BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

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NEWSLETTER

Belgian Charcot Foundation
Public interest foundation

Under the Patronage of Her Majesty The Queen

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ONLINE GIFT

The future is taking shape

Within the past 20 years, the number of MS drugs has increased considerably. In this issue, Dr. Danny Decoo describes the 3 latest medications used in severe progressive and relapsing forms of the disease. Lemtrada® was introduced in Belgium in 2015 and is a monoclonal antibody that destroys various types of lymphocytes. Mavenclad® was introduced on 1st August 2018 and inhibits the proliferation of activated lymphocytes. Finally, Ocrevus® was introduced on 1st March 2019. This monoclonal antibody destroys a specific group of lymphocytes known as B lymphocytes.

All three drugs have one thing in common: they were initially used to treat leukaemia or lymphoma. In the case of MS, they are used over longer periods and/or at lower doses, with the aim of changing or remodelling the functioning of the immune system. The results have been very encouraging, even though the risks of side effects are higher.

The hoped-for reconstitution of immunity occurs spontaneously, and we have no control over the new immunity, which we can only hope is no longer autoimmune. This calls for a degree of modesty. The other question is when these treatments should be used, and for which patients. Obviously, not all forms of MS require such aggressive treatment, and for this reason new disease-activity biomarkers could prove very useful. The biomarker in which researchers and neurologists currently place their highest hopes is a blood assay for neurofilament light chain (NfL), a protein specific to the nerve fibres of neurones. A high level signals axon degeneration and loss, either acute in the event of an attack, or chronic in the case of underlying cell death in the nervous system. Indeed, the disease continues to have a hidden side on which so far, we have been able to have little effect – the slow degeneration of the neuronal networks inside the brain and spinal cord, and hence the gradual progression of the symptoms of the disease. Future medications will need to address neuroprotection and remyelination. Although the results achieved thus far give cause for optimism, a great deal remains to be done before we are able to correct each of the pathological mechanisms of MS.

Prof. Dr. **Christian Sindic**
President

Visit our website : www.fondation-charcot.org

FUNDAMENTAL RESEARCH

Laureates of the Charcot Fund 2019

The two major avenues for research which may change the lives of MS patients are being confirmed. In future, multiple sclerosis will become a treatable and controllable disease. The Belgian Charcot Foundation has allocated over €500,000 to 11 teams of university researchers throughout Belgium so that this indispensable research can be started this year.

Jury of the Charcot Fund 2019

Prof. Dr. Christian Sindic, President of the Fondation Charcot Stichting.

Dr. Pierrette Seeldrayers, President of the Belgian Study Group for Multiple Sclerosis.

Prof. Dr. Alex Michotte, Professor of Neuroanatomy at the Faculty of Medicine of the VUB. Head of Clinic Department of Neurology and Anatomo-Pathology of UZ Brussel.

Prof. Dr. Alain Maertens de Noordhout, Head of Department of Neurology of CHR Citadelle Liège.

Prof. Dr. Gilles Edan, Professor of Neurology, Head of the Neurosciences Cluster at the Pontchaillou University Hospital in Rennes (France).

The selected projects

Neuroimmunology
and Immunology

Prof. Jerome Hendriks, Prof. Johan Swinnen and Dr. Jeroen Bogie
UHasselt - BIOMED
€ 53,000 / 2 years

"Lipid metabolism is key in driving the function of immune cells in multiple sclerosis lesions.In this study, we unravel whether targeting key enzymes involved in lipid metabolism promotes the beneficial features of macrophages in MS."

Neuroimmunology

Prof. Tom. Vanden Berghe and Prof. Peter Vandenabeele
UGent
€ 54,550

"Our aim: Therapeutic exploration of novel inhibitors of biological rust in multiple sclerosis"

Neuroimmunology

Prof. Anne des Rieux
UCLouvain
€ 40,000 / 2 years

"Our objective is to develop a treatment to repair the neurological damage of multiple sclerosis based on the non-invasive delivery of a therapeutic molecule protected by nanoparticles."

Neuroimmunology

Dr. Debbie Le Blon and Prof. Peter Ponsaerts
UAntwerpen
€ 43,000 / 2 years

"In previous studies performed by us, we have been able to demonstrate that modulation of the first line immune response, including microglia and macrophages, by administration of interleukin-13, leads to protection of myelin in a mouse model for MS. In a next step, we want to study this effect in a human context."

“Thanks to our donors’ generosity, this contribution to research will enable significant progress to be made in fighting multiple sclerosis over the next 5 years

– Prof. Dr. Christian Sindic

Immunology

Prof. Muriel Moser
and Dr. Isabel Vogel
Université Libre de Bruxelles
€ 45,530

“We examine the effect of the T-cell costimulatory molecule CD27 on different immune-cell subsets to explore the possibility of reducing autoimmunity and, at the same time, of restoring regulatory mechanisms.”

Immunotherapy

Dr. Judith Fraussen
and Prof. Veerle Somers
UHasselt - BIOMED
€ 45,000 / 2 years

“Age-associated B cells are elevated in the blood of 1/5 of individuals with MS and show pro-inflammatory functions which makes them an ideal target for a specific and efficient new therapy.”

Immunotherapy
and Immunology

Prof. Dr. Guy Laureys,
Prof. Veerle Somers
and Dr. Judith Fraussen
UZ Gent and UHasselt - BIOMED
€ 42,000 / 2 years

“Autologous stemcell transplantation offers us a unique opportunity to study how B cells can help in the regeneration of a normal functioning immune system in MS.”

Immunotherapy
and Immunology

Prof. An Goris
and Prof. Patrick Mathys
KU Leuven
€ 40,000 / 2 years

“In this project two KU Leuven research groups combined their expertise to understand the role of immunoregulatory B-cell subsets in multiple sclerosis and to use this knowledge in the clinic.”

Neuroimmunology,
Immunotherapy and Immunology

Dr. Inna Afonina
and Prof. Rudi Beyaert
VIB-UGent
Center for Inflammation Research
€ 47,424 / 2 years

“There is a great unmet medical need for new therapeutic strategies to improve remyelination in MS patients. The project aims to study the pathological role of interleukin-33 in MS and to analyze the therapeutic effect of a new IL-33 blocker in preclinical mouse models of MS.”

Neuroimmunology,
Immunotherapy and Immunology

Prof. Anje Cauwels
VIB-UGent
Center for Inflammation Research
€ 50,000 / 2 years

“Cytokines are potent immune modulators, but also cause toxic side effects. We develop AcTakines, dampened cytokines targeted to specific cells, and investigate their potential to treat cancer and autoimmune diseases.”

Neuroimmunology
and Neurobiology

Prof. Tim Vanmierlo,
Prof. Daniel Van de Hove
and Mme. Assia Tiane
UHasselt
€ 40,000 / 2 years

“In our project, we aim to identify epigenetic DNA imprints as a marker for ongoing remyelination in progressive MS patients.”

The recipients were awarded these subsidies during an academic session at the University Foundation in Brussels. For further information on these research projects and/or how you can support innovative research:
www.fondation-charcot.org

DIAGNOSTICS

A clue in a blood sample

Searching for a blood marker for active multiple sclerosis: the use of neurofilament light chain protein (NfL).

During an inflammatory attack of the disease, a MRI scan of the brain or spinal cord shows well-defined lesions that have captured the intravenously injected contrast agent. It is the breakdown of the blood-brain barrier caused by the inflammation that enables these active lesions to capture the contrast agent. They may be associated with new clinical signs (a relapse), or appear silently in areas which do not provoke easily identifiable external symptoms.

Basically, inflammation destroys the membranes and hence the "super-membrane" that is the myelin sheath. However, in many cases, the inflammation may also break the nerve fibre (axon) inside the sheath. Once the nerve fibre has been "transected", its protein content may be released into the cerebrospinal fluid, and finally end up in the circulating blood. This is particularly true of neurofilament light chains (NfL), which are specific to axons.

- Using state-of-the-art techniques 1,000 times more sensitive than those used in the 80s, it is now possible to assay the NfL protein directly in circulating blood. Various studies have shown that the concentration of NfL in the blood is in direct proportion to that observed in cerebrospinal fluid, so that a spinal tap is not required.

- A recent study published in March 2019 supplies information concerning the considerable potential of systematically assaying NfL in MS patients. It was performed on blood samples taken during two clinical trials on a placebo group or a group treated with interferon, compared with a group treated with fingolimod (Gilenya®). Control subjects were also tested at the same time.

This study yielded five important pieces of information:

1. the mean concentration of NfL in the blood was almost twice as high before the start of the clinical trial in the MS patients than in the control subjects.
2. prior to beginning the treatment, the concentration of NfL in the blood was correlated to the total number of lesions observed by MRI and with the number of active lesions that captured the contrast agent.
3. prior to beginning clinical testing, the concentration of NfL was predictive of this concentration at the end of the study, one or two years later.
4. a high NfL concentration at the beginning of the study was predictive of a more frequent occurrence of new lesions and new attacks, of more marked cerebral atrophy, and of a more marked increase in disability.
5. further to six months of treatment and thereafter, fingolimod reduced the concentration of NfL in the blood.

Of course, this marker is not specific to MS, since in all diseases in which there is degeneration of the nerve fibres, such as amyotrophic lateral sclerosis, cerebral thrombosis, Alzheimer's, etc., an increase in NfL content can also be observed.

Nevertheless, the fact remains that within the strict framework of MS, such testing, which hopefully will become available within the next two or three years, will make it possible to identify people at risk of developing a progressive and disabling disease, and to identify "good responders" to specific treatments.

The NfL blood levels of such good responders should typically return to normal values. However, before such a test becomes useful, the technique will need to be fine-tuned, its robustness and reproducibility checked, and reference values determined. We are nonetheless approaching a time when it will be possible to improve an individual's prognosis for MS by means of a blood test.

Prof. Dr. **Christian Sindic**

TREATMENT

An increase in the therapeutic arsenal against MS

Over the past four years, a number of immune treatments have become available. They are second-line treatments for patients with relapsing-remitting MS.

Lemtrada® (alemtuzumab)

Lemtrada® is a monoclonal antibody that acts against CD-52, an antigen present on the surface of many T and B lymphocytes. This causes lymphocyte depopulation and repopulation, which alters both their number and properties.

Lemtrada® is given intravenously for five days during the first year and for three days during the second year. The treatment then need only be repeated in the event of renewed disease activity.

Two major studies were performed to compare its effectiveness with that of an active comparator (IFN ß-1a, Rebif® 44µg, three per week, given subcutaneously).

- The CARE-MS I study was performed on patients who had never received therapy. A 55% reduction in the annualised relapse rate (ARR) was noted over two years of treatment with Lemtrada®. Statistically, the difference in sustained accumulation of disability (SAD) was insignificant.

- The CARE-MS II study was performed on patients suffering from attacks despite having been previously treated with interferon beta or glatiramer acetate. Compared with the IFN ß-1a treatment, a 49% decrease in ARR over a two-year period was noted, as well as a 42% decrease in SAD. Also, the number of patients with sustained reduction in disability (SRD) was 29% in patients treated with Lemtrada®, against 13% in those treated with Rebif®.

The 7-year follow-up data for both studies confirmed persistent efficacy. The EDSS score remained stable or improved in 78% of the MS-CARE I patients and 73% of the MS-CARE II patients compared with the initial score.

Side effects occurred on IV administration, or were delayed and had an auto-immune basis. 90% of the patients reacted to infusion. The reaction was usually slight to moderate and treated by the simultaneous administration of paracetamol, methylprednisolone and an antihistaminic drug. The symptoms chiefly included headaches, mild nausea, an itchy rash and an impression of fever. During lymphocyte repopulation, auto-immune events sometimes occurred, often between the second and fourth year following administration. The most frequent manifestations were thyroid problems (36%), a fall in platelet count with a risk of bleeding (1%) and auto-immune kidney disease (0.3%). Monthly blood and urine tests are required to detect these side effects. Finally, the risk of infection, among other things with shingles, increases during a one-month period following administration. In this case, treatment with Acyclovir is recommended.

Mavenclad® (cladribine)

Mavenclad® causes a long-lasting reduction in the number of lymphocytes. B and T lymphocyte depopulation is selective due to the fact that these cells contain a higher amount of the activating enzyme.

Mavenclad® is taken orally and the dose depends on body weight. The drug is taken for 4 or 5 days in the first and second month and the treatment is repeated after 1 year. No tablets need to be taken during the third and fourth years.

- Effectiveness was demonstrated by the CLARITY study, in which Mavenclad® was compared with a placebo over a period of 2 years. Initially, 2 doses were assessed, of 3.5 and 5.25 mg/kg. All results relate to the commercially sold dose, which is 3.5mg/kg.

- Cladribine treatment reduced ARR by 57.6% and 79.7% of the subjects remained free from attacks after two years, against 60.9% of those taking a placebo. The proportion of progression-free patients at the end of 6 months (EDSS score) increased by 47%. The number of patients who had not suffered attacks over a period of 2 years was 80%. The NEDA* rate was 47%.

The main side-effect of cladribine is lymphopenia. The lymphocyte count is therefore checked prior to beginning the treatment, then during the second and sixth months before completing each cycle. Shingles also occurs more frequently. Although care must be taken to avoid infections, there was no increase in rare infections during this study.

Ocrevus® (ocrelizumab)

Ocrevus® is a monoclonal antibody that specifically targets CD20+ B cells. This causes B lymphocyte depopulation. However, the cells which preserve long-term immune memory are not affected.

Ocrelizumab is administered intravenously every 6 months.

- 2 Phase III studies (OPERA I & II) assessed the drug's efficacy compared with an active treatment with IFN ß-1a (Rebif® 44µg, 3/week, given subcutaneously). Both studies yielded similar results: a reduction in ARR (46%/47%), a 40% increase in the number of patients whose disease had not progressed in 6 months (OPERA I & II). NEDA was achieved in 47.9 and 47.5% of cases respectively.

- Finally, the ORATORIO study should be mentioned, during which the use of ocrelizumab as a first-line treatment in primary progressive MS significantly reduced (25%) the number of patients whose disability continued to progress after 6 months (CDP).

Reactions may occur at the time of administration and drugs therefore need to be given preventively (as in the case of Lemtrada®). These side effects mainly occur at the time of the first administration. Particular attention needs to be paid to infections, especially Hepatitis B, which must be excluded prior to beginning the study. However, the studies show that severe side effects, especially severe infections, occur with about the same frequency as in the case of treatment with interferon beta-1a or a placebo.

Dr. **Danny Decoo**
Neurologist

**NEDA: No Evidence of Disease Activity*
This is a new goal in the treatment of multiple sclerosis. Patients with relapsing-remitting MS are treated with disease-modifying drugs (DMDs) so that they achieve a state in which:

- *they have no relapses*
- *their disability does not increase (as measured on the EDSS scale)*
- *no new or active (enhancing) lesions appear on their MRI scans.*

The references of all the studies mentioned are available on request to the Belgian Charcot Foundation.

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Brussels 20km on May 19th 2019. Please support our runners on www.fondation-charcot.org

With the support of

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