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Review article

French protocol for the diagnosis and management of familial Mediterranean fever

Protocole national de diagnostic et de soins de la fièvre Méditerranéenne familiale

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ABSTRACT

Familial Mediterranean fever is the most common monogenic auto-inflammatory disease in the world. It mainly affects people originating from the Mediterranean region. The mutated gene is *MEFV*, which codes for pyrin. Transmission is autosomal recessive. Patients present with recurrent attacks of fever since childhood associated with abdominal and/or thoracic pain lasting an average of 2–3 days and a biological inflammatory syndrome. Other symptoms include arthralgia or arthritis in large joints such as the knees and ankles, myalgia in the lower limbs and pseudo-erysipelas in the ankles. The most serious complication is inflammatory amyloidosis, which can lead to kidney failure. Treatment is based on colchicine, which helps to prevent flares and the onset of renal amyloidosis. This paper proposes national guidelines for the diagnosis, management and follow-up of familial Mediterranean fever in France, where we estimate there are between 5000 and 10,000 patients with the disease at all stages of life. The diagnosis is suspected on the basis of clinical and anamnestic factors and confirmed by genetic analysis. These guidelines also suggest a "treat-to-target" approach to disease management, particularly in case of suspected colchicine resistance – a very rare situation that should remain a diagnosis of elimination, especially after colchicine compliance has been verified. Two special situations are also addressed in these guidelines: kidney failure and pregnancy.

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RÉSUMÉ

La fièvre Méditerranéenne familiale est la maladie auto-inflammatoire monogénique la plus fréquente au monde. Elle touche principalement les sujets originaires du pourtour méditerranéen. Le gène muté est *MEFV* qui code la pyrine. La transmission est autosomique récessive. Les patients présentent des poussées récurrentes depuis l'enfance de fièvre associées à des douleurs abdominales et/ou thoraciques durant en moyenne 2 à 3 jours, associées à un syndrome inflammatoire biologique. Les autres symptômes sont des arthralgies voire arthrites des grosses articulations comme les genoux et chevilles, les myalgies des membres inférieurs et les pseudo-érysipèles de cheville. Sa complication la plus sévère est l'amylose inflammatoire, ou amylose AA, qui peut être entraîner une insuffisance rénale. Le traitement repose sur la colchicine qui permet de prévenir les poussées et l'apparition de l'amylose rénale. Ce travail propose les recommandations nationales de diagnostic et de prise en charge et de suivi de la fièvre Méditerranéenne familiale en France ou nous estimons qu'il y a entre 5000 et 10 000 patients atteints de cette maladie à tous les âges de la vie. Le diagnostic est suspecté sur des éléments cliniques et anamnestiques et confirmé par une analyse génétique. Ces recommandations proposent également une approche ciblée « treat-to-target » du traitement de la maladie en particulier en cas de suspicion de résistance à la colchicine, situation très rare qui doit rester une situation d'élimination, notamment après vérification de l'observance à la colchicine. Deux situations particulières sont également abordées dans ces recommandations : l'insuffisance rénale et la grossesse.

1. Abbreviations

AA	inflammatory amyloidosis
ACE	angiotensin-converting enzyme
ARBs	angiotensin-1 receptor blockers
CBC	complete blood count
CeReMAIA	Reference Centre for Auto-Inflammatory Diseases and Inflammatory Amyloidosis
CKD-Epi	Chronic Kidney Disease – Epidemiology Collaboration
CRF	chronic renal failure
CRP	C-reactive protein
FMF	Familial Mediterranean fever
GFR	glomerular filtration rate
HAS	French National Authority for Health
HIV	human immunodeficiency virus
IL	interleukin
ISSAID	International Society of Systemic Auto-Inflammatory Diseases
MDRD	modification of diet in renal disease
MEFV	MEditerranean FeVer
NSAID	non-steroidal anti-inflammatory drugs
SAA	serum amyloid A
TNF	tumor necrosis factor
TPE	therapeutic patient education
VAS	Visual Analog Scale

2. Key points for the family doctor

Familial Mediterranean fever is a rare hereditary, autosomal recessive disease that mainly affects patients from the Mediterranean region, especially Turks, Armenians, Sephardic Jews and North Africans. The prevalence of FMF is estimated at 100,000 worldwide. As it is a recessive disease, symptoms usually appear only if the patient has two pathogenic variants of the *MEFV* gene.

2.1. Etiology and pathophysiology

The mutated gene (*MEFV for MEditerranean FeVer*) encodes a protein called pyrin, which participates in the pathway leading to the synthesis of interleukin 1 by certain white blood cells. The pro-inflammatory cytokines will then induce the synthesis of inflammatory proteins (CRP in particular) by the liver. Raised CRP during attacks is the hallmark of auto-inflammatory diseases – group to which FMF belongs.

2.2. Clinical manifestations

FMF affects both children and adults as it usually starts early in life. FMF is characterised by attacks that last on average 24 to 72 hours, with sudden onset and end. The patient is asymptomatic between attacks. The interval between attacks is variable. FMF typically causes inflammation of the synovial, peritoneal, pleural, and sometimes pericardial serosa. Fever and severe abdominal pain, which may mimic peritonitis, are the most common symptoms described during FMF attacks. Other symptoms may include chest pain, arthralgia and inflammatory oedema in the ankles (pseudo-erysipelas). Stress and fatigue, or other factors such as menstruation in women, trigger the attacks. Untreated, FMF may induce inflammatory amyloidosis (AA amyloidosis) due to the uncontrolled chronic inflammation and ultimately may lead to end-stage renal failure.

2.3. Positive diagnosis

The diagnosis is based on clinical criteria (recurrent inflammatory and stereotyped attacks with elevated CRP) and confirmed by a genetic test.

2.4. Maintenance treatment

All patients with a positive diagnosis of FMF need a lifelong treatment with colchicine (starting dose of 1 mg/d or 0.5 mg/d in children under 5 years of age). The dose of colchicine should be adjusted if the patient experiences more than 4 attacks a year or if CRP in-between attacks remains above the laboratory standard. The maximum daily dose is 2.5 mg/d in adults. This treatment is effective in more than 95% of cases to prevent or substantially reduce the frequency and intensity of attacks. Colchicine is the only treatment that has been shown to prevent AA amyloidosis. Strict adherence to the prescription is imperative and must be explained to the patient. The preventive effect of colchicine can only be achieved with a very regular intake of a sufficient dose.

Precautions in relation to long-term colchicine use:

- colchicine has many potential drug interactions that must be considered if co-prescriptions are necessary. Colchicine has no negative impact on growth, puberty or fertility. It can be continued safely during pregnancy and breastfeeding. The decision to stop colchicine can only be made with the express agreement of the expert physician;
- in case of insufficient response and/or toxicity or intolerance to colchicine, other treatment options such as biological agents may be offered by expert centres.

2.5. Treatment of attacks

Patients with a well-balanced disease may still experience attacks that need a specific management: the first-line therapy should combine analgesics and antipyretics with non-steroidal anti-inflammatory drugs:

- child: paracetamol, 15 mg/kg every 6 h without exceeding the maximum adult doses, in combination with NSAIDs, e.g. ibuprofen 8 mg/kg/6 h without exceeding the maximum adult doses;
- adult: paracetamol (1 g/6 h) alternating with a ketoprofen-type NSAID 100 mg, 1 tablet × 2/d. In case of renal impairment, NSAIDs should be used cautiously;
- parenteral treatment may sometimes be necessary, especially in the presence of nausea or vomiting.

If the pain is not relieved by the aforementioned medications, level 2 or 3 analgesics may be necessary:[2]

- child:
  - tramadol: 1 mg/kg × 4/day without exceeding 400 mg/d,
  - if morphine is required (to be adjusted according to history):
    - intravenous (IV): loading dose, give a bolus of 50 micrograms/kg then boluses of 25 micrograms/kg to be administered according to pain, maximum 8 boluses every 4 hours,
    - intra-rectal: 0.3 mg/kg every 3 to 6 hours;
- adult: tramadol or tramadol-paracetamol combination or paracetamol-codeine combination, or even morphine in discontinuous IV or subcutaneous (SC) injections depending on the evolution of the pain.

3. Introduction

Familial Mediterranean fever is the most common monogenic auto-inflammatory disease with recurrent fevers [1–3]. It mainly affects patients of Middle Eastern and Mediterranean origin: Armenians, Turks, Sephardic Jews, Eastern and Western Arabs [1,2]. FMF is an autosomal recessive disorder that is common in these populations, particularly among Sephardic Jews and Armenians, where the frequency of heterozygous carriers of a variant of the (*MEditerranean FeVer* (*MEFV*) gene responsible for FMF may be as high as 1/5 of the population [4,5]. Other populations are also affected, but to a lesser extent: Kurdish, Druze, Lebanese, Italian, Greek, Ashkenazi Jewish, and even Japanese populations; FMF is more rarely observed outside the above-mentioned at-risk populations: its overall frequency in France is estimated at 1/5000 individuals, i.e. between 5000 and 10,000 patients [2].

The first attacks of FMF appear before the age of 20 in the majority of patients and most often within the first 10 years of life [1,3,6]. FMF is the prototypical disease of monogenic auto-inflammatory diseases: variants in the *MEFV* gene cause a disruption of the innate immune system, the immediate and non-specific immunity; this gene is mainly expressed in monocytes and neutrophils and its dysregulation will lead to increased secretion of pro-inflammatory cytokines such as IL-1β, IL-6, IL18 and TNFα, resulting in liver synthesis of acute phase proteins (CRP, SAA, fibrinogen. . .) and systemic inflammatory clinical signs (fever, muscle pain and serous inflammation) [1,7].

As this clinical and laboratory evidence is not very specific and can be found in a large number of different diseases, at present only a combination of clinical and laboratory-based arguments coupled with genetic testing will make it possible to make a diagnosis of FMF.

4. Objectives of the French guidelines for familial Mediterranean fever

The aim of this work is to explain to French health care professionals the current optimal diagnostic and therapeutic management and integrated care pathway for patients with Familial Mediterranean fever. The goal is to optimise and harmonise the treatment and follow-up of this rare disease.

It also identifies pharmaceutical specialties used in an indication not provided for in the marketing authorisation, as well as the specialties, products or services necessary for the management of patients but not usually paid for or reimbursed.

These guidelines can be used as a general reference for the general practitioner in cooperation with other medical specialists.

However, these guidelines cannot consider all specific cases, all comorbidities or complications, all therapeutic peculiarities, all hospital care protocols, cannot claim to be exhaustive in regard to treatment, nor can they be a substitute for the individual responsibility of the physician. The protocol does, however, describes a recommended treatment for patients with Familial Mediterranean Fever. It needs to be periodically updated, based on new and validated data.

These guidelines were designed using the "Methodology for the national protocol for the diagnosis and care of rare diseases" published by the French National Authority for Health (HAS) in 2012 (technical guide available on the HAS website: http://www.has-sante.fr/ (in French).

5. Diagnosis and initial assessment

5.1. Suspicion of diagnosis

In the presence of typical signs whose onset was paediatric, early or during adolescence, or in young adulthood, the interview with the patient and the analysis of the health record, the drawing of the family tree, and the collection of documents from the case file make it possible to confirm the presence of recurrent inflammatory, abdominal, thoracic and joint pain attacks. The precise description of attacks and precipitating factors is also an important part of the interview.

FMF onset occurs at a median age of 4 years, but 10% of patients have an onset before the age of 1 [3,6]. FMF should only be considered in children with Mediterranean ancestry, at least one grandparent on each side [1,6]. Attacks last a median of 48–72 hours but can be shorter or slightly longer, up to 4 days, in patients with severe disease; they are separated by free intervals of varying duration [2,3,6]. Attacks recur for months or years in a stereotypical manner; the presence of at least 3 episodes is necessary before the possibility of familial Mediterranean fever can be raised [6,8].

5.1.1. Typical presentation [2,3,6,8]

Fever is the "main symptom" and is generally high. It is accompanied by a series of symptoms, quite repetitive in the same patient,

[2] Repeated and prolonged use of these medications may be addictive.

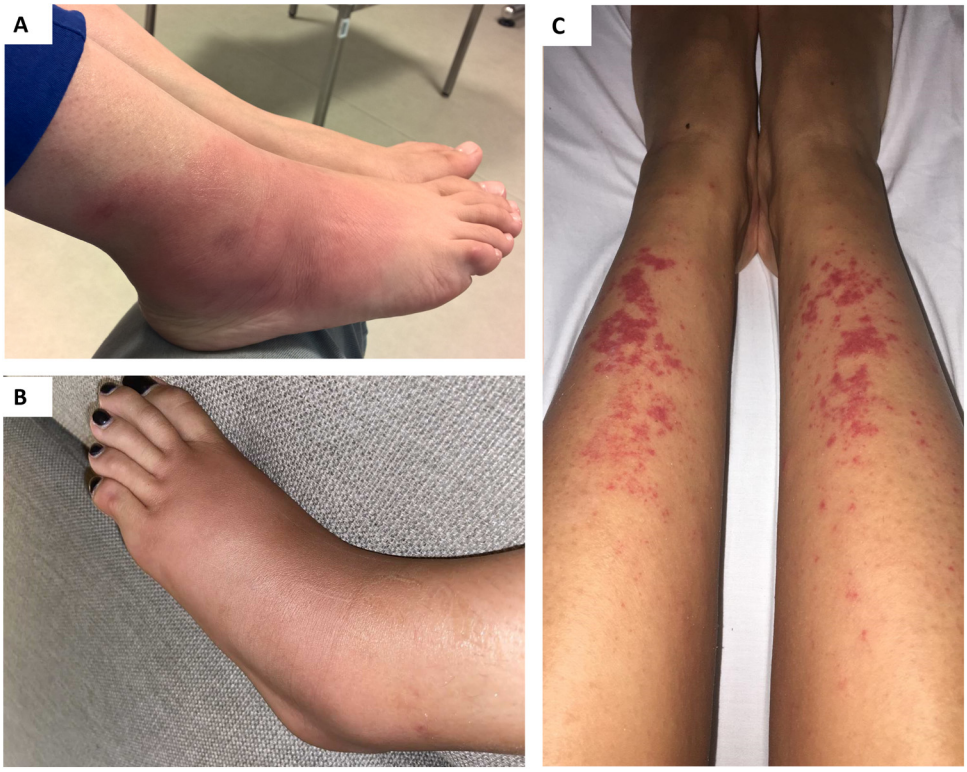

Fig. 1. A and B. Pseudo-erysipelas of the ankle in a young patient with familial Mediterranean fever (FMF). C. Purpuric eruption on the anterior aspect of the tibia, satellite of an attack of FMF confined to the lower limbs.

which reflect the inflammation of the serous membranes in various organs. In children under 1, the fever may be apparently isolated, which is a source of delay in diagnosis. Some adults have no fever, even if the CRP is high.

The onset of the attack is quite sudden, preceded in 50% of cases by prodromal symptoms: a feeling of general fatigue, irritability, sometimes headaches, myalgias and chills.

Abdominal pain begins in the epigastrium, migrates to the right iliac fossa and then to the entire abdomen. The pain is intense, resulting in a hard abdomen and the child lies in the foetal position or adopts a characteristic stooped posture, reflecting the inflammation of the peritoneum.

Chest pain is characterised by polypnea and/or a feeling of heaviness or punching in the lower thoracic region and shoulder, most often on the left side.

Arthralgias in the large joints (ankles > knees > hips) accompany the attacks and disappear with them. They may last beyond the attack in cases of true arthritis.

On the skin, a pseudo-erysipelas may occur [9] (Fig. 1). The ankle, which is the most affected, may be the site of significant inflammatory oedema with an erythematous and shiny appearance of the skin; it is almost pathognomonic of FMF in a patient from a high-risk ethnic group. Vascular purpura on the lower limbs is also a typical feature of FMF, which heat, fatigue and prolonged sitting can promote [3,10].

Orchitis, actually an inflammation of the tunica vaginalis, may be present but is also quite rare (5–10% of boys) and is considered to be a feature of the severity of the attack.

Between attacks: patients can display fatigue and exertional myalgia in the lower limbs (thighs and calves).

In typical cases, the diagnosis of FMF can be made according to international diagnostic criteria (Yalcinkaya in children and Tel Hashomer in adults and simplified criteria from Livneh) (Table 1) [8,11].

Atypical presentations:

- chronic inflammatory forms: some patients, with at least one M694V variant, can display chronic pain syndrome with digestive discomfort and myalgia associated with laboratory evidence of a moderate but chronic, permanent inflammatory syndrome (CRP > 15 mg/L);
- rheumatological forms: some patients can display arthralgia in the lower limbs, rarely arthritis, with less marked febrile and abdominal features but laboratory evidence of a chronic, permanent inflammatory syndrome (CRP > 15 mg/L);
- forms revealed by vasculitis: localised vascular purpura, genuine Henoch–Schönlein purpura or periarteritis nodosa with laboratory evidence of intense inflammation may be indicative of FMF [12,13];
- forms revealed by protracted febrile myalgia: rarely, patients can present with prolonged unexplained fever associated with very intense myalgias preventing any mobility and associated with laboratory evidence of intense inflammation. A skin/muscle biopsy is not helpful and it is therefore only clinical intuition that will lead to FMF.

5.1.2. Laboratory evidence of attacks

Elevation of serum biomarkers of inflammation during an attack, C-reactive protein (CRP), is mandatory and is often accompanied by elevated neutrophil hyperleukocytosis [14]. Between attacks, biomarkers should normalise. If that is not the case, the treatment should be increased.

5.1.3. Special and/or difficult diagnostic cases in adults

- Thoracic attacks (such as “stitches in the side”), where a CRP sample may not have been taken.
- Oligoarthritis without abdominal pain.

Table 1
Clinical criteria for familial Mediterranean fever (FMF).

Tel Hashomer criteria
Major criteria
Recurrent febrile episodes with peritonitis, arthritis or pleurisy
Type AA amyloidosis with no identified cause
Favourable response to continuous colchicine treatment
Minor criteria
Isolated recurrent febrile episodes
Pseudo-erysipelas
FMF in a first-degree relative
Positive diagnosis of FMF if
Presence of 2 major criteria
Or presence of 1 major and 2 minor criteria
Probable diagnosis of FMF if
Presence of 1 major criterion + 1 minor criterion
Simplified Livneh criteria
Major criteria
Typical recurrent attacks (at least 3, with fever > 38 °C, lasting 12 to 72 hours)
Peritonitis (generalised)
Pleuritis (unilateral) or pericarditis
Monoarthritis (hip, knee, or ankle)
Isolated fever
Incomplete abdominal attacks[a]
Minor criteria
Incomplete attacks affecting one or more of the following sites:
Abdomen
Thorax
Joint
Pain in the lower limbs on exertion
Favourable response to colchicine treatment
Positive diagnosis of FMF if:
Presence of 1 major criterion
Or presence of 2 minor criteria
Yalcinkaya paediatric criteria
Criteria
Fever lasting 6 to 72 hours with at least 3 febrile episodes
Abdominal pain lasting 6 to 72 hours with at least 3 painful episodes
Chest pain lasting 6 to 72 hours with at least 3 painful episodes
Arthritis lasting 6 to 72 hours with at least 3 episodes of arthritis
Family history of FMF
Positive diagnosis of FMF if
Presence of at least 2 criteria for populations with high FMF endemicity
In a mixed population (of non-obligatory Mediterranean origin such as in France), the presence of 3 criteria will lead to a diagnosis of FMF with a specificity of 95% and a sensitivity of 77%
Gattorno classification criteria (ARD 2019)
Presence of a confirmatory MEFV genotype + at least 1 among:
Duration of episodes 1–3 days
Arthritis
Chest pain
Abdominal pain
OR
Presence of a non-confirming MEFV genotype[b] and at least 2 of these:
Duration of episodes 1–3 days
Arthritis
Chest pain
Abdominal pain

[a] Painful and recurrent, differing from typical attacks in 1 or 2 features, as follows: temperature is normal or lower than 38 °C, the attacks are longer or shorter than specified (but no shorter than 6 hours or longer than a week), no signs of peritonitis are recorded during the abdominal attacks, the abdominal attacks are localized, the arthritis is in joints other than those specified.

[b] Heterozygous for one pathogenic *MEFV* variant, or trans compound heterozygous for one pathogenic *MEFV* variants and one variant of uncertain significance (VUS), or biallelic VUS.

- HLAB27-negative spondyloarthritis manifesting primarily as sacroiliitis, with chronic unexplained inflammation (Fig. 2, panels B,C) [15–19].

- Digestive disorders, chronic diarrhoea, ileitis, without criteria for Crohn's disease.

- Hepatomegaly or liver disease complicated by cryptogenic cirrhosis [20].

- Unexplained inflammatory syndrome, prolonged or recurrent, with or without recurrent fever.

- AA amyloidosis (Fig. 2, panels D-F), which may reveal FMF, either in the context of kidney failure, proteinuria, or oedema revealing a nephrotic syndrome, or very rarely thyroid goitre. Kidney failure may thus be immediately very advanced or terminal, requiring immediate management by dialysis. Exceptionally, the diagnosis of FMF may be made at an even later stage, in a patient who has undergone a renal transplant for kidney disease of undetermined cause and who develops suggestive clinical signs [21–23].

Coxitis (Fig. 2, panel A), which develops in only less than 2% of FMF patients, mostly M694V homozygous; but in 73% of cases it is severe and may require the use of one or two prostheses [24].

Table 2 proposes a list of differential diagnosis of FMF.

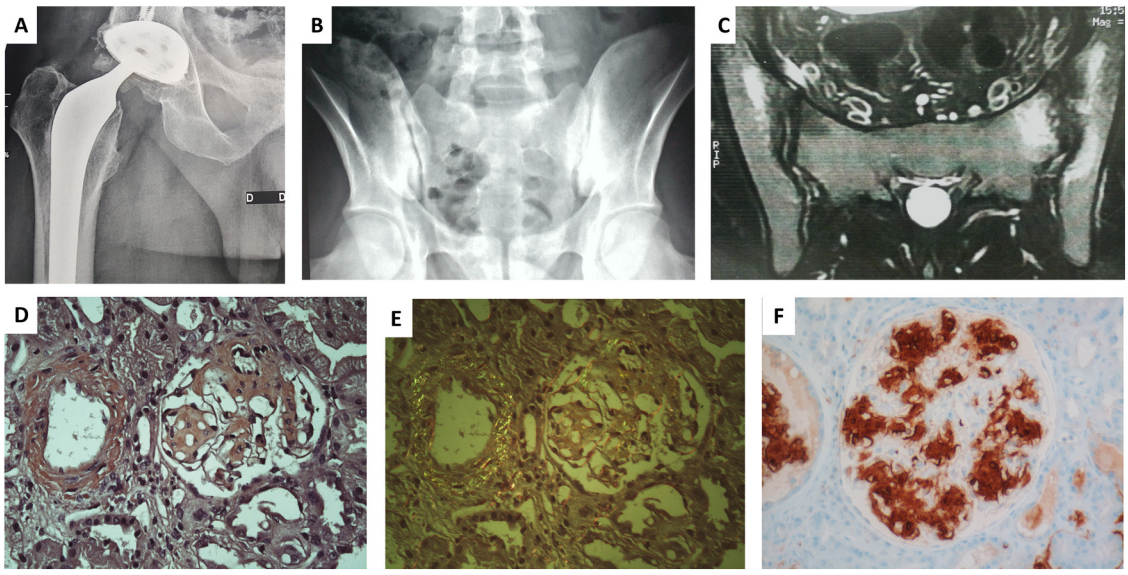

Fig. 2. A. Coxitis in a 42-year-old familial Mediterranean fever (FMF) patient who required hip replacement surgery. B, C. Spondyloarthropathy with bilateral HLA-B27-negative sacroiliitis in a 20-year-old FMF patient who required anti-TNF biotherapy in addition to colchicine. D, E, F. Histology of a kidney biopsy from an FMF patient showing amyloid deposits after staining with Congo red (D) birefringent in polarised light (E) with positive labelling by anti-SAA antibody in immunohistochemistry (photographs by Pr. David Buob).

Table 2
Main differential diagnosis of FMF.

Clinical features	Differential diagnosis
Acute abdominal attacks (recurrent peritonitis)	Appendicitis Diverticulitis Cholecystitis Pyelonephritis Inflammation of the peritoneum Pancreatitis Salpingitis
Recurrent abdominal pain (without peritonitis)	Gastric ulcer Renal colic Endometriosis Dysmenorrhoea Irritable bowel syndrome Acute intermittent porphyrias Cannabinoid syndrome Mast cell activation syndrome
Chest pain (recurrent pleurisy pain)	Pulmonary embolism Pleurisy (idiopathic, infectious, autoimmune) Pericarditis (idiopathic, infectious, autoimmune)
Recurrent arthritis (attacks of synovitis)	Microcrystalline arthritis: gout, chondrocalcinosis Spondyloarthritis Juvenile idiopathic arthritis
Recurrent febrile attacks	Lymphoma Infections (malaria, Q fever) PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and adenopathy)
Inflammatory diseases (recurrent febrile attacks involving at least 2 systems)	Inflammatory bowel diseases Other monogenic auto-inflammatory diseases (MKD, TRAPS, PAPA, PAAND) Behçet's disease Panarteritis nodosa Castleman's disease Lupus connectivitis (Adult onset Still disease)

FMF: familial Mediterranean fever.

5.2. Confirmation/genetics

Genetic testing is now required to confirm the diagnosis of FMF. Guidelines have been proposed by the International Society of Systemic Auto-Inflammatory Diseases ISSAID [25]. As FMF is an autosomal recessive disease, genetic confirmation of FMF relies on the identification of two mutated alleles of the *MEFV* gene: either the same genetic pathogenic variants on both chromosomes (homozygous status), or two different pathogenic variants (compound heterozygous status).[3] The vast majority of known *MEFV*

[3] In theory, as with all recessive diseases, phasing, i.e. genetic analysis of each parent, is necessary to confirm that each mutation is on a different chromosome.

variants are missense variants (change of one amino acid) with highly variable pathogenic effects. The variants located in exon 10 of the *MEFV* gene, p.Met694Val (M694V), p.Met694Ile (M694I), p.Met680Ile (M680I) and p.Val726Ala (V726A), which are very common in populations at-risk of FMF, are also those associated with the most typical phenotypes. Genotypes which include these 4 variants in the homozygous or compound heterozygous state clearly confirm the diagnosis of FMF (confirmatory genotype).

If a patient has one single pathogenic variant (e.g. p.Met694Val), but presents a clinical phenotype suggestive of FMF, seeking the opinion of an expert centre is strongly recommended.

The pathogenicity of some *MEFV* variants, especially p.Glu148Gln (E148Q), should no longer be reported according to international guidelines [6,25].

In patients without Mediterranean ancestry's, a pathogenic *MEFV* variant is (almost) never found despite a phenotype suggestive of FMF. Thus, genetic analysis should be confronted with the clinical evidence and if the genetic analysis is not conclusive, expert opinion is required to determine whether the diagnosis of FMF can be confirmed. Fig. 3 proposes a clinical-genetic course of action to establish the diagnosis of FMF and to better recognise and identify patients who require long-term treatment and monitoring. In children with a non-confirmatory or inconclusive genotype, differential diagnoses such as PFAPA syndrome and age-related physiological susceptibility to infection should be considered (Table 2). In case of very early onset (especially before the age of 1) and/or atypical recurrent fever, an expert centre's opinion is needed to consider other causes of auto-inflammatory syndrome.

5.3. Disclosing the diagnosis and informing the patient

Apart from situations where genetic analysis confirms FMF, the complexity in interpreting the other results requires that the diagnosis disclosure be made in an expert center. Unless it is a very severe phenotype, such as AA amyloidosis, it is recommended to wait for the results of the genetic tests before starting treatment (Fig. 3).

Beyond the transmission of medical information, the diagnosis disclosure appointment requires active listening and support that takes into account the patient's personal and family characteristics. The disclosure of familial Mediterranean fever diagnosis can sometimes justify the intervention of a clinical psychologist, as for any chronic hereditary disease.

In addition to the information directly concerning the patient, the diagnostic disclosure must also be accompanied by genetic counselling for the patient and their relatives, but without offering screening for asymptomatic subjects, specifying that there is no indication for prenatal diagnosis.

6. Therapeutic management

6.1. Treat-to-target approach

As in the majority of chronic diseases, the treatment of FMF should follow a treat-to-target approach. The ultimate goal of FMF treatment is [2,6]:

- to achieve complete resolution of attacks without triggers;
- to normalise subclinical inflammation between attacks (as measured by CRP below the laboratory's normal upper limit, measured in between inflammatory attacks);
- and to prevent long-term complications, including AA amyloidosis.

In order to achieve these goals, the disease should be minimally active.

The definition of a minimally active disease is as follows (*all criteria should be met*):

- ≤ 3 attacks (with fever or abdominal pain or thoracic pain) in the last 12 months;
- no attacks without any trigger;
- ≤ 1 severe attack in 12 months;
- ≤ 5 days (successive or altogether) of school/work absence in 12 months (disease-related);
- CRP measured outside of an attack (minimum 10 days after the end of the attack) $\leq$ laboratory's normal upper limit;
- no occurrence of a complication (or no worsening of a pre-existing complication).

6.2. Drugs for maintenance therapy

6.2.1. Colchicine

Colchicine is licensed for use in FMF under the term "treatment of periodic illness" [26,27]. Colchicine (not combined with tiemonium and opium) should be prescribed on a long-term basis to all patients with FMF (unless contraindicated, which is actually rare) [6]:

- in order to avoid flare-ups of the disease;
- in order to avoid the development of secondary amyloidosis.

6.2.1.1. For adults. The starting dose is 1 mg/day orally. This dose may need to be titrated in clinically unresponsive patients to find the minimum effective daily posology in order to achieve minimal disease activity. Increase of the posology will be 0.5 mg by 0.5 mg, in minimum 3-month increments, until a maximum dose of 2.5 mg/day.

For patients with AA amyloidosis, higher doses are used, regardless of clinical response (1.5 mg/day).

Increased monitoring and dose reduction is required for patients with hepatic or renal impairment. In patients with end-stage renal disease on dialysis, colchicine should be continued at a very low dose (0.5 mg/day) but should be carefully monitored for signs of colchicine toxicity, such as diarrhoea and neuromyopathy.

6.2.1.2. For children. The starting dose is based on the child's age, not body weight.

For children under 5 years of age, the starting dose should be 0.5 mg/day and for children over 5 years of age 1 mg per day. For children under 10 years of age, this dose should be adjusted in 0.25 mg increments without exceeding 2 mg/m^2 daily. For children over 10 years of age, the dose should be adjusted in the same way as for adults, in 0.5 mg increments according to gastrointestinal tolerance, without exceeding the maximum adult dose.

6.2.1.3. Adjusting colchicine dosage. If a patient does not meet one or more criteria of minimal disease activity (as defined above):

- assess adherence to treatment (compliance). Testing for colchicine in the hair can be discussed (see Box 1) [28];
- rule out a cause of inflammation not related to FMF: search for infections (notably *Helicobacter pylori*, *Clostridioides difficile*) and causes of systemic inflammation (neoplasia, etc.);
- in case of good compliance, intensification of therapy (increase of colchicine doses) should be considered: stepwise increase with increments of 0.5 mg (0.25 mg under 10 years of age) every

In practice, experience in FMF shows that the probability of finding 2 pathogenic variants in exon 10 on the same chromosome is almost zero.

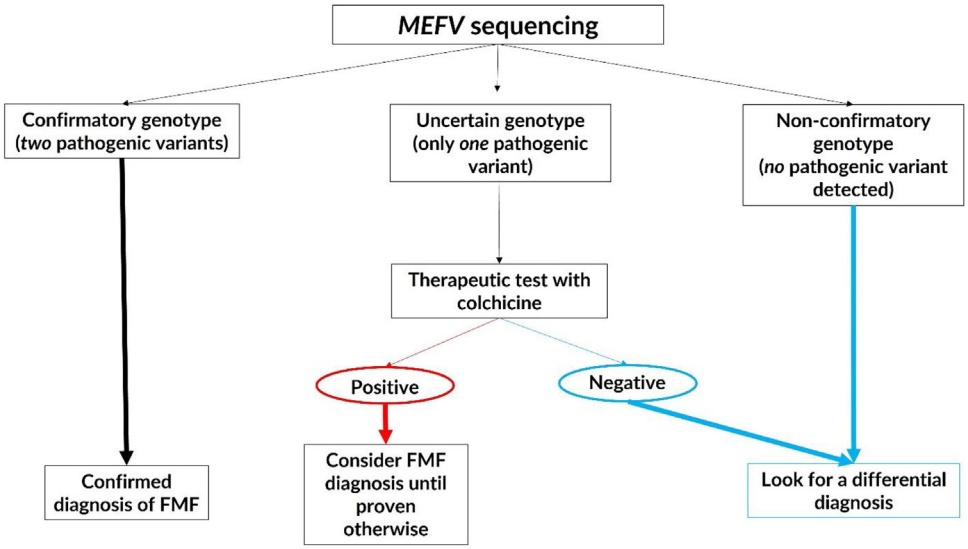

Fig. 3. How to interpret genetic results in familial Mediterranean fever (FMF)?

Box 1: Colchicine determination in hair (Supplemental)

Select a pencil-sized strand of hair from the top and back of the skull. Tie a thick thread about 1 cm from the root to distinguish the root from the tip, with the tests being performed on the segments of hair extending from the root. Cut flush with the scalp using a pair of fine scissors. Leave the thread in place and if possible use a clamp to prevent the hair from slipping.

Do not use sticky paper or other adhesives. Store and transport at a temperature between 15 °C and 25 °C. To be sent in an envelope to the pharmacology-toxicology laboratory of the Raymond-Poincaré hospital in Garches, France.

3 months or more, to a maximum dose of 2.5 mg/day in adults and 2 mg/day in prepubertal children;

- in case of maximum doses of colchicine (2.5 mg/day in adolescents and adults, 2 mg/day in prepubertal children) or in case of colchicine toxicity (exceptional situation), treatment with an IL-1 inhibitor may be considered (see below). This decision to intensify treatment with a biological agent should be made, justified and documented by an expert FMF physician after ruling out the other causes of insufficient response to colchicine (see checklist in Table 3).

6.2.1.4. Precautions when prescribing colchicine. Colchicine is a potentially toxic drug and its therapeutic index is low (therapeutic doses close to toxic doses) (Table 4). Furthermore, renal failure and, to a lesser extent, hepatic failure, increase the risk of side effects and require dose adjustment. The following precautions therefore apply to the prescription of colchicine:

- the concomitant use of colchicine and drugs that inhibit the ABCB1 transporter and/or cytochrome CYP3A4 can lead to drug interactions with potentially serious or even fatal consequences. The main drugs that interfere with the ABCB1 transporter and the CYP3A4 cytochrome are detailed in Table 4. These drugs must therefore be used cautiously, and the benefit-risk ratio of each prescription must be assessed on a case-by-case basis, with adjustment of colchicine doses if necessary (Table 5);
- regular assessment (1–2 times/year) of renal and hepatic function and adjustment of colchicine doses if necessary. Dose adjustment in elderly patients;
- formal contraindication of drug combinations that interact with the ABCB1 transporter or cytochrome CYP3A4 in patients with renal or hepatic failure;
- colchicine boxes should be kept out of sight and reach of young children;
- therapeutic education of the patient in order to check the compatibility of a potential drug combination with a doctor;
- in case of massive ingestion (accidental or voluntary), there is no antidote and no possibility of purification. Special precautions should therefore be taken in case of patients at high-risk of suicide.

In practice, we recommend writing the following sentence on each prescription for colchicine: "Do not combine with certain treatments or antibiotics in particular: macrolides and pristinamycin. Report this treatment to your doctor or pharmacist."

6.2.2. IL-1 inhibitors [6,28]

IL-1 inhibitors (anakinra and canakinumab) are approved only as a second-line treatment in FMF in France. However, they may be considered as a first-line treatment in patients with a contraindication or true intolerance to colchicine. These contraindications are severe hepatocellular failure and severe chronic renal failure (GFR < 30 mL/min).

IL-1 inhibitors can also be used after the advice from an FMF expert in addition to colchicine as a second-line treatment after a failure of colchicine (minimal disease activity not achieved with colchicine alone) or severe complications such as AA amyloidosis (see dedicated chapter). A checklist is available in Table 3 before considering a patient resistant to colchicine.

6.2.2.1. Anakinra [28,31–36]. Anakinra is indicated for the treatment of familial Mediterranean fever (FMF) as a second-line treatment in combination with colchicine, if appropriate. Anakinra treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of FMF. The recommended dose for patients weighing 50 kg or more is 100 mg/day by subcutaneous injection. For patients weighing less than 50 kg treatment should be dosed according to body weight, with a recommended dose of 1–2 mg/kg/day.

Table 3
Checklist before starting biotherapy for a patient with FMF.

1 – Check that the FMF genetic diagnosis is correct
2 – Check whether the reported symptoms are related to inflammation (measure inflammatory biomarkers, especially CRP during attacks)
3 – Eliminate common causes of fever and pain (infections, especially *H. pylori* and *C. difficile*)
4 – Ask the patient about personal, social or psychological problems that may trigger flares
Suggest behavioural approaches to stress management, if appropriate
5 – Ensure that the full dose is maintained for at least 3 to 6 months. If the maximum dose is not reached, gradually increase the dose by 0.5 mg (0.25 mg before the age of 10 years) every 3 months
6 – Ensure tolerance to colchicine with the following measures
Dietary modification (limiting lactose intake)
Splitting the total daily dose
Combining antidiarrhoeal agents and antispasmodics with colchicine
7 – In patients with sudden worsening of FMF despite full compliance with colchicine, other causes of inflammation should be considered
Inflammatory rheumatism, vasculitis
Haemopathy (in people over 50)
Chronic peritonitis or peritoneal mesothelioma (in people over 50)
8 – Prospectively document the recurrence of attacks for 3 to 6 months in order to confirm the number of inflammatory episodes reported

FMF: familial Mediterranean fever.

Table 4
Drug interactions with colchicine.

Colchicine is eliminated mainly by biliary and faecal excretion. The multidrug resistance transporter ABCB1 plays a major role in the elimination of colchicine. Cytochrome P450 plays a lesser but significant role in colchicine metabolism and must be taken into account when prescribing drug combinations, especially as a number of cytochrome P450 inhibiting drugs also inhibit the ABCB1 transporter
Main drugs that interact with the ABCB1 transporter (non-exhaustive list)
Erythromycin, clarithromycin
Ciclosporin, tacrolimus
Verapamil
Statins
Fexofenadine
Anti-H2
Fenofibrate
Certain chemotherapies
Tricyclic
Digoxin
Antiretrovirals
Corticoids
Ketoconazole
Main inhibitors of cytochrome CYP3A4 (non-exhaustive list)
Grapefruit juice (industrial juice and with high daily volume > 300 mL)
Anti-vitamin K
Amiodarone
Diltiazem, verapamil
Ketoconazole, itraconazole
Voriconazole, posaconazole
Fluconazole, miconazole
Ritonavir, nelfinavir, amprenavir, indinavir, atazanavir. . .
Erythromycin, clarithromycin, josamycin
Telithromycin
If for medical reasons the drug combination cannot be avoided, it is advisable to reduce the duration of the drug combination and/or the dose of colchicine as much as possible, and to monitor carefully for any signs of overdose (diarrhoea, vomiting, muscle weakness, tingling in fingers and toes, paleness of lips and palms, recent or increased hair loss)

Table 5
FDA recommendations for adjustment of colchicine doses.

FDA classification	Drugs concerned (non-exhaustive list)	Adjustment of colchicine doses in adult FMF	Adaptation of colchicine doses in FMF in children
Strong inhibitors of the P-gp transporter	Cyclosporine, ranolazine tacrolimus	Maximum dose 0.5 mg per day	25% of the usual dose (not to exceed 0.5 mg/m^2)
Strong CYP3A4 inhibitors	Ketoconazole, atazanavir, clarithromycin, darunavir/ritonavir, indinavir, itraconazole, lopinavi/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranivir/ritonavir	Maximum dose 0.5 mg per day	25% of the usual dose (not to exceed 0.5 mg/m^2)
Moderate inhibitors of CYP3A4	Diltiazem, verapamil amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice	Maximum dose 1.25 mg per day	50% of the usual dose (not to exceed 1 mg/m^2)
Weak CYP3A4 inhibitors	Cimetidine	No dose adjustment necessary	No dose adjustment necessary

FMF: familial Mediterranean fever.

Anakinra may also be used as a treatment option for FMF attacks – but in this indication its use is off-label (see treatment of attacks).

6.2.2.2. Canakinumab [29,30]. The recommended starting dose of canakinumab in patients is:

- adults, adolescents and children ≥ 4 years of age:
  - 150 mg for patients with body weight > 40 kg,
  - 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg,
  - 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg;
- children 2 to < 4 years of age:
  - 4 mg/kg for patients with body weight ≥ 7.5 kg.

It is administered every eight weeks as a single-dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (minimal disease activity) has not been achieved one week after treatment initiation, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 150 mg or 2 mg/kg every 4 weeks should be maintained. If a satisfactory clinical response has not been achieved 1 week after this increased dose, a third dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 300 mg or 4 mg/kg every 4 weeks should be considered, based on individual clinical judgement.

6.2.2.3. Precautions when prescribing IL-1 inhibitors as maintenance therapy. According to current knowledge, the main complications associated with IL-1 inhibitor treatments are as follows:

- frequent pain and local adverse reactions at anakinra injection sites, which can be limited by prior application of lidocaine cream (1 h) and ice packs (15 min). In the event of post-injection inflammatory plaques, creams containing steroids, such as hydrocortisone, may alleviate this adverse effect;
- increased frequency of invasive *Streptococcus pneumoniae* infections and susceptibility to other invasive bacterial infections;
- drug-induced hepatitis (rare – usually associated with high doses of anakinra);
- excessive weight gain and risk of dyslipidaemia (rare);
- an excess risk of secondary neoplasia has not yet been established (preliminary data on the use of these molecules in other aetiologies are reassuring), but must remain the subject of prospective epidemiological surveillance.

Before starting IL-1 inhibitors, it is therefore strongly recommended to [28]:

- complete vaccination against streptococcus pneumoniae;
- update the rest of the vaccination schedule, which remains identical to that of the general population;
- vaccinate against influenza annually;
- check immunological status against VZV and, in the absence of seroconversion, carry out a varicella vaccination, ideally 3 weeks before starting IL-1 inhibitors;
- check for the absence of primary tuberculosis infection;
- remember that all live attenuated vaccines are contraindicated during biological therapy (see chapter on vaccinations);
- have any pregnancy monitored by a specialist team (see chapter Fertility and pregnancy);
- perform pre-treatment blood tests: blood count, CRP, liver function test, cholesterol. If in doubt, check for primary or secondary immunodeficiency (HIV), as well as serological status against hepatitis B and C in the absence of vaccination;
- eliminate cavities and other dental infections at a dentist's office.

6.3. Treatment of remaining attacks

Patients with a well-balanced disease may still experience attacks that need a specific management: the first-line therapy should combine analgesics and antipyretics with non-steroidal anti-inflammatory drugs:

- child: paracetamol: 15 mg/kg every 6 h without exceeding the maximum adult doses in combination with NSAIDs, e.g. ibuprofen 8 mg/kg/6 h without exceeding the maximum adult doses;
- adult: paracetamol (1 g/6 h) alternating with a ketoprofen-type NSAID 100 mg, 1 tablet × 2/d. In case of renal impairment, NSAIDs should be used cautiously;
- parenteral treatment may sometimes be necessary, especially in the presence of nausea or vomiting.

If the pain is not relieved by the aforementioned medications, level 2 or 3 analgesics may be necessary:[4]

- child:
  - tramadol: 1 mg/kg × 4/day without exceeding 400 mg/d,
  - if morphine is required (to be adjusted according to history):
    - IV: loading dose, give a bolus of 50 micrograms/kg then boluses of 25 micrograms/kg to be administered according to pain, maximum 8 boluses every 4 hours,
    - intra-rectal: 0.3 mg/kg every 3 to 6 hours;
- adult: tramadol or tramadol-paracetamol combination or paracetamol-codeine combination, or even morphine in discontinuous IV or SC injections depending on how the pain evolves.

The "on-demand" use of a short-acting anti-interleukin-1 biological therapy, in this case anakinra, in case of an attack not relieved by analgesics, although performed in some expert centres, has not yet been validated by randomised trials. There are only case reports of its use in FMF [33,35]. Caution should be exercised in the absence of a well-conducted published trial, as this treatment is more expensive than simple analgesics, requires a subcutaneous injection and must be kept cool at +4 °C. Its unsupervised use could be detrimental to good adherence to colchicine by patients. Nevertheless, this treatment should be preferred to the use of morphine in case of severe attacks.

Other measures recommended in the literature have limited effects and benefits and cannot be recommended:

- systemic steroid therapy is not recommended in 2023;
- the transient increase in the dose of colchicine should be avoided due to the lack of scientific evidence of its efficacy in this indication, the unknown effect of this short-term treatment on the inflammatory attack and the increased risk of side effects. Indeed, colchicine is not a treatment for FMF attacks;
- intravenous colchicine should not be used due to the risk of lethal overdose. This formulation is no longer available in France.

6.4. Treatment of special situations

6.4.1. Special case of patients with AA amyloidosis

The therapeutic management of AA amyloidosis has several components: the first concerns systemic inflammation and the sec-

[4] Repeated and prolonged use of these medications may be addictive.

ond concerns the kidney, the main target organ of this complication of the prolonged inflammatory context of uncontrolled FMF over the long-term. The renal component of this management is divided into two parts: nephroprotection and management of end-stage renal failure (see our French recommendations for AA amyloidosis [37]).

6.4.2. Treatment of systemic inflammation in established AA amyloidosis

Colchicine is the only drug proven to be effective in preventing amyloidosis secondary to FMF and remains the first-line long-term treatment [26]. Colchicine alone, at the maximum dose (2.5 mg per day provided renal function is normal), can reduce or even eliminate a nephrotic syndrome. If the nephrotic syndrome is resistant to colchicine, anti-IL-1 biological therapy can be added on, while keeping 1 mg of colchicine per day.

In advanced renal failure (GFR < 30 mL/min), colchicine should be discontinued (or continued at a maximum dose of 0.5 mg/d) and replaced with an IL-1 inhibitor, usually anakinra in the haemodialysis setting, at a dose of 100 mg subcutaneously on dialysis days [6,37]. When a kidney transplant is performed, we recommend maintaining anakinra for a few months after transplantation, resuming colchicine usually at a dose of 1 mg/d as soon as renal function permits, and gradually discontinuing anakinra over 6 months if CRP and SAA are normal (they should be closely monitored, CRP every month and SAA every 3 months). If biomarkers stay above 10 mg/L we suggest discussing the case in an expert centre and maintaining anti-IL-1 biological therapy.

Any other source of even minimal inflammation should be actively sought and treated, as it would contribute to the persistence of an amyloidogenic situation:

- intercurrent/chronic infections (especially tuberculosis);
- associated inflammatory diseases which lead to discussing other anti-inflammatory molecules: spondyloarthritis and inflammatory bowel disease which will require anti-TNF-alpha or other treatments for complete control;
- obesity (through appropriate nutritional management and regular physical activity).

6.4.3. Nephroprotection

Non-specific nephroprotective measures are proposed in the majority of kidney diseases with renal failure and/or proteinuria, in order to preserve the nephron capital in the long-term. These therapeutic interventions have never really been evaluated in the specific context of AA amyloidosis secondary to FMF.

6.4.3.1. Anti-proteinuric treatment. The use of anti-hypertensive treatment such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) are typically proposed in glomerular nephropathy with albuminuria > 300 mg/24 h.

However, the clinician must be very careful when prescribing these molecules in the context of amyloidosis, as these patients often have multifactorial arterial hypotension due to the amyloidosis itself or to comorbidities (deteriorated general condition, adrenal insufficiency, hypovolaemia due to capillary leak, other anti-hypertensive drugs, etc.), which these treatments may aggravate.

In addition, patients on ACE inhibitors or ARBs should be warned that this treatment should be suspended in the event of an intercurrent event, such as diarrhoea or other causes of dehydration. Indeed, the occurrence of hypovolaemia in a patient with an inhibited renin/angiotensin system may expose the patient to the risk of severe acute renal failure, usually transient but sometimes permanent, especially if the patient is receiving diuretic treatment for the oedema syndrome induced by the nephrotic syndrome.

6.4.3.2. Adjusting the diet. Protein restriction usually proposed in chronic renal failure (CRF) should not be systematic in renal amyloidosis. Indeed, nephrotic patients present with hypoproteinaemia requires the maintenance of significant dietary protein intakes above 1.2 g/kg/d. Sodium intake should be limited when there is a significant oedema but should be adjusted to daily losses when there is chronic diarrhoea or adrenal insufficiency secondary to amyloidosis. Water restriction should only be imposed when there is hyponatraemia.

6.4.3.3. Avoidance of nephrotoxic drugs. Whenever possible, nephrotoxic drugs (such as non-steroidal anti-inflammatory drugs, aminoglycosides, nephrotoxic chemotherapies such as platinum salts, etc.) should be avoided in patients with CRF. Furthermore, radiological examinations with injection of iodinated contrast media must be proposed with caution and preceded by prior hydration to limit tubulopathy secondary to these potentially nephrotoxic molecules when they are prescribed in a patient with renal failure and/or hypovolaemia.

6.4.3.4. Control of other metabolic and cardiovascular risk factors. Controlling glycaemic balance in case of diabetes mellitus, smoking cessation, and managing dyslipidaemia (often aggravated by the nephrotic syndrome) are essential elements in slowing down the progression of nephropathy, but also in limiting the cardiovascular risk, which is the leading cause of mortality in patients with renal failure.

6.4.4. Management of end-stage renal disease

Patients with end-stage renal disease can be treated with peritoneal dialysis or haemodialysis, but peritoneal dialysis may worsen hypoalbuminaemia. The prognosis of dialysis patients with AA amyloidosis is severe with a mean survival of 20 to 50 months depending on the cohort. Only one study reports no benefit of biological therapies on the survival of haemodialysis patients. Renal transplantation improves the prognosis and overall survival of patients, but this is less than that of patients transplanted for end-stage CRF from other causes. In contrast, graft survival is similar to other causes of end-stage renal disease.

In case of severe CRF (GFR < 30 mL/min), in agreement with the nephrologist, colchicine should be reduced to a maximum of 0.5 mg/day and if CRP remains high, a short-acting anti-IL-1 biological therapy should be added on (anakinra 100 mg/day if the patient is not dialysed and 100 mg/dialysis day in dialysed patients). In the renal transplant patient who recovers normal renal function, colchicine can be resumed, checking for the absence of inflammation or anti-IL-1 biological therapy; we strongly recommend an expert centre's advice in this situation.

7. Fertility, pregnancy and breastfeeding

Fertility is an important issue in FMF as it affects young patients who are or will be of childbearing age. These are very common questions asked in consultations by young men and women.

In women, the disease has long been considered to have a negative impact on fertility due to the risk of tubo-ovarian adhesions related to the peritoneal fibrosis sequelae of inflammatory episodes. The causes of infertility remain discordant to this day. Factors associated with infertility in FMF are a significantly higher number of attacks, earlier onset of the disease, 2 severe mutations such as genotypes M694V and M680I, and patients diagnosed and treated late, non-compliant patients or non-responders to colchicine [38,39].

The effect of pregnancy on the disease varies by patient. Some can no longer have attacks, other patients can display an exacerbation of their disease. In a Turkish study comparing pregnancy outcomes of patients with and without FMF, a significantly increased risk of preterm delivery was found [40]. However, there were no significant differences in perinatal outcomes (APGAR score, malformations, and mortality). In the recent study by Sotskiy et al. the majority of pregnancies achieved after infertility treatment were uncomplicated, with no significant difference compared to the control population [38].

Colchicine should be continued at usual doses throughout pregnancy. Its use in pregnancy has been shown not to be associated with an increased risk of miscarriage or foetal malformation. There is no longer an indication for routine amniocentesis. European guidelines endorse and recommend its use during pregnancy and lactation. For breastfeeding, it is recommended to take colchicine at the time of a feed, as its peak concentration in breast milk occurs about 2 hours after oral intake. It is also advisable to take the treatment in the evening, as night feeds become less frequent and the child is less exposed. In some countries, colchicine pills can contain tiemonium methylsulphate and opium powder, which are contraindicated during breastfeeding.

Obstetrical monitoring of the pregnancy is not different from patients without FMF. We recommend closer monitoring in consultations, every two months with a blood count and especially CRP each time. FMF is not associated with an increased risk of thrombosis. There is no indication for increased antenatal monitoring. The risk of pre-eclampsia is not increased in cases of normal renal function.

In case of renal amyloidosis, pregnancy is at-risk and requires multidisciplinary follow-up with the nephrologist, the FMF specialist and obstetricians. In case of renal failure, there is a risk of worsening renal function, pre-eclampsia, intrauterine growth retardation and premature delivery.

In men, fertility is preserved in the vast majority of patients. Various studies have shown that the sperm quality of men treated with colchicine was not impaired. In case of infertility while on colchicine, it may sometimes be suggested that colchicine be discontinued temporarily for at least three months and the sperm count reassessed. Patients can then be treated during this period without colchicine with IL-1 inhibitors.

For anti-IL-1 biological therapies, continuation of treatment during pregnancy should be discussed with the patient and expert centres. Data on the use of IL-1 inhibitors in pregnancy is still scarce but reassuring. Two cases of renal agenesis have been reported in two patients treated with anakinra who had other potential risk factors for renal malformations, but a causal link cannot be formally excluded. The data on infectious complications are reassuring (Smith and Chambers, 2018; Youngstein et al., 2017). Given the potential for transplacental transport of IgG class antibodies from 30 weeks of pregnancy onwards, it is suggested that canakinumab should not be administered from 22 weeks of pregnancy. With less data available and a longer half-life, we prefer to use anakinra as first-line therapy. The data on breastfeeding of newborns of patients on IL-1 inhibitors is also in favour of its continuation if the patient so wishes [41,42].

8. Non-pharmacological treatments

8.1. Psychological care

Patients in social difficulty and in conflict with their family or in the workplace are likely to have a greater number of attacks, even if the causal link is sometimes not obvious. Moreover, adolescence is a delicate period in the psychological development of every child and chronic illness is a disruptive element in this development. Adherence can be a more problematic issue at this pivotal time in life. Thus, psychological care should be offered to each patient:

- at the time of adolescence, to help the adolescent to appropriate and invest in his or her different body, to accept comparison with peers and to give up the secondary benefits created by the strength of the bonds of care, and thus to facilitate the discovery of the world and empowerment;
- to optimise adherence to treatment;
- in case of FMF with a strong social and family impact and/or generally in case of unbalanced FMF;
- whenever there is evidence pointing to a psychological involvement of the somatic manifestations of FMF;
- in addition, a consultation with a clinical psychologist may be offered by the FMF specialist at the time of diagnosis.

8.2. Rehabilitation, physiotherapy

Joint rehabilitation may be necessary in case of chronic joint damage.

Manual lymphatic drainage of the lower limbs can be offered to prevent exertional myalgia in the lower limbs and pseudo-erysipelas in the ankle.

8.3. Therapeutic education and lifestyle adaptation

Therapeutic patient education (TPE) includes activities (awareness-raising, information, learning and psychosocial support) designed to help the patient (and his or her relatives) to understand the disease and treatments, participate in care, improve adherence, maintain or improve quality of life and thus maintain the resources needed to manage life with the disease optimally. Patients need to be reassured about their fears, expressed or not. The objective presentation of recent medical data often helps to mitigate the pejorative connotation that remains attached to FMF in at-risk populations, via a painful family history or the reading of outdated information or unduly alarmist data available on the Internet. A specific labelled TPE program for FMF is available in the adult reference centre for FMF in Tenon hospital, Paris, France.

Patients may be offered an adapted workstation to minimise the factors that trigger attacks (i.e. teleworking, avoiding prolonged standing. . .).

8.4. Use of patient organisations/associations

A dedicated association framework is often helpful, especially to help some patients to overcome social isolation due to the disease. Health professionals and patients should be informed of the existence of patient associations through reference centres, institutional websites and Orphanet. These associations contribute to a better overall management of the disease by promoting cooperation between patients and caregivers.

The contact details of the FMF patient organisation should be given to the family at the time of diagnostic consultations and/or at the first meeting with a specialised centre treating FMF patients. In France, there is a patient association for FMF (AFFMF).

9. Vaccination and FMF

The following guidelines for vaccination among FMF patients are proposed.

9.1. Vaccination of FMF patients treated with colchicine

Patients with FMF treated with colchicine have no special risk compared with the general population with regard to live and inert vaccines.

They also have no additional risk factors for specific infections.

Vaccination recommendations for FMF patients on colchicine are identical to those for the general population.

9.2. Vaccination of FMF patients treated with biotherapies (anti-IL-1, anti-TNF)

Treatment with biotherapy increases the risk of infection, so the vaccination schedule needs to be adjusted.

The initiation of biotherapy for FMF is not an emergency. It should therefore be delayed as long as possible until all vaccinations have been completed.

Before starting treatment, check that all vaccinations (compulsory and recommended, including the HPV vaccine for boys and girls) are up to date according to the general vaccination schedule.

If the vaccination schedule is not up to date, arrange for a catch-up vaccination according to the usual catch-up rules.

In addition to the vaccines recommended for the general population, specific vaccines are recommended:

- pneumococcal vaccination: 13-valent conjugated polysaccharide vaccine according to the age-appropriate schedule for children, or 1 dose of vaccine for patients who have not had a full course of conjugated polysaccharide vaccine, followed in all cases by a dose of 23-valent unconjugated polysaccharide vaccine;
- varicella vaccination for naïve patients, with two doses, 4 to 8 weeks apart;
- annual influenza vaccination.

Due to slightly lower immunogenicity and slightly faster loss of immunity after vaccination in patients treated with biotherapy, the vaccination posology or schedule should be adapted as follows:

- diphtheria-tetanus-polio booster vaccination every 10 years;
- 3-dose schedule for HPV vaccine, also in children under 14 years of age, with the option of catch-up vaccination up to 26 years of age;
- polysaccharide pneumococcal vaccination every 5 years.

10. Follow-up

10.1. Main objectives [6]

The main objectives of monitoring are:

- to prevent as many FMF attacks as possible so that the patient can lead as normal a life as possible;
- to detect and treat complications related to the disease or treatments;
- to detect and manage any treatment failures at an early stage in an appropriate manner;
- to avoid, and if necessary, detect and treat early the side effects of the disease (or treatments);
- to provide patient education (see dedicated paragraph)
- to assess the psychological, family and socio-professional impact of the disease and limit its negative consequences.

10.2. Clinical follow-up

The patients should be followed up every 6 to 12 months with a full clinical examination (including the musculoskeletal system).

The effectiveness of the treatment should be assessed by the following set of parameters:

- residual attack frequency per 12 months;
- severity of residual attacks: a severe attack is defined as an attack involving more than two sites and/or lasting > 72 hours and/or pain with a VAS score > 5 and/or pain not relieved by level 1 and 2 analgesics;
- number of days of school or work absence (related to the disease) in the last 12 months;
- impact on activities of daily living;
- onset or worsening of chronic complications (stunting, anaemia, symptomatic splenomegaly, persistent arthritis, joint destruction, chronic liver disease/hepatic cirrhosis, AA amyloidosis);
- the status of blood inflammatory markers outside of an attack (at least 10 days after the end of the last attack): CRP.

The assessment of the doctor and the patient should be taken into account when assessing the activity and severity of the disease.

During monitoring (every 6–12 months) of colchicine treatment (apart from treatment response), it is essential to assess through history taking:

- adverse events of the treatment and potential toxicity:
  - daily stools: number and consistency,
  - nausea, digestive discomfort;
- adherence to treatment (compliance) as measured by the number of omissions per week and the management of colchicine stocks;
- the patient's perspective: knowledge and beliefs about colchicine, its usefulness, potential side effects and how to deal with digestive discomfort and possibly loose stools on initiation of treatment or when changing dosage.

An insufficient effect of colchicine must be determined by a physician specialised in the management of FMF.

More sustained follow-up and additional investigations may be required for patients with severe or complicated FMF and treated with IL-1 inhibitors with specific assessments due to these medications:

- monitor bodyweight every 3–6 months;
- monitor local tolerability of injections and potential dizziness;
- offer flu vaccination at the start of each winter season.

10.3. Paraclinical follow-up

The annual follow-up must include at least:

- laboratory testing to detect poorly balanced and/or complicated FMF:
  - laboratory testing for inflammation. The choice of marker of residual inflammation depends on age:
    - in children, an annual CRP test seems necessary (and once at the beginning, a joint CRP and SAA test to check for dissociation, especially outside of an attack) (Çakan et al., 2021; Stankovic Stojanovic et al., 2017),
    - in adults, monitoring can be based on CRP alone, if there has been at least one check to ensure that there is no dissociation between SAA and CRP (low CRP while SAA is high). In the latter case, as in children, residual inflammation should be monitored based on CRP and SAA,

Box 2: Serum amyloid A protein

Serum amyloid A protein is a protein from the acute inflammatory phase whose kinetic evolution is comparable to that of C-reactive protein, but with an amplitude of increase that can be higher than that of CRP [15]. Therefore, the initial concentration of SAA in the acute inflammatory phase can be multiplied by 1000. Its plasma half-life is about 10 hours, slightly shorter than that of CRP (≈19 hours) and, like CRP, its concentration is low in healthy subjects.

SAA levels are determined by immunoprecipitation in liquid: nephelemetry or turbidimetry. SAA levels are usually available within a week after blood punction.

In normal clinical practice, the information provided by SAA levels is similar to that of CRP. Therefore, these two inflammatory markers are not measured simultaneously, especially in acute cases. In the presence of diagnosed AA amyloidosis or a potentially amyloidogenic disease, this suggestion may be nuanced, as SAA protein is the direct precursor of amyloid fibrils and its serum concentration may better reflect amyloidogenic risk. However, the prevalence of dissociation between serum concentrations of these proteins in chronic inflammatory diseases is not well understood and the literature may show conflicting results.

In practice, it is important to remember that:

- SAA is only a ubiquitous marker of inflammation; **its elevation is not synonymous with AA amyloidosis**. In fact, in the presence of elevated SAA, without renal abnormalities or proteinuria, *there is no need to perform a biopsy to look for amyloidosis*;
- normal CRP/SAA levels do not exclude the diagnosis of AA amyloidosis, as inflammation could have been marked in the past and then normalized;
- the most important factor in terms of amyloidogenic risk is the demonstration and quantification of a prolonged inflammatory syndrome over time;
- we recommend that if CRP is normal, SAA should be checked at least once;
- if SAA is elevated but CRP is normal, a *SAA1* promoter mutation could be considered.

  - in case of authenticated AA amyloidosis, it is recommended to check at least once that CRP and SAA protein levels are normal (Box 2);
  - renal assessment with creatininaemia and proteinuria testing on urine sample with urine creatinine to calculate the protein/creatinine ratio,
  - liver panel;
- laboratory testing to detect potential side effects of colchicine treatment:
  - blood count, creatinine levels,
  - liver function test,
  - CPK.

More sustained follow-up and additional investigations may be required for patients with severe or complicated FMF and treated with IL-1 inhibitors with specific assessments due to these medications:

- complete blood count (CBC), liver enzymes, bilirubin, γGT 4 weeks after starting treatment, then every 3 to 6 months;
- total LDL and HDL cholesterol and triglyceride levels, every year.

Testing for AA amyloidosis secondary to FMF includes assessment of renal function (creatininemia) and proteinuria testing (urine dipstick screening and, if appropriate, confirmation by a urine protein to urine creatinine ratio sample) at least annually.

If there is permanent proteinuria or unexplained renal failure, amyloidosis should be investigated through histological sampling. This sample can be fixed and taken to the laboratory for accurate analysis of amyloid deposits by Congo red and immunohistochemical testing (Fig. 2).

The sites of biopsy are in first-line (practices which can vary according to the habits of the centres):

- the labial accessory salivary glands;
- abdominal fat;
- the upper and lower digestive mucosa and submucosa.

Renal biopsy is discussed as a second-line procedure.

Rarely, AA amyloidosis is revealed by digestive disorders such as diarrhoea or thyroid goitre [43].

Disclosure of interest

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The other authors declare that they have no competing interest.

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Authors' contributions

SGL, VH, GG, JJB and LS wrote the first draft of the manuscript; LC, GB, MD, RB, J-B M, IT and IKP participated to writing. All authors participated to edition. All authors read and approved the final version of the manuscript.

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The French version is available free of charge on the following link: Haute Autorité de santé – Amylose AA (http://www.has-sante.fr/).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.revmed.2023.10.441.

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