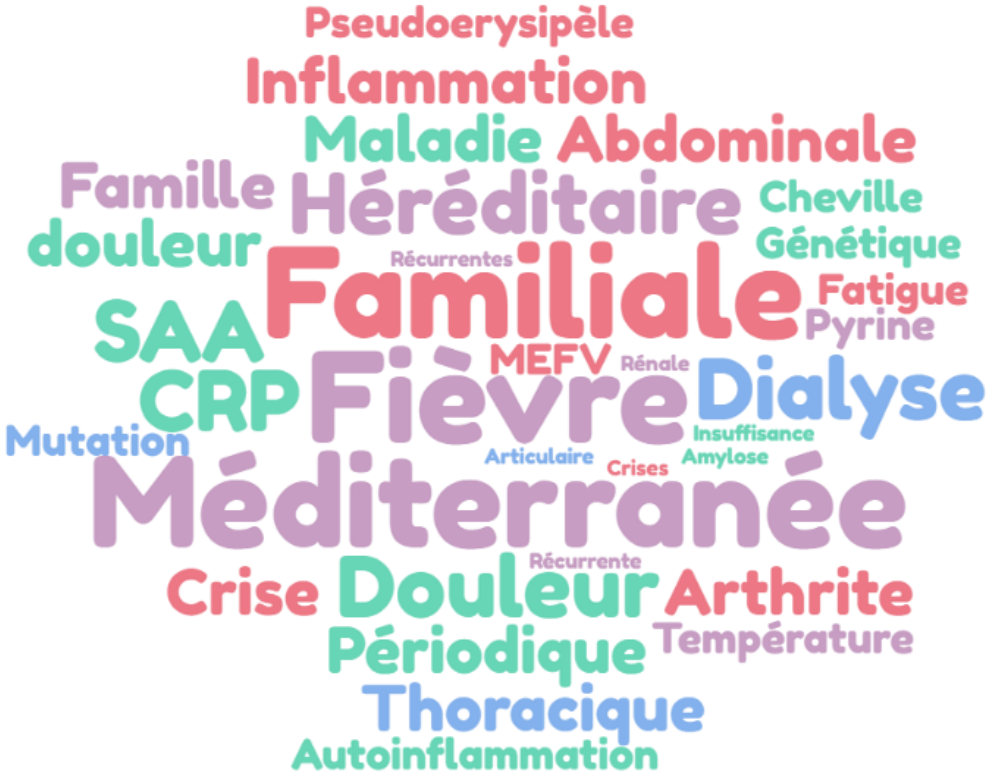


Familial Mediterranean Fever

Booklet for patients and their families and friends

CeRéMAIA

affmf

Coordination: Pr Sophie Georgin-Lavialle, Dr Véronique Hentgen and Dr Rim Bourguiba

Editors: Pr Sophie GEORGIN-LAVIALLE, Dr Véronique HENTGEN, Dr Rim BOURGUIBA, Pr Isabelle KONE-PAUT, Pr Isabelle TOUITOU, Pr Gilles GRATEAU, Dr Léa SAVEY

Proofreaders: Dr Caroline VINIT, Dr Marion DELPLANQUE, Zohra AKNOUCHE, Keshia KOUTEKISSA, Valentine GUYAU, Charlène ALZON, Patrick BELAMICH, Max AMOR, Mortier SIMONE, Gaelle BENDAVID, Maya BEN TOLILA-PANCER, Claire BAYADO, Jonathan BENAZRA

Layout: Zohra AKNOUCHE and Valentine GUYAU

SUMMARY

1. What is an autoinflammatory disease?

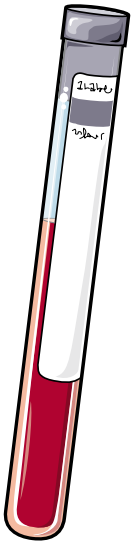
These are conditions caused by one or more defects or deregulation of the very first phase of the immune response, characterized by:

- Recurrent or ongoing inflammation (elevated blood markers of inflammation such as C-reactive protein (CRP)
- The absence of an abnormality of the adaptive immune system (absence of autoantibodies).

2. What are C-reactive protein (CRP) and serum amyloid A protein (SAA)?

C-reactive protein (CRP) is often used as a marker of a significant inflammatory response in the body. CRP is a protein that the liver makes when it detects an injury, infection or inflammation in the body. This protein will help the immune system heal the injury or fight the infection. It can be measured by a simple blood test.

Serum Amyloid A protein (SAA) is a protein synthesized by the liver. It is a protein of the inflammatory reaction that can be measured by a simple blood test. Its increase in the body is early and important in case of inflammation. It is monitored as part of the screening and follow-up of inflammatory amyloidosis (AA), a rare complication of FMF (see question 12).



3. What is familial Mediterranean fever (FMF)?

Formerly called periodic illness, it is an inherited disease that belongs to the group of innate immunity diseases: auto-inflammatory diseases. It is considered a rare disease with less than 1 case in 2000 depending on the country. It affects preferentially people from the Mediterranean area.

The prevalence (number of cases in a given population at a given time) of FMF is about 1/200 to 1/1000 in certain populations around the Mediterranean, about 100,000 cases worldwide and 5 to 10,000 cases in France.

The first symptoms of the disease appear early in life: generally before 5 years of age in 75% of cases and before 1 year of age in 10% of cases.
FMF does not manifest itself permanently but rather in the form of bouts or "attacks" of fever, often high (38.5°C and 39°C and up to 40°C) and accompanied by a feeling of malaise and cold (chills).

The crisis can be announced by the onset of great fatigue and loss of appetite. It lasts on average 2 to 3 days.

Along with fever, the most common sign is extreme abdominal pain (hard stomach sensation) that can lead to a "bent-over" position, with the legs tucked under the body or the torso bent forward to reduce pain. Because of the intensity of the pain and the appearance of the abdominal area, the attack can be mistaken for appendicitis or peritonitis, which is why it is important to know that you have FMF to avoid unnecessary surgery.

Patients may also experience pain in the lungs, due to damage to the membrane that protects them, called the pleura, which manifests itself as chest pain, shoulder pain or difficulty breathing.

Leg pain is very common in the muscles and joints, especially in the ankles and knees. The joints may sometimes swell due to arthritis. The FMF attack can also manifest itself by pain in the ankle with a red appearance of the skin in front of it called "pseudo erysipelas of the ankle".
Outside of the attacks, it is common to feel pain in the calves, under the heels or under the soles of the feet during prolonged effort, with more rarely a localized swelling.

4. What is the cause of FMF?

FMF is a genetic disease, which means that it is associated with a mutation in a gene, the *MEFV* gene *(for MEditerranean FeVer)*. It is recessive, which means that in order to express the disease, patients carry 2 mutations of the *MEFV* gene, one inherited from each parent.

Genes are carried by our chromosomes within all the cells of our body. They are used to program the production of proteins that are essential for the functioning of our body. In the case of the *MEFV* gene, it programs a protein, pyrin, whose role is to produce inflammation to eliminate microbes (intestinal microbes in particular).

Patients with FMF have a mutation in this gene that causes them to produce much more inflammation than normal and inappropriately.

Researchers have shown that this excess of inflammation would have been acquired to better fight against certain infections such as the Black Plague, which killed many people in the Middle Ages. This could explain the particular distribution of FMF around the Mediterranean.

5. How is FMF transmitted?

FMF is an autosomal recessive inherited disease (see question 4). It affects males as well as females and consanguinity increases the risk of transmitting the mutation (figure 1).

As shown in the figure below, the risk for healthy carrier parents (i.e. having a single mutation and not expressing the disease) to have an affected child is 1/4.

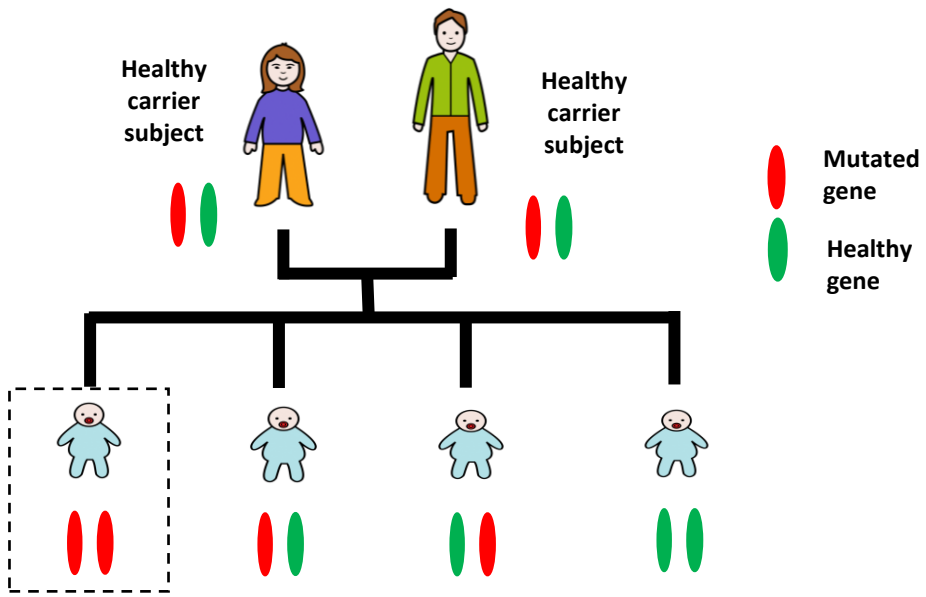


Figure 1: Mode of transmission of FMF

6. Which patients are affected by the disease?

FMF mainly affects populations around the Mediterranean. It seems to have appeared several thousand years ago in the Mesopotamian basin, in the region where Israel is located today (Figure 2). The number of patients remains significantly higher in the Armenian, Sephardic Jewish and Turkish populations. Today, FMF is found worldwide but in patients of Mediterranean origin.

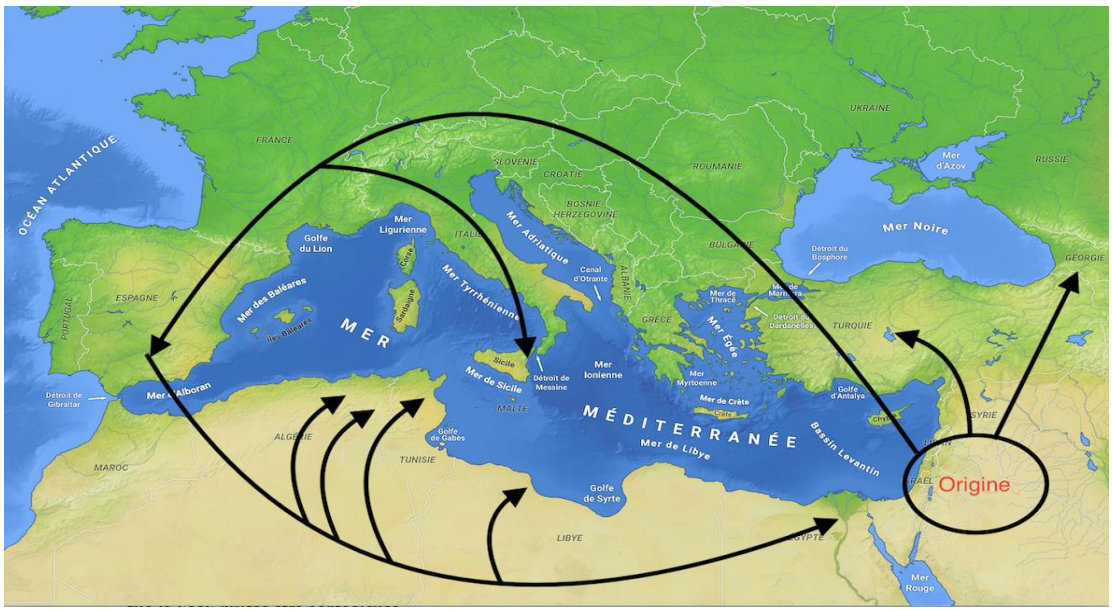


Figure 2: Populations at risk for FMF.

7. How is FMF diagnosed?

The diagnosis of FMF is based on the notion of fever attacks as described above associated with the presence of inflammation in the blood. This is why a blood test will be prescribed during an attack to measure the inflammation with the dosage of CRP: C-reactive protein and a blood count to look for an increase in white blood cells including neutrophils. *(The blood count is a simple blood test to count the number of red and white blood cells and platelets.)*

At present, a genetic test is available which allows to confirm the diagnosis of FMF in the vast majority of typical forms with 2 mutations. It consists in taking a blood sample in a city or hospital laboratory, after obtaining informed consent.

The result of this test must be returned to the physician who ordered it and he will explain the results. In most cases where the clinical signs are typical and the patient belongs to an ethnic group at risk, there is no equivocation and the genetic diagnosis confirms the clinic. However, some cases are not genetically confirmed (as two mutations in the *MEFV* gene are theoretically required) and require an opinion by an FMF expert.

8. When should medical tests be done to manage FMF? Which ones?

As part of the follow-up of the disease, the inflammation (the CRP marker) should be monitored once or twice a year and liver and kidney function should be checked once a year by blood and urine tests.

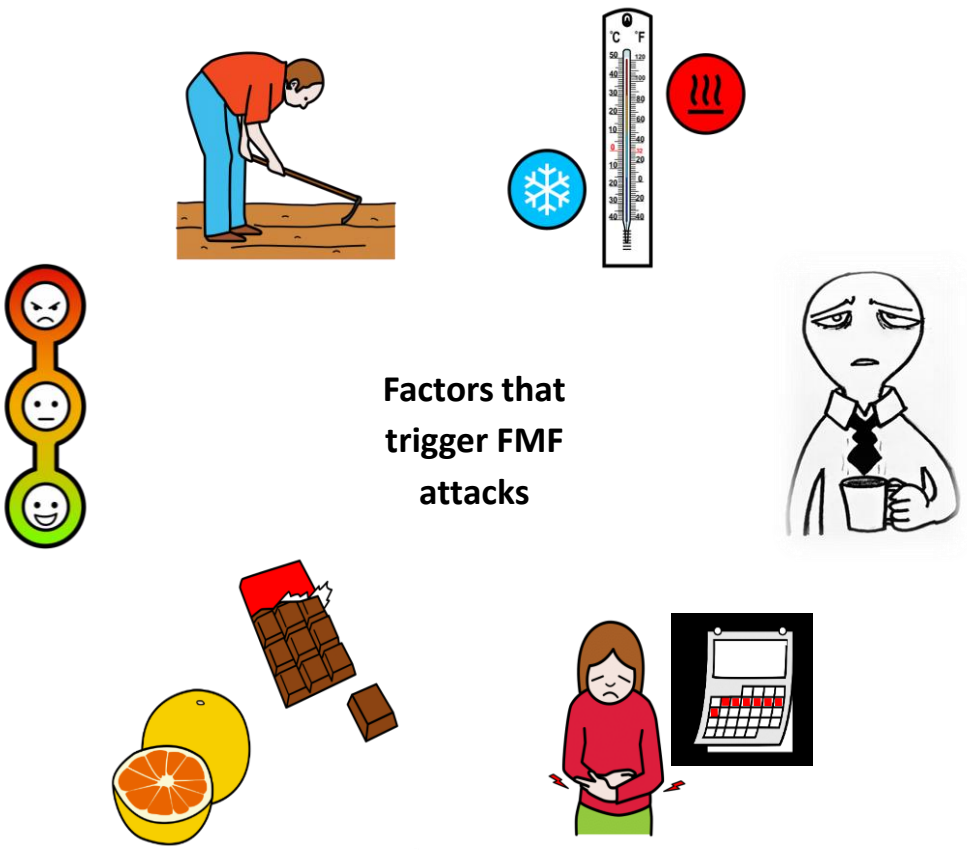
9. Is FMF contagious?

ARASAAC

No, because it is not caused by a germ (bacteria or virus), so there is no reason to think that FMF can be contagious.

10. What triggers FMF attacks?

The factors that cause the attacks are known; they are emotions, stress, unusual physical activity, lack of sleep, menstruation, cold or hot weather, and sometimes even certain foods like chocolate.



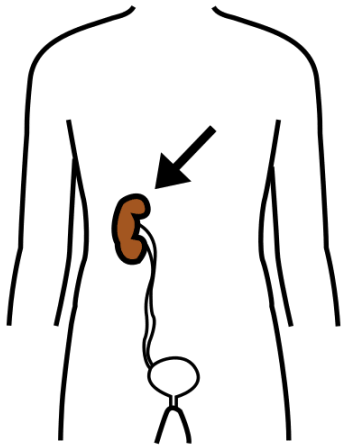
11. How is FMF evolving?

FMF is a chronic disease that progresses in attacks/flare-ups, potentially for life, although it may subside with age. Prolonged inflammation can lead to complications, the most serious of which is inflammatory amyloidosis (IA), which primarily affects the kidneys.

Daily intake of the basic treatment (Colchicine) allows to reduce the number of attacks or even to eradicate them.

12. What is the risk of developing AA amyloidosis?

FMF can be complicated by inflammatory amyloidosis or AA amyloidosis. Amyloidosis results from the deposition in certain organs of an inflammatory protein called SAA (which is an equivalent of C-reactive protein or CRP).
The risk of developing amyloidosis is globally proportional to the degree and duration of inflammation. Thus, when FMF is untreated or insufficiently treated, the blood inflammation is strong and can exist even outside of the attacks and the risk of developing amyloidosis in the long term is then higher. This amyloidosis, called AA amyloidosis, mainly affects the kidneys and the digestive tract.
Detection of AA amyloidosis is based on monitoring kidney function, including urine protein and blood creatinine levels. Confirmation of amyloidosis is based on histology via biopsy of an organ, most often the accessory salivary glands *(Histology: is the medical specialty that studies organs and/or tissues under the microscope to diagnose diseases; for example: to make the diagnosis of amyloidosis, amyloid deposits must be seen on a biopsy).*
AA amyloidosis is secondary to prolonged blood inflammation which suggests that well-controlled blood inflammation with Colchicine makes the likelihood of amyloidosis occurrence very low. For this reason, it is essential to take Colchicine on a regular basis even if you feel well.



13. What diseases may be associated?

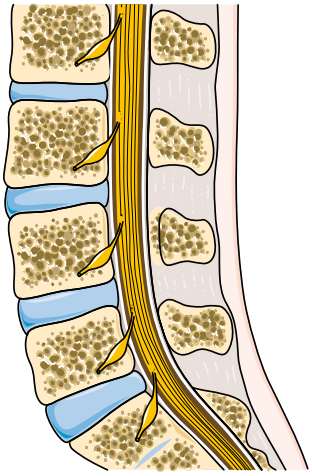
FMF promotes inflammation in general and some patients may develop certain inflammatory diseases.

1. Rheumatoid purpura:

Rheumatoid purpura is a rare inflammation of the vessels that may occur somewhat more frequently in children with FMF. It manifests as red/purple pimples, sometimes bruises, on the legs and buttocks, Knee and ankle joints may be swollen and painful. Belly pain can be very intense and uncomfortable and is sometimes accompanied by vomiting and signs of paleness. Rest is the treatment most often applied and often sufficient. Healing occurs most often after a few weeks.

2. Inflammatory rheumatism:

Spondyloarthropathies and psoriatic arthritis are inflammatory rheumatic conditions that may be present in FMF. They may involve inflammation of the spine and joints of the pelvis (sacroiliac, hip) and toes; rarely the hip joint (coxitis).



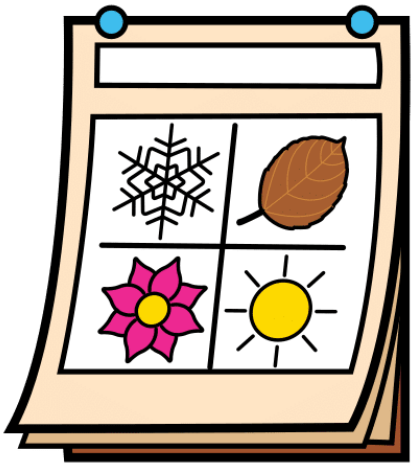
3. Certain skin diseases:

Psoriasis, usually of the vulgar type, may be present in patients with familial Mediterranean fever. It usually manifests as scaly patches frequently on the knees, elbows, navel, lower back and ears.

Verneuil disease or hidradenitis suppurativa is a skin disease characterized by the formation of nodules and abscesses in the areas where the sweat glands are located (under the arms, breasts, groin folds...) and areas of mechanical friction.

14. Is FMF chronic?

FMF is a lifelong condition, making it a chronic disease, even though it occurs primarily in attacks. Some patients do not really identify an attack and experience chronic fatigue and pain, which can be disabling and may be partly related to poor control of the inflammation. These pains are sometimes indicative of a state of anxiety and/or depression requiring specific complementary treatment.



ARASAAC

15. Is FMF a serious disease? Will I die from this disease?

FMF is not a serious disease in the sense that it does not reduce life expectancy in France to date, and that it is only exceptionally fatal. It also has a very effective treatment accessible to all because it is inexpensive and well supported.

16. How to treat FMF: main principles?

Patients should benefit from regular care and follow-up involving, as far as possible, an expert team (essential in children) in an expert center (see list of reference centers) and local caregivers (general practitioner or pediatrician, and/or nurse) and, if available, a city-hospital network. Patient and family associations can also be of great help.
The current treatment of FMF does not provide a definitive cure. Its objectives are to reduce the number of attacks, to normalize the quality of life and to avoid long-term complications which are essentially renal.

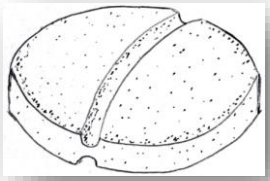
A background treatment is taken chronically throughout the year for life, it allows one to prevent attacks.
A crisis treatment is only taken when there is a severe attack of the disease.

17. What is background treatment and is it risky?

A disease-modifying therapy is a long-term treatment, lasting several months or years, which reduces the activity of the disease. The main objectives are:

1. Improve quality of life by reducing the number of accesses.
2. Reduce the use of inflammatory drugs and avoid complications from these drugs.
3. Avoid long-term complications of the disease (inflammatory amyloidosis).

Colchicine is the current standard of care for FMF.
In some specific cases, other drugs called biotherapies may be used as background treatment.

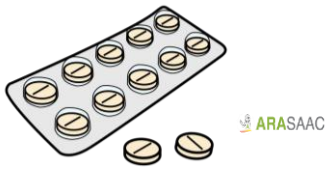


@antoinefayand

18. What should I know about Colchicine?

Colchicine is a medicine made from a flower: colchicum. It acts directly on the inflammation and is very effective in preventing the occurrence of new attacks if given in sufficient doses and taken very regularly. It is not toxic for fertility or liver at therapeutic dose in FMF.

The treatment of FMF is simple, inexpensive and does not involve drugs with significant side effects, as long as the doses are respected. The reference treatment is Colchicine, which prevents the occurrence of new attacks if given in sufficient doses and taken very regularly. Attacks disappear in about 60-70% of cases; the response is partial in 30% of cases and the treatment is ineffective only in very exceptional cases. Regular use of the drug prevents the development of renal complications (AA amyloidosis) that could lead to renal failure and dialysis.



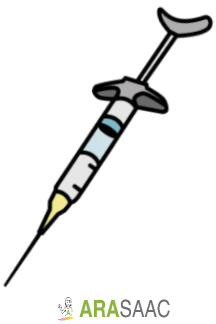
It is extremely important to follow the dosage prescribed by the doctor, as compliance is very important. In this case, a person with FMF can lead a normal life with a normal life expectancy. Doses should never be changed without consulting a physician first.

Colchicine comes as a 1 mg tablet in boxes of 20, in other countries such as the United States and Israel, the tablet is dosed at 0.6 mg. The prescribed dose varies from 1 (0.5 mg for young children under 5 kg) to 2.5 mg/d. The dosage is adapted to each person according to their weight, disease activity and age. Colchicine does not interfere with growth in children.

In case of an attack it is sometimes difficult to make all the signs disappear, but anti-inflammatory and painkillers can help. In any case you should not take a higher dose of colchicine, it does not work and it is dangerous. It is necessary to rest and try to practice relaxation: mindfulness breathing, yoga, calm atmosphere by limiting sensory stimuli (noise, light etc..).

19. What is a biotherapy?

A biotherapy is a protein made by humans to block inflammation at a specific point, particularly at the level of inflammation where certain proteins from immune cells (white blood cells) are known to be produced in excess, such as interleukin 1 and interleukin 6 in FMF. Those that have marketing authorization in France for FMF are Anakinra (Kineret) and Canakinumab (Ilaris). These are 2nd intention treatments that are only given in cases of proven resistance to Colchicine correctly taken at maximum dose (a very rare situation) or in cases of AA amyloidosis with renal impairment responsible for end-stage renal failure that no longer allows Colchicine to be taken.



20. Are there any risks (side effects) of the treatment?

Colchicine, at the beginning of treatment, can accelerate the intestinal transit and give diarrhea but this regresses after a few weeks. A treatment to fight diarrhea can be prescribed. Another therapeutic option, Colchimax®, associating Colchicine and opium, allows a better digestive tolerance. Severe diarrhea may require a reduction or even a discontinuation of the treatment as it may also reveal incipient intoxication. Digestive intolerance may also manifest itself by nausea, stomach pains or loss of appetite.

Colchicine should not be taken with large amounts of grapefruit juice and with certain allopathic or naturopathic drugs which may increase its toxicity. Every physician should be informed about the long-term use of Colchicine and should check that there is no interference before prescribing another drug. Any self-medication, even with plant extracts, requires a check with the pharmacist or treating doctor to see if the new medication is compatible with the long-term use of Colchicine.

Anti-IL1 biotherapies can promote the occurrence of certain infections. Therefore, before starting a biotherapy, it is recommended that the vaccination schedule of the general population be updated, and that the vaccine against seasonal influenza and pneumococcus be added. This infectious risk is not observed with Colchicine, which therefore does not require any particular vaccination apart from those recommended for the general population.

Blood tests for white blood cells (CBC), renal function and liver (transaminases) should be monitored at least once a year for patients on Colchicine and 2-3 times a year for patients on biotherapy.

A good patient-physician dialogue is important so that treatment can be adjusted if a side effect occurs. At each step, caregivers try to find the right balance between the potential benefits and risks of each treatment.

21. What is the cost of treatment?

Colchicine is an inexpensive treatment in France (less than 5 euros per month) but its price varies greatly depending on the specialties and countries. Biotherapies can cost several thousand euros each month. In France, the cost is covered by the health insurance system for the insured, as this is a disease for which the treating doctor can request 100% coverage in the event of a biotherapy prescription or the need for dialysis in the event of kidney damage.

22. Aren't the treatments too strong for a child?

Whether it is old treatments such as Colchicine or the most recent biotherapies, the doses have been well studied and the children tolerate these treatments well, which pose few problems in the long term.

23. Can we use complementary treatments such as naturopathy, homeopathy, acupuncture, hypnosis, yoga?

Complementary treatments can have a real benefit on well-being (pain reduction, stress management, etc.), particularly in chronic pain patients. However, they have no direct proven efficacy on FMF and cannot replace the basic treatment which must absolutely be continued; as their name indicates, they are therefore "complementary". Some herbal or naturopathic medicines (such as St. John's wort extract) can interact with Colchicine, so it is important to inform the referring physician and the caregivers who are following the patient in order to manage the whole treatment. In case of doubt, do not hesitate to ask the pharmacist or the treating doctor for advice.

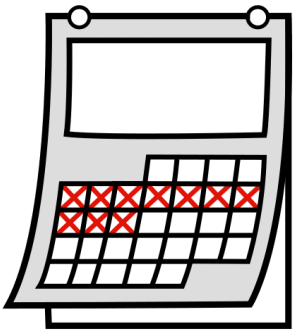
24. Are the injected treatments painful?

Injections of certain medications such as Anakinra can sometimes be painful for some patients, so it is important to discuss with the doctor and nurse what small adjustments can be made to improve this discomfort. An ice pack can be placed on the skin before the injection, and a hydrocortisone ointment can be applied to the painful area after the injection. Most of the time, the treatment can be continued because the pain subsides in 15-21 days, but in some cases it may be necessary to change the treatment.

For more information, you can consult our medication sheets by following the link https://ceremaia.fr/information2.php

25. How long will my treatment last?

In the current state of knowledge, Colchicine is prescribed for life. It does not cure the disease but it prevents attacks and complications from occurring. In case of a good response to treatment, the minimal effective dose is maintained with clinical and biological monitoring. However, it is important not to interrupt the treatment without medical advice, otherwise there is a risk of a rebound with new attacks or even a complication of the disease.



26. Will I be able to get the vaccine normally?

For patients on colchicine treatment, all vaccines for the general population are recommended and can be safely administered. On the other hand, patients undergoing biotherapy (a rare situation) require special attention with regard to vaccines, as biotherapy can make them more fragile with regard to certain infections. In addition to the vaccines recommended for the general population, it is recommended to receive the annual flu vaccine and the pneumococcal vaccine. Some live vaccines (MMR (Measles, Mumps, Rubella), BCG (against tuberculosis), rotavirus (Yellow Fever)) are theoretically contraindicated under immunomodulatory treatments, including biotherapies.

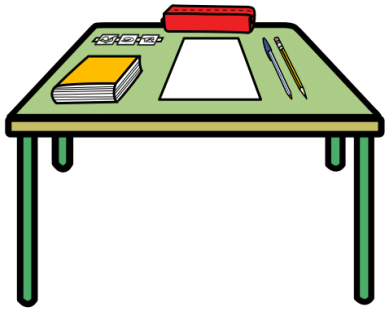
27. Who can advise me for my illness in France?

In France, there is a network for the management of rare inflammatory diseases, through centers of the national network of rare autoimmune and auto-inflammatory diseases (FAI2R, r.org/"www.fai2r.org). These are centers of competence or reference that form a care network of multidisciplinary teams capable of managing this disease. Internists (specialists in internal medicine) and pediatric rheumatologists are particularly involved in the management of FMF. They orchestrate the diagnostic investigations and the follow-up of patients, which may involve several other health care providers (city pediatricians, general practitioners, psychologists, nurses, etc.) or social workers.

The list of FAI2R Competence Centers with their contact information is available at the end of the booklet.

28. How can I explain my illness to my school/family?

FMF is a generally fluctuating disease with alternating inflammatory crises and periods of remission when the patient feels quite well. It can therefore be difficult and sometimes destabilizing for those around the patient to understand that the patient has a chronic disease. Therefore, it is important to explain how the disease manifests itself and evolves to those around him, in order to avoid misunderstandings. This is particularly important in the school setting where the child may feel isolated and left out by his or her peers. Explaining the disease to the teachers also allows the child to be listened to differently and to be evaluated according to his or her state of health (for example, adjustments to sports activities).



ARASAAC

29. How can I explain the disease to my child?

Children, regardless of age, feel when something is happening in their family. It is therefore important to explain the disease to them in age-appropriate language and with an optimistic outlook. As a rule, for young children the parent can say that he/she has an illness and that he/she is taking care of him/herself to get better. The main manifestations such as fever, pain and fatigue can be explained to help the child better understand the changes related to the disease in the daily routine.

If you are an adult patient and your child is worried about catching your disease, it is important to explain that the disease is not contagious.
There are therapeutic education programs on FMF for both children and adults.

30. Can my child go to school with his treatment?

Yes, the goal of the treatment is for the child to live as normally as possible: he/she can (and should!) live the same life as other children of his/her age. Medication (Paracetamol and/or NSAIDs: Non-Steroidal Anti-Inflammatory Drugs) can be left at school so that the child can be treated quickly in case of an attack. Children who are receiving biotherapy can also attend school normally, especially since most of the medication is administered at home. Regular absences can be reported to the school team in case of hospital infusion treatment.

31. What if my classmates or colleagues are sick and I have to be around them?

The hygiene rules of the general population must be applied. In case of background treatment by biotherapy, reinforced hygiene rules are to be applied (hand washing, wearing of masks for sick people, etc).

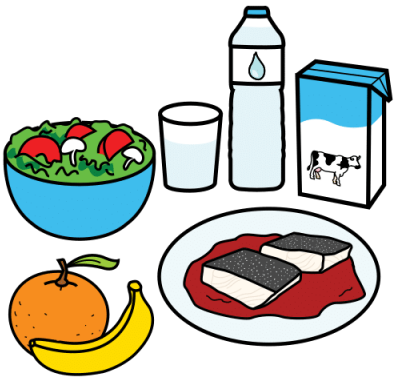
32. Do my parents and/or spouse need to get a flu shot if I have FMF?

There is no particular interest in having relatives vaccinated against influenza, unless the patient is being treated with biotherapy. It is important to know that if the parents are less than 60 years old or are not on ALD (Affection Longue Durée), the vaccine is not reimbursed.

33. Do I need to adjust my diet?

There is no need for a special diet when taking Colchicine: a balanced, healthy, normo-caloric diet is recommended as for the general population. For the rare patients who still have diarrhea or abdominal pain, reducing the lactose intake can improve the gastric embarrassment (prefer yoghurt to milk, drink milk without lactose, etc.).

Some biotherapies may cause a slight imbalance in the fat balance, but this does not generally require dietary adjustments in children or adults, especially since this imbalance is generally transient. We must always insist on the importance of a balanced and healthy diet to ensure a balanced digestive microbial flora.



34. How can I help my child in addition to medication?

The first thing to do is to help him/her by giving him/her a positive vision of life and by reinforcing his/her self-confidence. We must allow him to have a normal life, at school, with his friends, with activities that he likes (moving around with his illness is generally beneficial), sometimes with the help of professionals such as physiotherapists.

Some teams offer therapeutic education programs that allow children and their parents or adults and their partners to take more control of their disease.

Often, the activities and meetings proposed by the patients' associations are also useful: they allow him to understand his disease and the reason for the medication, and also allow him to understand that he is not the only one suffering from this disease even if it is rare.

35. Will I be fine and live normally?

The medical management of FMF is aimed not only at relieving pain and disabling symptoms but also at maintaining the best possible quality of life for patients. Colchicine is generally very effective provided it is taken strictly every day. It allows to reduce or even make disappear the attacks of FMF and prevents the complications in particular the most serious which is the AA amylose. So yes, in the vast majority of cases, one lives normally with FMF.

36. Is there a risk of cancer?

Studies have shown that FMF is quite protective against cancers in general, with the exception of mesothelioma (a tumor of the peritoneum) which can be benign or malignant.

37. How can I manage severe pain or flare-ups while waiting to see my doctor?

It is necessary to know how to use the medication prescribed to face these situations, starting, when it has been validated by a doctor, with anti-inflammatory medicines such as Ibuprofen, Naproxen or Indometacin at the prescribed doses (which are generally higher than those in the medical dictionaries), analgesics: Paracetamol Codeine or Tramadol. Physical measures (moving in hot water in the shower or bath, applying cold or heat to the painful area) can help.

However, if it is a real flare-up or attack, a quick consultation may be necessary, often preceded by a phone call or email. Do not hesitate to contact the health care team. Many departments also have therapeutic education nurses who can answer (by phone or email) a number of questions and provide therapeutic advice.

Finally, the role of the general practitioner is important, as he or she is often the "first resort" and can prescribe symptomatic treatment to reduce pain while the patient meets the specialist.

38. What are the signs that I need to go to the emergency room?

If the attack is easily recognized, follow the emergency protocol provided and wait at home.

You should go to the emergency room if:

1. Despite the treatments applied, the pain is unbearable.
2. If there are non-typical signs that may raise suspicion of a cardiac, neurological, renal or infectious complication.
3. If the crisis lasts more than 5 days.

Note that there are FMF emergency cards available from doctors at the reference centers and the FAI²R network.

ARASAAC

39. Will my fertility and sexuality be affected by FMF?

Men and women with FMF who take their treatment theoretically have no decrease in fertility compared to the general population and can have children like other adults. Decreased fertility has been reported in the past, but in older studies in which most patients did not receive colchicine treatment.

It is important to remember that treatment with Colchicine does not alter fertility, either for women or for men. Colchicine can and should be continued during pregnancy because it limits the number of attacks that can be unpleasant and probably lead to premature delivery. Non-steroidal anti-inflammatory drugs (such as Ibuprofen, Naproxene, etc.), which are usually prescribed during attacks, are formally contraindicated from the third trimester of pregnancy. The CRAT website (https://lecrat.fr/) can be consulted freely for information on the risks of medication during pregnancy and breastfeeding.

Anakinra has been taken by pregnant and breastfeeding women, but it is advisable to discuss this with your specialist and obstetrician gynecologist if possible before starting a pregnancy: clinical and ultrasound follow-up arrangements should also be discussed with the gynecologist.

Sexuality is not usually affected by the disease or its treatments, so there are no known effects of the disease or its treatments on libido, nor are there any reported cases of impotence.

The majority of FMF patients are able to work, live as a couple and have children if they wish.

40. Can a woman with FMF be able to have children?

ARASAAC

Yes, if a woman with FMF wishes to have children, there is no contraindication. It is recommended that the disease be controlled and that she not take any medication that would be harmful to the growth of the fetus.

Colchicine, contrary to what is written on the drug, can and should be continued during pregnancy and lactation.

Anakinra has been taken by pregnant and breastfeeding women, but you should discuss this with your specialist and obstetrician gynecologist if possible before starting a pregnancy.

41. Can you breastfeed your child if you have FMF?

Breastfeeding is possible under Colchicine, it is advised to take it in the evening at the same time as the last feeding. The quantities present in the milk during the following feedings are low and are not toxic for the baby. It is important to talk to your doctor and pediatrician about any treatment you are taking. In case of doubt, prescribers and patients are advised to consult the CRAT website before taking any treatment (https://lecrat.fr/). (https://lecrat.fr/spip.php?page=article&id_article=426).

42. Can you travel if you have FMF?

Yes, you can travel by air or other modes of transportation if you have FMF. However, it is important to consult with your doctor prior to travel to ensure that you have all the necessary medications and to discuss any vaccinations.

If you are traveling by air and need to take injectable products with you, you must ask your doctor for a bilingual (French/English) medical certificate stating that the treatment must be carried in the cabin, which will be requested at the airport.

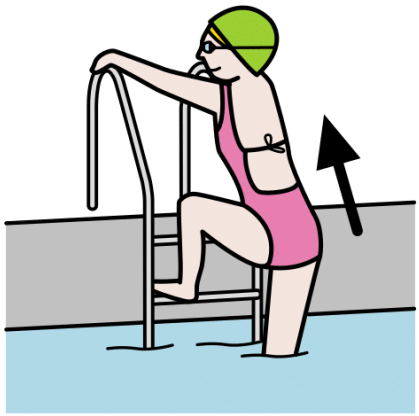
In addition, biotherapies (such as Anakinra or Canakinumab) should be stored in an insulated bag (12 hours duration) (https://ceremaia.fr/information2.php).

43. Can I have pets in my home with FMF?

Yes, there are no contraindications.

44. Is sport indicated with this disease?

Yes, sport is generally recommended because it strengthens muscles and bones, prevents joint stiffness and pain due to inactivity, and improves physical ability and well-being. Regular sports activity also plays an important role in the prevention of seizures, cardiovascular risk factors and weight control. It also has beneficial effects on sleep quality, psychological state and quality of life.

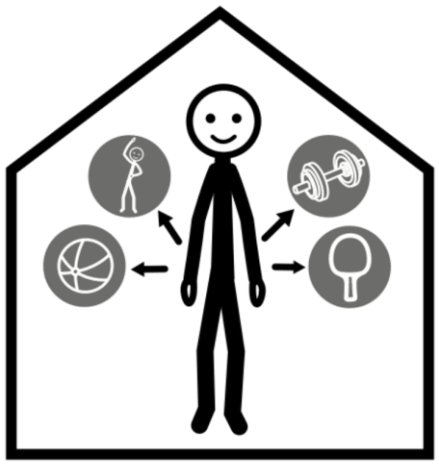


ARASAAC

45. Can I practice all activities and sports?

All physical activities and sports can be practiced with FMF. However, it is advisable to adapt physical activities and sports according to the physical condition of the patient and the stage of the disease. On the other hand, it is preferable to limit sports activities during inflammatory attacks or flare-ups. It is also advisable to adapt the intensity and rhythm of activities so as not to trigger the appearance of painful attacks.

In general, activities such as walking, cycling, swimming are to be preferred as well as gentle activities such as tai chi, chi gong or yoga; whereas sports with high constraints (e.g. boxing) require special physical preparation to be practiced safely.



ARASAAC

46. Should I tell my employer about my illness?

Each case is different, depending on the job and the employer, the size of the company and the occupational physician. This can sometimes be useful to be better understood, but you should not let it be a disadvantage. The best thing to do is to ask your specialist or attending physician for advice; some patients wait until they have a permanent job to talk about it for fear that it will harm them.

47. Can you work/study normally with FMF?

In theory, there is no reason why one should not be able to do the studies or the work one wants to do. The rhythm imposed by studies or work must be in accordance with the patient's state of health and fatigue. During attacks, fever, fatigue and abdominal pain can make it difficult to get to work or school. An adjustment of school or work schedules can be considered during attacks of the disease. Outside of the attacks, the patient must adapt to his or her feelings and form.

48. What is the purpose of patient organizations in FMF?

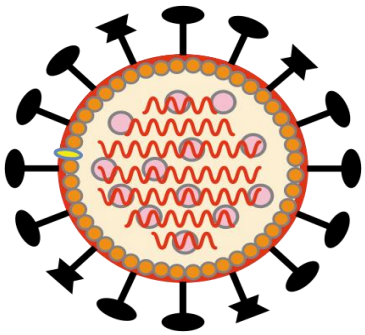
Patient associations play an essential role in supporting patients and their families in their health care and daily life. Their main actions are :

- To make diseases known and recognized, all the more so if they are rare diseases
- Accompanying patients and their families in their health care journey and in their relationships with the various caregivers.
- To improve the quality of life of patients through better dissemination of information on the disease, the various care options and patients' rights.
- Organize meetings with other sufferers and caregivers to allow patients to feel listened to, to exchange on the difficulties linked to the disease and treatments and to have advice on how to live better on a daily basis.
- To promote and participate in the realization of medical research.

49. Is FMF a risk factor for developing a severe form of COVID19 infection?

FMF does not appear to be a risk factor for developing a severe form of Covid -19 infection in FMF patients taking their Colchicine daily, compared with the general population.

Nevertheless, FMF patients infected with SARS-CoV-2 should be well monitored and receive appropriate medical care.

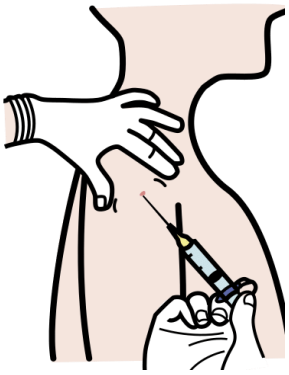


One should continue to take their Colchicine daily even if they are Covid-19 positive. Studies have shown that FMF patients taking long-term Colchicine on a daily basis are affected in the same way as the general population.

50. Does the COVID-19 vaccine protect me against severe forms?
Can it be a trigger for crises?

Yes, the vaccine protects against severe forms of COVID-19.

Usually it does not trigger attacks, but it can happen in some rare cases.



Useful links

https://www.maladiesautoinflammatoires.fr/la-fi%C3%A8vre-m%C3%A9diterran%C3%A9enne-familiale

https://ceremaia.fr/patients.php

https://www.fai2r.org/les-pathologies-rares/fievre-mediterraneenne-familiale/