

My prog-MS ezine

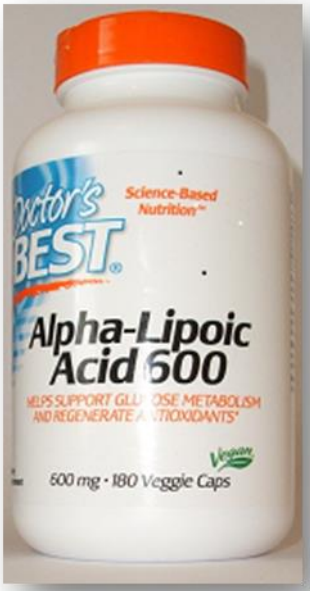
For people with progressive MS and other interested people

Issue number 37, May/June 2021

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 six pages of prog-MS news stories. There are also two features. One on page 5 is about new research showing yet more links between HIV medications and improvements in patients' MS. There's also a feature on Alpha Lipoic Acid, a supplement that has been proven to improve symptoms of progressive MS and which I and others take . See page 10 for details.

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News

Several existing drugs to be tested to treat worsening MS

UK researchers are to test several drugs at once to speed up identification of those that slow or reverse MS symptoms in a trial that bears similarities to the MS SMART trial - a trial which looked at re-purposing three existing drugs and which reported in 2020.

Doctors in the UK are to launch the new multi-drug clinical trial to assess whether drugs already on the market can prevent progressive from worsening over time and even reverse the disabilities it causes.

The new trial called Octopus , so named because of its various arms, will allow researchers to investigate the potential benefits of several drugs at once, in the hope of identifying effective new treatments three times faster than if the medicines were trialled separately.

The idea bears similarities to the MS-SMART trial which looked at three drugs (fluoxetine, riluzole and amiloride) for progressive MS. Sadly, none of these drugs was found to be suitable for being re-purposed for progressive MS

Hundreds of patients signing up for the Octopus trial will be randomly assigned to have either standard care for progressive MS or standard care plus one of three drugs that doctors hope will aprotect their neurons from MS if not repair the damage done.

The team hope to start recruiting patients for the trial, which is funded by the MS Society through its Stop MS appeal, later this year, provided the coronavirus crisis does not interfere with its plans.

The Octopus trial is intended to accelerate the search for drugs to treat progressive MS. The design means that as soon as a drug shows any benefit, more patients can be recruited to gather further data on its efficacy and any side-effects.

Patients who volunteer for the trial will have a brain scan after 18 months to see whether the drug they are receiving have slowed down the brain shrinkage that MS causes. If a drug is having no effect, it can be replaced with another medicine and the trial continues.

Other tests may look at electrophysiology to see how well signals move around the central nervous system, biological markers that reveal when nerve damage is being repaired and levels of disability. Doctors are expected to decide which drugs form part of the trial this summer.

For details of sources for all news stories go to page 13

New Remyelinating Compound To Be Tested in Healthy Volunteers

US Pharmaceutical company Pipeline Therapeutics has started a Phase 1 safety clinical trial to investigate PIPE-307, a new remyelinating treatment for MS which it is hoped will help with progression.

The trial (NCT04725175) will assess the compound's safety, tolerability, and pharmacokinetics, or how the drug moves through the body of people without MS (so-called "healthy volunteers"). Up to 72 people, ages 18 to 55, will be enrolled at the trial's single testing centre in Western Australia. Recruitment is currently taking place. Results from the Phase 1 study are expected to inform the design and optimal dose for a future Phase 2 trial to take place in MS patients.

PIPE-307 is designed to help regrow myelin, a fatty substance that surrounds nerve cells like a sheath and is important for these cells to efficiently transmit electrical signals. Myelin is damaged in MS patients, leading to nerve damage and chronic disability. Yet, effective treatments that induce myelin regrowth, or remyelination, to counteract disease progression in MS patients are lacking.

PIPE-307 works by inactivating the muscarinic receptor type 1, which stimulates oligodendrocyte progenitor cells to grow into mature, myelin-producing oligodendrocyte cells. Oligodendrocytes are the myelinating cells of the central nervous system, comprised of the brain and spinal cord.

The ongoing clinical trial will be conducted in three parts. In part one, some 48 participants will receive a single ascending dose of oral PIPE-307 or a placebo over six weeks. Part 2 will assign 24 participants to either multiple ascending doses of PIPE-307 or a placebo over seven weeks. Finally, Part 3 will evaluate how food affects the bioavailability of PIPE-307 — meaning how much ingested medicine reaches the blood and is actively used for therapeutic effect — among approximately eight participants from the single ascending dose section. This part of the study will last for six weeks.

Researchers will assess the therapy's safety through periodic electrocardiograms, blood laboratory analyses, vital sign measurements, physical examinations, and monitoring for adverse side effects. Pipeline expects to announce results in the second half of the year.

Earlier this year, Pipeline raised $80 million in support of its neurodegenerative development programs. In addition to PIPE-307, other candidate therapies include compounds targeting remyelination and neuroinflammation, axonal (or nerve fibre) repair, and sensorineural hearing loss.

For details of all stories go to page 13

Re-purposed asthma drug slows brain shrinkage in prog-MS

A new drug has been shown to slow brain shrinkage in MS patients, according to a preliminary trial conducted in part with the US University of Iowa (UI) .

The study, published this week in the New England Journal of Medicine, tested the drug ibudilast on individuals with progressive MS.

Ibudilast inhibits the enzyme phosphodiesterase. It reduces inflammation and acts on a number of biochemical processes in cells associated with nerve damage and myelin repair. Previous studies have suggested it may have a neuroprotective effect.

Ibudilast is used in Japan and Korea to treat asthma and some complications of stroke. It is taken as a tablet twice daily

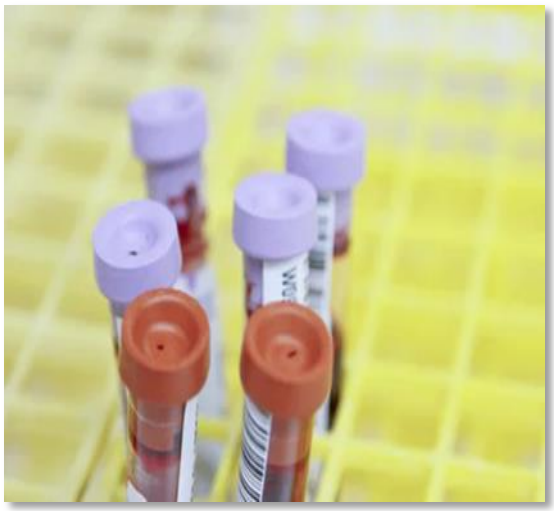
Of the 255 patients with progressive MS in the study , it was found that ibudilast slowed brain atrophy - or brain shrinkage - by 48 percent compared with the patients who took a placebo over the course of 96 weeks, said Dr. Robert Fox, lead researcher on the study and staff neurologist at the Mellen Center for Multiple Sclerosis at the Cleveland Clinic in Ohio.

'The patients treated with ibudilast had about 2.5 milliliters less of brain tissue loss or shrinkage compared to the placebo-treated patients," Fox told The Gazette.

While there's no clear clinical benefit at this stage, the study is what Fox described as a 'proof of concept" trial, meaning it provided evidence that 'this drug does slow something researcher think is important - shrinkage of the brain in MS.

The next step for the drug ibudilast would be another trial to demonstrate the clinical benefit to justify its approval for widespread use. The next trial would require more patients and be more expensive - a price tag of about $103 million. However, It is believed the process of starting such a clinical trial is already taking place.

For details of all stories go to page 13



More links between HIV drugs and MS symptom relief

One of the perks of being a freelance journalist is that people "tip you off" about interesting new developments in MS research. These "tip offs" are often stories ignored by the mainstream medical press.

One "tip-off" that came to me recently was a phone call from another MSer telling me about an academic paper titled "HIV infection and multiple sclerosis: a case with unexpected 'no evidence of disease activity' status".

It outlines the case of a patient diagnosed with MS who saw his MS substantially improve following subsequent HIV infection and treatment. The patient achieved No Evidence of Disease Activity (NEDA) without any MS disease-modifying drugs and continues to have no disease activity more than ten years after first diagnosed with MS. The authors speculate that antiretroviral therapy, which the man is still taking for his HIV, may be responsible for his MS "disappearing" with the HIV medication perhaps treating MS as well.

Of course, MS is not a retroviral infection like HIV so what is going on? One theory is that this patient's MS, and all MS, is caused by something called a HERV or Human Endogenous (inherited) Retrovirus. HERVs share similarities to exogenous (ie: non-inherited) retroviral illnesses like HIV and perhaps respond to HIV drugs as is shown in the above study .

Not a lot is known about HERVs but basically they are remnants of retroviral infections which infected our ancestors and which entered our DNA being inherited by subsequent generations . Amazingly they make up around 8% of the human genome and several disorders are thought to be associated with the re-activation of HERVs. The "MS-HERV" theory hypothesises that under certain circumstances, like infection with another virus, Epstein Barr virus (EBV) for example, HERVs can spring back to life causing illnesses like MS. HIV drugs being anti-viral help keep these HERVs "under control" in the same way that they keep HIV under control.

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Continued from page 5. A case report was published in 2011 in the European Journal of Neurology saying the same thing as the latest 2020 study. It was titled "Could antiretroviral drugs be effective in multiple sclerosis?" and outlined the case of an Australian man with HIV and MS who also experienced a marked improvement in his MS after taking anti-retroviral HIV drugs.

The 2011 Australian case study led to two important developments in exploring the theory that a HERV could be involved in MS. First, a 2015 survey of people with HIV found that far fewer of tpeople with HIV had MS than would be expected. The thinking was that the HIV drugs used by patients who had both HIV and MS were also treating the patients' MS like in the two case studies already mentioned.

Secondly, in 2019, an anti-retroviral HIV drug raltegravir (Isentress) was tried out on a small group of MSers. Sadly, raltegravir did not lead to any improvement in the MSers' condition. It was later suggested that raltegravir was the wrong HIV drug to use on its own. This idea makes sense because HIV patients like the above two take a "cocktail" of drugs, sometimes ten or more, and choosing the right anti-retroviral drug or drugs would obviously be crucial to success.

As far as I am aware there is no current project to try out other HIV drugs on MS. But I emailed the 2020 paper to Prof. Julian Gold, who led the raltegravir trial and published the 2011 case study. I asked him for his view. He said he would send the 2020 paper to his colleague, Professor Gavin Giovannoni from London University and added he was personally still "very committed" to the concept of viral or HERV involvement in MS although he acknowledged that research in this area is "very sporadic."

Sporadic, of course does not mean non-existent and there is some work going on right now exploring the idea that HERVs and MS are connected. A bio-tech company based in Switzerland called Geneuro is currently pursuing the HERV theory for treating MS using a drug it has developed specially rather than using an existing HIV drug like Gold did in his 2019 trial. Geneuro recently announced that enrolment of MS patients had been completed for a 48 week Phase 2 study of the drug called temelimab . Results are due to be reported in the first three months of 2022. This could be the big breakthrough we have all been waiting for, and certainly something to look out for next year. In the mean-time I shall look out for further stories similar to ones mentioned above. There is a steady stream of them, and it's a shame that mainstream MS research doesn't give them the attention their investigation so richly deserves.

More information on page 13. Page 5 Picture: National Cancer Institute / unsplash

Ocrevus delays PPMS patients' wheelchair need by 7 years

Ocrevus (ocrelizumab) treatment may delay the need for a wheelchair by seven years in patients with primary progressive MS (PPMS), a study reports.

This delay, drawn from clinical trial data on treatment- versus placebo-group patients - and supported by real-world findings, likely translates to long-term benefits for PPMS patients, its researchers wrote.

The study, "Risk of requiring a wheelchair in primary progressive multiple sclerosis: Data from the ORATORIO trial and the MSBase registry," is published in the European Journal of Neurology.

Ocrevus, marketed by Genentech, is the first and only approved disease-modifying therapy in the U.S. and European Union for PPMS. Its favourable benefit-risk profile has been consistently shown in several clinical trials. New analyses of a Phase 3 study called ORATORIO show that taking Ocrevus reduced the risk of a patient reaching a 24-week EDSS score of seven or greater by 46% compared with those on placebo.

Reaching an EDSS score of 7.0 or higher "is a key clinical disability milestone, as this represents an inability to walk more than 5 metres, even with an aid, essentially leading to the requirement for a wheelchair," the researchers wrote.

When these results were extrapolated to estimate the median time to requiring a wheelchair, the researchers found it was 19.2 years for patients on Ocrevus and 12.1 years for those on placebo, meaning Ocrevus may delay need for a wheelchair by seven years.

The researchers, however, are cautious about generalizing the results: "It is important to note that due to the restricted eligibility criteria for ORATORIO, patients were generally younger, had a shorter disease duration and had lower levels of disability than a typical population; therefore, it may be difficult to generalize these results to a broad real-world PPMS population," the researchers wrote. Further studies are needed, they added.

Nonetheless, based on the results obtained, the team concluded that "compared with placebo, ocrelizumab [Ocrevus] significantly delayed time to 24-week confirmed wheelchair requirement in ORATORIO." The researchers also emphasized that "time to requiring a wheelchair is a well-defined outcome that allows comparisons to be made across studies and across cohorts. Furthermore, it is a clinically meaningful outcome for patients; high levels of disability are associated with a number of physical, emotional and financial challenges, and an overall reduced quality of life. **For details of all news stories go to page 13**

Measuring Blood Proteins Can Predict Disability in SPMS

People with inactive secondary progressive MS (SPMS) who have high levels of the blood proteins neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) have an increased risk of worsening disability.

That's according to new research presented at the 2021 annual meeting of the American Academy of Neurology, in a talk titled "Plasma Neurofilament Light Chain and Glial Fibrillary Acidic Protein Levels Are Prognostic of Disability Worsening: A Biosignature That Helps Differentiating Active From Non-active SPMS."

NfL is released into the blood when neurons or nerve cells are damaged or destroyed. As such, levels of NfL in the blood indicate injury in the nervous system. GFAP, meanwhile, is associated with the activity of star-shaped neural support cells called astrocytes, and also is a marker of nervous system injury. Prior research has suggested that NfL and GFAP have predictive use in MS. This led researchers to hypothesize that combining the two markers could provide additional useful information.

To test this idea, the scientists analysed data from the EXPAND Phase 3 clinical trial (NCT01665144), which evaluated the safety and efficacy of the Novartis drug Mayzent (siponimod) in people with SPMS. EXPAND included a total of 1,651 patients, who were randomly assigned to receive Mayzent or a placebo, taken by mouth once a day, for up to three years. Following the trial's conclusion, participants could then enter an extension study and receive Mayzent for up to 10 years.

The team examined samples for 1,369 SPMS patients, including 665 with active disease — meaning they experienced relapses and/or evidence of new disease activity on an MRI scan in the two years prior to the trial. The remaining 704 SPMS patients had non-active disease. Among individuals with non-active SPMS, those with high levels of both NfL and GFAP had significantly worse disability than those with low levels of both proteins.

Among those with non-active SPMS, high levels of NfL, but not GFAP, also were associated with significantly shorter times to worsening disability, as compared with low levels of both proteins. In contrast, high levels of GFAP, but not NfL, were not significantly linked with disability progression.

"So, high plasma NfL seems to be more important than high plasma GFAP in non-active SPMS," said Jens Kuhle, MD, of the University Hospital and University of Basel, in Switzerland, who presented the findings. **For details of all news stories go to page 13**

NurOwn cell therapy is safe and effective for prog-MS

NurOwn cell therapy led to significant improvements in the physical abilities, vision, and cognition of people with progressive MS in a Phase 2 clinical trial,. That is according to trial data. In addition to these positive results, BrainStorm Cell Therapeutics, NurOwn's developer, announced that its cell-based therapy showed a good overall safety profile.

Trial participants received three injections, with two-month intervals between each treatment. The company reported that levels of neuroprotective molecules increased in the treated MS patients while neuroinflammatory biomarkers decreased.

NurOwn is produced from a patient's own bone marrow-derived mesenchymal stem cells (MSCs). These are grown under specific conditions that stimulate cells to release neurotrophic factors (NTFs). These factors induce the growth and development of brain cells. MSC-NTF cells are designed to deliver NTFs and other important factors directly to the site of damage to slow the progression of the disease.

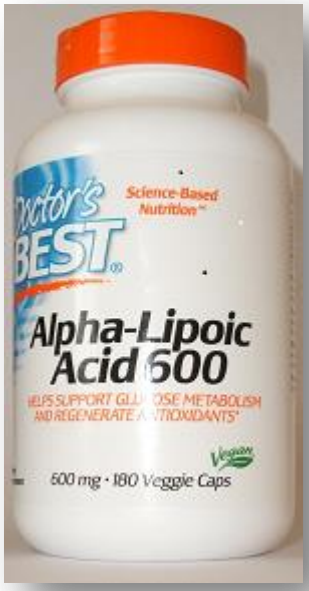
Brainstorm evaluated the safety and efficacy of NurOwn in progressive MS in a Phase 2, open-label, multicentre trial (NCT03799718). Altogether, 20 primary and secondary progressive MS patients were enrolled in the trial. Three injections of 100-125 million MSC-NTF cells were given intrathecally, or directly into the spinal canal. There were two-month intervals between each treatment, and patients were followed for a total of 28 weeks (about seven months) after the first injection.

Among the NurOwn-treated patients, 14% showed 25% improvements in the T25-FW (Timed 25 foot walk test) by 28 weeks. And 13% of MS patients treated with NurOwn showed improvements by 25% in the 9-HPT (Nine hole peg test). None of the matched controls showed improvements in these measures.

Biomarkers from cerebrospinal fluid (CSF) were analysed before each NurOwn injection. While levels of molecules with neuroprotective effects such as VEGF and HGF increased, proteins associated with neuroinflammation — namely MCP-1, SDF-1, and osteopontin — decreased.

Brainstorm plans to present its findings on efficacy and biomarker analyses at an upcoming scientific meeting and to publish the results in a peer-reviewed journal.

For further information on news stories go to page 13



Research shows Alpha Lipoic acid is neuroprotective in secondary progressive MS

There are two main processes involved in the progression of MS: immune dysfunction and neurodegeneration. Whether or not, and how, they interact is not yet clear. However, what is clear is that drugs which just modify the immune system do not work in those of us with progressive MS.

Among several "over the counter" health supplements which may have a benefit for people with MS, Alpha Lipoic Acid (ALA), also known as Lipoic Acid (LA), has attracted a lot of interest recently. ALA helps a number of enzymes in the body work, especially those involved in energy metabolism. It is also a powerful antioxidant that scavenges highly toxic free radicals that cause oxidative stress. It regenerates other antioxidant molecules too.

ALA – which I take - has been shown to reduce measures of both oxidative stress and immune dysfunction in animal models of MS. In addition, long-term treatment with ALA reduced the amount of demyelination and axonal damage.

This has motivated researchers, like the eminent neuroscientist Professor Alan Palmer (who has SPMS and is pictured on next page), to consider antioxidant molecules as potential treatments for progressive MS.

Interest in ALA as a neuroprotective treatment for progressive MS has been growing for the past decade but increased dramatically in 2017 following publication of the results of a clinical trial in the USA. This two-year study showed that ALA slowed both the rate of brain shrinkage and deterioration in walking performance in people with SPMS. Specifically, progressive MSers taking ALA for two years saw a 68% reduction in annualised PCBV (percentage brain volume) loss. In addition, those with a disability score (EDSS) of six or less showed faster times in the expanded Timed Up and Go (TUG) task when compared to a group of SPMSers taking the placebo or dummy pill (the control group). Thus, there is clear and convergent evidence for ALA having a neuroprotective effect. **Continued on page 11**



Continued from page 10 In November 2020, a paper in the Journal of Neurology, Neurosurgery and Psychiatry looked at the possibility of re-purposing several licensed drugs and supplements for treating progressive MS. One of the candidates for re-purposing was ALA. From a list of 55 potential treatments, the authors of this paper recommended four for clinical testing in progressive MS: (i) R-α-lipoic acid, (RALA, the biologically active form of ALA), (ii) the anti-diabetes drug metformin, (iii) the combination treatment of R-α-lipoic acid and metformin, and (iv) niacin (vitamin B3).

Professor Alan Palmer (above) who has SPMS was one of several researchers and MSers involved in this process. He's a visiting Professor at the University of Reading, as well as CEO of Elixa MediScience, a biopharmaceutical company focused on developing first-in-class disease-modifying therapeutics for neurodegenerative disorders. He remembers the background to the 2020 research well.

"I joined the MS consortium tasked with identifying drugs that could be repurposed for the treatment of SPMS at the beginning and served until the group was disbanded, about two years later (September 2019). I have been taking RALA (the active form of ALA) on and off for about 2 years, but consistently for the past 6 months. It is difficult to ascribe any definite effect of this treatment, but it's important to note that the neuroprotective efficacy described in the 2017 US research was seen over a 2-year period."

As readers of the MS press may be aware, OCTOPUS, a multi-arm trial, will start this Summer. (See page 2) It will investigate the possibility of repurposing drugs already on the market as potential treatments to slow or halt the progression of disability in MS. The study will be funded by the MS Society and will recruit hundreds of patients with progressive MS. Researchers are in the process of selecting the three therapies to be included in the trial but say that OCTOPUS has enough flexibility to include new treatments as they are discovered and drop others that don't look so promising. Alan Palmer has been following its progress closely. "As I understand it, the MS Society plan to make a decision with regard to which three compounds will be included in the OCTOPUS study. It remains to be seen whether or not RALA is selected." **Continued on page 12**

Continued from page 11. The multi-arm approach of testing existing drugs for progressive MS was tried in the MS-SMART study in 2018. Three existing licensed drugs (riluzole, amiloride and fluoxetine) were tried out in progressive MS, but none showed any evidence of neuroprotection.

The possibility of slowing disability progression in MS has recently been rekindled with the approval by the National Institute for Health and Clinical Excellence (NICE) of a drug used to treat RRMS for SPMS. The drug is from the Swiss pharmaceutical company Novartis and is called Mayzent (siponimod). Like all medicines approved to treat RRMS, it is an immunomodulatory drug. It has the same mechanism of action as an earlier Novartis drug, Gilenya (fingolimod).

Although Mayzent slowed disability progression at both 3 and 6 months, there is not yet evidence to show that disability progression is slowed over the long-term. In addition, Mayzent's use is restricted to only people with SPMS showing active inflammatory plaques with MRI, which is a minority of the total SPMS population. Therefore, there remains an urgent unmet need for a therapeutic agent that slows the progression of disability in all people with SPMS. Such a treatment would allow SPMSers to remain independent, carry on working and stay connected with family and friends. It will also substantially reduce the economic cost of MS, which is largely driven by increasing disability.

There is a good chance that the planned OCTOPUS trial will identify such a compound, especially if RALA is included. However, Professor Palmer points out that "the big problem with ALA/RALA is that it is an unapproved health supplement and not a drug that has been approved by regulatory agencies for the treatment of MS. Because of this: (i) the quality of ALA/RALA supplements is often not assured, (ii) combination therapy (e.g. with metformin) is more challenging and (iii) claims regarding the treatment of disease are not permitted."

In spite of all this I do hope that OCTOPUS succeeds and, as a sign of my optimism, I will, like Prof. Palmer continue to take ALA. It's inexpensive, and, who knows, it might just work. I hope it does. As someone with SPMS I have little to lose and possibly lots to gain by swallowing the pills.

"**For further details of all features go to page 13**

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