JUNE 2023

[Logo: "Knowledge and Understanding: Advances in Research"]

ADVANCES in myasthenia gravis

> myasthenia gravis
> *myasthenia gravis*
> *ocular myasthenia gravis*
> *generalised myasthenia gravis*

Myasthenia gravis is a rare disease that manifests as fluctuating muscle weakness and fatigue of varying intensity and duration which can affect any of the voluntary muscles. It is often accompanied by thymus gland irregularities such as hyperplasia and occasionally thymoma.

This document, published to coincide with the AFM-Téléthon General Meeting 2023, presents myasthenia gravis research news from the past year (ongoing studies and clinical trials, scientific and medical advances, etc.).

It can be downloaded from the AFM-Téléthon website where further information in the scientific, medical, psychological, social and technological fields relating to myasthenia gravis can be found:

WEB www.afm-telethon.fr

AFMTÉLÉTHON
CURE THROUGH INNOVATION

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What is myasthenia gravis?

*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.*

Myasthenia gravis is a rare disease that affects between 10 and 20 people in every 100,000. According to the preliminary results of a study conducted in France which were shared during the Myology 2022 conference organised by AFM-Téléthon in September 2022 in Nice, it is estimated that over 20,000 people in France suffer from myasthenia gravis.

- The disease is most common in women between 20 and 40 years old. After the age of 40, the male/female distribution tends to reverse.

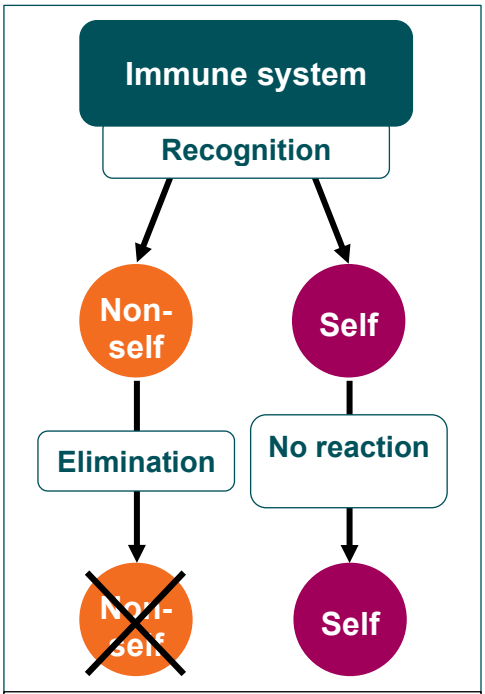
- Myasthenia gravis is characterised by varying weakness and fatigue in the affected muscles which fluctuate over time. In nearly half of all cases, the first manifestations are purely ocular in nature (drooping of the upper eyelids (ptosis), double vision (diplopia), etc.). After one year of progression, other muscles are also affected in the majority of cases.

A malfunctioning of the immune system

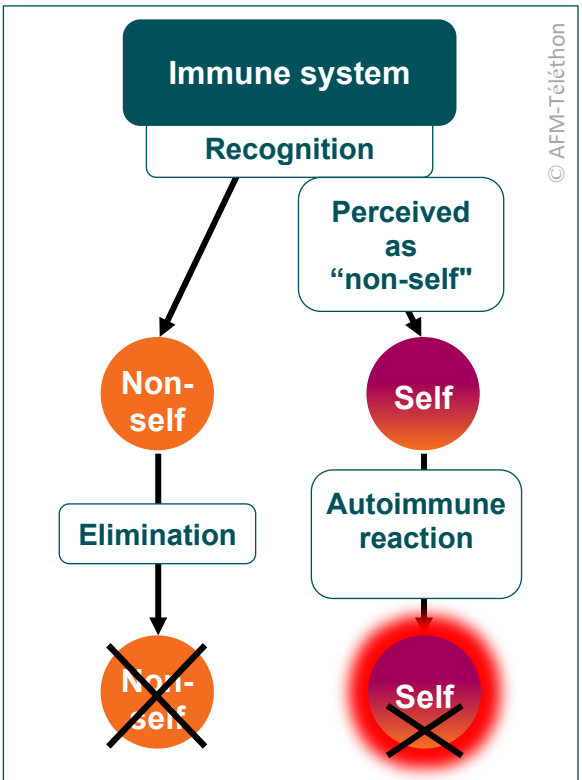
*The **neuromuscular junction** is the site of communication between the nerve through which the contraction signal (nerve impulse) arrives and the muscle that contracts due to the nerve impulse.*

Myasthenia gravis is caused by an inappropriate reaction of the immune system which is directed against the neuromuscular junction. This results in a defect in transmission of nerve impulses.

"Autoimmunity" means that the immune system (responsible for protecting the body from external attacks from bacteria, viruses, etc.) is faulty. In myasthenia gravis, it produces autoantibodies directed against a component of the neuromuscular junction.



Self-tolerance of the immune system
The immune system defends the body against external elements ("non-self") such as bacteria, viruses, etc., while respecting the cells that belong in the body ("self").



In autoimmune diseases
The immune system goes beyond its defensive role and attacks the body's own cells as though they are "non-self".

Autoantibodies

The majority of people (around 85%) with myasthenia gravis make autoantibodies directed against **acetylcholine receptors** (or AChRs).
By binding to these receptors, anti-AChR autoantibodies can increase AChR degradation and cause complement-mediated destruction of the postsynaptic membrane. They can also just block their function or cause the acetylcholine receptors to disappear into the muscle membrane (internalisation). In doing so, the number of functional acetylcholine receptors decreases.

Autoantibodies *are antibodies that react with parts of an individual's own body, such as the neuromuscular junction.*

Complement *is a complex system composed of different proteins that is involved in the immune system's defence of the body. By binding to antibodies, it forms a complex which is able to attack membrane receptors. It is the main anti-acetylcholine receptor antibody mechanism in myasthenia gravis.*

Fewer functional AChRs
Acetylcholine can no longer bind to its receptors and transmission of the nerve impulse to the muscle is poorly executed, therefore, the muscle contracts less well and gets tired. What follows is muscle weakness of varying intensity and duration which worsens with movement and can affect any voluntary muscle.

- Others have autoantibodies directed against the muscle-specific tyrosine kinase (MuSK) protein. This **MuSK protein** plays an important role in the development and stability of the neuromuscular junction, namely by inducing clustering of acetylcholine receptors during the formation of the neuromuscular junction.

- Some people with myasthenia gravis have neither anti-AChR nor anti-MuSK autoantibodies, but instead have autoantibodies against the **LRP4 protein** (low-density lipoprotein (LDL) receptor-related protein 4).
Bound to the MuSK protein, this protein is an agrin receptor at the neuromuscular junction. By binding to its LRP4 receptor, agrin contributes to the maintenance of AChR clustering beneath the nerve ending.

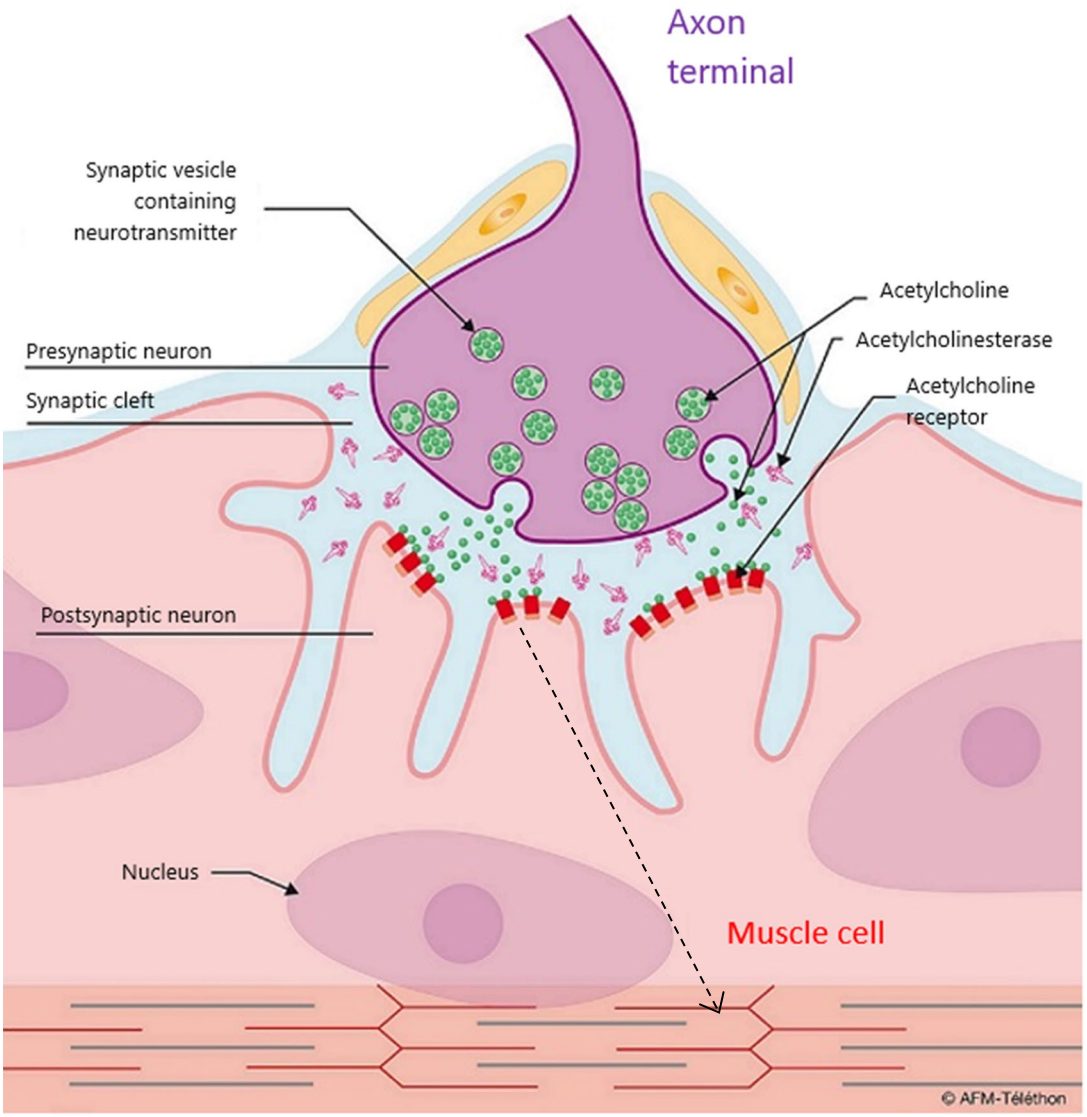
Did you know?

Dispersal of acetylcholine receptors
Anti-MuSK and anti-LRP4 autoantibodies inhibit clustering of acetylcholine receptors at the neuromuscular junction, resulting in poor nerve impulse transmission. Consequently, the muscle does not contract as well and becomes tired.

- Some people with myasthenia gravis do not have anti-AChR, anti-MuSK or anti-LRP4 autoantibodies ("seronegative" myasthenia gravis). A number of these people have "low-affinity" anti-AChR autoantibodies which are not detectable using traditional tests.

- Other types of autoantibodies have been identified in people with myasthenia gravis, in particular those directed against:
- cortactin, a protein located at the neuromuscular junction involved in the clustering of acetylcholine receptors;
- titin, a protein involved in the development and structure of sarcomeres.
These antibodies do not seem to be specific to myasthenia gravis.

Sarcomeres *are the basic units of myofibrils and the cellular structures responsible for the contraction of muscle fibres. The repetition of sarcomeres forms regular striations all along the myofibril which are visible under a microscope.*



The neuromuscular junction - where the movement order is transmitted

- *All voluntary movement is triggered by a nerve impulse which travels along a nerve and arrives at the junction between the nerve and the muscle.*
- *The neurotransmitter acetylcholine is stored in synaptic vesicles in the nerve's axon terminal (presynaptic part).*
- *The arrival of the nerve impulse at the nerve ending causes the vesicles to fuse with the presynaptic membrane.*
- *The vesicles release the acetylcholine into the synaptic cleft.*
- *The acetylcholine molecules released will then bind to acetylcholine receptors on the membrane of the muscle cell (postsynaptic membrane).*
- *This binding causes ions to pass through the muscle fibre membrane which, through a cascade of chemical reactions, makes the muscle fibre contract.*
- *At the same time, the acetylcholine molecules in the synaptic cleft are broken down by acetylcholinesterase, the products of which are reabsorbed to make more acetylcholine.*
- *The synaptic transmission mechanism is then ready to transmit another nerve impulse to the muscle.*

The thymus

Located in the chest behind the sternum, the thymus is an organ which reaches its peak activity and size around puberty before decreasing as adulthood approaches. Its role is to "teach" immune system cells (T cells) how to recognise characteristic proteins of infectious agents while being able to differentiate between what belongs to the body ("self") and what has come from the environment ("non-self").

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.

Common abnormalities
In cases of **anti-AChR** autoantibody positive myasthenia gravis, the thymus often has either an increased volume (hyperplasia) linked to the abnormal presence of B cells which form ectopic germinal centres (generally in young patients), or a thymoma (often in older patients).

The main treatments in 2023

The current methods used to treat myasthenia gravis come from knowledge acquired regarding the function of the neuromuscular junction and the immune system mechanisms involved in the disease.
There are non-medicinal treatments (surgery, physiotherapy, etc.) as well as medications such as:
- **those that treat symptoms**: anticholinesterases take effect quickly (within one hour) and have a limited duration of action (a few hours).
- **those that target the immunological causes**: corticosteroids and immunosuppressants take longer to take full effect. The action of new biological therapies is quicker.
- **those that are used to treat myasthenic crisis**: plasmapheresis and intravenous immunoglobulin therapy.

Anticholinesterases

- These drugs (Mestinon®, Mytelase®) inhibit the action of acetylcholinesterase, the enzyme that breaks down acetylcholine. By preventing acetylcholine from being broken down in the synaptic cleft, more acetylcholine is able to bind to the receptors, thereby improving neuromuscular junction function.
- This treatment is less effective in those with anti-MuSK autoantibody positive myasthenia gravis. For patients with anti-LRP4 autoantibodies, there is not yet enough data from which to draw a conclusion.

Corticosteroids and immunosuppressants

- These treatments aim to stop the autoimmune reaction by decreasing immune system activity.
- Azathioprine (Imurel®), mycophenolate mofetil (CellCept®), cyclosporin (Néoral®) and tacrolimus (Prograf®) are immunosuppressants.

Biological therapies

- These medications are made from a biological source. They modulate immune system activity and can therefore also be referred to as "immunomodulators".
- Immunoglobulins, monoclonal antibodies (rituximab, efgartigimod, ravulizumab, zilucoplan, etc.) and stem cells all fall into this category.

Plasmapheresis

- This treatment consists of removing certain substances from the blood, such as autoantibodies.
- It is used in the event of severe symptoms.

Thymectomy

- This surgery consists of removing the thymus in order to eradicate the cells that take part in the autoimmune response.
- Offered to those with anti-AChR autoantibodies, it is essential in cases of thymoma.

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

Did you know?

Stem cell transplantation - an exceptional treatment option

Haematopoietic stem cell transplantation enables new immune cells to be produced which are tolerant to the part of the body in which they were implanted.

▪ A real "reset" of the immune system, this treatment strategy for autoimmune diseases is currently used in particular in anti-MuSK and anti-AChR autoantibody positive myasthenia gravis. It first requires high-dose immunosuppression (chemotherapy, anti-T-cell antibodies, etc.) to eradicate the self-reactive immune cells causing the disease.

▪ According to French guidelines published at the end of 2022, this treatment option is indicated up to the age of 65 in cases of severe myasthenia gravis which is resistant to various immunosuppressants. It is an extremely rare situation according to data in the European Society for Blood and Marrow Transplantation Registry - out of the 3,789 people who have received this type of transplant for an autoimmune disease in Europe since 1997, only 10 of them had myasthenia gravis.

Sources: Mathec – FAI2R – MaRIH HAS website. October 2022 Greco R et al. EBMT. 2022 Feb. Beland B et al. Muscle Nerve. 2023 Feb.

__Corticosteroids__ are hormones secreted by the adrenal glands and are essential for the body's survival. Synthetic corticosteroids are used as medications, mainly to reduce inflammatory, allergic and immune reactions (anti-inflammatories, antiallergics and immunosuppressants). Because they also act on other bodily functions, they have several possible side effects. Taking corticosteroids should never be stopped abruptly and always requires strict medical supervision.

Aggressive, fast-acting treatment - an option that could be a winner

Results published these last few months advocate for early treatment which acts quickly.

▪ A Japanese team showed that, in 700 subjects with generalised myasthenia gravis, intravenous immunoglobulin therapy, plasmapheresis or high doses of intravenous corticosteroids led faster and more often than other drugs to complete remission or improvement such that a daily dose of oral corticosteroids of less than 5 mg is sufficient.

▪ According to an analysis led by the same team on 204 subjects, this time in ocular myasthenia gravis, intravenous high-dose corticosteroids administered within three months of starting treatment for the disease have comparable benefits (minimal manifestations, daily dose after infusion less than 5 mg).

Uzawa A et al. Neurotherapeutics. 2023 Jan.
Uzawa A et al. J Neurol Neurosurg Psychiatry. 2023 Jan.

- A third study conducted in South Korea showed that removal of the thymus (thymectomy) less than two years after the onset of myasthenia gravis resulted in more disease remissions (67.7%) than if it were removed after this period (50%) or not at all (25.2%). This result is based on the analysis of data from nearly 300 patients with generalised or ocular myasthenia gravis (7% of thymectomy cases) with anti-AChR autoantibodies and no thymoma who were monitored for up to nine years.
Chung HY et al. J Neurol Neurosurg Psychiatry. 2023 Apr.

The need to continue research

Progress still needs to be made in order to improve our understanding of the mechanisms involved in myasthenia gravis but also the treatments, as indicated by several recent publications.

Unmet medical needs

The persistent burden of myasthenia gravis in the real world

Even when treated, myasthenia gravis continues to have a significant impact on everyday life according to the preliminary results of the MyRealWorldMG study, which AFM-Téléthon helped to design. For the first 834 people enrolled in this "real-life" study, myasthenia gravis often has significant consequences despite treatment (pyridostigmine, corticosteroids, azathioprine, etc.) and regardless of the type of the disease (ocular, generalised).

*In addition to clinical trials, **"real-life"** observational studies are conducted without altering the patients' treatment. They rely on data that can come from different sources such as medical records, reimbursements for care, connected objects, patient questionnaires, etc. These studies reflect the "real life" of patients more and can also include a very large number of participants.*

- In practice, food shopping or working proved to be problematic for a third of participants. Nearly half of the respondents mentioned difficulties getting up from a chair, brushing their teeth or combing their hair due to muscle fatigue. Almost a third reported suffering from significant anxiety, and a fifth from moderate to severe depression. One in eight respondents reported difficulty breathing, and nearly three in 10 reported double vision and/or drooping eyelids. Finally, discomfort or significant pain was experienced by 12% to 53% of participants, depending on the severity of the myasthenia gravis.

Dewilde S et al. BMJ Open. 2023 Jan.

It's in the eyes

In a study conducted in China in 185 patients aged 14 to 77 with myasthenia gravis, the symptoms that are reported the most in both the ocular and generalised forms of the disease are the ones that affect the eyes, and impact perceived quality of life more than muscle weakness in the arms or legs.

Wu X et al. Front Neurol. 2023 Jan.

The issue of unpredictability

In the United States, an analysis of interviews conducted with 28 individuals with generalised myasthenia gravis showed that they reported an average of 16 symptoms each, the most troublesome being blurred or double vision, difficulty breathing or swallowing and fatigue. The fluctuating and unpredictable nature of these symptoms has a significant impact on the wellbeing of those with the disease and requires more thinking ahead and planning. Symptom stability was also one of the main treatment goals for the participants in this study, along with reducing fatigue and muscle weakness.

Jackson K et al. Neurol Ther. 2023 Feb

Comorbidities

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

In England, out of 1,149 adults with a generalised form of myasthenia gravis monitored between 1997 and 2016, nearly 6% had a "refractory" form of the disease where the symptoms are resistant to properly carried out conventional treatments. They experienced more exacerbations (8.71 vs 3 in 10 years) and hospitalisations related to myasthenia gravis (5 vs 1.79 in 10 years) than those with a non-refractory form of the disease. On top of this, having a refractory form of the disease is associated with an increased

risk of high blood pressure, diabetes and heart failure. Nevertheless, this study showed that mortality was comparable between patients with refractory and non-refractory myasthenia gravis and those who did not suffer from the disease.
Harris L et al. BMC Neurol. 2022 May.

Two additional ways of advancing treatment

Treatment research for myasthenia gravis takes two main paths for achieving progress.

Improving the "classics" *(drugs, surgery, etc.) with the aim of improving the benefit (efficacy) / risk (of side effects) ratio and specifying the scope of each one (when, for which form of the disease).*

Developing innovative treatments *(CAR-T cells, biological therapies, etc.) which act more selectively on the immune system and therefore are potentially more effective, better tolerated and act faster than classic immunosuppressants.*

Menon D et al. Drugs. 2022 Jun.

Drug trials in France

Drug	Approach	Phase	Recruitment
Rozanolixizumab 165 participants worldwide	Anti-FcRn	III	Completed
Inebilizumab *(MINT trial)* 270 participants worldwide	Anti-CD19	III	Recruiting
Nipocalimab 190 participants worldwide	Anti-FcRn	III	Recruiting
Zilucoplan (*RAISE-XT trial*) 200 participants worldwide	Anti-C5	III	Completed
Pozelimab +/- Cemdisiran (*NIMBLE trial*) 235 participants worldwide	Anti-C5	III	Recruiting
Satralizumab 240 participants worldwide	Anti-IL-6	III	Recruiting
Efgartigimod in children 12 participants worldwide	Anti-FcRn	II/III	Recruiting
Efgartigimod two regimens *(ADAPT NXT trial)* 72 participants worldwide	Anti-FcRn	III	Recruiting
Gefurulimab 200 participants worldwide	Anti-C5	III	Recruiting

Four highlights from the past year

1. Ever intense research

Once again, this year, knowledge of myasthenia gravis and research into new treatments have continued to advance. The consistently monumental number of scientific publications and clinical trials is evidence of this.

Over 800 scientific and medical publications between May 2022 and May 2023

(Source PubMed)

Almost 70 clinical trials underway or in preparation worldwide, including 9 in France, as of 01 June 2023

(Source ClinicalTrials.gov)

2. Three biological therapies now available in France

After ravulizumab (Ultomiris®) in May 2022, two other next-generation treatments obtained **early access authorisation** for myasthenia gravis from the HAS (Haute autorité de santé [French National Authority for Health]) - efgartigimod (Vyvgart®) in July 2022 and zilucoplan in March 2023. In order to make these decision, the HAS relied on positive results from various clinical trials demonstrating the efficacy and safety of using these three drugs in myasthenia gravis.

What do they do?

Ravulizumab is a complement component 5 (C5) inhibitor (anti-C5 antibody) and is administered intravenously every eight weeks.
Efgartigimod is a neonatal Fc receptor blocker (anti-FcRn antibody) administered intravenously every week for four weeks followed by a schedule determined by the response of the myasthenia gravis symptoms.
Zilucoplan is a once-daily subcutaneously self-administered complement C5 inhibitor (anti-C5 antibody).

▪ These products are not "repositioned", that is, already indicated for another autoimmune disease. Their early access authorisation for the moment only applies to myasthenia gravis, more specifically the generalised form with anti-AChR autoantibodies in adults who are unresponsive, intolerant or have contraindications to other available treatments. The PNDS (Protocole National de Diagnostic et de Soins [French National Diagnosis and Care Protocol]) for myasthenia gravis must now be updated accordingly and a national registry for the disease should be set up.

HAS website www.has-sante.fr. May 2022.
Vanoli F et al. Expert Opin Biol Ther. 2023 Mar.
HAS website www.has-sante.fr. December 2022.
HAS website www.has-sante.fr. March 2023.

3. A first in Europe

Associations from seven countries (including AFM-Téléthon representing France) met at the All United for MG coalition and are organising the first **European Myasthenia Gravis Day** for 2 June 2023 - the start of MG awareness month which is observed around the world. The aim is to raise

*The **PNDS (Protocoles Nationaux de Diagnostic et de Soins [French National Diagnosis and Care Protocols])** are guidelines for healthcare professionals. "The objective of a PNDS is to provide explicit instructions to professionals regarding the current optimal diagnostic and therapeutic management and care pathways for patients with a specific rare disease. Its aim is to optimise and harmonise the care and follow-up of rare diseases throughout the country" (Haute autorité de santé [French National Authority for Health]). All PNDSs published are available on the Haute Autorité de Santé website.*

WEBSITE https://www.has-sante.fr/

awareness of the disease and its consequences among the general public, healthcare professionals and institutions through stories from patients and carers, which are available to watch on the coalition's Instagram account and YouTube channel (in English). The disease affects between 56,000 and 100,000 people in Europe, and its care remains inconsistent depending on the country.
AllUnitedForMG. Presse release 2023 February.

4. Lessons from the COVID-19 pandemic

People with myasthenia gravis were 10 times more likely to contract COVID-19 in 2021 (6%) than in 2020 (0.6%) according to a survey conducted in one thousand people on the Myasthenia Gravis Foundation of America's registry.

▪ Other studies confirmed the increased risk of developing COVID-19 and of it being a severe form when myasthenia gravis was previously poorly-controlled. In contrast, these studies also confirmed that mRNA COVID-19 vaccines were well tolerated in the short-term in cases of stable myasthenia gravis.
De León AM et al. Muscle Nerve. 2023 Jan. *Aktoz G et al. Neurol Res. 2023 Jan.*
Karimi N et al. Clin Neurol Neurosurg. 2022 Nov.
Tugasworo D et al. Egypt J Neurol Psychiatr Neurosurg. 2022 Jul.
Gamez J et al. Muscle Nerve. 2022 Nov.

Did you know?

An insightful flashback

FILNEMUS, the French rare neuromuscular diseases healthcare network, with the support of AFM-Téléthon, conducted a survey to measure the impact of the first lockdown in France (from 17 March to 11 May 2020) in 1,351 adults with a neuromuscular disease (myasthenia gravis in 9% of cases). According to the results:

- 56% of respondents who used home help or care services (such as physiotherapy) had to stop these interventions completely or partially;
- 57% of respondents reported a deterioration in their muscle strength and/or their joint suppleness as a result of the lockdown;
- 18% of participants said that they were "severely impacted" mentally by the lockdown (stress, lack of sleep, sense of injustice, etc.);
- 59% received information on the epidemic and the challenges related to their disease from associations, including AFM-Téléthon.

Source: Merret et al. Cah. Myol. July 2022.

▪ Partial results from the French Vacnemus online survey were shared during the Myology 2022 conference organised by AFM-Téléthon in September in Nice. They indicated, at the end of a follow-up period of nearly eight months on average, that over half (51.7%) of the vaccines received by nearly 300 people with myasthenia gravis had no side effects.
In the other cases, the side effects reported were not specific to myasthenia gravis and were "moderate" (pain at the injection site, fatigue, headaches, body aches, etc.). Vaccination did not lead to any changes in the disease in nearly eight out of 10 cases. Only 20 vaccinations (out of 578) were followed by a temporary worsening of the manifestations of myasthenia gravis, with intravenous immunoglobulin therapy needed in only two cases.
Barnay M. YouTube video. Myoloy 2022.

Clinical trials of innovative treatments

Clinical trials explained

Clinical trials consist of assessing a potential treatment (drug candidate, medical device, etc.) in order to ensure that it is well tolerated and effective in treating a disease.

Did you know?

The four phases of clinical trials

- **Phase I: Safety/tolerability**

A drug candidate is tested for the first time on a small group of individuals to assess its safety/tolerability and its movement through the body (pharmacokinetics).

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

Phase II, conducted on a comparable group of volunteers with the disease, studies the safety and efficacy of the product and will determine the optimum dose to be used.

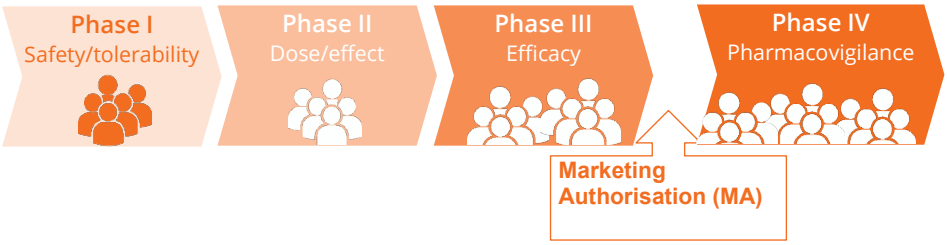
- **Phase III: Therapeutic efficacy**

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

- **Phase IV: Pharmacovigilance**

The goal of phase IV, which is conducted after the drug has been launched on the market, is to fine-tune knowledge of the product and to identify any serious and/or unexpected side effects caused by its administration.

*A **placebo** is a product whose appearance is identical to a particular medicine but does not contain any active substances. 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.*



- According to the Ministère des solidarités et de la santé [French Ministry of Health and Solidarity], on average, it takes **15 years** from a drug candidate being identified for it to be launched on the market, with a **10 to 12 year period** between the start of preclinical studies and the end of phase III clinical trials. However, it is possible for the process to be accelerated for treatments intended for rare diseases, such as with early access authorisation.

Trialling CAR-T cells - a cell and gene therapy

A **CAR-T cell** starts off as a T cell (a type of white blood cell) capable of recognising and destroying specific cells such as cancerous cells, cells infected by a microorganism, etc.

- This T cell, which is usually collected from the patient to be treated (autologous), is genetically modified in the laboratory to make it capable of recognising an antigen that is present on the surface of the cells to be eliminated.
- Once modified in this way, the T cell becomes a CAR-T cell (CAR stands for chimeric antigen receptor) and is then injected into the patient.

CAR-T cells are already used to treat certain types of blood cancer linked to the proliferation of lymphocytes. This treatment method is now being studied in various autoimmune diseases such as refractory systemic lupus erythematosus.
Oh S et al. Immune Netw. 2022 Sep. *Mackensen A et al. Nat Med. 2022 Oct.*

Did you know?

AFM-Téléthon funds research into CAR-T cells
With the support of AFM-Téléthon, several teams of researchers in France are working on the use of CAR-T or CAAR-T cells to treat various neuromuscular diseases, such as:
- Prof. Olivier Boyer's team (CHU Rouen [Rouen University Hospital]) who are working on developing CAAR-T cells in immune-mediated necrotising myopathy;
- Inès Barthélemy's team (École Nationale Vétérinaire d'Alfort [National Veterinary School of Alfort]) is getting ready to launch a research project on CAR-T cells to tackle fibrosis in Duchenne muscular dystrophy.

Generally against B cells

The pharmaceutical company **Cartesian Therapeutics** has developed autologous CAR-T cells (Descartes-08) which target the B-cell maturation antigen (BCMA). It is expressed on the surface of plasma cells, the cells that produce antibodies, including autoantibodies. Descartes-08 is administered in six successive infusions. Unlike in stem cell transplants, no prior immunosuppressant treatment is necessary.

- Cartesian Therapeutics is conducting an open-label clinical trial consisting of three parts: assessment of ascending doses of Descartes-08, an extension including administration of six infusions using a different regimen depending on the participants, and a comparison between Descartes-08 and a placebo. The comparison part of the trial started in January 2023.
Cartesian Therapeutics. Press release 2023 Jan.

*An **open-label trial** is a clinical trial in which the doctors and participants are aware of the treatment being given.*

Preliminary results
During the 14th Myasthenia Gravis Foundation of America (MGFA) conference in May 2022 in the United States, the principal investigator of the trial announced the preliminary results of the first part.
- Three participants with severe generalised myasthenia gravis received three ascending doses of CAR-T cells one week apart.
- This treatment was well tolerated and led to a reduction in disease activity in all participants, which was demonstrated most notably by an improvement in the Myasthenia Gravis Composite (MGC) score of more than 50% of participants three months after the trial had started.

Source: Granit V et al. MGFA Abstracts. Muscle & Nerve 2022 May.

- In a press release published in May 2022, Cartesian Therapeutics stated that two participants enrolled in the second part of the trial who received the six infusions in a weekly regimen also saw a significant improvement - 10 weeks after the trial had started, one of the participants' MGC score had gone from 27 to 2, and the other's had gone from 23 to 3.
Cartesian Therapeutics Press Release 2022 May.

Phase II
Dose/effect

Phase II trial of Descartes-08 cells

In the United States

30 participants (over 18 years old)

Recruiting

5.5 months of follow-up

December 2019 – December 2023

NCT04146051

The treatment developed by the biopharmaceutical company **Nanjing IASO** uses CAR-T cells which are also against BCMA. Tongji Hospital in Shanghai (China) is assessing the safety and efficacy of these cells in various autoimmune diseases, including generalised and refractory myasthenia gravis, using an open-label clinical trial called CARTinNS.

Phase I
Safety/tolerability

Phase I CARTinNS trial

In China

18 participants (18 to 75 years old)

Recruiting

2 years of follow-up

September 2020 – May 2024

NCT04561557

*In the United States, it falls to the Food and Drug Administration (FDA) to authorise, or not authorise, the sale of new drugs. The "**fast track** drug development program" was set up in 1997 with the aim of facilitating development and accelerating the regulatory review of marketing applications for new drugs for serious diseases which do not yet have a treatment.*

Particularly against anti-MuSK autoantibody-producing B cells

The company **Cabaletta Bio** in the United States is developing CAAR-T cells (with two "As" for AutoAntibody) which only target anti-MuSK autoantibody-producing B cells. The American health authorities granted them "fast track" designation at the start of 2022.

- The clinical trial announced last year officially started in November 2022. The "MusCAARTes™" trial has two parts: a phase involving the administration of ascending doses in order to be able to select the most appropriate dose, followed by a phase in which all the participants will receive the treatment at this dose. The pharmaceutical company expects to publish the preliminary results in the first half of 2024.
Cabaletta Bio. Press release. 2023 March.

- The final results of the preclinical studies will be published in 2023. They show a reduction in anti-MuSK autoantibodies without a concomitant fall in B cell or overall antibody levels, reflecting a probable specific depletion of B cells expressing anti-MuSK autoantibodies.
Oh S et al. Nature Biotech. 2023 Jan.

Phase I, open-label trial of MuSK-CAART

Phase I
Safety/tolerability

In the United States

24 participants (over 18 years old)

Recruiting

3 years of follow-up

November 2022 – October 2028

NCT05451212

Biological therapies: Seven families, 17 drug candidates

Several clinical trials that are either ongoing or in preparation are evaluating different immunomodulators (or biological therapies) designed to modulate immune system activity.

Biological therapies *are made from a biological source. They modulate immune system activity and can therefore also be referred to as "immunomodulators".*

They are all antibodies or components of monoclonal antibodies. Each one targets a specific element (receptor, protein, etc.) involved in autoimmunity. They are often developed for several autoimmune diseases, including myasthenia gravis.

Mechanism of action	Drug candidate
Anti-neonatal Fc receptor (anti-FcRn)	• Efgartigimod (Vyvgart®) • Rozanolixizumab (UCB7665) • Nipocalimab (M281) • Batoclimab (HBM9161)
Anti-complement	• Zilucoplan (RA101495) • Cemdisiran (ALN-CC5) • Pozelimab (REGN3918) • Ravulizumab (Ultomiris®) • Eculizumab (Soliris®) • Vemircopan (ALXN2050) • Gefurulimab (ALXN1720)
Anti-interleukin	• Tocilizumab (RoActemra®) • Satralizumab (Enspryng®)
Janus kinase inhibitors	• Tofacitinib (Xeljanz®)
Anti-CD19	• Inebilizumab (Uplizna®)
Anti-BLyS and anti-APRIL	• Telitacicept (RC18)
Anti-CD20	• Rituximab (MabThera®)

The respective role of biological therapies being developed to treat myasthenia gravis is yet to be defined - what are the indications for each of them? At this stage, the issues of when best to start treatment (upon diagnosis, after having tried more conventional drugs, in the event of a

flare-up, etc.), the required duration, how to discontinue treatment if necessary, occasionally the cost, and whether there is a need to combine it with background therapy are also raised.

FcRn blockers

Neonatal Fc receptors
Immunoglobulin G (IgG) is the main type of antibody produced by the immune system. Neonatal Fc receptors (FcRns) bind IgG, preventing them from being degraded. In doing so, they contribute to prolonging the time that IgG circulates in the blood, and therefore prolong immunity. The autoantibodies produced in myasthenia gravis are also IgG. FcRns therefore contribute to prolonging their autoimmune action.

__Marketing authorisation__ (MA) enables a new drug to be sold. It is granted in France by the Agence nationale de sécurité des produits de Santé (French medicines agency) or, at a European level, by the European Commission, after consulting the European Medicines Agency. To be granted marketing authorisation, the pharmaceutical company must provide scientific data from the phases of development, in particular from clinical trials. The decision is made based on safety, efficacy and quality

Drugs being developed specifically target FcRns. They involve antibodies or fragments of antibodies directed against these receptors. By blocking them, they bring about a reduction in all circulating IgG and, in particular, autoantibodies.

- The action of FcRn blockers is very targeted and differs from that of immunosuppressants which slow down the activity of the entire immune system.

Efgartigimod (or ARGX-113)

Efgartigimod (Vyvgart®) is an FcRn blocker developed by the pharmaceutical company argenx. It has obtained marketing authorisation (MA) in the United States, Japan and Europe. In July 2022, France granted early access authorisation to Vyvgart® in combination with "standard" treatment in anti-AChR autoantibody positive generalised myasthenia gravis.

Dos Santos JBR et al. Expert Rev Clin Immunol. 2022 Sep.
HAS-Early access decision. December 2022.

Phase III
Safety/tolerability

- These authorisations are based on the results of the phase III, placebo-controlled ADAPT trial (NCT03669588). This trial included 167 adults from 16 countries, including France, who had a generalised form of myasthenia gravis, the majority of which had anti-AChR autoantibodies (six participants had anti-MuSK autoantibodies and 32 were seronegative). They were divided into two groups and monitored for six months. One group received an initial cycle of four weekly IV infusions of efgartigimod, which was repeated in accordance with the progression of the participants' symptoms. The other group received infusions of a placebo.

A __placebo__ is a product whose appearance is identical to a particular medicine but does not contain any active substances. 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.

The final results of the ADAPT trial
Efgartigimod led to a decrease in IgG levels in the blood of participants with anti-AChR autoantibodies. The average maximum decrease achieved was 61.3% for IgG and 57.6% for anti-AChR autoantibodies one week after the fourth infusion.
- The drug candidate also induced a significant and persistent improvement (at least four weeks) in the score that measures the impact of myasthenia gravis on activities of daily living (MG-ADL) and the score that quantifies the disease severity (QMG) more often than the placebo.
- Efgartigimod also led to a significant improvement in quality of life that was both fast (starting the first week of treatment) and long-lasting (up to eight weeks after the first infusion of cycles 1 and 2 of treatment). This benefit is correlated with lower IgG levels and a reduction in disease manifestations.

▪ In terms of tolerance, 77% of participants treated with efgartigimod and 84% of those who received the placebo reported side effects. The most common ones were headaches and colds.

Sources: Saccà F et al. J Neurol. 2023 Apr. Suzuki S et al. Expert Rev Clin Immunol. 2022 Dec

▪ The investigator sites for the ADAPT trial conducted an open-label extension called ADAPT+ (NCT03770403) lasting three years. The final results are awaiting publication.
Partial results were published in December 2022 which concerned 17 subjects who participated in the ADAPT or ADAPT+ trial who received influenza, pneumococcal or COVID-19 vaccines during their participation. Known to bring about a reduction in autoantibodies, efgartigimod also caused a reduction in other IgG autoantibodies, but this was only temporary (during the treatment period). In addition, the vaccinations administered while taking efgartigimod led to the production of specific protective antibodies (IgG) against influenza, pneumococcal infections and COVID-19. *Guptill JT et al. Autoimmunity. 2022 Dec.*

▪ The pharmaceutical company argenx are continuing their assessment of efgartigimod in several countries, including France, through an open-label trial in participants with anti-AChR autoantibody positive generalised myasthenia gravis to compare two dosing regimens.

*An **open-label trial** is a clinical trial in which the doctors and participants are aware of the treatment being given.*

Phase III ADAPT NXT trial

Phase III
Efficacy

In France and abroad

72 participants (over 18 years old)

Recruiting

Up to 2.5 years of follow-up

December 2021 – April 2025

NCT04980495

▪ Efgartigimod is also the subject of another trial in adults who have already participated in trials of the same drug (ADAPTsc, whose results are awaiting publication and ADAPT+) to assess subcutaneous administration.

Phase III ADAPTSC+ trial

Abroad (outside France)

183 participants (over 18 years old)

Recruitment completed

Up to 3.5 years of follow-up

April 2021 – December 2024

NCT04818671

▪ Finally, the pharmaceutical company argenx is sponsoring a trial and its extension in children and adolescents with anti-AChR autoantibody positive generalised myasthenia gravis. All participants will receive IV efgartigimod. France has two investigator sites, one in Marseille and one in Paris.

Phase II
Dose/effect

Phase III
Efficacy

Phase II/III trial of efgartigimod

In France
and abroad

12 participants
(2 to 18 years old)

Recruiting

6.5 months of follow-up

October 2021 – March 2024

NCT04833894

Phase II/III long-term trial

In France
and abroad

12 participants
(2 to 18 years old)

Recruiting

4 years of follow-up

August 2022 – July 2026

NCT05374590

*The **"orphan drug"** designation is applied to drug candidates (whose efficacy has not yet been demonstrated) in rare diseases, with the aim of facilitating the various stages of their development.*

Rozanolixizumab (or UCB7665)

Developed by the pharmaceutical company UCB Pharma, rozanolixizumab is administered subcutaneously on a weekly basis. In Europe, it has had orphan drug status for myasthenia gravis since 2020.

Phase III
Efficacy

▪ UCB Pharma conducted a phase III trial called MycarinG study (NCT03971422) and its open-label extension (NCT04124965) in several countries, including France, to assess two doses of rozanolixizumab (7 and 10 mg/kg) vs placebo in 200 adults with anti-AChR or anti-MuSK autoantibody positive myasthenia gravis.

The final results of the MycarinG study and its extension

Both dosages (7 and 10 mg/kg) of rozanolixizumab led to a significant improvement in MG-ADL scores at 43 days from the start of treatment compared with the placebo, with an average difference of -2.59 points for the 7 mg/kg dose and -2.62 points for the 10 mg/kg dose.

▪ A higher percentage of participants treated with rozanolixizumab saw an improvement of 2 points or more in their MG-ADL score, and 3 points or more in their QMG and MGC scores.

▪ Adverse events linked to the treatment occurred in 81% of participants treated with the 7 mg/kg dose, 83% of participants treated with the 10 mg/kg dose and 67% of participants in the placebo group, the most common being headaches, diarrhoea and fever.

▪ Encouraged by these results, the pharmaceutical company UCB Pharma applied for marketing authorisation (MA) in the United States and Europe.

Sources: Bril V et al. Lancet Neurol. 2023 May. UCB Pharma. Press release. 2023 Jan.

UCB Pharma is assessing additional treatment with rozanolixizumab (six weeks) in participants in the MycarinG study and its extension.

Phase III
Efficacy

Phase III trial of rozanolixizumab

In France and abroad

165 participants (over 18 years old)

Recruitment completed

Up to 4.5 months of follow-up

February 2021 – October 2023

NCT04650854

▪ A trial which is currently in preparation will assess open-label rozanolixizumab in generalised myasthenia gravis administered by the participants themselves (one injection per week for 18 weeks).

Phase III trial of self-administration

Abroad (outside France)

30 participants (over 18 years old)

Not yet recruiting

4 months of follow-up

April 2023 – April 2024

NCT05681715

Nipocalimab (or M281)

Developed by the pharmaceutical company Janssen, nipocalimab has orphan drug status in Europe for an autoimmune blood disorder.

Phase II
Dose/effect

▪ The phase II trial, called VIVACITY-MG, has assessed different dosing schedules for nipocalimab (5 mg/two weeks, 30 mg/four weeks, 60 mg/two weeks or one 60 mg dose) vs placebo in 68 adults with refractory generalised myasthenia gravis in North America and Europe (but not in France).

The results of the VIVACITY-MG trial

Published in 2021, the final results showed a rapid and significant reduction in total IgG and anti-AChR autoantibodies, correlated with a rapid improvement (within two weeks) in MG-ADL scores for all four dosing schedules.

▪ Just over half (51.9%) of the participants treated with nipocalimab saw a sustained improvement in their MG-ADL score vs 15.4% in the placebo group.

▪ None of the participants had to withdraw from the trial due to adverse drug reactions. The frequency of headaches and infections proved to be comparable among all of the participant groups.

Source: Menon D et al. Drugs. 2021 Jun.

▪ Janssen is sponsoring a new trial in adults with generalised myasthenia gravis which is assessing the effects of one infusion of nipocalimab administered every two weeks. It includes a placebo-controlled phase lasting five and a half months, followed by an open-label phase lasting two years.

Phase III
Efficacy

Phase III trial of nipocalimab

In France and abroad

190 participants (over 18 years old)

Recruiting

4 years and 8 months of follow-up

July 2021 – April 2026

NCT04951622

Nipocalimab is also part of an open-label trial in children and adolescents with refractory anti-AChR or anti-MuSK autoantibody positive generalised myasthenia gravis.

Phase II
Dose/effect

Phase III
Efficacy

Phase II/III trial of nipocalimab

Abroad (outside France)

12 participants (2 to 18 years old)

Recruiting

3 years of follow-up

July 2022 – December 2025

NCT05265273

Batoclimab (HBM9161)

Phase II
Dose/effect

Developed by Harbour BioMed, batoclimab was the subject of a phase II, placebo-controlled trial (NCT04346888) which was followed by an open-label period. Its results were published in April 2022.

Encouraging results for batoclimab

The trial included 30 participants with anti-AChR or anti-MuSK autoantibody positive generalised myasthenia gravis who received either a placebo or one of two doses of batoclimab (340 and 680 mg) subcutaneously.

- The drug candidate led to a significant clinical improvement more often than the placebo. MG-ADL scores changed more favourably in those receiving batoclimab, with a decrease (i.e. improvement) of 2.2 ± 0.9, 4.7 ± 0.6, and 4.4 ± 1.0 seen in the placebo, batoclimab 340 mg, and 680 mg groups respectively 43 days since starting treatment.
- The FcRn blocker led to a decrease of IgG levels in the blood of up to 74% one week after the sixth injection of the 680 mg dose, with no concomitant increase in the rate of infections compared to the placebo.

Source: Yan C et al. Neurol Ther. 2022 Apr.

*A **placebo** is a product whose appearance is identical to a particular medicine but does not contain any active substances. 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.*

- These encouraging results paved the way for a phase III trial (NCT05039190) conducted in China in 132 adults with generalised myasthenia gravis with anti-AChR autoantibodies, anti-MuSK autoantibodies or neither autoantibodies (seronegative), the results of which are awaiting publication.
- Two trials currently underway are assessing batoclimab, one open-label, the other placebo-controlled.

Phase III
Efficacy

Phase III trial of batoclimab

In China

144 participants (18 to 99 years old)

Recruiting

5.5 months of follow-up

June 2022 – December 2023

NCT05332210

Phase III
Efficacy

Phase III, placebo-controlled trial of batoclimab

In North America, Europe and South Korea

210 participants (over 18 years old)

Recruiting

1.5 years of follow-up

June 2022 – April 2025

NCT05403541

Complement inhibitors

Complement is an immune response mediator which circulates in the blood. It is made up of several proteins. Its components 5 to 9 form a so-called "membrane attack" complex (MAC or C5b-9) that binds to the surface of target microorganisms during infections.

Did you know?

C5 - a rational target

The MAC acts by binding to the surface of cell membranes, creating a pore through which ions and water can enter the cell, which in turn destroys it.

- Studies conducted in animal models and human patients have shown that this complex is involved in various forms of myasthenia gravis.
- Several drug candidates, at various stages of development, are antibodies that bind specifically to complement component 5 (C5) with the aim of preventing the formation of the membrane attack complex.

- A European team found complement activation in subjects with anti-AChR autoantibody positive myasthenia gravis but not in those with anti-MuSK autoantibody positive or seronegative myasthenia gravis. This complement activation persists even with immunosuppressants.

Stascheit F et al. Eur J Neurol. 2023 May.

Zilucoplan (or RA101495)

Developed by UCB Pharma, zilucoplan is a once-daily subcutaneously self-administered complement C5 inhibitor. It received early access authorisation in France in March 2023 for refractory anti-AChR autoantibody positive generalised myasthenia gravis.

HAS. Early access decision. March 2023.

Phase III
Efficacy

This decision from the French health authorities was largely based on the results of a phase III trial called RAISE (NCT04115293) which assessed zilucoplan vs placebo in moderate to severe anti-AChR autoantibody positive generalised myasthenia gravis in 174 adults in around ten countries, including France. Its final results were published in May 2023.

The results of the RAISE trial

Participants treated with zilucoplan saw a rapid (from week one) and more significant improvement in their MG-ADL scores compared to those in the placebo group (-4.39 vs -2.3 on average) 12 weeks after starting treatment.

- Other assessment scores (QMG, MGC, MG-QoL 15r) also saw comparable improvements.
- Side effects were experienced by 77% of participants in the zilucoplan group and 70% of participants in the placebo group, the most common one being bruising at the injection site.

Source: Howard JF Jr et al. Lancet Neurol. 2023 May.

- An open-label extension of the RAISE trial is currently underway.

Phase III
Efficacy

Phase III RAISE-XT trial

In France and abroad

200 participants (over 18 years old)

Recruitment

3 years of follow-up

December 2019 – April 2024

NCT04225871

- Another trial is evaluating switching from another intravenously-administered complement C5 inhibitor (eculizumab or ravulizumab) to zilucoplan (administered subcutaneously).

Phase III trial of zilucoplan

In the United States

20 participants (18 to 85 years old)

Recruiting

4 months of follow-up

October 2022 – January 2024

NCT05514873

Cemdisiran alone or in combination with pozelimab

Cemdisiran (ALN-CC5) is a small interfering RNA (siRNA) molecule directed against complement component 5. The European health authorities granted it orphan drug status in 2021 for an autoimmune kidney disease. Pozelimab (REGN3918) is a monoclonal antibody, which is also directed against C5, being studied in paroxysmal nocturnal haemoglobinuria, a disease of the blood.

siRNAs
A small interfering RNA (siRNA) molecule specifically binds to a messenger RNA molecule, to which it is complementary. In doing so, it prevents the expression of the corresponding genes into proteins.
In this study, the siRNAs used target the messenger RNAs that control the synthesis of BAFF and BCMA receptors.

▪ Cemdisiran and pozelimab were developed by the pharmaceutical company Regeneron, which is conducting an international trial to explore the efficacy and safety of the pozelimab - cemdisiran combination vs cemdisiran monotherapy or placebo in anti-AChR or anti-LRP4 autoantibody positive myasthenia gravis.

Phase III NIMBLE trial

Phase III
Efficacy

In France and abroad

235 participants (over 18 years old)

Recruiting

3 years of follow-up

December 2021 – May 2027

NCT05070858

Ravulizumab (Ultomiris®)

The French health authorities granted early access authorisation to ravulizumab (Ultomiris®) in May 2022. It is administered intravenously, however, a subcutaneous form is being trialled. Like eculizumab, this drug candidate was developed by Alexion, a company acquired by the pharmaceutical company AstraZeneca in 2021.

The results of the CHAMPION-MG trial
The phase III trial CHAMPION-MG was conducted in around 15 countries, including France. It included 175 participants with anti-AChR autoantibody positive generalised myasthenia gravis. After the two initial injections, they received an infusion of ravulizumab or the placebo every eight weeks for six months.
▪ Published in April 2022, the results of this trial showed that, compared to the placebo, ravulizumab led to a rapid (from the first week) and sustained improvement in disease manifestations. It significantly improved MG-ADL (on average -3.1 vs -1.4 for the placebo group) and QMG scores (−2.8 vs -0.8) after six months of treatment.
▪ The investigators reported no notable differences in the adverse drug reactions observed in the ravulizumab and placebo groups.
Source: Vu T et al. NEJM Evid 2022 April.

*In a **double-blind trial**, neither the patients nor the doctors know which treatment the patients are taking.*
➤➤ Essais cliniques et maladies neuromusculaires [Clinical trials and neuromuscular diseases], Savoir & Comprendre references documents, AFM-Téléthon

▪ The assessment of ravulizumab continues in children.

Phase III open-label trial

Phase III
Efficacy

In the United States

12 participants (6 to 17 years old)

Not yet recruiting

4 months of follow-up

June 2023 - July 2023

NCT05644561

Eculizumab (Soliris®)

Eculizumab has marketing authorisation in Europe for anti-AChR autoantibody positive generalised myasthenia gravis in adults and generalised myasthenia gravis that is resistant to conventional treatments, but is not officially available in France.

- An open-label trial is assessing eculizumab in children and adolescents with refractory anti-AChR autoantibody positive myasthenia gravis.

Phase III
Efficacy

Phase III trial of eculizumab

Abroad (outside France)

11 participants (6 to 17 years old)

Recruitment

4 years of follow-up

December 2018 – July 2025

NCT03759366

- In order to better understand long-term effects and safety, a registry (C5ITs) of people with myasthenia gravis who have received eculizumab or ravulizumab is currently being set up.

Observational study

In the United States

500 participants (over 18 years old)

Recruiting

5 years of follow-up

December 2019 – November 2024

NCT04202341

Vemircopan (or ALXN2050)

Developed initially by Alexion, which has since been acquired by AstraZeneca, ALXN2050 or vemircopan inhibits a compound (factor D) which is involved in a complement activation pathway, along with complement component 3 (C3).

- A placebo-controlled trial is assessing it in generalised myasthenia gravis.

Phase II
Dose/effect

Phase II trial of ALXN2050

In the United States and Italy

70 participants (over 18 years old)

Recruiting

2 years of follow-up

December 2021 – February 2025

NCT05218096

Gefurulimab (or ALXN1720)

Gefurulimab or ALXN1720, developed by Alexion/AstraZeneca, is an antibody directed against complement component 5 which is injected subcutaneously once a week. A phase III, placebo-controlled clinical trial is ongoing (including in France) in anti-AChR autoantibody positive generalised myasthenia gravis. An open-label trial will follow which will last nearly two years.

Phase III placebo-controlled trial

Phase III
Efficacy

In France and abroad

200 participants (over 18 years old)

Recruiting

6 months of follow-up

November 2022 – May 2027

NCT05556096

Three anti-complement approaches for the future

① Knowing who to use them in

*An Italian team is researching **biomarkers** of complement activation in anti-AChR autoantibody positive myasthenia gravis. The goal? Ultimately, having reliable indicators to be able to proactively identify the patients who will derive the most benefit from an anti-complement treatment.*
Iacomino N et al. Biomedicines. 2022 Jun.

② An anti-C5 siRNA

*Japanese researchers are developing a **small interfering RNA** (siRNA) molecule which binds to the messenger RNA molecule that controls the production of C5. It is encapsulated in lipid (fat) nanoparticles so that it is able to better reach liver cells, which make most of the complement components. The results of the preclinical studies (mice, non-human primates) of the intravenous injection of this siRNA are promising.*
Kuboi Y et al. Mol Ther Nucleic Acids. 2023 Jan.

③ A C6 inhibitor

*An international team is developing an antibody called CP010 which is directed **against complement component 6** (C6). In vitro, it prevents the formation of the membrane attack complex (MAC). Injecting it into rats produces the same effect. It also prevents experimental autoimmune myasthenia gravis.*
Gytz Olesen H et al. J Innate Immun. 2022 May.

Interleukin-6 inhibitors

Interleukin-6 (IL-6) is an important protein for T helper 17 cells (Th17) and follicular helper T cells (Tfh) as well as in B cell activation and antibody production. It may be involved in the pathogenesis of myasthenia gravis.

▪ Levels of IL-6 in the blood are higher in those with anti-AChR autoantibody positive myasthenia gravis than in those who do not suffer from the disease. These levels are even higher when myasthenia gravis is active. They decrease after immunosuppressive treatment is started.

Source: Uzawa A et al. J Neuroimmunol. 2021 Sep.

Tocilizumab (RoActemra®)

Tocilizumab is an antibody directed against IL-6 currently indicated for rheumatoid arthritis, an inflammatory disorder that affects the joints.

▪ In China, Tang-Du hospital is sponsoring an open-label trial and its extension to assess the efficacy and safety of a monthly infusion of tocilizumab in anti-AChR autoantibody positive myasthenia gravis.

Phase II
Dose/effect

Phase II tMG trial of tocilizumab

In China

64 participants (18 to 80 years old)

Recruiting

3.5 months of follow-up

July 2022 – September 2024

NCT05067348

Phase II
Dose/effect

Phase III
Efficacy

Phase II/III tMG-E trial of tocilizumab

In China

64 participants (18 to 80 years old)

Recruiting

3.5 months of follow-up

April 2023 – December 2024

NCT05716035

Satralizumab (Enspryng®)

The pharmaceutical company Roche's **satralizumab** is an antibody directed against IL-6 which is marketed in Europe for neuromyelitis optica spectrum disorder, an autoimmune disease.

▪ Roche is conducting a phase III trial called LUMINESCE. Presented in October 2022 at the World Muscle Society (WMS) conference, it assesses the efficacy, safety, pharmacokinetics (the movement of a drug through the body) and pharmacodynamics (the body's biological response to a drug) of satralizumab in seropositive (anti-AChR, anti-MuSK or anti-LRP4 autoantibodies) generalised myasthenia gravis which is symptomatic despite treatment. It involves 65 investigator sites around the world, five of

which are in France (Bordeaux, Garches, Marseille, Nantes and Nice), and will be followed by an open-label trial during which all participants will receive satralizumab for two years.
Kaminski H et al. Neuromuscul. Disord. 2022 Nov.

Phase III LUMINESCE trial

Phase III
Efficacy

In France and abroad

240 participants (over 12 years old)

Recruiting

Up to 2.5 years of follow-up

October 2021 – December 2025

NCT04963270

A Janus kinase inhibitor

Developed by Pfizer, **tofacitinib** (Xeljanz®) is a Janus kinase inhibitor of enzymes which are involved in inflammation and the immune response via the production of several interleukins (2, 4, 6, 7, 9, 15, 21) and interferons.

- Tofacitinib thus modulates the immune response. It is currently prescribed in autoimmune diseases such as rheumatoid arthritis and ulcerative colitis, and is being trialled in dermatomyositis. In myasthenia gravis, several publications from these past few years have reported seeing improvements in those taking tofacitinib.
- Huashan Hospital in Shanghai is conducting an open-label pilot study designed to assess the safety and efficacy of 10 mg of tofacitinib per day for six months in refractory anti-MuSK autoantibody negative myasthenia gravis.

*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.).*

Phase I trial of tofacitinib

Phase I
Safety/tolerability

In China

20 participants (18 to 60 years old)

Recruiting

6 months of follow-up

June 2020 - February 2023

NCT04431895

Did you know?

AG490, a new JAK inhibitor in development in myasthenia gravis
In a preclinical study conducted in China, a selective JAK2 inhibitor has demonstrated its efficacy in an experimental model of myasthenia gravis, leading in particular to an improvement of symptoms and a reduction in complement deposition at the neuromuscular junction.
Source: Lu Y et al. Int Immunopharmacol. 2023 Feb.

An anti-CD19 monoclonal antibody

Inebilizumab (Uplizna®) received early access authorisation in France in May 2022 to treat a type of neuromyelitis optica spectrum disorder. Developed by the pharmaceutical company Viela Bio, which was

acquired by Horizon Therapeutics in March 2021, this drug is a monoclonal antibody directed against a protein located on the surface of B cells - CD19.

▪ The pharmaceutical company Viela Bio is assessing inebilizumab vs placebo in anti-AChR or anti-MuSK autoantibody positive generalised myasthenia gravis in around 20 countries, including France. This trial is called MINT and will be followed by an open-label extension which will last for 18 months.

Phase III
Efficacy

Phase III MINT trial

In France and abroad

270 participants (over 18 years old)

Recruiting

1 year of follow-up

August 2020 – December 2024

NCT04524273

*The **"orphan drug"** designation is applied to drug candidates (whose efficacy has not yet been demonstrated) in rare diseases, with the aim of facilitating the various stages of their development.*

*An **open-label trial** is a clinical trial in which the doctors and participants are aware of the treatment being given.*

***Lupus** 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 to as a "butterfly rash". When several organs are affected, the disease is called "systemic" lupus erythematosus.*

A BLyS/APRIL dual inhibitor

The pharmaceutical company RemeGen is developing **telitacicept**, or RC18, in several autoimmune diseases, including myasthenia gravis. In 2021, China granted this drug candidate conditional marketing authorisation for systemic lupus erythematosus. In October 2022, the North American health authorities granted it orphan drug status for myasthenia gravis.

Telitacicept or RC18

Developed by the pharmaceutical company RemeGen, telitacicept is composed of an antibody (IgG) combined with a protein called TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor).

▪ TACI is naturally present on the surface of B cells where it binds to two molecules, BLyS and APRIL, which promote the development and survival of B cells (autoantibody-producing cells).

▪ Telitacicept binds to BLyS and APRIL (with its TACI part), preventing them from binding to TACI proteins on B cells and therefore limiting B cell development and survival.

RemeGen conducted a phase II, open-label trial (NCT04302103) in 29 adults with anti-AChR autoantibody positive generalised myasthenia gravis to assess two doses of telitacicept (160 and 240 mg) administered via subcutaneous injection once a week.

▪ At the end of 2022, the pharmaceutical company announced the preliminary results of this trial via a press release. Five and a half months after starting treatment, QMG scores had dropped an average of 7.7 points in the group that received the 160 mg dose and 9.6 points in the group that received the 240 mg dose, demonstrating a clinically significant efficacy. The final results are awaiting publication.
RemeGen Co Ltd. Press release. 2022 Nov.

▪ RemeGen is preparing a phase III trial to assess telitacicept vs placebo in anti-AChR or anti-MuSK autoantibody positive generalised myasthenia gravis.

Phase III
Efficacy

Phase III, placebo-controlled trial of telitacicept

In China

100 participants (18 to 80 years

Not yet recruiting

11 months of follow-up

May 2023 - May 2027

NCT04302103

An anti-CD20 monoclonal antibody

Rituximab (MabThera®, Truxima®, etc.) is a monoclonal antibody that binds specifically to the CD20 protein, which is only present on the surface of B cells. This binding induces killing of these B cells, with the aim of reducing autoantibody production.

Did you know?

A drug already on the market

Rituximab has been used for years in rheumatoid arthritis (another autoimmune disease) and certain blood cancers.

▪ In myasthenia gravis, it is used more and more as a course of treatment to treat refractory forms of the disease, as recommended by the Protocole national de diagnostic et de soins (PNDS) published in 2015.

▪ Rituximab could also prove beneficial without having to wait for other drugs to fail, as suggested by the results of a Swedish, placebo-controlled trial called RINOMAX. It included adults with new onset generalised myasthenia gravis (onset of symptoms no more than one year ago).

Three and a half months after a single infusion of 500 mg of rituximab, 71% of the 25 participants who received the infusion had few or no manifestations of the disease with only low doses of corticosteroids and no further treatment needed since the injection. Only 29% of the 22 participants who received the placebo had the same results. In addition, 4% of the participants in the rituximab group, vs 36% of the participants in the placebo group, needed further treatment (immunoglobulins, other biological therapies, etc.) within 5.5 months of receiving the injection. All three hospitalisations for worsening of the disease were in the placebo group.

Piehl F. JAMA Neurol. 2022 Nov. *Chuquilin M et al. JAMA Neurol. 2022 Nov.*

▪ A South African neurologist published follow-up results of 17 patients with refractory anti-AChR autoantibody positive, anti-MuSK autoantibody positive or double seronegative myasthenia gravis who again received a single infusion of low-dose rituximab (500 to 600 mg on average). This additional treatment led to an improvement in 13 participants (100% of which had anti-MuSK autoantibodies). Of these 13 participants, six became asymptomatic (no myasthenia gravis symptoms). This improvement meant that corticosteroids could be stopped or their dose reduced.

Heckmann JM. J Neurol Sci. 2022 Nov.

▪ In China, the First Affiliated Hospital of Sun Yat-Sen University is assessing the safety and efficacy of low-dose rituximab (100-200 mg/week) in refractory myasthenia gravis (ocular or generalised).

*The **PNDS (Protocoles Nationaux de Diagnostic et de Soins [French National Diagnosis and Care Protocols])** are guidelines for healthcare professionals. "The objective of a PNDS is to provide explicit instructions to professionals regarding the current optimal diagnostic and therapeutic management and care pathways for patients with a specific rare disease. Its aim is to optimise and harmonise the care and follow-up of rare diseases throughout the country" (Haute autorité de santé [French National Authority for Health]). All PNDSs published are available on the Haute Autorité de Santé website.*

WEBSITE https://www.has-sante.fr/

Phase III
Efficacy

Phase III trial of rituximab

In China

50 participants
(up to 80 years old)

Recruiting

6 months of follow-up

August 2020 – July 2022

NCT05332587

Three innovative approaches for the future in the preclinical stage

Before being tested in humans, a drug candidate must be subjected to "preclinical" studies, that is, trials on cells and animal models. Preclinical studies aim to check a drug's mechanism of action, measure its activity, study its pharmacokinetic and pharmacodynamic properties and assess its toxicity.

Blocking interleukin-23

Interleukin-23 (IL-23)
A mediator of inflammation and the immune response, interleukin-23 (IL-23) promotes the multiplication, differentiation and survival of T helper 17 cells, which play a major role in the abnormalities linked to myasthenia gravis observed in the thymus, but also in the skeletal muscles.

Supported by AFM-Téléthon, a team at the Institut de Myologie have shown that a monoclonal antibody directed against IL-23 has a positive effect on the thymus (reduction of inflammation, control over the formation of ectopic germinal centres) and the muscles (stimulation of muscle repair mediators, better transmission of the nerve impulse at the neuromuscular junction, etc.) in two mouse models of anti-AChR autoantibody positive myasthenia gravis. It reduces the production of anti-AChR autoantibodies in the blood and improves the symptoms of the disease.

▪ These initial results are paving the way for future clinical trials with one or more IL-23 inhibitors. Some are already available in France, such as ustekinumab (Stelara®) and guselkumab (Tremfya®) which are used to treat other autoimmune diseases such as psoriasis and Crohn's disease as well as ulcerative colitis.

Villegas JA et al. J Neuroinflammation. 2023 Jan.

Restoring self-tolerance

In myasthenia gravis, the immune system is faulty and produces autoantibodies directed against a component of the neuromuscular junction, most often the acetylcholine receptors (AChR).

▪ Spanish researches, helped by the previously-mentioned Institut de Myologie team, have managed to make mouse models of myasthenia gravis which are tolerant to their own acetylcholine receptors. Inspiration from the natural phenomenon of efferocytosis helped them to achieve this.

Cleansing the body
Efferocytosis is the process by which dead cells are removed by the immune system.

- This mechanism relies on a lipid molecule called phosphatidylserine being present on the surface of dead cells.
- Its presences enables the immune system to recognise dead cells and remove them, limiting the risk of the body becoming sensitised to the components of these cells.

- Using the principle of efferocytosis, the Spanish team developed microscopic lipid nanoparticles (liposomes) rich in phosphatidylserine in which they encapsulated a fragment of acetylcholine receptor (AChR), all of which "replicated" a dead cell to be removed. Seven weeks after injecting them into mouse models of anti-AChR autoantibody positive myasthenia gravis, their levels of these antibodies had decreased and their motor scores had improved.

- This project is continuing in order to test different doses and injection methods. The interest of such a treatment is not to modify the whole immune response (unlike immunosuppressants) and to be specific to one type of autoantibody (anti-AChR autoantibodies in this case, anti-MuSK autoantibodies if MuSK proteins were encapsulated in liposomes, etc.).
Almenara-Fuentes L et al. Nanomedicine. 2023 Feb.

Dual inhibition of autoantibody-producing cells

CD269 receptors (or BCMA) are specific to the B-cell maturation antigen and are only present on the surface of plasma cells, immune cells that produce autoantibodies. CD268 receptors (or BAFF-R) are mainly expressed by the precursors of plasma cells - mature B cells. Blocking these two receptors can affect the production of autoantibodies.

- Supported by AFM-Téléthon, a team of researchers at the University of Texas (United States) has combined antibodies (Ab) directed against BAFF-R and BCMA proteins with small interfering RNAs (siRNAs) which are active against the same targets.

siRNAs
A small interfering RNA (siRNA) molecule specifically binds to a messenger RNA molecule, to which it is complementary. In doing so, it prevents the expression of the corresponding genes into proteins.
In this study, the siRNAs used target the messenger RNAs that control the synthesis of BAFF and BCMA receptors.

The injection of the Ab-siRNA combination into mouse models of myasthenia gravis led to a substantial reduction in the two receptors and levels of anti-AChR autoantibodies, with a significant improvement in the signs of myasthenia gravis (mobility, grip strength, etc.).
The team is continuing to work on this project in order to optimise the Ab-siRNA conjugates. Their advances could also eventually be applied to other autoimmune diseases.
Ibtehaj N et al. J Autoimmun. 2023 Feb.

*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.*

What's new with "classic" treatments?

The conventional treatments for myasthenia gravis continue to be studied and, for some, be part of clinical trials with the aim of refining their use (indications, route of administration, etc.) and improving their efficacy/tolerance balance.

Pyridostigmine - effective but with side effects

Pyridostigmine (Mestinon®), the first treatment to be launched for myasthenia gravis, inhibits the action of acetylcholinesterase, the enzyme that breaks down acetylcholine at the neuromuscular junction. By preventing acetylcholine from being broken down, pyridostigmine increases the rate of it binding to the receptors.

*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.).*

- Over 400 participants on the Dutch-Belgian registry of neuromuscular junction diseases assessed its efficacy to be, on average, 60 on a scale from zero (no effect) to 100 (complete resolution of symptoms). For them, fatigue was the symptom that was least responsive to the action of pyridostigmine.

- 91% of the participants currently using it reported side effects. Out of those who no longer use pyridostigmine, a quarter stopped taking it mainly because of these side effects, the most common of which being diarrhoea and abdominal or muscle cramps.
Remijn-Nelissen L et al. Neuromuscul Disord. 2022 Oct.

- A trial conducted by the pharmaceutical company DAS Therapeutics assessed DAS-001 (a drug currently being developed) in anti-AChR autoantibody positive myasthenia gravis. It combines pyridostigmine with ondansetron, a product already marketed for preventing and treating nausea and vomiting. The aim is to reduce the gastrointestinal side effects of pyridostigmine.

Phase II
Dose/effect

Phase II trial of DAS-001

In the United States

24 participants (over 18 years old)

Recruiting

6 weeks of follow-up

April 2021 – April 2023

NCT04226170

Immunoglobulins under the skin

Immunoglobulins in a nutshell
In myasthenia gravis, polyvalent immunoglobulins (Ig) have been shown to be capable of modulating immune system activity. They are administered intravenously (IVIg) or subcutaneously (SCIg). Doctors use them today to treat severe flare-ups of the disease. Prescribed in a growing number of diseases, Igs are subjected to regular supply pressures.

In recent months, the results of a study conducted in France at CHU de Bordeaux and a North American clinical trial have confirmed the efficacy and good tolerance of SCIgs.
Barnay M et al. J Neurol. 2022 Dec. *Pasnoor M et al. Eur J Neurol. 2023 May*

A repositioned drug

Drug repositioning consists of using a drug for condition that is different from what it was initially indicated for.

Sold under the name **Firdapse®** by Catalyst Pharmaceuticals, **amifampridine phosphate** (or 3,4-diaminopyridine or even 3,4-DAP) facilitates the release of acetylcholine into the synaptic cleft by prolonging the depolarisation of the presynaptic membrane at the nerve ending.

Firdapse® is indicated as a symptomatic treatment for Lambert-Eaton myasthenic syndrome in adults and certain congenital myasthenic syndromes (other neuromuscular diseases which involve neuromuscular junction dysfunction).

- The results of an Italian clinical trial (15 participants) shows its benefits in anti-AChR autoantibody positive myasthenia gravis. One hour after taking just one tablet of Firdapse® 10 mg led to a significant improvement in disease manifestations (demonstrated by improvements in QMG scores and lung capacities) and an improvement in electrical activity in the muscles (electromyogram) in the participants most severally affected by the autoimmune disease.

- The only notable side effects were temporary sensory issues (tingling, pins and needles, etc.) in the mouth, fingers and toes which have already been associated with this drug.

- These results reinforce the idea that Firdapse® could be an additional treatment option in certain cases of myasthenia gravis, for example, when conventional treatments are not able to sufficiently control disease manifestations or in cases of poor tolerance to anticholinesterases.
Ceccanti M et al. Front Pharmacol. 2022 Aug.

- Catalyst Pharmaceuticals is conducting a long-term study assessing amifampridine phosphate in anti-AChR and anti-MuSK autoantibody positive myasthenia gravis.

***Congenital myasthenic syndromes** are caused by abnormalities in the genes that code for neuromuscular junction components (acetylcholinesterase, acetylcholine receptors). Unlike myasthenia gravis, congenital myasthenic syndromes are genetic conditions.*

*The **neuromuscular junction** is the site of communication between the nerve through which the contraction signal (nerve impulse) arrives and the muscle that contracts due to the nerve impulse.*

Phase III MSK-003 trial

Phase III
Efficacy

In the United States

70 participants (over 18 years old)

Recruitment

21 months of follow-up

July 2018 – April 2023

NCT03579966

From one thymectomy technique to another

Thymectomy (a surgery that consists of removing the thymus) has been used for decades to treat generalised myasthenia gravis with thymoma. A phase III, international trial called MGTX showed that thymectomy is also beneficial in the absence of thymoma in anti-AChR autoantibody positive myasthenia gravis.

- A thymectomy can be performed transsternally or by using a minimally invasive method (video-assisted thoracoscopic surgery or VATS, or robot-assisted surgery). These methods continue to be assessed and compared by various clinical trials in Europe (NCT04158661) and Asia (NCT03613272, NCT02317224, NCT05262582).

- Dutch doctors analysed the records of 230 patients with anti-AChR autoantibody positive myasthenia gravis who had a DaVinci® robot-assisted thymectomy between 2004 and 2018. One third had a thymoma. The vast majority (82.4%) of patients saw an improvement thanks to the thymectomy. Nearly half (47.8%) were in remission two years after the procedure. These improvements were comparable in patients who had a thymoma and those that did not.
Marcuse F et al. Neuromuscul Disord. 2023 Mar.

Therapeutic patient education

Therapeutic patient education
Therapeutic patient education (TPE) enables people with a chronic disease to acquire or maintain useful skills to better manage their daily lives.
- Its aim is to help them to better understand their disease (or a relative or friend's disease) and treatments, as well as how to live better with it and manage it more effectively, therefore improving the disease's care and outcome.
- TPE is often offered by a team of healthcare professionals in the form of a comprehensive programme which combines individual and group activities.

CHU de Grenoble, Toulouse and Marseille offer myasthenia gravis-specific TPE programmes. CHU de Strasbourg has also developed this type of programme. A study will assess its effects.

Efficacy of a therapeutic patient education programme

In France

100 participants (over 18 years old)

Not yet recruiting

6 months of follow-up

January 2021 – May 2025

NCT04714658

Observational studies of the gut microbiota

The exact origin of the immune system dysfunction in myasthenia gravis is still poorly understood. Researchers are working on finding genetic and/or environmental factors that predispose someone to developing this disease. The gut microbiota could be one of these factors. Its imbalance (dysbiosis) could play a part in the pathological mechanisms of myasthenia gravis.

*The human **gut microbiota** is made up of microorganisms (bacteria, viruses, fungi, etc.). Its imbalance (or dysbiosis) can foster the development of diseases such as obesity, cardiovascular diseases, etc.*

Billions of useful bacteria

The gut microbiota is made up of 100,000 billion microorganisms (the majority of which are bacteria) which are involved in numerous essential functions such as digesting food, vitamin synthesis, educating the body's defence system, etc. The gut microbiota is being studied by applying human gene analysis techniques (sequencing) to the genome of the microorganisms that are present in the digestive system.

These past few years, various observational studies have found significant differences in the composition (less diversity) of the gut microbiota in subjects with myasthenia gravis. In recent months, new publications have confirmed these findings and reiterate that these abnormalities:

- are shared by other autoimmune diseases;
- could serve as biological markers for monitoring the course of the disease;
- may open treatment avenues such as faecal microbiota transplantation, probiotics, prebiotics or certain plants used in traditional Chinese medicine, which still need to be tested in myasthenia gravis.

Kang Y et al. Clin Immunol. 2022 Dec. *Wu N et al. Front Neurol. 2023 Feb.* *Kapoor B et al. Autoimmun Rev. 2023 May.* *Schirò G et al. Neurol Int. 2023 Mar.* *Zhao M et al. Front Microbiol. 2023 Jan.*

*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. These markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

Did you know?

In the mouth too!

An article published in July 2022 reported abnormalities in the microbiota of the mouth. The microbiota of people with anti-AChR autoantibody positive myasthenia gravis has significant differences in composition and function compared to the microbiota of those who do not suffer from the disease.
Source: Huang C et al. Front Neurol. 2022 Jul.

▪ The pharmaceutical company ProgenaBiome is conducting a study of the gut microbiota in myasthenia gravis.

Correlating the gut microbiota to myasthenia gravis (pilot study)

In the United States

100 participants (children and adults)

Recruiting

3 years of follow-up

March 2020 – July 2023

NCT04224506

Databases and registries

Databases and **registries** accumulate data which can be analysed to determine the natural history of a disease, monitor its prevalence and help recruit patients for clinical trials.

*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.*

Two times more common or two times better diagnosed?

According to the analysis of reimbursement requests from a German database of over six million insured persons, the number of people with myasthenia gravis doubled in Germany between 2011 and 2020, going from 15.7 to 28.2 people in every 100,000.

▪ The results of a study conducted in Japanese hospital departments are similar - myasthenia gravis affected 23.1 people in every 100,000 in 2017 compared to half as many ten years earlier. In addition, the age of onset of the disease seems to be decreasing (59 years old on average) and the male/female distribution is becoming more balanced.

Sources: Wartmann H et al. Neuroepidemiology. 2023 Feb. Yoshikawa H et al. PLoS One. 2022 Sep.

Research in France

The database created by Sonia Berrih-Aknin (Institut de Myologie, Paris) with the support of AFM-Téléthon was not designed to be exhaustive but to aid research projects which advance our understanding of myasthenia gravis.

▪ It collects information (symptoms, blood test results, muscle biopsy analyses, thymus analyses, etc.) on around 50 new patients every year who have myasthenia gravis, with or without thymoma.

*A **muscle biopsy** is a procedure which involves removing a small fragment of muscle tissue under local anaesthetic. The fragments of muscle tissue are then studied under a microscope. The different methods used to prepare the tissue enables abnormalities in the morphology and/or structure of the muscle fibres to be detected and/or deficiencies in certain proteins to be identified.*

➤➤ Diagnostic des maladies neuromusculaires [Diagnosis of neuromuscular diseases], Savoir & Comprendre references documents, AFM-Téléthon.

French myasthenia gravis database

In France

Created in 1986

Recruiting

2,083 patients

At a European level

European Database for Myasthenia Gravis

Abroad (outside France)

Created in 2006

Recruiting

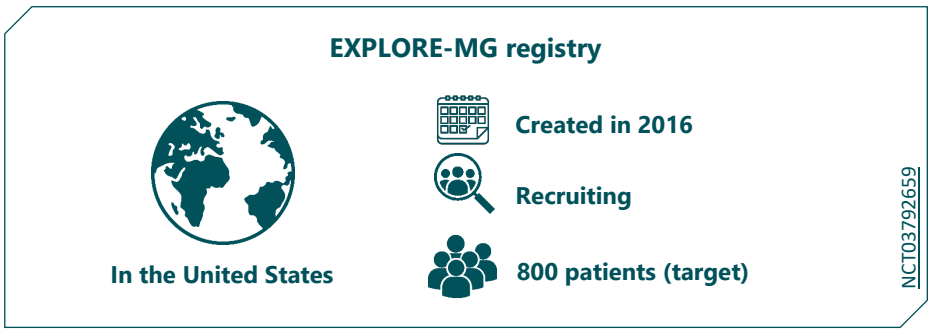
5,000 patients

Three North American registries

EXPLORE-MG registry

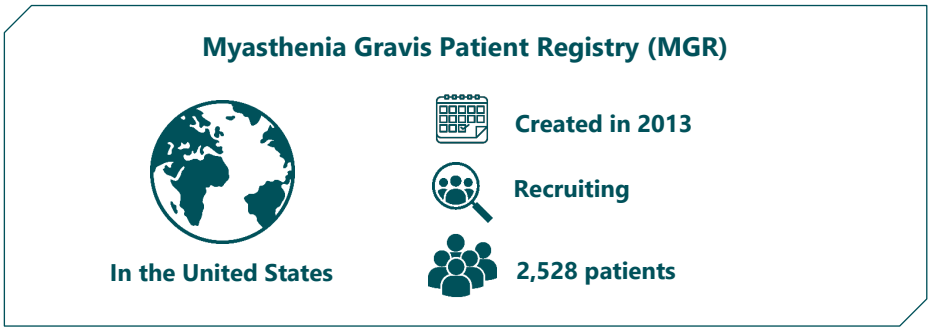
Created by Yale University (United States), this registry collects data on people with myasthenia gravis who are monitored by Yale New Haven

Hospital. The registry should be closed after eight years, i.e. in March 2024. The data collected is used for research purposes.



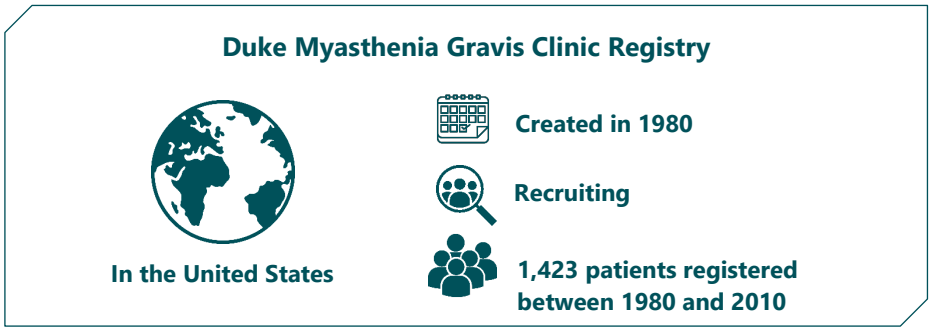
Myasthenia Gravis Patient Registry (MGR)

This registry is run by the University of Alabama at Birmingham (United States) under the supervision of the Myasthenia Gravis Foundation of America (MGFA). It collects data on adults with myasthenia gravis residing in the United States for the purpose of research, treatment and information for patients. Registration takes place on a dedicated website (www.mgregistry.org/). The data is entered by the patients and their doctors.



Duke Myasthenia Gravis Clinic Registry

Duke University in Durham (United States) has been developing a registry for myasthenia gravis for several decades. One of its benefits is being able to use its data to conduct analyses on the course of the disease and its treatment over time.



Progress in understanding of myasthenia gravis

*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.*

Like other autoimmune diseases, myasthenia gravis results, not from the mutation of a gene, but from the combination of a genetic predisposition (particular versions of several genes) and environmental factors, which remain to be formally identified. All of this causes the immune system to be faulty, which causes the disease.

Risk-bearing genetic characteristics

Three new genes in the hot seat

An international team of researchers compared the entire set of genetic information (genome) of nearly 1,900 people with anti-AChR autoantibody positive myasthenia gravis to that of over 36,000 people without the disease. They also compared the RNA molecules transcribed from the genome (transcriptome).

▪ The results showed that certain versions (or alleles) of the CHRNA1 and CHRNB1 genes, each coding for a type of acetylcholine receptor subunit, seem to increase the likelihood of having myasthenia gravis one day. They had not been identified as such until now. Moreover, the ERBB2 gene seems to be underexpressed in the muscles of those with myasthenia gravis, however, it codes for a protein that also regulates the expression of subunits of the same receptor.

▪ The same study also found differences based on whether myasthenia gravis started earlier or later in life. These two forms of the disease seem to have distinct genetic bases. Conversely, the researchers found genetic risk factors which are common in myasthenia gravis and other autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and even type 1 diabetes.

Chia R et al. Proc Natl Acad Sci U S A. 2022 Nov.

Skewed X-chromosome inactivation in women

The predominance of women among myasthenia gravis patients can be explained by hormonal factors, but not just that. The skewed inactivation of one of the two X chromosomes in some women also seems to contribute to increasing the risk of developing myasthenia gravis one day, according to the results of an Italian study.

Did you know?

X-chromosome inactivation - a natural egalitarian process

Humans have two sex chromosomes (men have XY chromosomes and women have XX chromosomes), one from their father and one from their mother. In theory then, women have twice as many genes carried by an X chromosome as men, and should therefore produce twice as many proteins coded by these genes.

▪ A spontaneous mechanism exists which restores the equal expression of these genes - the inactivation of one of the two X chromosomes, or lyonisation. It occurs during embryonic development and silences the inactivated X genes. Therefore, there is only one functional X chromosome in both men and women.

▪ Not all cells inactivate the same X chromosome. In general, each X chromosome is active in half of the body's cells and inactive in the other half. However, in some women, this ratio is not equal and the X chromosome is inactive in 75 to 90% of nuclei. This unequal ratio can lead to a higher level of expression of certain genes linked to immunity. In a

study conducted in Italy, women with myasthenia gravis had skewed X-chromosome inactivation more often than women without the disease (47% vs 17%).
Nicoli V et al. Genes (Basel). 2022 Apr.

A suspected virus

Certain infections could be part of the environmental factors facilitating the development of myasthenia gravis, the microorganism responsible for causing chronic inflammation of the thymus. A team of Chinese doctors have released a hypothesis that parvovirus B19 could play such a role.

Parvovirus B19
Parvovirus B19 is a virus that infects humans only and is transmitted through respiratory secretions, like in colds and the flu, and through blood. The infection may have no symptoms (in around a quarter of cases) or cause fifth disease (erythema infectiosum) in children. Fifth disease is most often a mild illness but is very contagious. It is associated with a red rash on the skin, flu-like symptoms and joint pain.

A study conducted in China analysed the thymuses of 708 patients who had undergone thymoma surgery, a third of whom had myasthenia gravis, looking for traces of a past parvovirus B19 infection (presence of the virus' DNA or proteins of the envelope (capsid) that surround this DNA).

- Initial results confirmed the discovery made in 2020 by a team at the Institut de Myologie, supported by AFM-Téléthon - in cases of thymoma, germinal centres (B cell activation site) are detected more often in the thymuses of myasthenia gravis patients (51%) than in those of people who do not suffer from the disease (25%).

- Moreover, there were only traces of B19 in the thymuses with germinal centres. They were mainly located in diseased cells (thymoma) and in ectopic germinal centres - the virus could be an essential contributor to the formation of these.

- However, no thymuses were found to be positive for the Epstein-Barr virus, which was recently implicated in the development of another autoimmune disease, multiple sclerosis.

Gong L et al. Ann Surg Oncol. 2023 Mar. *Lefeuvre CM et al. J Autoimmun. 2020 Jan.*
Bjornevik K et al. Science. 2022 Jan.

Innate immunity too

Did you know?

Two defence barriers - one innate, the other acquired
The immune system has two ways of defending the body against infections.
- Intrusion of a pathogen first activates innate immunity, which relies on "phagocytes" such as monocytes, macrophages, dendritic cells and neutrophils. They remove the microbe immediately, nonspecifically and without remembering this first encounter.
- Adaptive or acquired immunity mobilises other cells, such as T cells and B cells. In adaptive immunity, the time it takes to produce antibodies specific to the microbe to be fought is slower but it lasts longer as the immune system remembers this reaction, which will be faster and often more intense during subsequent contact with the same microbe in the future.

In myasthenia gravis, like in other autoimmune diseases, researchers have already identified dysregulation in adaptive immunity cells.

▪ The team at the Institut de Myologie led by Rozen Le Panse have just identified abnormalities in innate immunity cells too, such as monocytes. To achieve this, she used a technique (mass cytometry), which is able to identify immune cells much more precisely, to analyse the blood of 24 people with anti-AChR autoantibody positive myasthenia gravis without thymoma and 16 people without the disease.
Verdier J et al. Front Immunol. 2023 Jan.

A central role for macrophages in the thymus

Anti-AChR autoantibody positive myasthenia gravis is characterised by an increased expression of a type I interferon (IFN), interferon beta (IFN-β), in the thymus but not in the blood.

Interferons
Interferons (IFNs) are produced by the immune system and participate in the body's defence against infections.
▪ There are three types of IFN: type I, type II and type III. There are type I interferon genetic diseases (or interferonopathies) which result in chronic and inappropriate IFN secretion.
▪ Some autoimmune diseases (lupus, dermatomyositis, etc.) are considered to be "acquired" interferonopathies, not genetic. They are characterised by an inappropriate secretion of type I interferons (high levels in the blood and sometimes in the muscles, skin, etc.) and an increase in the level of expression of genes stimulated by the interferons which is called an "interferon signature".

A study conducted in France, and supported by the Institut de Myologie, confirmed an interferon beta (IFN-β) signature in the thymus, an organ in which there was also a significant decrease in macrophages.

▪ In mice, a decrease in thymic macrophages was accompanied by an increase in necrotic thymic cells and IFN-β expression. In humans, the decrease in thymic macrophages could reduce the thymus' ability to remove dead thymocytes (T cells undergoing education in the thymus), which would then release their contents and, in particular, their nucleic acids (DNA and RNA). However, these nucleic acids are capable of activating the same inflammatory pathways that a virus would, as well as inducing an IFN-β signature.

▪ Thus, when there is a local macrophage deficiency, stress (infection, major anxiety, etc.), which causes an increase in thymocyte death, may trigger the production of INF-β and changes to the thymus, which causes the disease.
Payet CA et al. Ann Neurol. 2023 Apr.

Advances in diagnosis and monitoring

Juvenile myasthenia gravis - a particular form of the disease

Researchers at a Canton hospital (China) analysed studies conducted on juvenile myasthenia gravis (1,109 children and adolescents in total) and compared their results to those from studies on over 900 people diagnosed as adults.

▪ As a result, they concluded that juvenile myasthenia gravis starts with ocular symptoms more often (60% vs 40%) and with bulbar symptoms such as difficulty swallowing or talking much less often (7.5% vs 39.3%), progresses to a generalised form less often (22% vs 32%), is rarely accompanied by thymoma (2% vs 13%) and is ultimately in complete stable remission much more frequently (24% vs 9%).
Lin Y et al. Front Neurol. 2023 Mar.

The refractory forms being studied

According to international criteria, **myasthenia gravis is considered to be "refractory"** to medication when it does not improve and even worsens following treatment with corticosteroids and at least two other immunosuppressants taken at the appropriate dose during a sufficient period of time. Symptoms or side effects persist that limit function, as defined by patient and doctor. This affects around 10 to 20% of patients.

Source: Sanders DB et al. Neurology. 2016 Jul.

*We use the term **"complete stable remission"** when there has been no signs or symptoms of myasthenia gravis for at least one year with no myasthenia gravis treatment being taken during this period. There is no muscle weakness when examined by a doctor, with the possible exception of weakness in the muscles involved in eyelid closure.*

Things in common

In Spain, 15 hospitals retrospectively analysed the medical records of 990 of their patients. Out of the 990 patients, 8.5% had a refractory form of myasthenia gravis.

▪ These patients were more often women, younger at the time of diagnosis, with anti-MuSK autoantibodies, a generalised form, bulbar symptoms and decompensation of the disease. At the end of a 10-year follow-up, on average, nearly 43% of the patients with refractory forms (100% of which had anti-MuSK autoantibodies) and just under 80% of the patients with non-refractory forms were finally in remission or had minimal disease manifestations.
Cortés-Vicente E et al. Ann Clin Transl Neurol. 2022 Feb.

A relapse marker on rituximab

Anti-MuSK autoantibody positive myasthenia gravis responds well to rituximab, which induces CD20-mediated B cell depletion. However, relapses often occur eventually.

▪ An international team has attempted to understand why by studying autoantibody-producing lymphocytes in nine subjects with anti-MuSK autoantibody positive myasthenia gravis who were taking rituximab. In two participants who saw an improvement on rituximab then had a relapse, anti-MuSK autoantibody-producing B cell clones reappeared several months before the relapse, which could make them a useful biomarker in the choice of treatment.
Fichtner ML et al. Acta Neuropathol Commun. 2022 Oct.

Possible genetic predispositions

A team at a hospital in Wuhan (China) hypothesised that resistance to conventional myasthenia gravis treatments could be linked, at least partly, to genetics.

▪ The study of six genes which are potentially involved in the transformation of immune-targeting drugs in 131 subjects with myasthenia gravis, 13 of which had a refractory form, showed a significant association with certain variants of the HSP90AA1 and CYP3A5 genes in these 13 subjects. These results still need to be confirmed by other studies.
Zhang Q et al. Ann Transl Med. 2022 Nov.

*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. These markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

Going the extra mile for personalised treatment
Identifying reliable biomarkers (genetic, cellular, etc.) that allow myasthenia gravis that is refractory or non-refractory to a specific drug to be distinguished before any treatment is given is a key issue.
▪ This gives hope for the future of personalised medicine, which consists of choosing the treatment that will be most beneficial to a specific patient, according to the specifications of the individual patient and their disease.
▪ The European project MG-PerMed (which stands for Myasthenia Gravis - Personalised Medicine) aims to identify biomarkers for resistance to treatments and then develop an algorithm to help doctors make treatment decisions (MG-CDST) which will ensure safer and more effective personalised care. ▪ Led by an Italian neurologist, this project involves partners from five countries, one of which is France (Rozen Le Panse's team (Institut de Myologie) supported by AFM-Téléthon).
Source: ERAPerMed 9th Newsletter January 2023.

Age matters when taking ICIs

Taking immune checkpoint inhibitors (ICI), used to treat a growing number of cancers, may cause myasthenia gravis.

▪ By studying a North American database with over 5.5 million adverse drug reaction reports, a Japanese team have shown that the risk of developing myasthenia gravis while taking ICIs increases with age. It is 2.4 times greater after the age of 75 than before.
Niimura T et al. J Clin Pharmacol. 2023 Apr.

Associated health issues to look out for

Anaemia - another reason to be fatigued

In Japan, a team of doctors studied the medical records of 215 women who were being monitored for myasthenia gravis. Their analysis showed that 40% of them had had anaemia (haemoglobin levels below 11 g/dL).

▪ Nothing differentiated them from the non-anaemic women (age, disease duration, autoantibodies, thymectomy, etc.) apart from their disease being more severe and a greater frequency of immunosuppressive treatment (corticosteroids, tacrolimus, cyclosporin, complement C5 inhibitors, etc.). Nearly six out of 10 women had an iron deficiency, the most common cause of anaemia in women in the general population. In a third of the cases, as none of the other usual causes of anaemia were found, the doctors attributed it to long-term immunosuppressant treatment.
Sekiguchi K et al. PLoS One. 2022 Sep.

Anxiety and depression - often undiagnosed

According to the results of a German study of 1,399 people with myasthenia gravis, 31% showed signs of depression (which are sometimes confused with those of the autoimmune disease) and 36% showed signs of anxiety disorders. These figures are much higher than in the German general population. Additionally, 4% showed signs of post-traumatic stress disorder (PTSD), a condition which was more common after a flare-up of the disease or a myasthenic crisis.

▪ Allowing these conditions to progress without appropriate medicinal or non-medicinal treatment is to risk seeing quality of life deteriorate. Depression in myasthenia gravis patients also has an impact on the burden of caregivers, as shown in this study. It also emphasized the value of psychotherapy: 94% of participants who underwent psychotherapy said that they benefited from it.

Marbin D et al. Sci Rep. 2022 Nov.

Low vitamin D levels

A Spanish researcher analysed five studies on vitamin D, which included 219 subjects with myasthenia gravis. Vitamin D deficiencies were more common in the myasthenia gravis subjects than in those without the disease. Vitamin D levels were on average 5.39 ng/ml lower than those of people without myasthenia gravis, a statistically significant difference.

Bonaccorso G. CNS Neurol Disord Drug Targets. 2022 Sept.

The heart can become inflamed

In a study conducted in South Korea, 10% of 247 subjects with myasthenia gravis experienced inflammation of the heart muscle (myocarditis). Two factors were linked to the significantly increased risk of developing this rare condition: producing autoantibodies directed against titin, a protein found in skeletal and heart muscle, and having had myasthenic crises.

Kim S et al. J Neurol. 2023 Mar.

A new tool for remote consultations

At the height of the COVID-19 pandemic, Italian neurologists designed a new scale (the Myasthenia Gravis TeleScore or MGTS) in order to be able to continue to monitor their myasthenia gravis patients during lockdown via video conferencing. The Italian team then demonstrated the validity and reliability of this new tool by comparing it, in 131 participants, to another scale (the INCB-MG scale) used in face-to-face consultations. Their results were comparable in 82% of cases.

Pasqualin F et al. Neurol Sci. 2022 Jul.

The impact on pregnancy is getting clearer

After analysing 974 births to women with myasthenia gravis over a ten-year period in the United States, Canadian researchers concluded that this disease does not increase the risk of caesarean section or the use of forceps.

▪ However, having myasthenia gravis seemingly comes with the increased risk of premature birth of the baby as well as a prolonged hospital stay. It is also associated with a greater risk of respiratory failure for the future mother. These results advocate for the need for expectant mothers with myasthenia gravis to be monitored by a specialised multidisciplinary team.

▪ Another large-scale study conducted on 824 pregnancies by a second Canadian team in Toronto supports this recommendation. According to its results, if the myasthenia gravis remains stable or even improves in two thirds of pregnancies, the possibility of an exacerbation of symptoms justifies close expert monitoring. The risk of myasthenic crisis is low but real during pregnancy (6.4%) and after delivery (8.2%). In the same study, 13% of newborns also experienced transient neonatal myasthenia gravis linked to autoantibodies from their mother. This possibility is a good reason to monitor any newborns born to a mother with myasthenia gravis for a few days in a specialised department.

Nicholls-Dempsey L et al. J Perinat Med. 2020 Oct.
Banner H et al. Obstet Med. 2022 Jun.

Autoantibody levels - an unclear marker

A group of European experts, including two from France, investigated fluctuations in autoantibody levels by sharing their experiences and reviewing 42 studies published on the subject.

▪ Ten of the studies reported a correlation between autoantibody levels and the severity of the disease, a link which is particularly true for anti-AChR, anti-MuSK and anti-titin autoantibodies. However, due to a lack of sufficient statistical evidence, the experts could not draw definitive conclusions as to the usefulness of these assays in the monitoring of people with myasthenia gravis.

Meisel A et al. Eur J Neurol. 2023 Jan.

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