JUNE 2022

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

ADVANCES in inflammatory myopathies

> dermatomyositis (DM)
> polymyositis (PM)
> inclusion body myositis (IBM)
> overlap myositis
> antisynthetase syndrome
> immune-mediated necrotising myopathy

Inflammatory myopathies (or myositis) are diseases that involve muscle inflammation. These so-called "autoimmune" diseases are not hereditary.

They are characterised by muscle weakness (ranging from simple discomfort to complete paralysis), and often by muscle pain. Certain forms of myositis are accompanied by joint pain or skin manifestations, or even cardiac and/or pulmonary involvement, making these conditions very serious.

This document, published to coincide with the AFM-Téléthon General Meeting 2022, presents research news from the past year regarding inflammatory myopathies, such as ongoing studies or clinical trials, scientific and medical publications, etc.

It can be downloaded from the AFM-Téléthon website, where other information regarding scientific, medical, psychological, social and technical fields relating to inflammatory myopathies can also be found:

WEB www.afm-telethon.fr

AFMTÉLÉTHON
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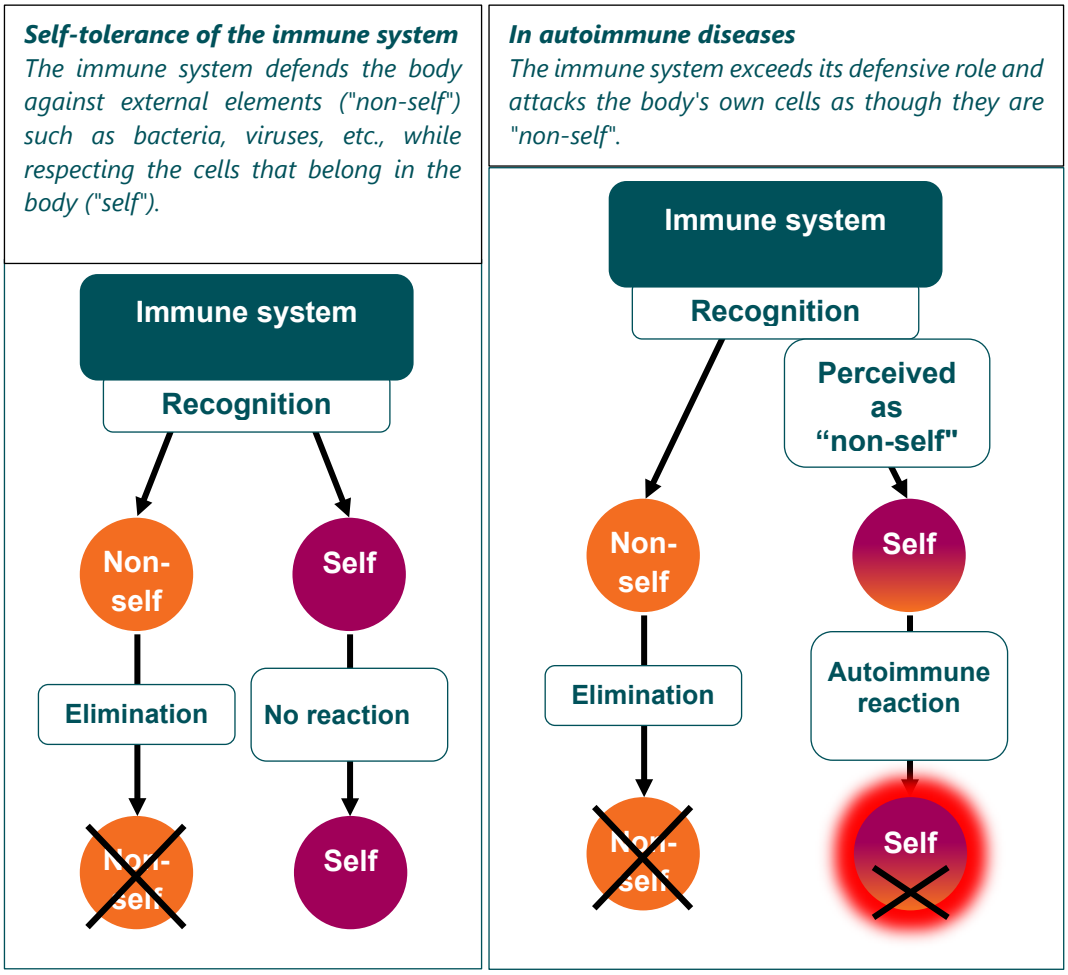
Myositis, an overview

*A **disease** is said to be **rare** if it affects less than 1 in 2,000 people. Rare diseases are subject to common public health policy in the areas of research, information and therapeutic management.*

Idiopathic inflammatory myopathies (or myositis) are a group of rare diseases affecting approximately 6 to 7 people in every 100,000.

Immune origin

Myositis are so-called "autoimmune" diseases: the immune system (in charge of protecting the body from external attacks such as bacteria, viruses, etc.) becomes deregulated and attacks constituents of the body.



__Autoantibodies__ are antibodies that react to elements of one's own body, such as the muscles.

▪ The classification of the different types of myositis is established based on the symptoms, immunological characteristics (autoantibody type) and appearance of the muscle tissue under a microscope (histological criteria). It changes year by year and **continues to be debated**. To date, the classification that still serves as the international reference distinguishes between **5 main types of myositis**:

- dermatomyositis (DM),
- inclusion body myositis (IBM),
- immune-mediated necrotising myopathy,
- overlap myositis,
- polymyositis (PM), a condition now considered to be rare, whose very existence is contested by certain experts who believe that individuals diagnosed with polymyositis in the past actually have another form of inflammatory myopathy (antisynthetase syndrome, immune-mediated necrotising myopathy, etc.).

Leclair V et al. Cur Opin Rheumatol. 2021 Nov

Unique mechanisms

While all types of myositis have an autoimmune component, each one has its own unique immune mechanism.

- In **dermatomyositis (DM)**, the immune system, via type I interferons, initially attacks the blood vessels of the skin and muscles, where an abnormal accumulation of complement is produced. This causes destruction of the blood vessels, which in turn is responsible for a decrease in blood supply, especially to muscle fibres. The muscle fibres then decrease in volume - they atrophy. The immune cells then invade the damaged area (inflammatory infiltrate), causing a deterioration in the state of the muscle fibres.
- In **polymyositis (PM**), immune cells, cytotoxic T lymphocytes (CD8+ T cells), attack muscle fibres and destroy them.
- In **inclusion body myositis (IBM)**, toxic protein aggregates (beta-amyloid, phosphorylated tau, etc.) are seen in muscle fibres - these are known as "inclusion bodies". Additionally, certain muscle fibres are invaded by immune cells, especially CD8+ T cells, as is the case in polymyositis.
- **Immune-mediated necrotising myopathy** is characterised by significant muscle necrosis with little or no inflammatory infiltrate. This necrosis is induced by the presence of specific autoantibodies called anti-SRP and anti-HMGCR autoantibodies, that attack muscle.
- **Overlap myositis** is defined by extra-muscular or extra-cutaneous manifestations and/or the presence of autoantibodies specific to myositis. For example, antisynthetase syndrome (a form of overlap myositis) involves a combination of the presence of antisynthetase autoantibodies (such as anti-Jo-1), a myositis condition, and joint, skin and lung involvement.

Complement *is a complex molecular system composed of different proteins that is involved in the immune system's defence of the body.*

Cytotoxic T lymphocytes (CD8+ T cells) *are specialist immune system white blood cells. They attack their target cells by releasing toxic proteins that cause these cells to die by a process known as "apoptosis".*

Cell necrosis *is the accidental death of cells due to external factors (lack of oxygen, toxins, disease, etc.). If the cell is too damaged, it undergoes necrosis: the cell takes on water until it bursts. This leads to the contents of the cell spilling into the surrounding environment, causing inflammation and damage to the surrounding tissue.*

Autoantibodies

The majority of individuals with myositis produce **autoantibodies**, i.e. antibodies directed against parts of our own body, such as skeletal muscles. They are produced by the B cells.

Did you know?

Two broad groups of autoantibodies

- Autoantibodies **specific** to myositis are found solely in individuals with myositis.
- Autoantibodies **associated** with myositis can also be present in other autoimmune diseases (such as lupus).

- The presence of these autoantibodies has now been linked to certain characteristics, such as the type of myositis, associated manifestations, progression of the disease, and response to different treatments.

For example, the presence of anti-SRP or anti-HMGCR autoantibodies signals immune-mediated necrotising myopathy. Similarly, anti-SAE, anti-MDA5, anti-TIF1-γ, anti-NXP-2 and anti-Mi2 autoantibodies are considered to be specific to dermatomyositis.

Lupus *erythematosus can affect a number of organs such as the skin, joints, blood vessels, kidneys and lungs. The skin is sometimes the only one affected (cutaneous lupus erythematosus) with the appearance of a red rash (erythema) on the face referred as a "butterfly rash". When several organs are affected, the disease is referred to as "systemic" lupus erythematosus.*

The main treatments in 2022

With the exception of inclusion body myositis, the current treatment for inflammatory myopathies is based on various medicines aimed at **modulating the activity of the immune system** (corticosteroids, immunosuppressants or immunomodulators).

Corticosteroids, immunosuppressants, immunomodulators

- These medicines reduce the activity of the immune system.
- Methotrexate, azathioprine, cyclophosphamide, tacrolimus and cyclosporine are immunosuppressants.

Targeted therapies

- A targeted therapy is a treatment directed specifically against a particular biological target (cell, protein).
- Rituximab (MabThera®) is a targeted therapy that binds to B lymphocytes to reduce antibody production.

Polyvalent immunoglobulins

- These are antibodies collected from healthy donors who have the ability to modulate immune system activity during myositis.

Plasmapheresis (plasma exchange)

- This treatment uses a machine that purifies the blood and filters out various substances, such as autoantibodies.

▪ **Inclusion body myositis** is a special case because it responds very little or not at all to the medicines currently being used. Several clinical trials are underway to test new medicines for this disease.

Very active research

Knowledge regarding the different types of myositis and the development of new treatments are progressing every year. The growing number of scientific publications and clinical trials is evidence of this.

1251 scientific publications between May 2021 and May 2022

+67% in 10 years

> 80 clinical trials

underway or in preparation worldwide as of 01 June 2022

11 in France, 6 of which relate to medicines

▪ In the last few years, new therapeutic avenues have presented themselves, including for inclusion body myositis, thanks mainly to a better **understanding of the mechanisms** causing these diseases.

The treatments being studied are **increasingly selective**, targeting the mechanism or mechanisms in a specific myositis subgroup. Janus kinase inhibitors acting against the interferon in dermatomyositis, an anti-C5 antibody acting against the complement in immune-mediated necrotising myopathy, rapamycin acting against the T cells (also called T lymphocytes) and autophagy in immune-mediated necrotising myopathy, etc.

▪ Treatment avenues currently being explored in myositis are organised into **two broad categories**.

OPTIMISATION OF CURRENT TREATMENTS

The objective is to improve their benefit/risk ratio and to better clarify the role of each medicine (when to use them, which form of myositis to use them for, etc.).
Immunosuppressants, immunoglobulins, physical exercise, etc.

ASSESSMENT OF INNOVATIVE TREATMENTS

These candidate medicines, which are already marketed or still in development, are more targeted, and so potentially more effective and better tolerated than current medicines.
Biotherapies, cell therapies, etc.

Certain treatments must undergo clinical trials, others need a prescription on a case-by-case basis, as is often the case with rare diseases.

Did you know?

A long journey

On average, it takes 15 years from when a candidate medicine is identified until it is brought to market, with a 10 to 12 year period between the start of preclinical studies and the end of phase III clinical trials. However, there is a possibility for the process to be accelerated in the case of treatments intended for rare diseases.

Source: Ministère des solidarités et de la santé - Le développement du médicament (2016).

Understanding clinical studies and clinical trials

There are different types of so-called "clinical" research, i.e. research conducted in individuals with a disease or based on their examination data.

Clinical trials

These consist of assessing a potential treatment in order to ensure that it is well tolerated and effective in treating a disease. A candidate medicine is assessed over the course of successive trials, corresponding to different phases: I, II, III and IV.

Did you know?

The 4 phases of a clinical trial

- **Phase I: Safety/tolerability**

A candidate medicine is tested for the first time on a small group of individuals (often healthy volunteers) to assess its safety/tolerability and its movement throughout the body (pharmacokinetics).

- **Phase II: Optimum dose/Effect**

Phase II, conducted on a homogeneous group of volunteers with the disease, studies the safety and efficacy of the product and determines the optimum dose.

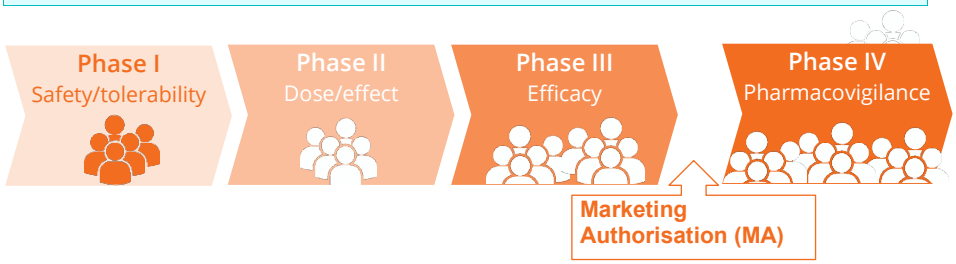
- **Phase III: Therapeutic efficacy**

Phase III is conducted on a larger number of participants who have the disease in order to determine the therapeutic efficacy compared to an existing treatment or a placebo. At the end of this phase, the medicine may obtain marketing authorisation (MA).

- **Phase IV: Pharmacovigilance**

The goal of phase IV, which is conducted after the medicine is brought to market, is to fine-tune knowledge of the product and to identify any serious and/or unexpected side effects.

*A **placebo** is a product whose appearance is identical to a particular medicine but does not contain any active substance. In a clinical trial, a placebo is used to measure the true action of a medicine by comparing the effects of the medicine (which contains the active substance) to those of the placebo.*



Clinical studies

Clinical studies, consisting of observational studies, databases or registries, help us to learn more about a disease and to identify better diagnostic and follow-up tools. They are essential to improving therapeutic management and exploring future clinical trials.

Did you know?

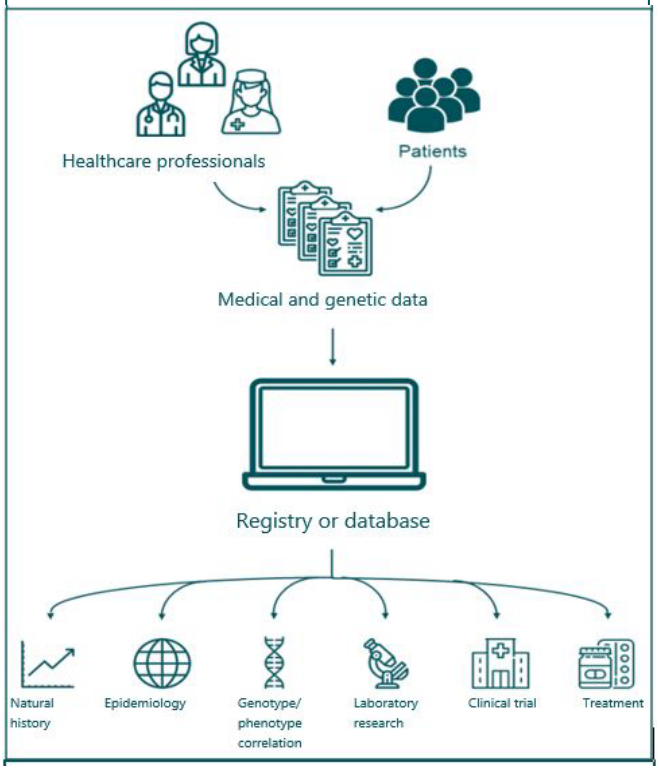
There are two types of observational clinical studies

- **Cross-sectional** studies describe how a disease manifests in a group/population of patients at a specific point in time.
- **Longitudinal** studies describe the progression of a disease over time (for example, a natural history protocol).

Databases and **registries** capitalise on molecular and medical data from patients with a particular disease, with their consent. Analysis of these data helps, in particular, to determine the natural history of a disease. It also helps in the recruitment of participants for clinical trials.

Registries and databases

Patient registries and databases are collections of molecular and medical data from patients with a particular disease (collected with their consent).



Clinical trials currently underway for myositis in France

Treatment	Approach	Phase	Recruitment
Stem cells (*ADSVF-in-IBM trial*) 32 participants ➥ Inclusion body myositis	• Cell therapy	• I	• In preparation
Ravulizumab 180 participants worldwide ➥ Refractory dermatomyositis	• Pharmacology	• II/III	• Underway
Abatacept 150 participants worldwide ➥ Refractory myositis	• Pharmacology	• III	• Completed
Sodium thiosulfate (*ITS-PILOT trial*) 40 participants ➥ Calcinosis due to dermatomyositis	• Pharmacology	• II	• Underway
Cyclophosphamide + Azathioprine *versus* Tacrolimus (*CATR-PAT trial*) 76 participants ➥ Antisynthetase syndrome	• Pharmacology	• III	• Underway
IgPro20 (Hizentra®) *(RECLAIM trial)* 126 participants worldwide ➥ Dermatomyositis	• Pharmacology	• III	• Underway

2022: the third year shaped by the COVID-19 pandemic

COVID-19 has continued to impact research in 2022. Certain clinical trials that should have started have been postponed. Several teams have also conducted specific studies on COVID-19 and its vaccination in cases of neuromuscular disease.

Researchers at the ready

Experts in the FILNEMUS rare neuromuscular diseases healthcare network, with the support of AFM-Téléthon, have been conducting:

- **national monitoring** of COVID-19 cases among patients with neuromuscular diseases including myositis since the beginning of the pandemic;
- surveys to measure the **impact of the pandemic** on this population;
- a study called CANNEMUSS on the **efficacy of vaccination** against COVID-19 in cases of severe muscle atrophy.

▪ Since March 2021, CHU de Bordeaux [Bordeaux University Hospital] has been conducting the Va-C-NEMUS national study in order to **learn more about the effects of COVID-19 and its vaccines** in neuromuscular patients.

Did you know?

Whether vaccinated or not, **any adult with neuromuscular disease** may participate in the Va-C-NEMUS observational study. After an initial questionnaire, each participant receives a text message once a month for a period of one year inviting them to fill in a follow-up questionnaire online.

Va-C-NEMUS observational study

France

5000 participants (18+ years)

Recruitment underway

1 year of follow-up (online)

March 2021

Va-C-NEMUS

A safety and efficacy study specific to China

A team from the Chongqing University Hospital is about to launch an observational study on the effects of a COVID-19 vaccine in patients with myasthenia gravis or myositis. However, this is a so-called "inactivated" vaccine produced in China with a different principle of action compared to those used in France and many other countries.

Source: NCT04941079

Less infected by COVID-19

According to the results of a study conducted by FILNEMUS, with AFM-Téléthon, patients with neuromuscular diseases in France were less likely to contract COVID-19 compared to others during the first wave: 17/10,000, versus 26/10,000 in the general population.

This difference would appear to be due to "particular care of patients to follow self-isolation and hygiene measures", as well as "actions taken by the

neuromuscular patient associations and FILNEMUS", according to the conclusions of this national study.

▪ During the first lockdown in France, 84 patients with a neuromuscular disease developed COVID-19 symptoms and/or tested positive (only two of whom had myositis). Hospital admission was more common (42%) than among the general population, but the death rate was lower. The long-term use of corticosteroids or immunosuppressants did not seem to be associated with a significant increased risk of severe COVID-19 in this study.
Pisella LI et al. Orphanet J Rare Dis. 2021 Oct.

The lockdown had an impact on mood and care

In the United Kingdom, paediatricians conducted a survey among the parents and carers of 139 children with juvenile dermatomyositis to assess the effects of the COVID-19 lockdown.

▪ These participants expressed a feeling of worry and anxiety in connection with this period, which was a difficult time for them and for the children they were looking after. COVID-19 often led to a disruption in their treatment (over 40% of cases), cancellation of medical appointments, use of virtual appointments and long gaps between blood tests.
Wilkinson MGL, et al. Rheumatol Adv Pract. 2021 Sep.

Specific precautions in cases of immunosuppression

In France, experts in the FILNEMUS network have called on patients who are immunosuppressed (being treated with Cellcept®, Imurel®, Endoxan®, rituximab, or high-dose corticosteroids) and appropriately vaccinated against COVID-19 to monitor the efficacy of the vaccine by having a blood test to measure antibodies directed against the Spike protein (anti-S antibodies).

▪ Anti-S antibody levels provide evidence of the degree of protection that the body has against the COVID-19 virus. If this level is too low, then depending on the vaccine status and health of the patient, another booster jab or administration of antibodies directed against SARS-CoV2 (Ronapreve®, Evusheld®, Xevudy®) may be justified. These antibody medicines bind to the coronavirus, preventing it from penetrating into the cells and multiplying there, thus reducing the risk of developing a serious form of the disease.
ANSM. January 2022.

Protecting yourself from infections - an absolute necessity

▪ A number of treatments for myositis, beginning with corticosteroids, reduce resistance to infections, a phenomenon that must be taken into account for patients to better protect themselves, especially through vaccination and hygiene care. The validity of these precautions is confirmed by a study conducted in the United States.

▪ This study, conducted using a large healthcare database, concludes that infections are the third biggest cause of hospital admissions (13%) for patients with myositis, and the biggest cause of death in hospitals (34%).
Source: Pavon MR et al. J Clin Rheumatol. 2022 Mar.

Improving the efficacy of vaccination in non-responders

In the United States, the National Institute of Allergy and Infectious Diseases is conducting a multicentre clinical trial among patients with different autoimmune diseases (including juvenile dermatomyositis) receiving

immunosuppressant treatment who have not responded or responded poorly to two Moderna, Pfizer or Janssen COVID-19 vaccine doses.

▪ All the participants will receive an additional (booster) dose of the same vaccine. Some will continue their immunosuppressant treatment without any changes. Others will discontinue their treatment just prior to and after receiving the booster vaccine dose, then will resume their treatment. The main evaluation criterion for this trial is the anti-S antibody level four weeks after the booster dose.

Phase II
Dose/Effect

Phase II trial of a COVID-19 vaccine booster dose

In the United States

2340 participants (5+ years)

Recruitment underway

11 months of follow-up

August 2021 – August 2023

NCT05000216

A review of vaccination (in general) among young subjects

A Swiss team has analysed 37 studies conducted among a total of 2571 children and adolescents with different autoimmune diseases (including dermatomyositis) being treated with immunosuppressants. It concluded conventional vaccines (flu, tetanus, etc.) are safe and confer good immunity in this population. They should, therefore, be encouraged, especially since autoimmune diseases and their treatments increase the risk of infection.

Source: Keller M et al. Eur J Pediatr. 2021 Dec.

Post-COVID-19 and even post-vaccine myositis?

Myositis seems to occur in individuals with a genetic predisposition, influenced by factors related to the "environment" in the broad sense of the word, such as infections. COVID-19 is a viral infection.

▪ A centre of expertise in Paris found undetected COVID-19 in 2 of the 10 children who developed or experienced a relapse of juvenile dermatomyositis between April 2020 and March 2021. No other factors likely to trigger the disease or its relapse were found. COVID-19 may facilitate the development of juvenile dermatomyositis, possibly via interferon alpha; both children had very high levels of interferon alpha in their blood.

Rodero MP et al. J Clin Immunol. 2022 Jan.

▪ A review conducted by a team in London of all the publications (up to the end of October 2021) on possible muscle involvement related to COVID-19 found:

- 86 cases of rhabdomyolysis, with muscle pain and the need to perform dialysis in 28% of cases, the muscle lysis possibly being caused by viral infection and/or medicines,
- 10 cases of viral muscle involvement without rhabdomyolysis,
- 6 possible cases of myositis or myositis relapse, a number too small to be able to confirm a cause/effect relationship with COVID-19 according to the British authors.

Hannah JR et al. Clin Exp Rheumatol. 2022 Feb

***Rhabdomyolysis** involves the more-or-less severe destruction of muscle tissue, caused for example by trauma, infection or a medicine. It causes a massive release of muscle components (proteins, ions, etc.) into the blood stream, some of which are particularly harmful to the kidneys.*

▪ Out of a population of 232,603 subjects vaccinated against COVID-19, a team of neurologists from a German hospital identified a total of 21 adults who developed (17 cases) or experienced a relapse (4 cases) of a neurological or muscular autoimmune disease in the six weeks that followed. Three of these cases involved myositis.
According to the authors of this study, these results do not call into question the utility of COVID-19 vaccination, given the potential seriousness of this infection. Furthermore, research on a much larger population would be necessary to confirm or deny an increased incidence of neuromuscular autoimmune disease since the deployment of COVID-19 vaccination.
Kaulen LD et al. Eur J Neurol. 2022 Feb.

Advances in inclusion body myositis

None of the immunosuppressant treatments generally used in inflammatory myopathies are beneficial in inclusion body myositis, but different therapeutic avenues are currently being pursued.

Cell therapy trials are starting soon

Cell therapy, which is currently being studied for different neuromuscular diseases, consists of transplanting therapeutic cells, most often obtained from stem cells collected from the patient or a donor.

__Stem cells__ possess both the ability to multiply to produce new identical stem cells (self-renewal) and the ability to produce differentiated cells under specific conditions (blood cells, liver cells, muscle cells, etc.).

▪ These stem cells could repair or regenerate a damaged organ or tissue. They also appear to undertake an immunomodulating action, an effect that is giving rise to a large number of research projects for various inflammatory diseases. Thus, in 2017, researchers from Toulouse reported positive results (possible improvement in muscle strength) for stem cell transplantation in a mouse model of inclusion body myositis at the 22nd World Muscle Society Congress.

Fabry V et al. Neuromuscular Disorders 2017 Oct.

Benefits in inclusion body myositis

An international team has reviewed cell therapy research in muscle diseases. This treatment approach is all the more justified in inclusion body myositis since this condition does not respond to the usual immunosuppressant treatments. The fact that it affects only certain muscles (the thighs, finger flexors, etc.) suggests the possibility of a local injection into these muscles, or a local-regional injection into the artery that supplies blood to these muscles.

Source: Boyer O et al. Front Genet. 2021 Aug.

In France

Prof. Benveniste (Hôpital Pitié-Salpêtrière, Paris) is preparing for the launch of a cell therapy trial (called ADSVF-in-IBM) among patients with inclusion body myositis. This phase I, open-label trial, which is supported by AFM-Téléthon, should have two investigating centres in Paris and in Marseille.

▪ The objective is to assess the safety and tolerability and, to a lesser extent, the efficacy (muscle repair and inflammation control) of escalating doses of stem cells taken from the fat tissue of the patient. They will be injected into the finger flexors of the forearm. One group of participants will be treated with rapamycin (sirolimus) for a period of six months prior to the cell therapy, and the other group will not.

Phase I
Safety/tolerability

ADSVF-in-IBM trial

In France

32 participants (45 to 80 years)

Trial in preparation

7 months of follow-up

September 2021 – April 2024

NCT05032131

In the United States

A team from the University of Kansas Medical Center will conduct a cell therapy pilot study (IBM-ADRC), smaller than the one in France, on inclusion body myositis in order to assess the safety and efficacy of the injection of stem cells into the finger flexors and quadriceps (thigh muscle).

IBM-ADRC trial

In the United States

9 participants (45+ years)

Trial in preparation

1 year of follow-up

March 2022 – December 2024

NCT04975841

Rapamycin is continuing to progress

Rapamycin (or sirolimus) is an immunosuppressant medicine that has been used for years in the prevention of rejection after a kidney transplant. It acts on three targets (effector T cells, regulatory T cells and autophagy) that are involved in the development of inclusion body myositis.

- A clinical trial called RAPAMI, which was conducted in France with the support of AFM-Téléthon, included 44 patients with inclusion body myositis. This trial's definitive results were published in January 2021 and showed that one year of treatment with rapamycin resulted in stabilisation of 6-minute walking distance and lung function, but did not have an effect on the strength developed while performing different movements (knee and elbow flexion and extension, hand grip).

Benveniste O. et al. The Lancet Rheumatology January 2021.

- These results are sufficiently positive to justify the implementation of a phase III, placebo-controlled clinical trial. Sponsored by the University of Kansas Medical Center, it is expected to be conducted in the United Kingdom, Australia, the Netherlands and the United States.

Phase III trial for rapamycin

Abroad (outside France)

140 participants (45+ years)

Trial in preparation

19 months of follow-up

January 2022 – November 2023

NCT04789070

Regulatory T cells *(or* ***Tregs****) play a crucial role in "self-tolerance" by modulating the activity of other immune cells.*

Autophagy *is a process that allows a cell to cause a part of its contents to be degraded.*

A ***placebo*** *is a product whose appearance is identical to a particular medicine but does not contain any active substance. In a clinical trial, a placebo is used to measure the true action of a medicine by comparing the effects of the medicine (which contains the active substance) to those of the placebo.*

Phase III
Efficacy

ABC008 delivers its first results

ABC008, which is administered subcutaneously, is being developed by the American pharmaceutical company, Abcuro. It obtained the status of orphan drug from the American health authorities in June 2020.

Journey from understanding a mechanism to candidate medicine

At the end of 2019, a team led by Dr Steven A Greenberg (United States) showed that inclusion body myositis is characterised by the presence of highly differentiated cytotoxic T lymphocytes in the muscles and the blood that are positive for a surface marker: KLRG1 (killer cell lectin-like receptor G1).

- The activation of these cells by a muscle antigen could be the mechanism that initiates inclusion body myositis. And yet, they are resistant to the usual corticosteroids and immunosuppressants.
- *Abcuro*, the pharmaceutical company that was co-founded by Dr Steven A Greenberg, is developing ABC008, an anti-KLRG1 antibody designed to reduce the subpopulation of KLRG1 cytotoxic T lymphocytes without impacting other lymphocyte populations.

In an article published in March 2022, the same team confirmed and completed its first results, showing that the KLRG1 surface protein is, in inclusion body myositis, overrepresented on highly differentiated CD8+ and CD4+ T cells, but hardly expressed on regulatory T cells (Tregs). And yet, the latter play an important role in limiting autoimmunity. ABC008, a monoclonal antibody targeting KLRG1, could therefore reduce the number of cytotoxic T cells without compromising the capabilities of Tregs.
Goyal NA et al. Neurology. 2022 Mar. *Mammen AL. Neurology. 2022 Mar.*

__T cells__ are white blood cells that specialise in certain immune reactions. There are several different types of T cells, each one with a specific function. Unlike B cells, T cells do not secrete antibodies.

- Abcuro has been assessing the tolerability and safety of escalating doses of ABC008 in inclusion body myositis since 2021.

Phase I
Safety/tolerability

Phase I trial of ABC008

In Australia

27 participants (40+ years)

Recruitment underway

5.5 months of follow-up

May 2021 – December 2023

NCT04659031

At the end of 2021, the pharmaceutical company presented preliminary results from its trial at the American College of Rheumatology Convergence annual meeting.

- In three participants, injection of ABC008 at the lowest dose resulted in a reduction in the number of KLRG1+ CD8+ T cells (-68% on average) which was maintained four weeks later. The Treg cells remained stable, with no moderate or serious adverse reactions reported.

Goel N et al. Arthritis Rheumatol. 2021 Oct.

A study of phenylbutyrate

Sodium **phenylbutyrate** is already used in other rare diseases and is undergoing an open-label pilot study in the United States, sponsored by the University of Kansas Medical Center. The objective of this study is to assess the safety and tolerability of 3 mg of phenylbutyrate taken twice a day for three months.

Did you know?

Phenylbutyrate

Designated an orphan medicine in Europe and the United States, sodium phenylbutyrate is indicated in urea cycle enzyme deficiencies.

- It is being or has been trialled in different diseases, especially neuromuscular ones such as amyotrophic lateral sclerosis (ALS) or SMN1-related proximal spinal muscular atrophy (SMA).
- According to a study conducted in 2014, it improves lysosomal dysfunction and reduces amyloid-β protein deposits in a cell model of inclusion body myositis.

Source: Nogalska A et al. Neurobiol Dis. 2014 May

***Lysosomes** are small sacks (vesicles) that are found in cells, whose role is to digest material from cell function into small molecules. These are either evacuated and eliminated as waste, or recycled and reused by the cell. Lysosomes degrade and recycle materials from outside the cell (heterophagy) as well as those from inside the cell (autophagy) using a large number of different enzymes capable of digesting large molecules.*

Phase I trial of sodium phenylbutyrate

In the United States

10 participants (18+ years)

Recruitment completed

6 months of follow-up

August 2020 – January 2022

NCT04421677

Phase I
Safety/tolerability

Pain - still an understudied symptom

In Germany, a university hospital is conducting a study on muscle pain in different diseases, including inclusion body myositis. The challenge is to measure its frequency, severity and type, but also to establish correlations between muscle pain, function and stiffness.

Study of musculoskeletal nociceptive pain

In Germany

90 participants (18+ years)

Recruitment underway

1 day of follow-up

April 2021 – August 2022

NCT04907162

Learn more about the natural history of the disease

The University of California, Irvine (United States) is conducting an observational study called INSPIRE-IBM at 13 investigating centres in North America.

Its objectives are to study the influence of anti-NT5c1A autoantibodies on the progression of inclusion body myositis, describe the lesions observed on muscle biopsy, and quantify the decline in lung function.

INSPIRE-IBM study

In the United States

150 participants (40+ years)

Recruitment underway

2 years of follow-up

October 2021 – November 2024

NCT05046821

A dedicated database

In collaboration with the Myositis Association and the Muscular Dystrophy Association, Yale University (United States) is developing a database dedicated to inclusion body myositis - the IBMR (Inclusion Body Myositis Disease Registry). Patients who wish to be included must complete an online questionnaire.

▪ On its website, this registry offers a personalised index calculator (IBM-PIC) inspired by a functional rating scale (IBM-FRS) used by doctors. In a study conducted by telephone among 35 patients included in this registry, the IBM-PIC has been proven to reliably reflect the IBM-FRS clinical score. It could, therefore, help to remotely assess the seriousness of the myositis and its progression.

Roy B et al. J Neurol Sci. 2022 May.

IBMR database

In France and abroad

Created in 2012

Recruitment underway

1000 patients

WEB https://publichealth.yale.edu/ibmregistry/

The GSK3 avenue kills two birds with one stone

What is GSK3?

Glycogen synthase kinase 3 (GSK3) is involved in the formation of Tau protein deposits found in both the brains of individuals with Alzheimer's disease and muscles affected by inclusion body myositis. However, this enzyme also plays a role in the innate immune response which if deregulated can result in chronic inflammation.

*An **enzyme** is a protein that specifically allows, facilitates or accelerates a particular chemical reaction in our bodies (cell digestion, protein synthesis, DNA replication, etc.).*

The use of GSK3-inhibiting drugs, such a **Tideglusib**, could help to combat both protein deposits and inflammation in inclusion body myositis. This orphan medicine is currently in the clinical trial stage in Alzheimer's disease and amyotrophic lateral sclerosis, and also in Steinert's disease.

Piazzi M et al. Cells. 2021 Nov.

Results published in 2022

The benefits of blood flow restricted physical exercise

A randomised, controlled clinical trial (NCT02317094) conducted in Denmark has assessed the effects of a 12-week programme of training during which the arteries supplying the muscles that are performing the exercise are compressed in order to restrict blood flow.

▪ In 22 patients with inclusion body myositis, divided into two groups, this very special type of training resulted in an improvement in exercise capacity and the strength of certain muscles. These activities, which are supervised by a healthcare professional, could reduce muscle function decline.

N Jørgensen A et al. Scand J Med Sci Sports. 2022 Feb.

Botox to improve swallowing difficulties

The cricopharyngeus muscle, located in the throat, relaxes when we swallow, allowing food to pass into the oesophagus. A procedure performed under general anaesthesia (a myotomy or dilation) can help with this relaxation in cases where inappropriate contraction is causing swallowing difficulties (dysphagia).

▪ Danish doctors have assessed an alternative to this operation, i.e., the injection of botulinum toxin, the active substance in Botox®, into the cricopharyngeus muscle. Out of 10 patients aged 71 to 84 with inclusion body myositis complaining of moderate to severe dysplasia, eight improved after one to three injections.

Witting N et al. J Neurol. 2022 Mar.

Advances in dermatomyositis and polymyositis

Treatment avenues in 2022	In practice
Stem cells from umbilical cord blood	• Phase I trial in the United States
Stem cell mitochondria	• Phase I/II trial in China
CAR-T cells	• Phase I trial in China
PF-06823859	• Anti-interferon beta 1 antibodies • Phase II trial in the United States
Sodium thiosulfate	• To treat calcinosis • Two phase II trials (one in France)
Subcutaneously administered immunoglobulins	• IgPro20 (Hizentra®) in phase III trial, including in France
Janus kinase inhibitors (ruxolitinib, tofacitinib, baricitinib, etc.)	• Phase III trial in France • Phase II trial in the United Kingdom and phase IV trial in China
Ravulizumab	• Anti-C5 antibody • Phase II/III trial, including in France
Zetomipzomib (KZR-616)	• Immunoproteasome inhibitor • Two phase II trials
Lenabasum	• Cannabinoid receptor type II agonist • Phase III international trial
Ustekinumab	• Anti-interleukin-12 and -23 antibody • Phase III trial in Japan
Apremilast	• Phosphodiesterase-4 inhibitor • Phase II trial in the United States
Physical exercise	• Three trials underway (one in France)

Asking patients for their point of view - what a good idea!

In the UK, 20 adults with dermatomyositis used a smartphone app to record the intensity of their symptoms (pain, fatigue, etc.) every day on a numbered scale, and any flare ups in their disease once a week over a three-month period.

▪ Flare ups proved to be frequent (on average once every five weeks) and were associated with a concomitant increase in symptom intensity (especially fatigue) reported by the participants. Their assessment does indeed help to identify and characterise a myositis flare up.

▪ Nevertheless, calling on patients with myositis to assess the activity of their disease is not yet a widespread habit, as demonstrated by an Australian analysis of 20 clinical trials conducted between 1993 and 2020 on dermatomyositis in children or adults.

▪ Out of a total of 34 evaluation criteria categories, only 4 come directly from trial participants, 17 are clinical (assessment of muscle strength, for example) and 13 are based on the results of laboratory examinations (autoantibodies, imaging, etc.).

Sources: Oldroyd AGS et al. Rheumatology (Oxford). 2022 Mar. Kelly AH et al. Clin Exp Rheumatol. 2022 Feb.

Three cell therapy trials

Stem cells

The University of Florida is assessing the tolerability, safety and feasibility of a single infusion of stem cells from umbilical cord blood in dermatomyositis and polymyositis.

Stem cells *possess both the ability to multiply to produce new identical stem cells (self-renewal) and the ability to produce differentiated cells under specific conditions (blood cells, liver cells, muscle cells, etc.).*

Umbilical cord blood, a precious gift

Stem cell transplantation is being studied or is already being used to treat severe forms of autoimmune disease such as lupus and scleroderma.

- In a sense, the challenge is to reset the immune system (re-induce self-tolerance) or to trigger immunomodulation.
- Stem cells can be extracted from a bone marrow sample, a blood sample, or even from an umbilical cord or placenta donated at the birth of a baby by the parents.
- Because they are more immature, the stem cells from umbilical cord blood are potentially better tolerated by the recipient than other types of stem cell. They have been used since the 1980s to treat conditions, in particular, blood diseases (lymphoma, leukaemia, sickle-cell disease, etc.).

WEB Thérapie cellulaire dans les maladies auto-immunes [Cell therapy in autoimmune diseases]: MATHEC network website

- The trial conducted by the University of Florida uses three different doses of stem cells (50, 100 and 200 million).

Phase I trial of umbilical cord stem cell transplantation

Phase I
Safety/tolerability

In the United States

22 participants (18 to 90 years)

Recruitment underway

24 hours of follow-up

October 2021 – April 2022

NCT04723303

Stem cell mitochondria

The Korean biotech company Paean is developing **PN-101**, a treatment based on the mitochondria of stem cells extracted from umbilical cord blood. Mitochondria are the "powerhouse" of the cell. A deterioration in their function would induce abnormal inflammation. The transplantation of mitochondria, intended to replace abnormal mitochondria with healthy ones, would therefore have a potential therapeutic benefit in inflammatory diseases.

Cell ***signalling pathways*** *transmit messages within a cell in order to modulate its activity (growth, division, differentiation, death, etc.). A message can originate from other cells in the body or from the external environment. Its arrival at a cell receptor triggers a cascade of reactions that modify the cell's behaviour.*

- In support of this hypothesis, researchers from this biotech company published the results of a study conducted in vitro and in mice. The intravenous injection of PN-101 seems to lessen the inflammatory reaction by inhibiting the signalling pathway of the nuclear factor kappa B (NFκB), a protein involved in the immune response and responsible for the expression of pro-inflammatory genes.

Yu, S. H. et al. BMB reports 2022 Mar.

Did you know?

Advances in heart attacks and strokes too

The transplantation of mitochondria is currently undergoing clinical trials in two diseases caused by the stopping or reduction of blood flow into a tissue (ischaemia): stroke, caused by the obstruction of a blood vessel in the brain, and ischaemia of the heart muscle (heart attack). In both cases, the injected mitochondria are extracted from a sample of... muscle tissue!

▪ Paean Biotechnology is sponsoring a trial to define the safety, tolerability and efficacy of a single injection of PN-101 at three different doses in refractory dermatomyositis and polymyositis.

Phase I
Safety/tolerability

Phase II
Dose/Effect

Phase I/II trial of PN-101

In China

18 participants (19+ years)

In preparation

12 weeks of follow-up

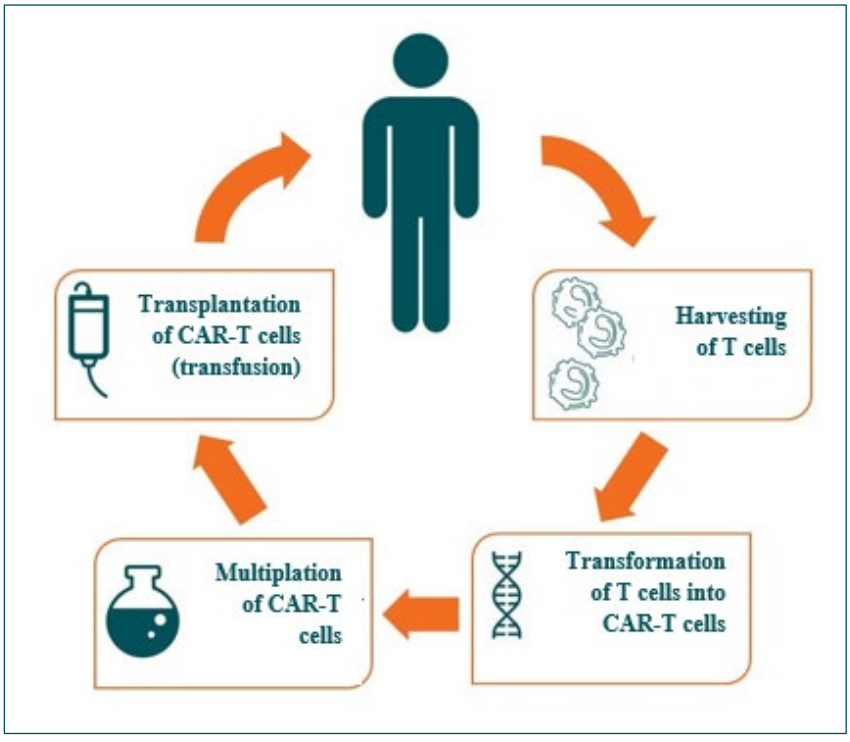
August 2021 – December 2022

NCT04976140

CAR-T cells

A CAR-T cell starts off as a T cell, capable of recognising and destroying specific cells: cancerous cells, cells infected by a microorganism, etc. This T cell, which is usually collected from the patient with the disease to be treated, is genetically modified in the laboratory to make it capable of recognising an antigen that is present on the surface of the cell to be eliminated.

▪ Once modified in this way, it becomes a CAR-T cell (CAR stands for chimeric antigen receptor) and is then injected into the patient.



Did you know?

Medicines and trials

CAR-T cells are already being used to treat blood cancers (leukaemia, lymphoma, etc.). This treatment method is also starting to be explored in different autoimmune diseases, such as myasthenia.

▪ In China, Zhejiang University is conducting an open-label clinical trial to assess the safety and efficacy of **targeting CD7 CAR-T cells**. CD7 is a protein present on the surface of mature T cells in autoimmune diseases that are resistant to the usual treatments, including dermatomyositis.

Phase I trial of CD7 CAR-T cells

Phase I
Safety/tolerability

In China

75 participants

Recruitment underway

2 years of follow-up

February 2022 – December 2024

NCT05239702

PF-06823859 passes phase I

Developed by Pfizer, **PF-06823859** has had the status of orphan medicine in Europe since 2021. It is an antibody directed against interferon beta 1, which has been identified as being involved in myositis by several studies.

▪ A phase I clinical trial conducted among 62 healthy subjects assessed the safety and tolerability of PF-06823859 administered intravenously or subcutaneously and showed that there were no serious adverse effects.
Neelakantan S et al. Clin Pharmacol Drug Dev. 2021 Mar.

▪ Pfizer is sponsoring a new trial and its extension study assessing the candidate medicine in moderate to severe dermatomyositis in the United States and Europe (but not in France).

Phase II trial of PF-06823859

Phase II
Dose/Effect

Abroad (outside France)

57 participants (18 to 80 years)

Recruitment completed

3 months of follow-up

January 2018 – December 2022

NCT03181893

Extension study of the phase II trial of PF-06823859

Phase II
Dose/Effect

Abroad (outside France)

30 participants (18 to 80 years)

Recruitment underway

3 months of follow-up

December 2021 – October 2023

NCT05192200

Sodium thiosulfate times two

Patients with dermatomyositis may present with calcification under the skin (calcinosis), made up of calcium crystals.

In France, a pilot study conducted by CHU de Limoges [Limoges University Hospital] is assessing **sodium thiosulfate** injected into the calcifications in three diseases, including dermatomyositis.

Phase II
Dose/Effect

Phase II ITS-PILOT trial

In France

40 participants (2+ years)

Recruitment underway

1 year of follow-up

January 2020 – March 2023

NCT03582800

A trial involving the treatment of calcinosis by sodium thiosulfate administered as an intravenous infusion is underway in the United States, sponsored by the National Institute of Environmental Health Sciences.

Phase II trial of intravenous thiosulfate

In the United States

250 participants (7 to 99 years)

Recruitment underway

1 year of follow-up

October 2017 – June 2025

NCT03267277

Janus kinase inhibitors, a promising class of medicines

Janus kinases, a target that makes sense

The different myositis conditions, in particular dermatomyositis, appear to be interferon diseases or interferonopathies. Interferons (IFNs) are produced by the immune system and participate in the body's defence against infections.

- There are three types: I, II and III. Dermatomyositis involves an overexpression of genes that are dependent on interferon I, and this "interferon signature" correlates with skin and muscle manifestations of the disease.
- Interferon I activates the Janus kinase (JAK) signalling pathway.
- Janus kinase inhibitors (JAKi) are already on the market, and are prescribed in autoimmune diseases (rheumatoid arthritis, etc.) and inflammatory diseases (ulcerative colitis, etc.)

*A **gene** is a "segment" of DNA located in a very specific position (locus) on a chromosome. Each gene contains information that constitutes the "manufacturing plan" for a protein.*

*The usual medicines do not always help to improve the manifestations of dermatomyositis and polymyositis. Their efficacy can also prove to be insufficient. In such situations, doctors call this a "**refractory**" form of the disease.*

Back in 2018, Prof. Benveniste's team (Hôpital Pitié-Salpêtrière, Paris), supported by AFM-Téléthon, provided a proof of concept of the efficacy of the first JAKi, **ruxolitinib**, in adult refractory dermatomyositis. Since then, results have been accumulating, reporting the efficacy of different medicines in this same therapeutic class.

▪ In the past year, reviews of preclinical and clinical research have underlined the benefit of blocking interferon alpha (a variety of type I IFNs), for example with JAKis, to treat autoimmune diseases such as dermatomyositis, especially its juvenile form.
De Ceuninck F et al. Drug Discov Today. 2021 Oct. *Ll Wilkinson MG et al. Pediatr Rheumatol Online J. 2021 Sep.*

▪ Results published in March 2022 by Bénédicte Chazaud's team, supported by AFM-Téléthon as part of the Lyon-based MyoNeurALP strategic centre, show that type I interferon significantly reduces (-31% to -43%) the proliferation of muscle stem cells in vitro, thwarting the repair of lesions manifesting during the course of dermatomyositis. This could explain the persistent muscle weakness observed in the severe forms of the disease.
Blocking IFN pathways, with ruxolitinib in particular, restores a normal level of muscle stem cell multiplication in vitro.
Gallay L et al. Neurology. 2022 Mar. *Pinal-Fernandez I et al. Neurology. 2022 Mar.*

Baricitinib

Baricitinib (Olumiant®), which is produced by Lilly, is presently indicated in the treatment of progressive forms of another autoimmune disease - rheumatoid arthritis.

Did you know?

Advances in COVID-19 too!
Baricitinib has been assessed in patients with COVID-19 and has shown a certain degree of efficacy.
▪ In order to explain this, doctors have put forward the hypothesis that Janus kinase inhibition could repress immune system overreaction, which can occur with COVID-19.
▪ At the beginning of 2022, the World Health Organization added baricitinib to the list of five medicines that it recommends for certain cases of COVID-19.
Source: Update to living WHO guideline on drugs for covid-19. BMJ. 2022 Jan.

▪ Conducted by Dr Yves Allenbach (Hôpital Pitié-Salpêtrière, Paris), a randomised, double-blind, placebo-controlled clinical trial called BIRD will assess the efficacy of baricitinib among patients with active dermatomyositis, those who are in relapse or treatment naïve with respect to any specific treatment.

*A **placebo** is a product whose appearance is identical to a particular medicine but does not contain any active substance. In a clinical trial, a placebo is used to measure the true action of a medicine by comparing the effects of the medicine (which contains the active substance) to those of the placebo.*

Phase III BIRD trial

In France

62 participants (18 to 74 years)

Trial in preparation

5.5 months of follow-up

May 2022 – December 2025

NCT04972760

Phase III
Efficacy

▪ The University of Manchester (United Kingdom) is conducting a trial on baricitinib in refractory dermatomyositis and polymyositis.

Phase II
Dose/Effect

Phase II MYOJAK trial

In the United Kingdom

25 participants (18+ years)

Recruitment underway

8 months of follow-up

October 2021 – October 2023

NCT04208464

Tofacitinib

Developed by Pfizer, **tofacitinib** (Xeljanz®) underwent an open-label clinical trial between 2017 and 2020 (NCT03002649) among 10 patients with refractory dermatomyositis, who were treated for three months. All the participants experienced a significant improvement in disease activity, muscle strength and skin lesions.
Paik JJ et al. Arthritis Rheumatol. 2021 May.

- Two centres of expertise in Boston (United States) conducted a retrospective study on data from 11 patients aged 19 to 74 with refractory dermatomyositis treated with tofacitinib alone or in combination with another medicine after failure of at least four other treatments. All the patients experienced a significant improvement in their muscles, skin, and rashes. Tofacitinib was well tolerated, and in 10 cases allowed the other systemically administered treatments to be stopped or reduced.
Min MS et al. J Am Acad Dermatol. 2022 Feb.

- A university hospital in the city of Xi'an (China) is undertaking an open-label trial of the efficacy, safety and tolerance of tofacitinib in combination with corticosteroids for adult anti-MDA5 antibody-positive dermatomyositis.

Phase IV
Pharmacovigilance

Phase IV trial of tofacitinib

In China

20 participants (18 to 70 years)

Recruitment underway

1 year of follow-up

April 2020 – December 2021

NCT04966884

Anti-MDA5 antibodies and interferon alpha

Rheumatologists in Shanghai (China) have studied blood samples from almost 300 patients with dermatomyositis, versus those from patients with other autoimmune and non-autoimmune diseases.
- The presence of anti-MDA5 autoantibodies, found in 76.1% of the participants with dermatomyositis, has proven to correlate with high levels of IFN alpha in the blood.
- The immune complexes formed by the antibody and its antigen (MDA5) appear to be powerful inducers of IFN alpha production.
Source: Wang K et al. Front Immunol. 2021 Oct.

Ravulizumab here and elsewhere

Ravulizumab (Ultomiris®), which was developed by Alexion, is already being marketed in Europe to treat other rare diseases.

Like eculizumab and zilucoplan, it is a monoclonal antibody designed to bind specifically to the C5 complement fraction, with the goal of preventing the formation of the membrane attack complex.

Did you know?

Complement is present in the blood and is composed of several proteins involved in the immune response.

- Its fractions 5 to 9 form a **so-called "membrane attack" complex** that binds to the surface of the target microorganisms. Studies have shown its involvement in different autoimmune diseases.

Alexion Pharmaceuticals is the sponsor of an international, randomised, double-blind, placebo-controlled trial that has been recruiting patients in France since the beginning of 2019, in order to assess the safety and efficacy of ravulizumab in patients who have refractory dermatomyositis or who are intolerant to two or more treatments (corticosteroids, immunosuppressants/immunomodulators).

- France has four investigating centres located in Lille, Paris, Strasbourg, and Toulouse.

*In a **double-blind trial**, neither the patients nor the doctors know which of the alternative treatments (candidate medicine or placebo) the patient is taking. This guarantees the objectivity of the assessment of a new treatment.*

➤➤ Essais cliniques et maladies neuromusculaires [Clinical trials and neuromuscular diseases], Savoir & Comprendre references documents, AFM-Téléthon.

Phase II/III trial of ravulizumab

In France and abroad

180 participants (18+ years)

Recruitment underway

11.5 months of follow-up

December 2021 – August 2024

NCT04999020

Phase II
Dose/Effect

Phase III
Efficacy

Zetomipzomib, formerly KZR-616

Developed by Kezar Life Sciences, **zetomipzomib** is a selective immunoproteasome ("ipzom") inhibitor ("ib"). It is currently undergoing clinical trials for different autoimmune diseases. It has had the status of orphan drug for dermatomyositis and polymyositis in the United States since the end of 2020.

Did you know?

In a nutshell

- **Proteasomes** are collections of enzymes (proteases) that are capable of fragmenting poorly-folded or denatured proteins.
- The **immunoproteasome** is a specific immune-cell proteasome that plays an important role in regulating immune cell function. Several studies have demonstrated the overexpression of the immunoproteasome by the inflammatory cells that have infiltrated the skin and muscles.

- Preclinical studies appear to show that the selective inhibition of the immunoproteasome has an anti-inflammatory effect in animal models of several autoimmune diseases, without immunosuppression.

▪ The pharmaceutical company Kezar is sponsoring a placebo-controlled clinical trial called PRESIDIO, and its open-label extension study, on active dermatomyositis and polymyositis in the United States and Europe, but not in France. It was announced that recruitment had been completed in August 2021.

▪ Preliminary results were announced at the beginning of May 2022 via a press release. According to this, the majority of participants saw an improvement, but with no significant difference compared to the placebo.
Kezar Press release 2022 March. Kezar Life Sciences. Presse release 2021 Aug. Kezar Press release 2022 May

Phase II
Dose/Effect

Phase II PRESIDIO trial

Abroad (outside France)

24 participants (18+ years)

Recruitment completed

3.7 months of follow-up

January 2020 – July 2022

NCT04033926

Open-label extension study of PRESIDIO trial

Abroad (outside France)

24 participants (18+ years)

Recruitment upon invitation

1.5 years of follow-up

November 2020 – April 2023

NCT04628936

Mixed results for lenabasum

Lenabasum was developed by Corbus Pharmaceuticals and received the status of orphan medicine from the European health authorities for several diseases, including dermatomyositis.

A highly targeted mechanism of action
Lenabasum, also known as JBT-101 or anabasum, binds to the cannabinoid type 2 (CB2) receptors expressed on immune cells.
In doing so, it activates these receptors, thus appearing to have an immunomodulating effect, stopping the inflammatory processes without causing immunosuppression. It does not have a psychoactive effect since it does not activate CB1.
Source: Burstein S. Mol Pharmacol. 2021 Feb.

▪ US researchers have shown that CB2 receptors are overexpressed in the skin of patients with dermatomyositis and tend to be found on dendritic cells, B cells, T cells and macrophages, and cells that produce inflammation mediators such as interleukin 31 and IFN gamma and beta.

After 12 weeks of treatment, lenabasum causes a repression of the CD4+ T cells, CB2 receptors and IFN-β and -γ in the skin, which is probably the root cause of its anti-inflammatory effect.
Maddukuri S et al. Arthritis Res Ther. 2022 Jan.

▪ This year, dermatologists have reported the results of a placebo-controlled trial of lenabasum conducted in the United States between 2015 and 2017 among 22 adults with refractory dermatomyositis. These results show a difference in terms of improvement in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) in favour of lenabasum, becoming significant at day 113 of treatment.
Werth VP et al. J Invest Dermatol. 2022 Apr.

*A **placebo** is a product whose appearance is identical to a particular medicine but does not contain any active substance. In a clinical trial, a placebo is used to measure the true action of a medicine by comparing the effects of the medicine (which contains the active substance) to those of the placebo.*

▪ Corbus Pharmaceuticals is conducting the DETERMINE trial, an international, randomised, double-blind, placebo-controlled trial to assess two doses of lenabasum in dermatomyositis that is active despite the use of another treatment.
According to the preliminary results released in June 2021, the candidate medicine appears not to have achieved its main evaluation criterion (increased Total Improvement Score (TIS)) after 6.5 months of treatment. Significant improvements in disease activity and skin severity, however, appear to have been observed in cases of dermatomyositis with no muscle involvement.
Corbus Pharmaceuticals. Press release 2021 June.

Phase III DETERMINE trial

Abroad (outside France)

176 participants (18+ years)

Data currently being analysed

1 year of follow-up

December 2018 – September 2022

NCT03813160

Phase III
Efficacy

Ustekinumab targets two interleukins

Developed by Janssen, **ustekinumab** (Stelara®) is mainly prescribed in chronic inflammatory bowel diseases and psoriasis. It is a monoclonal antibody (the suffix "ab" stands for "antibody") that binds to interleukins 12 and 23.

Key mediators
Interleukins 12 and 23 are inflammation messengers that contribute to the activation of natural killer (NK) cells and certain T cells (CD4+). An impairment in the regulation of these two interleukins appears to be associated with various autoimmune disorders.

***NK (natural killer) cells** are lymphocytes that are capable of eliminating tumour cells and infected cells.*

▪ A placebo-controlled clinical trial sponsored by Janssen involving around 30 investigating centres is being conducted in Japan to assess ustekinumab in refractory dermatomyositis and polymyositis.

Phase III
Efficacy

Phase III trial of ustekinumab

In Japan

51 participants (18 to 75 years)

Recruitment completed

5.5 months of follow-up

July 2019 – April 2023

NCT03981744

Apremilast and the skin

Apremilast (Otezla®), which is used in the treatment of psoriasis, is an inhibitor of phosphodiesterase-4 (PDE4), which modulates different mediators involved in inflammation.

Phase I
Safety/tolerability

The results of a Japanese phase I trial on refractory dermatomyositis that is active with respect to skin manifestations, but not with respect to respiratory and muscular manifestations, were published at the beginning of 2022. Only three of the five participants received 12 weeks of treatment, with a 39.4% reduction on the CDASI compared to the beginning of the trial. Gastrointestinal adverse effects (diarrhoea) occurred in three of the five cases.

Konishi R et al. J Dermatol. 2022 Jan.

▪ Tulane University (United States) is conducting an open-label trial of apremilast on refractory dermatomyositis skin lesions.

Phase II
Dose/Effect

Phase II trial of apremilast

In the United States

10 participants (18 to 75 years)

Data currently being analysed

6 months of follow-up

June 2018 – April 2021

NCT03529955

Results and a trial for immunoglobulins

Did you know?

Human polyvalent **immunoglobulins (Igs)** are one of the treatments for inflammatory myopathies.

▪ They are usually administered in hospital by intravenous (IV) infusion.

▪ Immunoglobulins can also be injected by infusion into the tissue located beneath the skin (hypodermis). This subcutaneous (SC) administration can be performed at home by the patients themselves after receiving training.

Update on the ProDERM trial

Phase III
Efficacy

Octapharma has assessed its IVIgs, **Octagam®**, administered once every four weeks over a 16-week period to 95 adults with dermatomyositis as part of the phase III, randomised, placebo-controlled trial, ProDERM (NCT02728752), followed by an open-label extension lasting 5.5 months. France was one of the investigating countries.

▪ The results of this trial, which were shared at the EULAR 2021 European Congress, show that a significantly larger proportion of subjects responded to the IVIg treatment (78.7%) compared to the placebo (43.8%).
Aggarwal R et al. Ann. Rheum. Dis. 2021.

Subcutaneous administration studied in countries including France

A placebo-controlled trial being sponsored by CSL Behring is assessing **IgPro20** administered subcutaneously (Hizentra®) in dermatomyositis. France is participating, with five investigating centres.

Phase III RECLAIIM trial

In France and abroad

126 participants (18+ years)

Recruitment underway

6 months of follow-up

October 2019 – February 2024

NCT04044690

▪ An Italian centre of expertise has conducted a retrospective study on IgPro20 among 14 patients with dermatomyositis and 16 patients with polymyositis who had learnt to perform infusions of this product into the skin of their abdomens.
The results of this analysis support the beneficial effects of these SCIgs and their good long-term safety/tolerability (3.5 years of treatment on average) with a significant improvement in muscle strength, skin lesions and disease activity.
▪ None of the participants experienced any general reactions to the SCIg injection. Local reactions (redness, swelling, etc.) lasted only a few hours in 80% of cases and all of them resolved spontaneously. Nine out of 10 participants had a good or very good opinion of this treatment.
Danieli MG et al. Front Immunol. 2022 Jan.

Exercise in all its forms

Exploring abilities

A trial sponsored by CHU de Strasbourg [Strasbourg University Hospital] aims to better understand why the ability to exercise is often reduced (feeling of lack of strength, poor endurance on exertion, etc.) in dermatomyositis, with the hypothesis being that there is a dysfunction in the mitochondria, the "powerhouse" of the cell.

Did you know?

Prior support from AFM-Téléthon

As part of a call for projects in 2019, AFM-Téléthon financed a previous project by the CHU de Strasbourg team that is conducting this study. The objective of this project was to better understand the role of mitochondrial dysfunction in the muscle inflammation of patients with dermatomyositis.

Ability to exercise in dermatomyositis

In France

45 participants (18+ years)

Recruitment underway

1 day of follow-up (biopsy)

November 2019 – January 2025

NCT03293615

Comparisons conducted in Brazil

The Federal University of Espirito Santo is comparing the effects of two training programmes involving three sessions per week for a period of 12 weeks in inactive or mildly active but stable dermatomyositis and polymyositis. One programme involves resistance exercises and the other involves repetitive tasks without resistance.

Trial of a training programme based on repetitive tasks

In Brazil

30 participants (18+ years)

Trial in preparation

2 years of follow-up

September 2021 – September 2023

NCT05027152

In Canada with supplements

A team at the Toronto Hospital for Sick Children is testing the benefit of combining two nutritional supplements, **creatine** and **coenzyme Q10**, with a physical exercise programme in juvenile dermatomyositis. These nutritional supplements could help the muscles to use energy and recover after exercise.

Trial of exercise combined with the use of creatine and coenzyme Q10 supplements

In Canada

15 participants (7 to 18 years)

Recruitment underway

6 months of follow-up

April 2021 – March 2023

NCT04286178

Advances in immune-mediated necrotising myopathy

Cell therapy to undergo phase I testing

A Chinese company, IASO Biotherapeutics, is developing a CAR-T cell-based treatment, **CT103A**, in different autoimmune diseases and blood cancers affecting B cells.

Did you know?

CAR-T cells - a brief overview

- A CAR-T cell starts off as a T cell, capable of recognising and destroying specific cells: cancerous cells, cells infected by a microorganism, etc.
- This T cell, which is usually collected from the patient with the disease to be treated, is genetically modified in the laboratory to make it capable of recognising an antigen that is present on the surface of the cell to be eliminated. Once modified in this way, it becomes a CAR-T cell (CAR stands for chimeric antigen receptor) and is then injected into the patient.

The cell therapy developed by the biotech company IASO uses CAR-T cells directed against the B-cell maturation antigen (or BCMA). It is expressed on the surface of mature B cells and their derivatives (plasma cells) which produce autoantibodies.

- The Tongji Hospital in Shanghai (China) is conducting an open-label clinical trial called CARTinNS, to assess the safety and efficacy of CT103A in different autoimmune diseases, including immune-mediated necrotising myopathy that is refractory or in relapse.

Phase I CARTinNS trial

Phase I
Safety/tolerability

In China

18 participants (18 to 75 years)

Recruitment underway

2 years of follow-up

September 2020 – December 2023

NCT04561557

Very early stage use of immunoglobulins

Polyvalent human immunoglobulins (Ig) are one type of treatment for inflammatory myopathies. One such treatment, **Gamunex®** produced by Grifols, is undergoing a placebo-controlled trial conducted by the University of Washington to assess initial IVIg treatment on its own among patients with immune-mediated necrotising myopathy.

Phase II MIGHT trial

Phase II
Dose/Effect

In the United States

10 participants (18+ years)

Recruitment underway

8 weeks of follow-up

February 2022 – July 2022

NCT04450654

Advances in myositis with lung involvement

Learning more about the disease

Assessing the risk of associated cancer

Antisynthetase syndrome
Antisynthetase syndrome is a form of myositis that combines involvement of the muscles, lungs (interstitial lung disease), skin and joints with the presence of antisynthetase autoantibodies (anti-Jo1, anti-PL7, anti-PL12, etc.) in the blood.

The CHU de Nancy [Nancy University Hospital] is conducting a retrospective study intended essentially to measure the incidence of cancers associated with antisynthetase syndrome, which might have been underestimated in the past. The Dijon, Reims, Strasbourg and Besançon university hospitals and the Metz private hospitals are participating in this study.

Retrospective study of association with cancer

In France

200 participants (18+ years)

Recruitment underway

Retrospective data

April 2021 – July 2022

NCT04941547

Researching environmental risk factors

Factors related to the environment, in the broad sense of the word (microorganisms, smoking, toxins, ultraviolet rays, etc.), could contribute to an increased risk of developing antisynthetase syndrome. This is what a large-scale observational study, conducted in the United States by The National Institute of Environmental Health Sciences, is committed to confirming.

Environmental study in antisynthetase syndrome

In the United States

450 participants (2+ years)

Recruitment underway

1 day of follow-up

February 2011

NCT01276470

Identifying advanced warning signs

In China, the Jiangsu Provincial People's Hospital is conducting an observational study on a large cohort of adults with dermatomyositis being monitored by 18 centres of expertise, in order to identify possible predictive factors for the onset of lung impairment (interstitial lung disease) in the next year.

CRAWFORD observational study

In China

1000 participants (18+ years)

Recruitment underway

1 year of follow-up

June 2020 – December 2022

NCT04747652

Improving treatment

Comparing European and US guidelines

The treatment of antisynthetase syndrome can involve different immunosuppressant medicines: cyclophosphamide (Endoxan®) then azathioprine (Imurel®) in Europe, tacrolimus (Prograf®) in the United States.

▪ Neither of these two treatment strategies has undergone a prospective study, and there are no comparisons of their efficacy or their safety and tolerance. This is the aim of the clinical trial called CATR-PAT being conducted by Prof. Olivier Benveniste's team (Assistance Publique–Hôpitaux de Paris).

Phase III CATR-PAT trial

Phase III
Efficacy

In France

76 participants (18+ years)

Recruitment underway

1 year of follow-up

February 2021 – January 2024

NCT03770663

Pirfenidone - an antifibrotic lung treatment

Pirfenidone (Esbriet®) is an immunosuppressant with antifibrotic and anti-inflammatory properties that is already being used in idiopathic pulmonary fibrosis - a rare disease.

In June 2022, a Lebanese team published positive results (decrease in lung inflammation and fibrosis) for pirfenidone in a murine model of antisynthetase syndrome.

Layoun H et al. Cytokine. 2022 Jun.

▪ A university hospital in the Shandong province is conducting an open-label trial to assess pirfenidone combined with an immunosuppressant, compared to an immunosuppressant alone. The participants have interstitial lung disease associated with different diseases, including myositis.

Phase IV
Pharmacovigilance

Phase IV trial of pirfenidone

In China

200 participants (18 to 80 years)

Recruitment underway

3 years of follow-up

August 2019 – June 2025

NCT04928586

Mycophenolate mofetil

Mycophenolate mofetil (CellCept®) is an immunosuppressant that has been on the market for a long time and is indicated in the prevention of organ rejection after transplantation.

▪ ERN-ReCONNET, a European network dedicated to rare muscular and connective tissue diseases, has conducted a survey involving centres of expertise in seven countries, including France, regarding the use of mycophenolate mofetil in an indication that does not feature on its marketing authorisation.

The expert doctors that responded reported that they often opted for this treatment, confident in its efficacy and safety. An analysis of data from 108 of their patients treated with mycophenolate mofetil confirmed its safety and tolerance and good clinical results, in particular for myositis conditions. *Bandeira M et al. Clin Exp Rheumatol. 2022 Mar.*

▪ A university hospital in the Shaanxi province (China) is assessing the effects of mycophenolate mofetil in interstitial lung disease associated with dermatomyositis or polymyositis and its impact on regulatory T cells (Tregs) in an open-label study.

Phase IV
Pharmacovigilance

Phase IV trial of mycophenolate mofetil

In China

20 participants (18 to 70 years)

Recruitment underway

1 year of follow-up

December 2020 – November 2023

NCT05129410

Advances in several types of myositis

Two exoskeletons being studied in France

An **exoskeleton** is a movement-assistive robotic device designed to compensate for muscle weakness, and thus increase autonomy. It can be used during physical rehabilitation sessions or on a daily basis to assist with movement.

▪ The Institute of Myology, founded by AFM-Téléthon, is conducting studies to assess the tolerability, safety and effects of two light exoskeleton models for the lower limbs (hips and knees) - **Keeogo™** and **MyoSuit™**. The objective is also to draft guidelines for the safe and effective use of these two devices in patients with neuromuscular disease.

▪ The participants recruited are already being followed up at the Institute of Myology and have different neuromuscular diseases, including myositis.

Exo-KGO1 trial of Keeogo™

In France

52 participants (18 to 70 years)

Recruitment underway

1 month of follow-up

December 2021 – April 2023

NCT05199246

Exo-NMD1 trial of MyoSuit™

In France

52 participants (18 to 70 years)

Recruitment underway

1 month of follow-up

January 2022 – April 2023

NCT05200702

Did you know?

To be continued

The Exo-KGO1 and Exo-NMD1 trials are the first stage of future trials that will assess the benefits of the long-term use of Keeogo™ and MyoSuit™ in the home.

Abatacept assessed in France

Abatacept (Orencia®), an immunosuppressant, targets T cells, modulating a signal needed for their activation.

▪ Bristol-Myers Squibb is conducting an international, placebo-controlled clinical trial of abatacept in adults with a refractory form of dermatomyositis, polymyositis, immune-mediated necrotising myopathy or overlap myositis.

Phase III trial of abatacept

In France and abroad

149 participants (18+ years)

Recruitment completed

5.5 months of follow-up

March 2017 – July 2022

NCT02971683

Phase III
Efficacy

*A **placebo** is a product whose appearance is identical to a particular medicine but does not contain any active substance. In a clinical trial, a placebo is used to measure the true action of a medicine by comparing the effects of the medicine (which contains the active substance) to those of the placebo.*

Subcutaneous immunoglobulins

A Canadian team has studied all the publications relating to the use of immunoglobulins (Igs) administered subcutaneously (SCIgs) in inflammatory myopathies, choosing three series of cases incorporating a total of 61 adults with different types of myositis.

▪ Their analysis shows that SCIgs are effective in these indications (improvement in strength, muscle enzymes and functional scores), both in patients previously treated with intravenous Ig and those who started with SCIgs.

Zhou AL et al. Rheumatol Adv Pract. 2021 Sep.

Physical exercise, again and again

It's better with a pro

A Czech team evaluated the effects of a five-and-a-half month training programme comprised of two one-hour supervised sessions per week and 30 minutes per day at home for the remaining five days, targeted at activities of daily living, muscle strengthening and balance. This programme was compared to daily, unsupervised exercises.

▪ The study included 50 participants with dermatomyositis, polymyositis or immune-mediated necrotising myopathy. Those who took part in the supervised programme saw a significant improvement in muscle strength (+26% on average), endurance (+135%), disability (39%) and depression (26%), the latter being attributed to functional improvement and the support of a physiotherapist.

Špiritović M et al. Arthritis Res Ther. 2021 Jun.

Benefits better understood

An American/Brazilian team analysed the muscle biopsies of 13 patients with dermatomyositis or immune-mediated necrotising myopathy who had followed a training programme comprised of two sessions per week for almost three months.

▪ At the end, their muscle cells showed an increase in the expression of genes involved in autophagy (the process by which a cell causes a part of its contents to degrade) and genes related to the production of lysosomes and mitochondria (the cell's powerhouses). As such, exercise appears to increase the recycling of damaged proteins and mitochondria, as well as the quantity of mitochondria, contributing to a higher production of energy and at the same time helping the repair, performance and endurance of muscles.

▪ The physical exercise programme also resulted in the overexpression of genes linked to the antioxidant capacity of muscle cells, which appears to help them combat free radicals in situations of oxidative stress.

▪ Finally, the training reduced the expression of muscle genes linked to the ubiquitin–proteasome system (UPS), an effect that is likely to lessen the loss of volume (atrophy) of the muscles affected by myositis.

Borges IBP et al. J Clin Rheumatol. 2021 Sep.

__Lysosomes__ are small sacks (vesicles) that are found in cells, whose role is to digest material from cell function into small molecules. These are either evacuated and eliminated as waste, or recycled and reused by the cell. Lysosomes degrade and recycle materials from outside the cell (heterophagy) as well as those from inside the cell (autophagy), using a large number of different enzymes capable of digesting large molecules.

An electronic wristband to assess amount of exercise completed

Activity-tracker watches are wristbands connected wirelessly to a smartphone/tablet app that can measure daily physical activity such as number of steps, distance travelled, heart rate, calories expended, etc.

A UK study compared the information provided by two electronic wristband models from the brand Fitbit™, which use specific medical devices such as accelerometers.

▪ This study, which was conducted among 110 patients with neuromuscular diseases, including myositis, concluded that the electronic watches are practical and useful in assessing daily physical activity. Participants said that they were more attentive to their levels of exercise when wearing them. However, these electronic watches are still less precise than medical devices, especially for measuring heart rate and number of steps.

Roberts-Lewis SF et al. Disabil Rehabil . 2021 Oct.

A high-intensity clinical trial

The *Rigshospitalet* Hospital (Copenhagen) is assessing the effects of a programme involving two sessions of high-intensity strength training per week in immune-mediated necrotising myopathy, dermatomyositis and polymyositis.

HI-STIM trial

In Denmark

34 participants (18+ years)

Recruitment completed

3.5 months of follow-up

August 2021 – January 2024

NCT04486261

Observational studies

Optimising the diagnostic process

Doctors in the Netherlands have announced the launch of a study (*ADAPT* study) based on the hypothesis that a diagnosis made using the results of a small number of preferably the least invasive examinations could prove to be as precise as one made using a complete panel of examinations (muscle biopsy, blood tests, electromyogram, MRI, etc.). This study will include 100 participants presenting signs suggestive of myositis.

Source: Walter HAW et al. BMJ Open. 2021 Dec.

In the United States, the National Institute of Environmental Health Sciences is conducting a large-scale study, the objective of which is to further our knowledge of the causes of different myositis, the immune disruptions involved and the other associated health problems.

Juvenile and adult myositis study

United States

1200 participants (2+ years)

Recruitment underway

1 to 5 days of follow-up

June 1995

NCT00017914

▪ The University of Manchester is the sponsor of a prospective clinical, laboratory, histological and imaging follow-up study of patients with recent idiopathic inflammatory myopathy (disease duration less than two years).

MYOPROSP study

United Kingdom

300 participants (18+ years)

Recruitment completed

5 years of follow-up

October 2016 – December 2030

NCT02468895

▪ Another study by the American National Institute of Environmental Health Sciences is committed to identifying the factors that facilitate the development of myositis.

Study of environmental risk factors

In the United States

36 participants (18+ years)

Recruitment completed

March 2014 – June 2022

NCT01734369

Valuable databases

*The so-called **natural history of a disease**, as doctors refer to it, is the description of different manifestations of a disease and their progression over time without treatment.*

Developing a database helps to identify patients with the same disease, determine the natural history of this disease, and facilitate recruitment for clinical trials.

▪ The **Groupe Hospitalier Pitié-Salpêtrière** [Pitié-Salpêtrière Hospital Group] (Paris) is the sponsor of a French database collecting data and biological samples (blood and/or muscle) from patients with myositis. The French name of the study, MASC, stands for Myosites, Muscles, ADN/ARN, Sérum, Cellules [Myositis, Muscles, DNA/RNA, Serum and Cells]. The collated data are enriching scientific research work.

MASC myositis database

In France

Created in October 2013

Recruitment underway

1600 patients

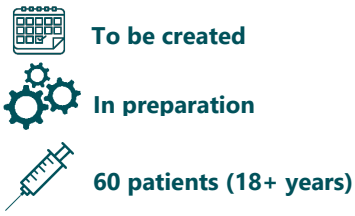
NCT04637672

▪ The **CHU de Brest** [Brest University Hospital] is preparing to create the "MAIA" database, a French acronym standing for Myopathies Auto-Immunes de l'Adulte [Adult Autoimmune Myopathies]. It will collate clinical

and laboratory (blood, urine, muscle, etc.) data from 60 patients suspected by doctors of having myositis.

MAIA adult myositis database

In France



To be created

In preparation

60 patients (18+ years)

NCT04792931

▪ The international **EuroMyositis** database encompasses different registries and databases, essentially from Europe but also from Asia and America.

EuroMyositis database

In France and abroad

Created in 2010

Recruitment underway

>3000 patients

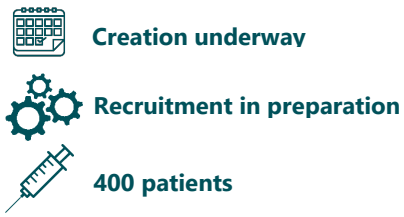
EuroMyositis (in English)

▪ In Spain, around 30 centres of expertise will participate in the **Myo-Spain** database, sponsored by the Spanish Society of Rheumatology. It will include patients with myositis, and its primary objective will be to analyse disease progression and clinical management at one year then at two years after inclusion.

Cobo-Ibáñez T et al. Reumatol Clin (Engl Ed). 2021 Apr.

Myo-Spain database

In Spain



Creation underway

Recruitment in preparation

400 patients

Myo-Spain (in Spanish)/

Advances in the understanding of myositis

The part played by genetics

The question of a genetic predisposition favouring the occurrence of myositis is the subject of ongoing research work.

*A **gene** is a "segment" of DNA located in a very specific position (locus) on a chromosome. Each gene contains information that constitutes the "manufacturing plan" for a protein.*

▪ At the beginning of 2022, results were published on the targeted sequencing of 1900 genes related to the immune system in a Scandinavian cohort of 454 patients with myositis, compared to 1024 subjects who did not have myositis. These analyses:
- identified two genes, *IFI35* and *PTGES3L*, certain variants of which appear to favour the occurrence of myositis,
- confirmed the existence of a genetic signature that provides evidence of the activation of the type I interferon pathway;
- identified genetic disruptions in the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway in a subgroup of different types of myositis;
- identified a specific genetic profile in cases of antisynthetase syndrome.
Bianchi M et al. Arthritis Rheumatol. 2022 Feb.

An original model to study inclusion body myositis

A North American team has transplanted muscle cells with inclusion body myositis into immunodeficient mice. This graft resulted in the formation of functional human muscle tissue, with blood vessels and nerves, hosted by the mouse, and presenting the two characteristics of inclusion body myositis: inflammation and degeneration. This new mouse model could prove very useful in better understanding the origin of inclusion body myositis, and therefore in developing new treatments.
Britson K. Doctoral dissertation to Johns Hopkins University. 2020

▪ The presence of TDP-43 protein deposits is one of the signs of degeneration visible on muscle biopsies in inclusion body myositis. TDP-43 aggregates are also visible in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS).
This protein from the cell nucleus appears to regulate the expression of genes by the sequestration of certain RNA molecules. Once it is trapped in the cytoplasm, aberrant maturation (splicing) of the RNA occurs.
The new mouse model for inclusion body myositis helped to show that reducing inflammation, by reducing the population of T cells, does not change muscle degeneration - TDP-43 deposits persist.
Britson KA, et al. Sci Transl Med. 2022 Jan.

Each type of myositis has its own type of lymphocyte

Precisely identifying the immune cells involved in a specific myositis condition can improve disease diagnosis and help identify new treatments targeted at these cells.
Knowledge in this area has progressed significantly in the last few years. This is demonstrated by a review of the literature published by Italian rheumatologists at the end of 2021, highlighting in particular the discovery of:
- an imbalance between the different lymphocyte subtypes in the muscles and the blood, with a predominance of CD4+ T cells and B cells in

dermatomyositis, and of CD8+ T cells in polymyositis and inclusion body myositis;
- new pro-inflammatory T cell subgroups (CD8+ T-bet+ and CD28-) in different types of myositis;
- abnormalities in the number and function of regulatory T cells (Tregs), particularly in dermatomyositis, polymyositis and inclusion body myositis;
- an increase in the amount of a type of T helper cell (T follicular helper cells or Tfh) in immune-mediated necrotising myopathy;
- the negative significance of a high neutrophil/lymphocyte ratio in dermatomyositis and polymyositis.
Franco C et al. Curr Opin Rheumatol. 2021 Nov.

T cells are white blood cells that specialise in certain immune reactions. There are several different types of T cells, each one with a specific function. Unlike B cells, T cells do not secrete antibodies.

Regulatory T cells (or Tregs) play a crucial role in "self-tolerance" by modulating the activity of other immune cells.

A parallel between lesions and antibodies in dermatomyositis

While re-examining the muscle biopsies of 256 patients with dermatomyositis, Japanese myologists showed that to each dermatomyositis-specific autoantibody (TIF1-γ, Mi-2, MDA5, NXP2, SAE), there corresponds a type of lesion that is observed in the muscle cells. This correlation suggests the existence of different underlying pathological mechanisms, specific to each dermatomyositis subtype, and associated with a specific autoantibody.
Tanboon J et al. Neurology. 2022 Feb.

The risk to muscles posed by statins

Statins, a class of medicines used to decrease cholesterol levels, sometimes cause muscle pain (myalgia), immune-mediated necrotising myopathy or even rhabdomyolysis. This type of adverse effect appears to occur in 1.5% to 5% of cases of treatment with statins during clinical trials, and 10% to 15% of cases in a real-life setting.

▪ This muscle toxicity does not vary according to the type of statin (hydrophilic or lipophilic), as was demonstrated by a study conducted using a British national registry, the Clinical Practice Research Datalink GOLD database, a rich source of anonymised data from more than 15 million subjects. In the year following the start of treatment with different types of statin, 98% of muscle effects reported were myalgia.
Mueller AM et al. J Gen Intern Med. 2021 Sep.

Rhabdomyolysis involves the somewhat severe destruction of muscle tissue, caused for example by trauma, infection or a medicine. It causes a massive release of muscle components (proteins, ions, etc.) into the blood stream, some of which are particularly harmful to the kidneys.

Progress in the diagnosis and follow-up of myositis

Best Practice guidelines

France - inclusion body myositis

Did you know?

An obvious need for guidelines

Outside of a hospital setting, a general practitioner will see an average of 1549 patients in consultation in one year, a neurologist slightly fewer, and a physiotherapist just over 200 patients. The probability that they have ever cared for a patient with inclusion body myositis is very low. It is therefore almost impossible for them to know the ideal way of caring for these patients inside out.
Source: French medical insurance – January 2022

The objective of the PNDS (Protocoles Nationaux de Diagnostic et de Soins [French National Diagnosis and Care Protocols]), which are veritable Best Practice guidelines, is to "provide explicit instructions to professionals regarding the optimal diagnostic and therapeutic management and treatment pathway for patients with a specific rare disease", explains the HAS (Haute Autorité de Santé [French National Authority for Health]), which provides these protocols for free on its website.

▪ Experts from the FILNEMUS network published a new PNDS dedicated to sporadic inclusion body myositis at the end of 2021. It is accompanied by a Summary for general practitioners that patients can bring to the attention of their local healthcare professionals.
HAS – November 2021

United Kingdom - treatments

The British Society for Rheumatology has published guidelines for the treatment of children, adolescents and adults with inflammatory myopathies, with the exception of inclusion body myositis.

▪ They specify the medicines that are useful in combating muscle and skin manifestations. They also insist on the need to be attentive to the risk of fractures, cancer and cardiovascular disease, as well as mental well-being and quality of life.
Oldroyd AGS et al. Rheumatology (Oxford). 2022 Mar.

Japan - lung involvement

As with other inflammatory diseases, antisynthetase syndrome and certain types of dermatomyositis are accompanied by interstitial lung disease, which can sometimes progress quickly.

▪ Its early diagnosis and treatment are essential. Japanese doctors have published a dedicated guide based on recent data from literature and their personal experiences. It fine-tunes the diagnostic criteria (especially clinical and radiological) for this type of lung disease, and offers recommendations for medicinal (corticosteroids, immunosuppressants, biotherapies, etc.) and non-medicinal (plasmapheresis, assisted ventilation, etc.) therapeutic management.
Kondoh Y et al. Respir Investig. 2021 Nov.

Considering myositis regardless of the patient's age

Immune-mediated necrotising myopathy is also possible in children

Immune-mediated necrotising myopathy, which was first described in 2003, was initially only attributed to adults taking a type of medicine (statins) to

reduce their high cholesterol levels. We now know that it can develop without this type of medicine being taken, and also in children.

▪ At the end of 2021, German doctors described two new cases of this disease in childhood, with the onset of rapidly progressive weakness in the limb-girdle muscles (shoulders, pelvis) before the age of 10. At first, genetically-caused muscular dystrophy was suggested before the presence of specific autoantibodies (anti-SRP, anti-HMGCR) was discovered, confirming immune-mediated necrotising myopathy, a disease that should be considered since early diagnosis allows rapid intensive treatment to be given, thus limiting the risk of chronic muscle deficit.

Della Marina A et al. Children (Basel). 2021 Aug.

Did you know?

A subject discussed at the JSFM 2021

▪ Over a period of three days, almost 400 researchers and doctors specialising in myology were able to share the latest advances in neuromuscular disease research in Saint-Etienne at the end of November 2021 during the annual JSFM (Journées de la Société Française de Myologie [French Society of Myology Days]).

▪ This edition was marked by the significant number of presentations regarding autoimmune diseases, and in the forefront was myositis, particularly the infantile forms of immune-mediated necrotising myopathy.

Muscle loss in elderly patients can disguise myositis

A gradual decrease in muscle mass and strength (or sarcopenia) is typical with old age. However, there are cases where this phenomenon may not be related solely to advancing age. In fact, in almost 35% of patients over 65 experiencing this phenomenon, this is the manifestation of a neuromuscular disease, in particular inclusion body myositis, a condition that is probably underdiagnosed.

▪ This underlines the importance of testing for neuromuscular disease when atypical sarcopenia symptoms are observed. Asymmetry and/or localised muscle deficit should serve as a warning and should prompt the measurement of muscle enzyme levels and the performance of an electromyogram and/or muscle biopsy, if applicable.

Hofmeister F, et al. BMC Neurol. 2021 Jun.

Specific autoantibody results under discussion

Anti-Jo-1, anti-HMGCR and anti-TIF1-γ are so-called "specific" autoantibodies and are valuable in confirming a diagnosis of myositis, but also in determining the type of myositis. However, their testing results are a matter of debate.

***Autoantibodies** are antibodies that react to parts of an individual's own body, such as muscles.*

Taking into account myositis manifestations...

Japanese doctors are arguing for supplementary parameters (such as clinical examination data) to be taken into account when interpreting results relating to autoantibodies, which can be falsely positive. In coming to this conclusion, they compared three antisynthetase testing techniques among 44 patients with myositis, and found they sometimes produced different results depending on the test being used.

Shinoda K et al. Intern Med. 2022 Feb.

... and also antibody levels

A team from Marseille recommends also taking into account specific autoantibody levels if the results are positive for several autoantibodies or

if there are no clinical signs suggestive of myositis. In their single-centre trial, 1% of a group of 3142 patients were positive for at least two specific autoantibodies. A diagnosis of myositis was retained in only 15 of these patients. The others, with lower specific autoantibody levels and no suggestive clinical signs, were considered to be false positives.
Briantais A et al. Semin Arthritis Rheum. 2022 Feb.

Combining them to improve performance

A US-Spanish team has confirmed the benefit of specific autoantibodies, detected in 68% of a group of 268 patients with myositis using a new technique (PMAT or particle-based multi-analyte technology) currently reserved for research work.

▪ To reduce the risk of incorrectly interpreting results, the same team has developed composite scores (MyoScores) which equate the test results for a set of autoantibodies, for example Jo-1, PL-7, PL-12 and EJ, to a score intended to diagnose antisynthetase syndrome.
Mahler M et al. Diagnostics (Basel). 2021 Nov.

Anti-cN1A antibodies (probably) not useful in IBM

CN1A is an enzyme that is found abundantly in skeletal muscles. The autoantibodies directed against it are said to be "associated with myositis", because they can also be present in other autoimmune diseases.

▪ Some teams believe that the presence of anti-cN1A antibodies could be a possible biomarker for inclusion body myositis.

▪ The results of a meta-analysis published in the autumn of 2021 contradict this point of view. Anti-cN1A antibodies do not appear to be useful in diagnosing inclusion body myositis, nor in diagnosing dermatomyositis or polymyositis.
Source: Mavroudis I et al. J Clin Neuromuscul Dis. 2021 Sep.

*A **biological marker**, also referred to as a **biomarker**, is a measurable characteristic that indicates a normal or pathological biological process. The identification of new biological markers for a disease is very important in monitoring the progression of the disease and the efficacy of new treatments, whether these markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

Relationship between type of autoantibody and disease expression

Necrotising myopathy with and without antibodies is different

A study conducted in China on the medical files of 127 patients with immune-mediated necrotising myopathy found that muscle pain (myalgia), cardiac involvement and improvement with immunotherapy were more common in cases of seronegativity (no anti-SRP and no anti-HMGCR autoantibodies).

▪ A second Chinese study conducted on a group of 60 patients with immune-mediated necrotising myopathy with anti-SRP autoantibodies found a higher incidence of short- or medium-term lung involvement (45%), with a generally favourable outcome (mild form).
Ma X et al. Front Neurol. 2021 Jul. *Ge Y et al. BMC Pulm Med. 2022 Jan.*

Atypical signs sometimes found with anti-HMGCR autoantibodies

According to a review of recent publications, immune-mediated necrotising myopathy with anti-HMGCR autoantibodies can be accompanied by more unusual signs such as particularly slow progression with symptoms similar to those of limb-girdle muscular dystrophy, or dermatomyositis-like or lymphoma-like skin lesions.
Kurashige T. Curr Opin Rheumatol. 2021 Nov.

An unusual clinical picture with anti-cortactin autoantibodies

Cortactin is a protein present in cell cytoplasm that controls the polymerisation of actin into filaments. Anti-cortactin autoantibodies were discovered in 2014 in different types of myositis and myasthenia gravis.

- At the end of a study that encompassed more than 1300 participants, an international team concluded that anti-cortactin autoantibodies are rarer in children who have myositis (2%) than in those who don't (4%).
- In contrast, these autoantibodies are relatively common in adults with myositis, especially dermatomyositis (15%) and even more so in dermatomyositis patients with coexisting anti-Mi-2 (24%) or anti-NXP-2 (23%) autoantibodies.

The presence of anti-cortactin autoantibodies in adults is usually accompanied by skin manifestations and difficulty swallowing (dysphagia). Levels are higher in cases with lung involvement.

Pinal-Fernandez I et al. Arthritis Rheumatol. 2022 Feb.

Anti-PL7 antibodies in more severe antisynthetase syndrome

Antisynthetase syndrome
Antisynthetase syndrome is a form of myositis that combines involvement of the muscles, lungs (interstitial lung disease), skin and joints with the presence of antisynthetase autoantibodies (anti-Jo1, anti-PL7, anti-PL12, etc.) in the blood.

Chinese doctors performed a retrospective study of medical records from 113 adults with this form of myositis. Twenty-five of these patients had had rapidly progressive interstitial lung disease as the first presentation and episodes of fever or inflammation. In this subgroup, 36% of patients had anti-PL7 antibodies, versus 12% of participants that were not in this subgroup.

Sun S et al. Front Immunol. 2021 Sep.

New and protective autoantibodies in dermatomyositis

North American researchers have investigated the immunological profile of patients with dermatomyositis in order to identify risk factors for cancer other than those already known.

- They identified 10 new autoantibodies, including anti-CCAR1, that seem to be protective. Their use could help to fine-tune cancer detection and monitoring protocols in dermatomyositis.

Fiorentino DF et al. J Clin Invest. 2022 Jan. *Turnier JL et al. J Clin Invest. 2022 Jan.*

Clues for assessing activity and predicting progression

Seeing muscles functioning

Did you know?

PET scan with or without glucose
A PET scan is an ultra-precise imaging examination that combines a CT scan with positron emission tomography (PET). It can be associated with studying the function of an organ or tissue, assessed by their consumption of a sugar similar to glucose (fluorodeoxyglucose (18F) or 18F-FDG) injected during the imaging examination.

A meta-analysis of several research projects, conducted among a total of 90 patients, has confirmed the good performance of PET scans with 18F-FDG to determine whether myositis is in the active phase or not.

Kim K et al. Hell J Nucl Med. 2021 Aug.

Testing for CD26 in muscle…

CD26 is a protein expressed on the surface of T cells that contributes to their activation. Italian researchers have shown that it is selectively expressed in the skeletal muscle of patients with myositis, with the highest levels being in cases of dermatomyositis.

__T cells__ are white blood cells that specialise in certain immune reactions. There are several different types of T cells, each one with a specific function. Unlike B cells, T cells do not secrete antibodies.

▪ The expression of CD26 is associated with a decrease in muscle performance and is predictive of the number of treatments that will be needed before the disease symptoms can be stabilised or improved.
De Lorenzo R et al. Clin Exp Rheumatol. 2022 Feb.

... or SIGLEC1 on macrophages

A connection with type I interferon
SIGLEC1 is a protein located on the surface of macrophages, which are a type of white blood cell present in tissue that participate in the immune response. The expression of the gene that codes for this protein is stimulated by type I interferon.

A Dutch study conducted among 21 children who recently developed juvenile dermatomyositis suggests that the expression of SIGLEC1 on macrophages correlates to disease activity. High levels of SIGLEC1 at the time of diagnosis is associated with an elevated risk of needing to intensify treatment in the next three months.
Lerkvaleekul B et al. Rheumatology (Oxford). 2021 Aug.

Taking care of your heart and blood vessels

The last 12 months have seen the publication of numerous medical articles on the link between myositis and cardiovascular disease.

A much-studied risk

These recent publications highlight:
- the higher incidence, in comparison to the general population, of heart rhythm disorders (arrhythmias), impairment of the arteries supplying the heart (coronary arteries), phlebitis, pulmonary embolism and heart failure in the **different types of myositis**, especially in adult polymyositis and dermatomyositis;
- a possible association between **juvenile dermatomyositis** after several **years of progression**, deterioration in heart function seen using ultrasound, and blood lipid (triglycerides, cholesterol) abnormalities, particularly in cases of active myositis;
- the possibility of detecting **subclinical impairment** (i.e. not yet manifesting with symptoms) of the heart using examinations such as an electrocardiogram or ultrasound scan.
Lin CY et al. Arthritis Rheumatol. 2022 Jan. Naaraayan A et al. Heart Rhythm. 2021 Sep. Witczak BN et al. Rheumatology (Oxford). 2021 Oct. Fairley JL et al. Rheumatology (Oxford). 2021 Dec. Qin L et al. Front Med (Lausanne). 2022 Jan. Xiong A et al. Rheumatology (Oxford). 2021 Nov.

Probably several intermingled causes
The increased risk of cardiovascular disease in myositis appears to be partly related to the corticosteroid and immunomodulating treatments and inflammation (especially of the blood vessels) that characterise these diseases.

North American rheumatologist have identified a reduction in the activity of paraoxonase-1 (PON1), a protein that protects the inner wall (endothelium) of blood vessels from oxidative stress (antioxidant effect), among 184 patients with myositis. This activity is even lower in cases where the myositis is active and is accompanied by lung involvement.

▪ The different variants of the gene coding for PON1 correlate to its activity and one of them is associated with more commonly favourable progression of the myositis.
Bae SS et al. Rheumatology (Oxford). 2021 Oct.

A modifiable risk
Far from being inescapable, the increased incidence of cardiovascular disease in cases of myositis can be reduced with changes to lifestyle (diet, physical exercise, etc.) and with regular monitoring to detect and treat abnormalities at an early stage.

At the beginning of 2022, the European Alliance of Associations for Rheumatology, known by the acronym EULAR, published an update to the guidelines dedicated to cardiovascular risk.
▪ In particular, they recommend screening for and closely monitoring the various contributing factors (smoking, poorly-controlled hypertension, diabetes, etc.), with an initial specialised medical check-up **within six months** of the diagnosis of myositis.
Drosos GC et al. Ann Rheum Dis. 2022 Feb.

No increased risk of cancer in immune-mediated necrotising myopathy

A team from the Mayo Clinic (United States) has conducted a study among 152 patients with immune-mediated necrotising myopathy plus follow-ups between 2000 and 2020, and a control group of subjects without myositis.
▪ The risk of developing cancer in the three to five years following diagnosis was not higher in the group with immune-mediated necrotising myopathy compared to the control group.
Shelly S et al. Rheumatology (Oxford). 2022 Mar.

The muscles, but not the brain in inclusion body myositis

Did you know?

Proteins in common with Alzheimer's disease
Abnormal deposits of beta-amyloid and tau proteins in the brain cause degeneration of neurons in Alzheimer's disease. These same proteins are also deposited in excess in cases of sporadic inclusion body myositis, not in the nervous system, but in certain muscles, causing degeneration.

A team of British doctors has shown that cognitive functions that are deficient at the beginning of Alzheimer's disease, such as remembering recent facts, thinking up a strategy to achieve an objective, resolving a problem or planning certain actions, are intact in inclusion body myositis, even after years of disease progression.
Lu K et al. Muscle Nerve. 2022 Jan.

Children a bit more likely to have asthma

Children whose mothers have myositis have an increased risk of being asthmatic up to their sixth birthday. This is the conclusion of a nationwide study involving more than 600,000 newborns in Taiwan.
Yang DH et al. Front Med (Lausanne). 2021 Aug.

A flexible brace being trialled for scapular winging

An adjustable, textile-based, Swiss brace prototype has proven to be beneficial in three neuromuscular diseases, including immune-mediated

necrotising myopathy. This orthopaedic support looks like an adjustable mini corset (or a very short vest) that leaves the arms and shoulders free.

▪ By pressing the scapula against the chest, the brace improves arm elevation to the front (+6.2° on average) and to the side (+5.8° on average). It also reduces the sensation of strain perceived when lifting according to the results of a small-scale trial.

Georgarakis AM et al. J Neuroeng Rehabil. 2021 Sep.

Better understanding of different symptoms

Oral issues

Difficulty swallowing (or dysphagia) is present and even very common in myositis according to the results of a study conducted in Italy among 54 patients with dermatomyositis, polymyositis or inclusion body myositis. These patients also frequently experienced burning sensations or dry mouth, taste disturbances or even jaw muscle pain - consequences of the disease or its treatments.

Crincoli V. et al. Int J Med Sci. 2021 Jul.

Digestion can be difficult

Dermatomyositis can also cause slow digestion, constipation, abdominal pain, or even blood in the stool. These types of symptoms relate to impairment of the smooth muscles of the gastrointestinal tract and usually occur in combination with another autoimmune disease, and after years of progression of the myositis.

Loftis C et al. Mod Rheumatol Case Rep. 2021 Nov.

Fatigue - frequent with multiple causes

Daily consequences

In myositis, fatigue impacts the ability to perform daily activities, quality of life and mood. It often results in a gradual inability to continue to perform long-lasting activities (driving, walking, etc.), with a tendency to decrease the duration of tasks and plan rest periods after particularly demanding activities.

An Italian team reiterates that in myositis, fatigue may have both a central origin (for example, inflammation impacting the brain's serotonin production), and a peripheral origin (deterioration of the architecture, blood vessels and metabolism of the muscles).

▪ Managing fatigue particularly calls for a physical activity programme, supervised by a professional. The benefit of psychostimulants (Ritalin®, etc.) in central fatigue and carnitine in peripheral fatigue have yet to be demonstrated.

Ricci G et al. Clin Exp Rheumatol. 2022 Feb.

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