyloidosis potentially causing cardiovascular problems, there are several reports on FMF-related pericardial inflammation and ischemic heart problems.[38] To prevent these cardiovascular events, the importance of prophylactic colchicine was highlighted.[39]

The recent study by Roitman *et al.*[40] analyzed the hospital admissions of any cardiovascular disease retrospectively over a period of 15 years. The authors compared 23 patients who were ≤55 years old with 40 FMF controls without a cardiovascular event. The results did not show an association between cardiovascular diseases and FMF as both the disease severity and the colchicine dose were similar in two groups. The cross-sectional study of 7670 patients from Israel, reported a higher prevalence of ischemic heart diseases (odds ratio [OR]: 1.33) and mortality (OR: 1.29) in univariate analysis.[41]

Another study on cardiovascular risks evaluated cardiac functions with speckle tracking echocardiography in 60 FMF patients and compared the results to 20 healthy controls.[42] Even though the results did not find a striking difference of clinical significance; the authors still suggested that FMF might deteriorate right ventricular function. Nevertheless, there are also studies denying an association between FMF and cardiovascular diseases.[43] So far, a pathologic mechanism specific to cardiac tissue has yet to be explained.

Cancer

The Israeli cohort of 8534 FMF patients studied the incidence of cancer.[44] The standardized incidence ratio of cancer was 0.66 (95% CI: 0.55–0.77) significantly lower in Jewish male patients ($P < 0.001$) as well as female patients (0.34, CI: 0.07–0.99,

$P < 0.001$). Even though no other studies on this condition were published, this one had a very large cohort with high generalizability.

Other rheumatologic conditions

FMF has a big list of rheumatologic comorbidities that are both autoimmune and autoinflammatory. Here, we wanted to selectively review the studies showing the associations with ankylosing spondylitis (AS) and vasculitis, specifically Behcet's disease (BD).

The review by Merashli *et al.*[45] analyzed the studies published up until 2017. Keeping in mind the high variability of the results in different studies, a special link was found between MEFV gene mutations and AS. However, the coexistence of FMF did not affect AS severity.

There is one recently published meta-analysis on the association with vasculitis by Abbara *et al.*[46] The authors included 58 articles: 12 on IgA vasculitis, 25 on polyarteritis nodosa and 7 on BD. The study concluded that homozygous MEFV mutation was found associated with IgA vasculitis and polyarteritis nodosa only, and not BD. Another study by Alparslan *et al.*[47] specifically investigated the coexistence of FMF and BD. The study analyzed the prevalence of BD and FMF from a cross-section of almost 5000 patients in total. Similarly, to the meta-analysis, this study also did not find an increased prevalence of BD in FMF patients therefore proving against the association.

Infertility

Although infertility in FMF was not studied as much as the aforementioned conditions, it is still a common long-term complication of the disease, and the treatment affecting the quality of life of the patients.

Atas *et al.*[48] studied the demographic, genetic, and disease-related features of 582 adult patients. Of these 582 patients, 64 (18.6%) was unable to conceive for at least 12 months, hence infertile. The OR was especially high among female patients (OR: 4.47, 95% CI: 1.75–11.42, $P = 0.002$). Besides gender, early disease onset and colchicine resistance seemed to be the independent predictors.

In conclusion, over the years numerous clinical associations were reported. However, the literature still lacks data on explaining the causality and prognostic importance of these associations. In addition, there is contradictory evidence on the association of some of these conditions. Before suggesting a screening modality or prophylactic approach in FMF patients, more studies with higher evidence value are needed.

Management

The disease management aims at preventing the attacks and controlling the subclinical inflammation.[49] For this purpose, daily prophylactic colchicine treatment is required, and in cases of colchicine resistance, biologic agents are preferred.[49] In this section, recent studies on each treatment modality will be reviewed.

Colchicine

The recent meta-analysis by Wu *et al.*[50] included nine randomized controlled trials with 249 participants. Oral colchicine treatment was studied in six of these studies. These studies overall reiterated the effect of the medication on reducing the number of attacks and increasing the overall quality of life.

Besides the clinical effectiveness of the drug, it has shed light on disease pathogenesis. Colchicine seems to inhibit the expression of the Toll-like receptor 2 (TLR2), especially on monocytes.[51] The elevated levels of TLR2 bring in a new explanation of the pro-inflammatory cytokine production and the inflammatory nature of the disease.

Colchicine currently has two different preparations at the market: Turkish produced-coated tablets (TP) and the French produced-compressed tablets (FP). From a clinical perspective, patients often respond differently to these medications. Two studies are focusing on their treatment response. Emmungil *et al.*[52] investigated the efficacy of FP in 50 patients resistant to TP. In 88% of the study population, there was a significant reduction in the attack count. The authors suggested the use of FP in patients who are resistant to TP. The other study by Baglan *et al.*[53] had a similar methodology. The results show a significant decrease in the mean attack duration, frequency, and the acute phase reactant levels during the attack-free periods. These two preliminary studies necessitate controlled trials in future studies.

Besides preparations, routes of administration are also important. The most abundant route of administration is oral colchicine. Grossman *et al.*[54] studied chronic intravenous (IV) colchicine treatment in patients who are resistant to oral colchicine. The data of 15 patients who were treated with IV colchicine for the mean duration of 5.16 years, had shown that long-term IV colchicine treatment is both effective and safe as both the attack count and severity decreased, and the adverse event rate was low.

Colchicine use during pregnancy has been an arguable topic. It has been studied for a while and the recent systematic review and meta-analysis of four studies is an important publication to summarize the work.[55] According to the results of the four studies, colchicine is not associated with an increase in the incidence of fetal malformations or miscarriages. The authors recommended the cessation of colchicine treatment during pregnancy.

Colchicine resistance and biologics

Colchicine resistance stems from the intolerance due to side effects and non-adherence. In 18.7% of the patients, effective colchicine dosing is not maintained.[56] The main side effects that warrant treatment cessation are diarrhea, elevated liver enzymes, leukopenia and renal impairment.

In these instances, IL-1 blockers are the choices of treatment (Fig. 2)[57] In a cohort of 250 FMF patients, 31 were treated with an anti-IL-1 (29 Anakinra, 2 Canakinumab) for a mean duration of 2 years.[58] The rapid response to anti-IL-1s was shown by the resolution of the FMF symptoms and inflammatory parameters in 2 ± 3 days. Also, the significant reduction in attack frequency and the overall disease severity enabled the authors to conclude that anti-IL-1s are effective. The rise in the quality of life of the patients was further emphasized with a prospective study of 44 patients.[59] The significant improvements in reported physical function, social function and general health reinforced the benefits of the treatment agent. A similarly designed, nationwide data of 172 FMF patients showed an additional effect on reducing proteinuria.[60]

Another important aspect of FMF management includes managing the attacks, and Anakinra is thought to be a great option for this purpose. A retrospective study from a cohort of 689 FMF patients identified 15 patients who were treated with on-demand use of Anakinra.[61] The attack severity and frequency

decreased significantly ($P = 0.002$ and 0.001) after a median duration of 6 months. This shows that on-demand Anakinra use can be a good treatment alternative in patients receiving maximum tolerated colchicine treatment and still having severe FMF attacks.

As an anti-IL-1 medication, Anakinra has yet to have adequate evidence for its safety during pregnancy. Venhoff *et al.*[62] published a case series on three patients who were treated with Anakinra during the whole pregnancy. No adverse events were reported related to the pregnancy, maternal health, and the health of the newborn except for one patient early cesarean section was done in Week 33. However, the safety of Anakinra should be further investigated in studies of higher statistical power.

Another anti-IL-1 medication, Canakinumab, is also preferred in colchicine-resistant patients. The recent trial has shown a significant decrease in its primary outcome of complete response by week 16 between the treatment arm and the control group (61–6%, $P < 0.001$)[63] In another Phase 3 trial, the authors compared the safety and efficacy of canakinumab in two subgroups treated with a cumulative dose of <2700 mg, or ≥2700 mg.[64] After a follow-up of 72 weeks, more than half of the patients had no attacks, and the median acute phase response nearly normal (median CRP < 10 mg/l and median SAA < 30 mg/l).

Canakinumab is usually preferred in patients who are also resistant to Anakinra. The retrospective analysis of 23 adult patients who were resistant to both colchicine and Anakinra, had shown the effectiveness and relative safety of this third-line treatment approach.[65] The significant improvement ($P < 0.01$) in attack severity, duration, frequency, acute phase levels enabled the authors to reach this conclusion. No severe adverse events were observed.

To sum up, in cases of colchicine resistance, anti-IL-1 agents seem effective and safe. Due to previously published data, they are routinely used in patient management.[66]

Prognosis and amyloidosis

The most morbid and mortal complication of FMF is systemic AA-Amyloidosis. It is still not possible to predict or prevent this complication in patients, besides treating the chronic inflammation.[67] Nevertheless, studies are investigating poor prognostic factors. The most acknowledged risk factors hinting towards both severe symptoms and amyloid deposition are homozygous mutations, especially M694V, and comorbid disorders.[68]

Two molecules were discussed as potential markers of amyloidosis.[69,70] The decrease in mitochondrial DNA amount was reported in FMF-related AA-Amyloidosis patients who also were homozygous M694V mutation carriers.[69] Even though the sample size of the study was quite small, the findings were promising. On the other hand, soluble triggering receptor expressed on myeloid cells-1 level was more questionable as an Amyloidosis marker.[70] The results showed that the molecule was associated with renal function due to amyloid deposition rather than the amyloidosis itself.

Another important aspect is the management of already developed amyloidosis. Tocilizumab, an anti-IL-6 inhibitor found to be effective in improving the condition and well-tolerated in a retrospective study by Colak *et al.*[71] of 15 patients. There are also two studies published, investigating the role of anti-IL-1 agents.[72,73] Varan *et al.*[72] found a significant decrease in proteinuria in 17 renal amyloidosis patients. Similar results were also observed by another retrospective study of 44 patients with a similar design.[73] However, the second one also showed its effects in different renal replacement therapies like hemodialysis and renal transplantation. In patients who were not on any renal replacement therapy, ∼80% had either improved or maintained renal function. The case series of four renal transplant recipients by Sendogan *et al.*[74] studies Canakinumab specifically. All of the patients were unresponsive to both colchicine and Anakinra. A complete response to treatment in terms of clinical signs and acute phase reactants were observed, and there were no serious adverse events.

Conclusion

As we improved our understanding of the disease, we started to notice numerous variations among patients based on their genetic information, clinical presentation, and treatment response. Patient history and physical exam should never be overlooked during the initial presentation, as well as family history. In order to optimize the medical counseling and treatment response, close follow-up with necessary laboratory tests is needed. Ways of improving prophylactic colchicine adherence should be practiced preventing the maintained inflammatory state and when necessary biologic agents should be considered.

Conflict of interest. None declared.

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