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Final report – Charcot Clinical Research Fellowship 2022-2024

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Metformin Add-on Clinical Study in Multiple Sclerosis to Evaluate Brain Remyelination And Neurodegeneration (MACSiMiSE BRAIN)

Project

Failure of remyelination and repair in multiple sclerosis (MS) is thought to be an important driver of disability progression in MS. Current disease modifying treatments (DMT) for MS mainly exert their effect via modulation of the adaptive immune system. Despite various efforts, treatments focussing on remyelinating and neuroprotection are not available to date. A great unmet need in MS research is to understand the mechanisms of remyelination and to construct treatment options to promote it. Due to its anti-inflammatory, antioxidant and remyelinating capacities, metformin was recently put forward as a highly promising repurposed drug to undergo immediate testing in clinical trials in progressive MS.
The MACSiMiSE-BRAIN project aims to reduce the societal and personal burden of progressive multiple sclerosis, by validating the therapeutic use of metformin in a randomised placebo-controlled clinical study.

Rationale

MS is a common neuroinflammatory and neurodegenerative disease of the central nervous system (CNS), affecting more than 2.9 million people worldwide. Pathophysiologically there is an auto-immune inflammation causing acute demyelination and neurodegeneration with concomitant chronic inflammation and axonal loss causing progressive disability accumulation. The neurodegenerative processes are thought to be driven by compartmentalised inflammation, oxidative stress, increased metabolic demand of demyelinating axons, iron accumulation and failure of compensatory mechanisms, such as neuroplasticity and remyelination. Current therapies for MS aim to control the inflammatory reaction and are not specifically targeted to neurodegenerative processes such as axonal protection and remyelination. One way to target the pathophysiology of the progressive form of the disease is to promote remyelination. Future treatment of MS will likely consist of a combination of immunomodulatory DMT with neuroprotective and remyelinating agents.
Metformin has been shortlisted as a highly promising repurposed drug to undergo testing in clinical trials in progressive MS (PMS). Metformin is traditionally used in the treatment of patients with type 2 diabetes mellitus, but may act on the pathophysiological pathways in MS by its anti-inflammatory, antioxidant and remyelinating capacities. Proof-of-concept is available for the use of metformin in PMS as evidenced by 2 different animal models. Moreover, a pilot clinical study in MS patients provided preliminary safety and suggested anti-inflammatory effects of metformin in this patient group. Consequently, our team set up a phase IIb randomised placebo-controlled clinical study to investigate the role of metformin in the treatment of PMS.

Progress

In the past two years I have worked on the FWO-TBM funded project MACSiMiSE BRAIN clinical trial (NCT05893225): a randomised clinical trial in patients with progressive multiple sclerosis, to evaluate the efficacy of metformin versus placebo. The aim is to investigate whether metformin is able to slow down or stop disease progression and maybe restore function in patients. I have a coordinating function in the trial and worked on the clinical trial protocol and amendments, investigator's brochure, informed consent forms and performed site initiation visits with the team of UZA Clinical Trial Center. Recruitment, inclusion and follow-up of study participants at UZA is also one of my tasks.
Additionally, I have set up a substudy for biomarkers in blood serum (Neurofilament-light (NFL) and Glial Fibrillary Acidic Protein (GFAP)) as potential biomarkers to monitor disease progression and treatment response in the clinical trial. This substudy is funded by a grant from the National MS Society USA.

Aside from the work on the MACSiMiSE BRAIN clinical trial, I have conducted a systematic review concerning remyelinating capacities of current DMT for MS, which was registered on PROSPERO (CRD42022385566). From the systematic review it was clear that some preclinical data suggest that various treatments could enhance remyelination, but clinical trials could not yet demonstrate a definite effect of DMT on remyelination, due to absence of availability of appropriate outcome measures of remyelination. Currently the manuscript is being edited with the final remarks. I hope to submit this manuscript for peer-review to an international peer-reviewed open-access journal (e.g. Neurology, neuroimmunology and neuroinflammation or Multiple Sclerosis Journal) at the end of 2024 (Deliverable 1).

During the last year, I have shared updates on MACSiMiSE BRAIN with the research community on several occasions, including a presentation at the online international Women in MS meeting (iWIMS) on April 3, 2023, and poster presentations at the interuniversity Flemish MS research days on May 11, 2023, ECTRIMS from October 11-13, 2023, and the European Charcot Foundation annual meeting on November 9, 2023. On June 1st, 2024, in the context of World MS Day, we also presented the MACSiMiSE-BRAIN study at a research event organized by University Hospital Antwerp, specifically aimed at patients and their family and friends.
I am the shared first author of a manuscript describing the clinical trial protocol which was published in Frontiers in Immunology (impact factor 5.7) in February 2024 (number of citations so far: 4) (Deliverable 2).

It took longer than expected to initiate the clinical trial. Firstly, there was a transitioning period to submit clinical trials to a new centralized European system (CTIS) to obtain ethical and regulatory approvals. Additionally, the organisation of study drug and placebo production and distribution to the sites was challenging. Moreover, setting up contracts between sites and amending study contracts for the biobank sub study took considerable time. However, all clinical trial sites are now fully initiated, operational and actively recruiting participants. We have started recruiting patients since December 2023. As of October 2024, we have screened 97 patients and randomised 84 patients. I act as sub-investigator and see patients in UZA for onsite visits (Deliverable 3). Once all patients are randomized, our group will analyse the baseline costs of illness in this patient population. I will be a co-author on the manuscript describing this data.

During the last year I worked part-time as a resident in neurology, with a special focus on multiple sclerosis and other neuro-inflammatory diseases. Two days a week, I conduct dedicated consultations for MS patients and patients with other neuro-inflammatory diseases, which gives me the opportunity to expand my knowledge on diagnostic approaches and treatment options. I attend a weekly team meeting concerning discussions of complex neuro-inflammatory patient cases, diagnostic questions and multidisciplinary services for MS patients. I have been taught to conduct clinical tests (Symbol Digit Modalities Test, 9-Hole Peg Test, Timed 25-Foot Walking Test, 6- Minute Walking Test), relevant for clinical follow-up and for clinical trials.
Furthermore, I am co-author on the ACTiMS study, an academic study investigating actigraphy for MS patients. This study was presented on ECTRIMS 2024 and a manuscript is currently being prepared for publication. Moreover, I have rated MS patients in commercial clinical studies (O'HAND (Roche), Remodel I/II (Novartis), cosMOG (UCB)) and recruited patients in academic studies (Acti-MS (Centre de Référence Liégeois des Maladies Neuromusculaires, Centre Hospitalier Régional de la Citadelle, Liège), ReMSCA (University Hospital Antwerp)) conducted in the university hospital of Antwerp.
I have obtained a Good Clinical Practice certificate and an Expanded Disability Status Scale-Neurostatus certification.

Future aims
As we wanted to avoid segmented publication and incidentally lower the impact of the final manuscript, our group decided not to publish baseline clinical and MRI characteristics from the MACSiMiSE BRAIN clinical trial. Data cleaning and analysis of all study data are planned in 2027 and we expect to publish the manuscript in a high impact journal. We aim to share the findings with the scientific, patient and lay community by Q4 2027.

During the last two years, my interest in unravelling the mechanisms of remyelination has grown even more, which resulted in the start of a doctoral research, focussing on remyelination as a treatment option in progressive MS, of which the MACSiMiSE BRAIN study is an integral part. Additionally, I have set up an observational, cross-sectional and longitudinal cohort study intended to investigate plasma biomarkers of remyelination in people with MS with distinct disease courses (and a control sample).
I am guided in my doctoral research by my two supervisors prof. Willekens and dr. Reynders, who have taken up the roles of promotors, after the emeritate of prof. Cras. It is my ambition to complete and defend my thesis by the end of 2027.

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Conclusion

I would like to express my profound gratitude towards the Belgian Charcot Foundation for granting me this clinical research fellowship.

With this grant I was able to dedicate myself as co-investigator to the start-up and co-coordination of a multicentre randomised placebo-controlled clinical trial aiming to reduce the burden of progressive multiple sclerosis by validating the therapeutic use of metformin.

This Charcot clinical research fellowship has provided me with many opportunities to grow as a clinician-researcher, as I was able to embark on a doctoral research programme investigating treatment options for progressive MS. Without this clinical research fellowship, it would not have been possible to dedicate myself to MS research in the same way. Through my doctoral research, I hope to gain better insights into remyelination and treatment of progressive MS patients. I will continue to strive to become an outstanding clinician- researcher in the field of MS and to have an impact on increasing the treatment options to stop or delay disability progression.

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Read and approved by
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Promotor