

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 39, September/October 2021

Hello and welcome to the later than usual edition of my ezine about progressive Multiple Sclerosis and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer from Birmingham, UK. I'm 63.

In this issue are seven pages of prog-MS news stories. There are also two features. One on page 5 is about walking and the question of whether the timed 25 foot walk test has any point. There's also a feature on a little talked about subject, but one that affects a lot of us and has recently affected me quite severely. The subject is going for a poo . See page 10 for details.

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News

MediciNova Planning Phase 3 Trial of Ibudilast for SPMS

Pharma company MediciNova is planning to launch a Phase 3 clinical trial that will test its experimental drug ibudilast (MN-166) in people with secondary progressive multiple sclerosis (SPMS) without relapses.

Originally developed by Kyorin Pharmaceutical, ibudilast is an orally available small molecule drug approved in Japan since 1989 to treat post-stroke complications and asthma. Because it's small molecule the drug can cross the blood-brain barrier — the highly selective membrane that prevents circulating microbes and potentially harmful molecules from reaching the central nervous system (CNS; brain and spinal cord) — overcoming a common obstacle of many other potential MS therapies.

Ibudilast is thought to potentially have anti-inflammatory action in the CNS by blocking the activity of four pro-inflammatory proteins — IL-1 beta, TNF-alpha, IL-6, and TLR4 — while possible activating the anti-inflammatory signalling molecule IL-10. The drug has received fast track designation from the U.S. Food and Drug Administration (FDA) for progressive MS, which is meant to accelerate its clinical development and regulatory review.

A previous Phase 2b clinical trial, called SPRINT-MS (NCT01982942), evaluated the safety, tolerability, and effectiveness of ibudilast in 255 adults with either primary MS or secondary progressive MS. Results showed that ibudilast significantly slowed brain volume loss (by 48%) and retinal thinning compared with a placebo. The retina, the light sensitive inside lining of the eye, is affected by MS, and its thinning is associated with brain shrinkage and other measures of MS activity and progression.

According to MediciNova, encouraging results were particularly pronounced among SPMS patients without relapses. After discussing the data with the FDA, the company is planning to recruit only this patient group in the upcoming Phase 3 trial. Its main goal will be to evaluate whether ibudilast can slow disease progression, as assessed through the proportion of patients with confirmed disability progression in the Expanded Disability Status Scale lasting at least three months.

The investigational therapy is also being tested in clinical trials for other neurodegenerative diseases, such as amyotrophic lateral sclerosis,

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Covid Severity and Deaths Linked to Age and Extent of MS Progression

Patients with MS and SARS-CoV-2 were at increased risk for severe disease and mortality if they were of advanced age and had progressive MS, according to study findings published in the journal Neurology Neuroimmunology and Neuroinflammation.

Study researchers from multiple hospitals around Spain assessed data from 326 patients with MS who tested positive for SARS-CoV-2, collected by the Spanish Neurology Society Registry. Clinical outcomes through June 2020 were associated with clinical features of MS.

Patients had an average age of 44.8 years and 67.8% were women. On average, they had been diagnosed 11.0 years previously, 80.7% had relapsing remitting MS, 13.2% had secondary progressive MS, 6.1% had primary progressive MS, 24.5% were using pulsed immunosuppressive therapies, and 16.2% reversible immunosuppressive therapies.

Patients who did not survive their COVID-19 infection were older, less likely to have relapsing-remitting MS had higher EDSS scores, did not receive disease modifying therapies and had longer MS duration.

This study was limited as the investigators were unable to determine whether patients received oxygen support or what the specific COVID-19 symptoms were. These data indicated that age and MS severity were significant predictors of severe COVID-19 infection and mortality. The study investigators did not observe a large effect of immunosuppressive treatments on SARS-CoV-2 outcomes.

In other research US scientists reported 7 cases of either new demyelinating disease post-vaccination or worsening of pre-existing MS (3 Moderna, 4 Pfizer). These occurred 1-21 days (on average 13.7 days) after either the 1st or 2nd dose of the vaccine. Those with pre-existing MS were disease activity free for 2.2-14 years (on average 7.5 years).**For details of all stories go to page 13**

News

Biotin Aids Walking Speed in Prog-MS after 12-15 months

High-dose biotin can aid walking speed in people with progressive multiple sclerosis after 12 to 15 months as an add-on treatment, an analysis of placebo-controlled clinical trials shows.

However, the therapy failed to improve other measures of disability, and was associated with inaccurate lab test results caused by high levels of biotin in the bloodstream — which can lead to complications due to incorrect diagnoses and treatment, the researchers said.

The review study, "High-dose biotin for multiple sclerosis: A systematic review and meta-analyses of randomized controlled trials," was published in the journal Multiple Sclerosis and Related Disorders.

Biotin, is a compound found in food that is necessary for the body to metabolize proteins, carbohydrates, and fats. In MS mouse models, high doses of biotin — 10,000 times higher than the daily recommended dose — prevented the loss of myelin, the protective sheath around nerve fibres that is damaged in people with MS.

MD1003, a pharmaceutical formulation of high-dose biotin that was being developed by MedDay Pharmaceuticals, was tested in the MS-SPI Phase 3 trial (NCT02220933). Study results suggested that one year of treatment (100 mg capsules three times a day) effectively reduced disability in people with non-active progressive MS compared with a placebo. However, MD1003 failed to significantly lessen disability in a subsequent trial, leading the company to stop MD1003's clinical development.

Researchers based at the University of the Philippines conducted a review and pooled analysis of all published clinical trials evaluating high-dose biotin versus placebo to clarify its impact on people with progressive MS.

Analyses found, after 12 to 15 months of high-dose biotin use, no significant differences in EDSS, or the combined EDSS-TW25 composite measure in patients with progressive MS. However, a significant improvement was seen in the TW25 (timed 25 foot walk) among progressive MS patients treated with biotin compared with those given a placebo.Based on "moderate quality evidence," the team concluded, "our review found potential benefit in favour of [high-dose biotin] administered for 12 to 15 months in terms of TW25 as adjunctive treatment in patients" with progressive MS.

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Becoming a medal winning T25FW walker

Every year I have a consultation with my neurologist. Due to Covid, these consultations now take place by phone. This means there isn't chance for "hands-on" tests like knee tapping, pushing and pulling to check for things like muscle strength and flexibility.

However, there is one test I can still do remotely and the neurologist asks me to do this test in my home and then records the result I give him. This test is the 25 foot timed walk test or T25FW where you walk 25 feet and your time is recorded. In pre-Covid days this test was done by the neurologist in the corridor outside his office. Now in the Covid era I mark out 25 feet on my living room floor and walk the distance, giving the neurologist my time during our phone chat. I am not sure that my self-reported test tells the neurologist very much about my MS or its progression but I suppose it's as good as any available measure.

One interesting thing about my T25FW test is that over the years of doing the test I have managed to do it faster and faster, improving my time year on year. This is despite a general decline in my condition. All of this begs the questions "how do I achieve this?" and "is the test really an accurate measure of MS and its progression?"

The answer to the first question, "how do I do it? ", is actually quite simple. I used to be a runner so know a little bit about how to move quickly. To improve my own T25FW test times I use my previous running experience and some of the techniques which I know are used by professional athletes and apply them to walking.

It is common knowledge among runners that getting the right stride is critical for maximum speed and this hinges on two events in the stride – the heel strike and the toe lift. Heel strike is where downward energy in the leg is transferred to the sole of your foot and then on to the toe lift where this energy is converted into an upward and forward propulsion giving you momentum and speed. The whole thing, I believe is based on something known as "gravitational torque". I reasoned that I could improve my T25FW test times by concentrating on improving heel strike and foot lift which would give me maximum gravitational torque.

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***Continued from page 5*.** As well as gravitational torque there's also the issue of what is the best number of strides to take? It may sound a strange question, but among elite athletes there has been a debate about how stride length affects your speed, in particular about the merits of taking fewer strides to achieve faster times. As a former runner I have always been incredibly impressed by the Jamaican sprinter Usain Bolt and his running technique.

Bolt's a legend and one of the reasons for his dominance of the 100m event has been the fact that he completes the distance using fewer strides than his opponents. To give one example - in the final heat of the 100m 2009 World Championship in Berlin, Bolt took 41 steps with an average length of 2.44m. His closest competitor Tyson Gay took 45.45 steps with the average length of 2.20m. Bolt won gold, Gay took silver, and subsequently Bolt won gold after gold using his "long strides" technique.

The next issue was whether I could transfer Bolt's longer stride and improved gravitational torque to my own more modest T25FW test. I started the experiment three years ago taking nearly 15 strides achieving a time of just under 12 seconds (1.6 feet a stride). I can now manage the T25FW in eight long strides (3.1 feet a stride) and in a time of about eight seconds, thus knocking a massive four second hole in my own personal record. It may not mean much to other people but it gives me some personal satisfaction to know I have "cracked" the T25FW test. Of course, the T25FW test is only a test of short distance walking in controlled conditions. I am no better at walking longer distances over more challenging surfaces than a hospital corridor or my living room floor. Sadly, in the great outdoors I am the same wobbler that I have always been, dependent on my elbow crutch, slow and at risk of falling.

So, to answer my second question "Is the T25FW test really an accurate measure of my MS and its progression?". The answer, in my opinion is probably "no". But you can't have everything. I will settle for my satisfaction at being in contention for a medal should the T25FW ever become an Olympic or Paralympic event. Hopefully, like Usain Bolt that medal will be gold too. **More information on page 13.** **Page 5 Picture: Chuttersnap at Unsplash**

Trial of new drug in Progressive MS To Start Later This Year

The U.S. Food and Drug Administration has cleared Immunic Therapeutics to start a clinical trial of its investigational medication IMU-838 (vidofludimus calcium) in people with progressive MS.

Enrolment in the trial called CALLIPER Phase 2 is expected to start later this year. It is expected to enrol about 450 people with progressive types of MS, which includes primary progressive MS (PPMS) and secondary progressive MS (SPMS). The trial will take place at more than 70 sites in North America and Europe.

Participants in CALLIPER will be given either 45 mg IMU-838 or a placebo once daily. The trial's main goal is to assess the effect of treatment on brain volume up to 120 weeks (over two years). Disability-related measures will be assessed.

"Our goal is to highlight IMU-838 as a therapy that combines truly differentiated safety and tolerability with neuroprotective activity such as slowing of brain atrophy and disability worsening," a spokesman said.

IMU-838 is designed to block the metabolism of active T-cells and B-cells. These immune cells help to drive the inflammation that causes nervous system damage in MS. Of note, because it is specifically designed to target active cells — immune cells that are actively participating in inflammation — IMU-838 is not expected to substantially affect the parts of the immune system that defend against infection.

IMU-838 has been tested in Phase 1 trials, and the Phase 2 clinical trial "Based on its very strong safety and tolerability profile along with its robust efficacy, which we are planning to further highlight with neuroprotective data from the CALLIPER trial, we believe that IMU-838 has the potential to become a well-differentiated new treatment option for MS patients," a spokesman said.

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News

Isoflavone-rich diets boost gut lessen MS severity, new study suggests.

A diet rich in Isoflavone may lessen MS severity, a new study in mice suggests. Isoflavones are plant-based compounds that resemble oestrogen. They are abundant in legumes such as soy and chickpeas and have anti-inflammatory and antioxidant properties.

The prevalence of MS is significantly lower in countries such as China and Japan, where citizens eat high amounts of isoflavones, compared to Western countries where isoflavone consumption is lower. MS is less common in women and oestrogen is a female hormone,

In a recent study, mice with MS that were fed a diet rich in isoflavone developed diverse and abundant gut bacteria, particularly isoflavone-digesting bacteria, which produced compounds that reduced inflammation in the brain and spinal cord.The study, “Isoflavone diet ameliorates experimental autoimmune encephalomyelitis through modulation of gut bacteria depleted in patients with multiple sclerosis,” was published in the journal Science Advances

Prior studies have shown that people with MS have different gut bacteria profiles compared to healthy people. Specifically, people with MS have higher quantities of some bacteria, while others, such as isoflavone-digesting bacteria, are diminished.

In the latest research a team from the University of Iowa sought to determine whether consuming a diet rich in isoflavones could prevent brain and spinal cord inflammation and potentially reduce MS severity. Mice with MS were fed an isoflavone-rich or isoflavone-free diet for six weeks, then injected with myelin oligodendrocyte glycoprotein (MOG) to induce brain and spinal cord inflammation — a condition called experimental autoimmune encephalomyelitis (EAE) that mimics MS in humans. Researchers then assessed inflammation by measuring immune cell numbers and inflammatory proteins in the brain and spinal cord. They also evaluated the diversity and numbers of gut bacteria.

Mice fed an isoflavone-free diet had more severe disease, with greater numbers of inflammatory cells than mice fed isoflavone-rich diets.

These results were confirmed in other animal models of MS. “In several models of autoimmune inflammation in the CNS [central nervous system, the brain and spinal cord], our results demonstrate that the presence of isoflavones in the diet significantly reduces the severity of EAE disease,” the researchers wrote.

“Ultimately, these studies will inform our use of diet and gut microbiome-based therapies as a complement to conventional disease-modifying therapies … for the treatment of MS and other diseases,” the research team concluded. **For details of all news stories go to page 13**

FDA backs further research into 'neurofilament light chain'

The International Progressive MS Alliance has received a Letter of Support from the U.S. Food and Drug Administration (FDA), marking a major milestone in the journey towards increasing the number and speed of clinical trials in progressive MS.

The letter from the FDA encourages the exploration and development of further studies on 'neurofilament light chain' (NfL), which is a molecule that enters the spinal fluid and blood when nerves are damaged. NfL can be used as a biomarker – an indicator of how the body is functioning and if a treatment is effective. NfL could potentially tell us whether or not an experimental therapy – tested in early clinical trials involving people with progressive MS – is working.

Studies of NfL have been underway to better define how this biomarker may be employed to help detect and predict disease activity and response to treatments, not only in MS but in other conditions. In early phase trials, NfL may give us a better picture of someone's ongoing disease course and be more responsive to the effects of treatments than traditional detection methods such as an MRI scan.

This is the first time the FDA has provided a Letter of Support for further research on any MS-specific biomarker for use in clinical trials. Because further steps and research are needed for NfL to be approved as an outcome measure, this letter can encourage further development by signalling to industry and other researchers that drug regulators are aware of the evidence supporting this biomarker. The Alliance has also submitted support materials to the European Medicines Agency to request a similar letter from them.

The FDA's Letter of Support resulted from an application that included a review of published research results on NfL that was compiled by the Alliance's Fluid Biomarkers Implementation Team, a panel that includes experts from the pharmaceutical/biotech industry, academic research and people living with progressive MS. The team had previously published recommendations outlining evidence and priority research for developing NfL as a biomarker for progressive MS.

The Alliance is also investing in other initiatives to develop biomarkers of therapies for progressive MS, and recently announced funding 19 new Research Challenge Awards to improve the understanding of mechanisms that drive progression, an area where the current lack of knowledge is hindering treatment development.

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The “tyranny of the toilet” and prog-MS

One of the depressing things about progressive MS is that problems you thought had been solved have a nasty habit of returning, often in a more severe form.

For years I have prided myself on the fact that although I have problems urinating, my bowels have been largely unaffected. A few years ago I did have a little problem with my bowels but this was quickly resolved when I bought a “squatty potty” - a little plastic frame you place it in front of the toilet and which raises your knees so you poo in a posture more typical of that adopted by your forefathers, and everything works normally.

The squatty potty worked well for a couple of years then in late Summer I went for a poo and nothing happened. I tried the following day and the day after but, although feeling like I needed to go, nothing was coming out. After four days I started to get worried.

Looking at research into MS and bowel problems I noticed that I am not alone, far from it. An Italian study just published revealed that “Neurogenic bowel dysfunction” (NBD) — the loss of normal bowel function due to a nerve problem — is present in up to 73% of MS patients who like me can experience extreme difficulty going for a poo , slow movement of poo through the bowel , and chronic constipation thus spending a long time in the smallest room. I think they call it “the tyranny of the toilet”.

Fortunately at the hospital where I see my neurologist there is a “poo nurse” or a “Clinical Nurse Specialist Functional Bowel Service” to give her the full title. The poo nurse sees lots of MS patients like myself and after making contact by email she arranged a phone chat the same day. Basically she said five days was far too long to wait to go for a poo and I had to tackle the problem immediately in one or two ways

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Continued from page 10 The poo nurse's first suggestion was a stool softener. It was explained to me that stools which sit in the bowel too long become hard and difficult to move. The solution is a stool softener which enables additional water and fats to be incorporated in the stool, making it easier for them to move through the bowel and out into the world.

If this failed then the next solution was suppositories. I guess I am vaguely aware of what these are but I have only a basic knowledge. Fortunately the poo nurse sent me a very helpful leaflet explaining how suppositories work. I discovered that Glycerine suppositories are like rectal "bullets". They are inserted into the back passage and you wait. Basically The melting of suppositories inside the bowel lubricates, irritates and softens poo. This lubricating and softening helps prevent straining during a difficult "bowel movement".

Glycerine is also a mild irritant which increases the frequency of bowel movements by stimulating bowel muscles to contract. The contractions help to move stools along the bowel and makes passing them much easier. In addition glycerine suppositories attract water from the bowel down towards the mass of hardened stool to relieve constipation quickly and effectively. Glycerine suppositories also cause the muscles in the rectum to move more effectively in order to facilitate a bowel movement.

Armed with all this information I made my way to the local pharmacist and bought the recommended laxative (called DulcoEase) and some suppositories to use if the DulcoEase wasn't enough. I took by first 100 mg DulcoEase capsule at teatime on day six and waited, and waited. Disappointingly nothing happened for a few hours but then shortly before I went to bed the earth moved for me, and I passed a stool which contained five days worth of waste material. I think you can picture the scene.

Since that time I have taken a laxative every couple of days and hope to wean myself off them very shortly. Things seem to be returning to normal and I hope my unpleasant experience in toileting is a one off and won't be repeated.

I am not sure whether this is hopeless optimism but I know from previous experience of MS related problems that even though problems crop up, a sort of hopeless optimism keeps you going in the face of adversity and for that reason I remain a hopeless optimist. After having MS for 30 years I think it is the only way to stay sane in the face of illness which seems to be doing its best to send your life in the opposite direction, down the toilet – if you will excuse the expression.

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News

Sativex Eased MS Spasticity as an Add-on Therapy

Sativex, a mouth spray that contains cannabis extracts, was found effective as an add-on therapy for easing spasticity in adult multiple sclerosis (MS) patients who failed to respond to other anti-spastic treatments, a real-world study from Belgium reports.

Overall, about 74% patients reported easing of spasticity — muscle stiffness or spasms — after 12 weeks of treatment, defined as a 30%-or-greater reduction in spasticity scores.

The study, "Sativex (nabiximols) cannabinoid oromucosal spray in patients with resistant multiple sclerosis spasticity: the Belgian experience," was published in the journal BMC Neurology.

Sativex, developed by GW Pharmaceuticals, is an oral spray that contains cannabidiol (CBD) and tetrahydrocannabinol (THC), two of the most abundant cannabinoids found in the cannabis plant. Sprayed under the tongue or inside the cheek several times a day, Sativex is available in 25 countries — including most of Europe and Canada, but not the U.S. — as an add-on therapy for adult patients with moderate-to-severe MS spasticity who fail to respond to other anti-spastic treatments.

Since its approval, real-world data has supported the therapy's efficacy, but health authorities in in Belgium requested further data on efficacy and safety for reimbursement purposes. In agreement with this request, researchers in Belgium conducted a retrospective analysis of 276 adult MS patients from eight different centres who received Sativex, as an add-on therapy, from March 2016 to December 2017.

A total of 73% of patients experienced at least a 20% improvement in spasticity after four weeks, and 89% achieved a 30% or greater improvement after eight weeks. This 30% improvement was maintained in 74% of patients at 12 weeks, meaning that these patients met the Belgian criteria for continued reimbursement of Sativex. In parallel with the easing of spasticity, patients' quality of life improved sustainably over the treatment course, with scores reaching 59 points at weeks 12 and 64 after one year, compared with a score of 39 before Sativex initiation.

About one third of the patients discontinued treatment, the most common reason was perceived lack of effectiveness (16.3%), followed by poor tolerability (6.5%).

Overall, "more than 60% of the patients with MS who started add-on treatment with cannabinoid oromucosal spray reported a clinically relevant symptomatic effect and continued treatment after 12 weeks," the researchers wrote. **For further details of all features go to page 13**

References contact details etc

Page 2 Ibudilast story

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Page 3 progressive MS + Covid severity

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Page 4 Biotin story

https://multiplesclerosisnewstoday.com/news-posts/2021/08/06/high-dose-biotin-md1003-aids-walking-speed-progressive-ms-but-risks-evident/

Page 5-6 Timed walking test

For feature on the bio-mechanics of walking and running See https://pubmed.ncbi.nlm.nih.gov/17933203/

Page 7 IMU-838 story

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Page 8 Isoflavines story

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Page 9 FDA backs research into Neurofilament-light-chain

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pages 10-12 Bowels.

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