My prog-MS ezine

For people with progressive MS and other interested people

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Hello and welcome to the latest edition of my ezine about progressive Multiple Sclerosis and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer who lives in Birmingham, UK. I'm 62 years old.

In this issue are 7 pages of prog-MS news stories. There are also two features. One on page 5 is on taking part in MS product trials – things like new disability aids and adaptations. There's also a feature on a new drug that targets a type of immune cells called mast cells that have until now had little interest to MS researchers. All that could soon change. See page 10 for details.

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Trial to Test drug in SPMS, PPMS Patients with little walking ability

An upcoming Phase 2 clinical trial, called ChariotMS, will test whether Mavenclad (cladribine) can slow a worsening of hand and arm function in people with progressive multiple sclerosis (MS) and very limited walking abilities.

Patients reliant on wheelchairs or aids to walk even short distances generally have advanced disease, often marked by progression to secondary progressive MS and scores of 6.5 or above on the Expanded Disability Status Scale (EDSS).

The trial is unusual in that advanced MS patients are typically not included in clinical trials, in part because the trials typically use walking ability as a key measure of effectiveness when testing potential disease-modifying therapies (DMTs).

Rather than focusing on changes in walking ability as an efficacy determinant, ChariotMS will use the Nine Hole Peg Test, a measurement of hand and arm function. Enrolled patients will also undergo MRI scans to assess the treatment's effect on brain lesions.

The U.K. trial aims to recruit 200 people with EDSS scores between 6.5 and 8.5, meaning they cannot walk more than 20 metres (about 65 feet) using two crutches, or are completely unable to walk. All eligible patients will still retain some function in their arms and hands. As such, the trial is open to people with advanced and progressive disease, regardless of whether their MS is primary progressive (PPMS) or secondary progressive (SPMS), without any upper age limit. Patients will be randomly assigned to either Mavenclad or placebo tablets over the study's 24 months. Mavenclad, approved to treat highly active relapsing MS, works by killing the immune cells that drive disease-causing inflammation in the nervous system of people with MS.

ChariotMS is being funded in part by Mavenclad's developer, EMD Serono (Merck KGaA outside of the U.S. and Canada); it is also supported by government agencies and charities, including the MS Society and Barts' Charity, both in the U.K., and the National MS Society in the U.S. ChariotMS is set to begin enrolment in 2021 at 20 centres across the UK, and plans are being put in place to limit the effects of the COVID-19 pandemic on the trial.

Individuals interested in this trial and who think they might be eligible are encouraged to get in touch with their doctors about a possible referral, or to email the study team at chariot@qmul.ac.uk. ***For details of sources for all news stories go to page 13***

Imaging Reveals Ibudilast's Neuroprotective Effect

A non-invasive retina imaging technique known as optical coherence tomography (OCT) provides evidence of the neuroprotective effect of ibudilast (MN-166) — a twice a day tablet designed to reduce inflammatory responses in people with primary and secondary progressive MS

The results of a new trial which show this effect were published in the study "Optical coherence tomography outcomes from SPRINT-MS, a multicentre, randomized, double-blind trial of ibudilast in progressive MS," published in the Multiple Sclerosis Journal.

Thinning of the peripapillary retinal nerve fiber layer (pRNFL), one of the eye's retina layers, is associated with the loss of brain volume and other measures of MS activity and progression. Thus, it has been proposed as a biomarker for MS progression, with OCT used as a way to measure it.

Ibudilast, developed by pharmaceutical company MediciNova, is thought to ease the neuroinflammation underlying MS symptoms by blocking the activity of four pro-inflammatory proteins while activating an anti-inflammatory signalling molecule. In the SPRINT-MS trial researchers measured the changes in brain atrophy in response to either ibudilast or a placebo over 96 weeks (about 22 months) among patients with primary or secondary progressive MS. OCT was used to track changes in the participants' pRNFL in response to treatment.

Previous data from the trial showed a 48% reduction in brain volume loss with ibudilast treatment compared with the placebo group. Now, the researchers analysed in more detail the OCT data. It was found pRNFL thickness increased overall in the ibudilast group (increase of 0.0424 micrometer per year) and decreased in the placebo group (decrease of 0.2630 micrometer per year).

Macular volume, an area within the central area of the retina, decreased less among patients receiving ibudilast than those receiving a placebo, also. Overall, the data suggested that ibudilast seems to reduce retinal thinning in progressive MS patients. According to the team, this was the first multicentre clinical trial to employ OCT as an outcome in studying progressive MS.

"Together," the researchers concluded, "these results potentially provide some support of a neuroprotective role for ibudilast in progressive MS and guide the use of OCT in future trials in progressive MS."

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Prog-MS Patients Urged to Enrol in Phase 3 Trials of Tolebrutinib

Investigators are looking for people with progressive forms of MS to participate in two Phase 3 clinical trials assessing the safety and effectiveness of tolebrutinib, an oral BTK (Bruton tyrosine kinase) inhibitor that is being investigated as a potential treatment, the US National Multiple Sclerosis Society announced in a press release.

Both studies — HERCULES (NCT04411641) and PERSEUS (NCT04458051) — are being sponsored by Sanofi Genzyme, the company that holds tolebrutinib's commercial rights. The trials are recruiting participants at several locations across the U.S., Europe, and Canada.

The studies intend to recruit about 2,280 adult patients, including 990 (ages 18–55) with primary progressive MS to be enrolled in PERSEUS, and 1,290 with non-relapsing secondary progressive MS (ages 18–60) to be enrolled in HERCULES.

Discovered originally by Principia Biopharma, tolebrutinib is an oral small selective inhibitor of the enzyme Bruton tyrosine kinase (BTK), which is important for the activity and survival of antibody-producing B-cells. These immune cells are thought to be one of the key drivers of brain and spinal cord inflammation in MS patients.

By lowering BTK activity, tolebrutinib is expected to reduce B-cells' activity and reduce inflammation associated with MS. In addition to those effects on B-cells, the experimental therapy also is thought to inhibit the activity of microglia (the immune cells of the brain), which has been linked to MS progression.

HERCULES and PERSEUS are both double-blind, randomized, placebo-controlled studies designed to compare the safety and effectiveness of tolebrutinib to that of a placebo, when given once daily for 24–48 months (two to four years).

Patients enrolled in both trials will need to visit their nearest study site up to 16 times. They will undergo several clinical exams, including standard blood tests and brain MRI scans, and will complete multiple questionnaires over the course of the studies.

Those who wish to know more information about the studies, including their eligibility to enroll, may contact Sanofi by email at US@sanofi.com,

Of note, two other Phase 3 clinical trials — GEMINI 1 (NCT04410978) and GEMINI 2 (NCT04410991) — comparing tolebrutinib with the approved MS therapy Aubagio, also marketed by Sanofi, are currently enrolling people with relapsing MS, which includes active secondary progressive MS.

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Why it pays you to take part in MS product trials

A friend of mine earns thousands testing new drugs in drugs safety trials. She says these trials, called Phase 1 trials, are a "nice little earner". My friend is young, healthy, knows the risks, and is prepared to take them and the money too.

Having a medical condition, I can't take part in these drugs safety trials, although I can take part in later stage unpaid MS drugs trials. I can also take part in MS product trials and here I do get paid. Yes, there are many products people with MS use which need to be tested and product testers get paid and quite nicely too. I am talking, of course, about trials of medical aids and adaptations. Here there is what you might call a healthy market for people to test out new products, as I know from personal experience.

About five years ago I was approached by a marketing company who wanted me to take part in a focus group to develop a name for a new MS drug. I have no idea why I was approached but as I have worked on TV consumer programmes for the BBC and, of course, written for the press about MS this may have played a part. At the focus group, various names were flashed for seconds on a screen and five MSers had to give their instant views on these names. I was paid more than £100 for a couple of hours work and made what I hope were intelligent and appropriate suggestions.

Someone must have been impressed by my contribution at the focus group because after that initial experience I became increasingly in demand as a tester of MS related products. Over the past few years, I have tested everything from apps to remind you to take drugs on time, auto injectors for injectable disease modifying drugs and also several trials for incontinence pads which can be obtained either on prescription or over the counter at a local pharmacist. Happily, as someone who has experience of product trials and also uses pads daily, I have all the credentials needed to test out these products.

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Continued from page 5 My latest survey last summer was once again a test of the design of male sanitary pads. This trial was slightly different to the previous trials because I was not allowed to see the 11 products I was testing out before a skype interview took place. I imagine the aim was to see my immediate response as I examined the products and capture visual images of my first impression as I opened the packages, but in reality you never know. Even if I did know I could never disclose because I signed a non-disclosure clause in the

contract and after the interview I was required, for reasons of preserving product confidentiality, to return all 11 products to the market research firm in a pre-paid envelope marked “confidential”.

Talking to other friends with MS I know I am not the only person who does this sort of product testing. A friend of mine was once a disabled mystery shopper for a supermarket chain and also once checked out the accessibility of trains for one of the train operating companies. Like me, she saw product testing as an interesting part-time job which paid her varying amounts of money. Another friend with MS, who uses a wheelchair, tests the accessibility of music festivals. He does this for an access group and gets free tickets in return. It may not earn him anything but he has had free access to some big music events including ones where tickets cost up to £200.

As everyone with MS knows, you take a big hit financially after diagnosis and this fact has been supported by research, doubtless carried out by well-paid academic researchers. The reason for this loss of earnings after diagnosis is that the illness takes away things like mobility, energy and mental sharpness, things that you previously relied on to get to work and earn money. That’s just how things are, particularly with progressive MS.

Product testing, therefore, is a small compensation for this loss of earnings, post-diagnosis. Since starting my product tests I have come to realise that although MS can rob you of much in your career it can also give you a new part-time occupation, that of testing products in the MS marketplace and for this you can get paid hundreds of pounds a year.

I would be first to admit the few hundred pounds I earn from product testing each year is nothing compared to the tens of thousands I earned previously and is a paltry sum compared to the thousands earned each year by my friend on her drug safety trials. However, it’s reassuring to know that despite MS I can still earn hundreds a year from my own small scale consumer trials.

Like my friend’s daughter I would agree, it can be a nice little earner.

Picture: Dario Martinez/ unsplash

News

Restoring Key Protein Level May Help Halt MS Progression

Levels of a protein called Neuregulin-1 beta 1 (Nrg-1beta1) decline with the progression of MS, a new study suggests. The finding support the potential of

this protein as a predictor of MS progression and suggest that restoring its levels may help halt it.

The study, "Neuregulin-1 beta 1 is implicated in pathogenesis of multiple sclerosis," was published in the journal Brain. Now, a team led by researchers at the University of Manitoba, Canada, discovered that the levels of a particular protein, called Nrg-1beta1, decline with MS onset and progression.

Using the experimental autoimmune encephalomyelitis (EAE) mouse model, a well-established model for human MS, the researchers found that the levels of Nrg-1beta1 declined within spinal cord lesions as well as in the blood and spleen before the animals showed symptoms (pre-symptomatic stage). That decline continued as the disease progressed.

Restoration of the levels of Nrg-1beta1 while MS is developing was sufficient to delay the onset of the disease and ease the effects of disease progression and severity in the MS mouse model.

Of note, therapeutic restoration of Nrg-1beta1 showed positive effects when given as a preventive treatment — prophylactically — before symptoms began, and also upon symptoms, known as symptomatically, and both acutely and chronically.

According to the team, Nrg-1beta1 exerted its therapeutic benefits not by suppressing the immune system but rather by balancing it out. Specifically, Nrg-1beta1 lessened the infiltration of certain immune cells into the central nervous system (CNS), comprised of the brain and spinal cord. Moreover, Nrg-1beta1 promoted the increase of immune cells that repair and help control the immune system in the MS mouse model.

"Taken together, our new findings in multiple sclerosis and experimental autoimmune encephalomyelitis have uncovered a novel regulatory role for [Nrg-1beta1] early in the disease course and suggest its potential as a specific therapeutic target to ameliorate disease progression and severity," the researchers wrote.

"We are hoping that we can use this study as a foundation to build on and hopefully at some point translate these discoveries into clinical therapies," they added.

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News

First results of NurOwn's Cell Therapy Trial expected in April

Patient dosing has finished in a Phase 2 clinical trial testing NurOwn, BrainStorm Cell Therapeutics' investigational cell-based therapy for people with progressive MS, the company has announced. The trial's first results are expected in April.

"Now that all dosing of the NurOwn Phase 2 progressive MS clinical trial is complete, we will shift our focus to completing all remaining patient clinical trial assessments and biomarker analyses," Ralph Kern, MD, BrainStorm's president and chief medical officer, said in a press release.

"We look forward to generating clinical trial top line results by the end of the first quarter 2021 and to advancing this promising treatment option based on a thorough analysis of the clinical trial outcomes," Kern added.

NurOwn involves collecting mesenchymal stem cells (MSCs) from a patient's own bone marrow, and expanding and maturating them into cells that produce high levels of neurotrophic factors (NTF) — molecules that promote nerve cell growth and survival. MSCs are stem cells that can generate a variety of other cell types.

The mature cells — called MSC-NTF cells — are then injected into the patient's spinal canal to promote and support nerve cell repair. Using a patient's own cells minimizes the risk of an immune reaction, as might occur with cells from a donor.

The open-label Phase 2 trial (NCT03799718) is evaluating NurOwn's safety and effectiveness in 20 adults, ages 18 to 65, with either primary progressive MS or secondary progressive MS. Patient enrolment started in March 2019, and the trial is taking place at five U.S. sites.

The study's main goal is to assess the safety of the procedure. Effectiveness goals include changes in patients' walking abilities or finger dexterity, as well as in the levels of neurotrophic and immunomodulatory biomarkers in their cerebrospinal fluid (the liquid that bathes the brain and the spinal cord).

BrainStorm also is evaluating NurOwn as a potential therapy for other neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease, as well as for autism spectrum disorder.

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News

Parasite May Protect Against MS, Study Suggests

Toxoplasmosis, an infection by the parasite Toxoplasma gondii, may confer a certain level of protection against MS, according to the results of an Italian study.

The study, "Toxoplasma gondii and multiple sclerosis: a population-based case-control study," was published in the journal 'Scientific Reports'.

Exposure to certain infectious agents early in life may serve as a protective factor for autoimmune diseases such as MS, according to a theory called the 'hygiene hypothesis'. This hypothesis theorizes that living in an environment with a high incidence of infectious diseases builds a resistance of sorts, protecting inhabitants in that area against allergic and autoimmune diseases.

T.gondii, as Toxoplasma gondii is known, is a parasite that is able to infect humans. Domestic cats and their relatives are the only known hosts for the parasite, which can infect most species of warm-blooded animals, including humans, according to the Centers for Disease Control and Prevention. Estimates suggest that at least one-third of the world's population is infected by T.gondii, yet this infection is generally asymptomatic in people with a healthy immune system. However, for people with compromised immunity, severe symptoms — like encephalitis, or inflammation of the brain — may occur. Previous studies have pointed to T.gondii as a protective factor for certain autoimmune diseases, such as rheumatoid arthritis and lupus, but its association with MS remains unclear.

To learn more about that association, researchers at the University of Catania, in Italy, collected blood samples from 129 MS patients (mean age 44.7 years) and 287 healthy individuals (mean age 48.1 years), who served as controls. About two-thirds of the individuals in both groups were women.

To determine whether someone had been infected with T. gondii, the researchers examined blood samples from each participant for the presence of antibodies against the parasite. These antibodies were detected in 38 MS patients (29.5%), and in 130 of the healthy controls (45.4%). The fact that more healthy individuals had been infected suggested that this parasite worked to protect against MS development. A statistical analysis demonstrated that people who had been infected were about 50% less likely to develop the autoimmune condition than those with no history of infection.

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Will lab research lead to a new licensed drug for non-active SPMS in 2021?

Although the cause of MS is still a mystery, there is general agreement that the disease and its progression involve a combination of two processes, neurodegeneration and autoimmunity.

Several types of immune cells, notably T and B cells, have traditionally been thought to play a central role in MS autoimmunity and neurodegeneration. However, there are many other types of immune cells in the body. Strangely, there has been until recently little interest in looking at the involvement of some of these other immune cells, in particular mast cells.

Mast cells are immune cells which cause sudden and severe inflammatory responses such as allergic reactions. When stimulated by a substance that causes an allergy, mast cells release a mixture of compounds into the surrounding tissues in a process called “de-granulation”. This causes sudden and sometimes potentially life-threatening reactions, something known as “anaphylaxis” or “anaphylactic shock”.

At the turn of the 20th century, it was found that mast cells accumulate at the edge of MS plaques. A century later, in 2001, researchers found the presence of mast cells and an increased concentration of mast cell constituents in MS plaques themselves. More recently, evidence has been found that mast cells play a crucial role in the inflammatory process and subsequent demyelination seen in MS. Evidence has also been found that several mast cell constituents are capable of causing demyelination and degradation of myelin proteins, with breakdown products stimulating further mast cell degranulation and contributing to activation of Myelin Basic Protein (MBP)-reactive white blood cells. Degranulation of mast cells next to myelin serves as a focus for inflammatory demyelination, leading to the damage of myelin sheaths by the action of enzymes as well as the discharge of “vasoamines” - substances which cause blood vessels to weaken or become leaky, and help circulating blood cells move across the blood brain barrier **Continued on page 13**

Continued from page 10 . If all this is correct then it would mean that mast cells should be a target for MS drug treatments. For some time it has been known that inhibitors of mast cells like anti-histamine drugs can effectively slow the progression and severity of an animal model of MS called experimental allergic encephalomyelitis (EAE) where these drugs limit the extent of mast cell degranulation, so mast cell research in MS is long overdue.

Now an MS drug which targets mast cells called masitinib is in trials. Masitinib is an experimental drug targeted at secondary and primary progressive MS. It is taken as a tablet, twice daily, and it blocks biochemical processes involved in inflammation and immune responses, targeting both mast cells. In clinical trials it has produced impressive results.

Last year, a Phase 2b/3 clinical trial reported masitinib's safety and effectiveness in 656 adults with primary or non-active secondary progressive MS. Participants were randomly assigned to receive either one of two doses of masitinib or a placebo (dummy drug), twice a day, for 96 weeks. The researchers also analysed the risk of disability progression and of reaching an EDSS score of 7.0 — reflecting a level of disability severe enough that you are restricted to a wheelchair. The results showed the patients treated with the low-dose masitinib had significantly slower disability progression than those in the placebo group, irrespective of their type of progressive MS. Those receiving masitinib's low dose were 39% more likely to have either reduced disability or fewer disability worsening events than those given a placebo. These masitinib-treated patients also showed a significantly lower risk of confirmed (3-month) disability progression by 37% over 96 weeks. The patients who received masitinib also had a 98% lower risk of reaching an EDSS of 7.0, compared with those in the placebo group.

Given that masitinib has been extensively researched and found to be effective, one is bound to ask when will masitinib become available? Here the situation is slightly unclear. At some point an application will be made to the licencing authorities. Will these authorities be satisfied that the Phase 2b/3 trial is enough proof? Here there is some suspicion that a further "confirmatory trial" will be sought. As one neurologist put it: "For Europe a second Phase 3 would be helpful." Another neurologist added: "We need a grant, i.e. money, to do this study. I predict it will cost in the order of £4M to do." As someone who has SPMS without relapses I am tempted to say I hope that masitinib gets approval as soon as possible. Those of us, like me, with progressive MS do not have time to wait.
Picture credit: Louis Reed/unsplash

News

Mayzent Aids Cognitive Processing in SPMS, Trial Suggests

Mayzent (siponimod) significantly improved cognitive processing speed in people with secondary progressive multiple sclerosis (SPMS) compared with

a placebo, according to additional analyses of two-year data from the EXPAND Phase 3 trial.

While no approved therapies in the U.S. currently target cognitive impairment in MS, "our study found that [Mayzent], which is prescribed to slow the progression of physical disability in MS, may also help improve cognitive processing speed in people with advanced MS," Ralph H. B. Benedict, PhD, the study's first author, said in a press release.

Benedict is a professor of neurology at the University of Buffalo in New York, and a member of the American Academy of Neurology.

Since significant improvements were seen in only one of the three cognitive function tests included in the trial, "more research should further examine how [Mayzent] affects scores on a broader array of thinking and memory tests," Benedict added.

These findings were reported in the study, "Siponimod and cognition in secondary progressive multiple sclerosis: EXPAND secondary analyses," published in the journal Neurology.

Mayzent, developed by Novartis, is an oral treatment approved in the U.S. for adults with clinically isolated syndrome, relapsing-remitting MS, and active SPMS.

In a Novartis-funded study, researchers evaluated the effects of treatment on patients' cognitive function over the first two years of the trial's placebo-controlled phase.

Participants underwent cognitive assessments before the start of treatment and every six months thereafter. Cognitive skills were assessed using the Symbol Digit Modalities Test (SDMT) and the Paced Auditory Serial Addition Test (PASAT) to measure cognitive processing speed, as well as the Brief Visuospatial Memory Test-Revised (BVMT-R) for visual or spatial memory. Results showed a significant improvement in SDMT scores among Mayzent-treated patients after one year, one-and-a-half years, and two years of treatment, compared with those given a placebo — whose scores remained stable. Based on SDMT scores, the therapy was found to be superior to placebo at lowering patients' risk of a sustained, clinically meaningful worsening in cognitive processing speed — by 21% — and at increasing their chances of a confirmed improvement (a four-point sustained increase in SDMT scores) — by 28%. **For further details of all news stories go to page 13**

References contact details etc

Page 2 Chariot trial story

https://multiplesclerosisnewstoday.com/news-posts/2020/11/19/new-trial-for-people-with-advanced-progressive-ms-starting-soon/

Page 3 Ibudilast story

https://multiplesclerosisnewstoday.com/news-posts/2020/11/12/ibudilast-neuroprotective-effect-in-progressive-ms-patients-revealed-via-non-invasive-oct-imaging-technique-sprint-ms-trial-shows/

Page 4 Tolebrutinib story

https://multiplesclerosisnewstoday.com/news-posts/2020/12/17/progressive-ms-patients-enroll-phase-3-trials-tolebrutinib

Page 5 Disability product testing

Among the many organisations offering this are abilitynet.org.uk
https://abilitynet.org.uk/careers/disabled-user-tester

Page 7 Neuregulin story

https://multiplesclerosisnewstoday.com/news-posts/2020/12/17/restoring-neuregulin-1-beta-1-protein-levels-may-help-halt-ms-progression-study-suggests

Page 8 Nurown story

https://multiplesclerosisnewstoday.com/news-posts/2020/12/21/dosing-finishes-phase-2-trial-nurown-cell-therapy-progressive-ms/

Page 9 Parasite story

https://neurosciencenews.com/microglia-ms-17178/

Page 10 masitinib story

For further details check out the MS Trust's website at
https://mstrust.org.uk/a-z/masitinib-ab1010 also look at the website
https://www.ab-science.com/ab-science-presents-phase-2b-3-study-results-in-progressive-multiple-sclerosis-at-the-worlds-largest-multiple-sclerosis-research-conference/

Page 12 Mayzent story

https://multiplesclerosisnewstoday.com/news-posts/2020/12/18/mayzent-aids-cognitive-processing-speed-spms-phase-3-expand-trial-suggests/

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