

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 28, November/December 2019

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

In this issue are seven pages of important prog-MS news stories plus two features about issues that matter to prog-MSers. In the first feature (page 5) I look at FES (functional electrical stimulation) and why I have given up using my FES device. The second feature looks at the issue of ageing and MS and its implications - something that is of particular interest to me now I have reached the grand age of 61. See page 10.

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Diabetes drug offers hope for treating MS and progression

Scientists have raised hopes of a new treatment for MS progression after animal studies showed a common diabetes drug can repair nerve damage caused by the disease. The effect of the drug was so striking that doctors in Cambridge are now planning a clinical trial next year.

If the treatment works as expected it could potentially halt the progression of the disease and even allow patients to recover from some of the disabilities that typically develop as the condition worsens.

"It's always a leap in the dark when you go from lab experiments to humans, but the data is as strong and as compelling as it is ever likely to get," said Robin Franklin, a professor of stem cell medicine at Cambridge University. "I am very optimistic that this is going to work."

Working with researchers in Australia, the Cambridge team administered the diabetes drug metformin to rats for three months before they had an injection that stripped myelin off some of the nerves in the brain. The rats continued to receive the drug for three more weeks afterwards. The treatment had a profound effect. Compared with animals that went without, those on metformin had a near complete recovery of the damaged myelin. "It is utterly unambiguous and very spectacular," Franklin said.

The scientists hope the drug will at least slow the progression of the disease. But a more optimistic possibility is to stop further neurological damage completely. If doctors can achieve that, the patient's nervous system may be able to rewire itself enough to recover from some of the disabilities.

Anna Williams, a professor of regenerative neurology at the University of Edinburgh MRC Centre for Regenerative Medicine, who was not involved in the study, said: "We know that repair generally gets worse with age, but this is exciting as it suggests that myelin repair in the brain and spinal cord in aged adult rodents can be improved. If this relatively simple, cheap and available drug can rejuvenate myelin repair in humans as well, then this may be really helpful in neurodegenerative diseases such as multiple sclerosis where efficiently restoring myelin will help avoid disability."

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Trial of ATA188 Shows "hints of Effectiveness" in Prog-MS

People with progressive MS and past exposure to the Epstein-Barr virus are responding to a potential immunotherapy known as ATA188, tolerating the treatment well with signs that suggest effectiveness. That's according to early updated data from an ongoing Phase 1 trial.

The research, "Preliminary safety and efficacy of ATA188, a pre-manufactured, off-the-shelf, allogeneic (Allogeneic cells are from donors with no family or genetic relationship to the recipient) Epstein-Barr virus-targeted T-cell immunotherapy for patients with progressive forms of multiple sclerosis," was presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) held in Stockholm (Sept. 11–13).

Infection with the Epstein-Barr virus (EBV) is linked to a greater susceptibility to MS. EBV promotes the expansion of immune B-cells, which can produce autoantibodies against myelin. People with MS are believed to be deficient in T-cells, which would normally kill EBV-infected B-cells. ATA188, by Atara Biotherapeutics, is designed to overcome this deficiency by providing allogeneic immune T-cells that target EBV in B-cells. (Allogeneic cells have an advantage in that these cells are available immediately or "off-the-shelf.")

The Phase 1 study (NCT03283826),which has been taking place in the U.S. and Australia, is assessing the safety and efficacy of ATA188 in progressive MS patients with a near equal mix of secondary progressive disease (SPMS) and primary progressive MS (PPMS) — ages 18 to 66. Patients were assigned to four groups, each testing a different cell dose: 5 x 106, 1 x 107, 2 x 107, and 4 x 107. In group 2 (1 x 107), all six patients showed either clinical improvement (two people) or partial clinical improvement (four people) at six months, or improvements in two or more or more MS scales. Data for this group did not stretch out 12 months. Additional efficacy and safety results from this study will be made available in 2020.

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Siponimod Reduces Risk of SPMSers Becoming Wheelchair users

Mayzent (siponimod) reduces the risk of people with secondary progressive MS (SPMS) becoming dependent on a wheelchair, a new study shows. These findings further corroborate prior trial data demonstrating that Mayzent use delays disability progression and cognitive decline in SPMS patients.

The results were disclosed at the 2019 Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), which ran Sept. 11-13 in Stockholm, Sweden. The presentation, titled "Siponimod delays the time to wheelchair in patients with SPMS: results from the EXPAND study," was given by Patrick Vermersch, MD, PhD, neurologist and researcher at the University of Lille, France.

Novartis' Mayzent is a sphingosine-1-phosphate (S1P) receptor modulator. It was approved in March by the U.S. Food and Drug Administration (FDA). The FDA's decision was based, in part, on data from the EXPAND Phase 3 clinical trial (NCT01665144). That data showed that SMPS patients taking oral Mayzent experienced a decrease in disability progression and in cognitive decline.

The trial included a total 1,651 people with SPMS, with moderate-to-severe disability, whose condition had deteriorated over the two years prior to the study's start. Participants, recruited across 31 countries, were randomly selected to receive 2 mg of Mayzent orally or a placebo, once per day, and were followed for up to three years. An open-label extension study for up to 10 years is ongoing.

In this new analysis, researchers used the trial's data to address whether Mayzent use could slow down disability to the point that it would prevent patients from progressing on the Expanded Disability Status Scale (EDSS), which quantifies disability in MS. Results showed that, compared with placebo, fewer patients at greater risk of worsening — those with an EDSS score of 6.5 — in the Mayzent group became dependent on a wheelchair. Specifically, the results showed 19.2% of the Mayzent group becoming wheelchair dependent versus 26.1% in the placebo group. This translated into Mayzent treatment leading to a 37.3% reduction in risk.

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When my FES stopped working for me

In 2012 my physio gave me an Odstock FES dropped foot stimulator. This is a walking aid that sends small pulses of electricity from a battery pack worn on your belt to sticky pads on lower leg muscles. Functional Electrical Stimulation (FES) powers lower leg muscles, and helps you raise your feet, stopping you tripping and falling.

For three years FES worked really well. Then, in 2016, I went shopping wearing my FES. On returning home I sat down and when I got up my leg suddenly gave way. This "leg collapse" happened a week later in similar circumstances. I wondered if the problem had been caused by wearing the FES and an online search uncovered an academic paper which said FES could "induce excessive neuromuscular fatigue." So, I wondered whether "excessive neuromuscular fatigue" had caused my leg collapse.

I phoned Paul Taylor, head of research at Odstock the company that makes my FES device. Had he ever come across my problem before? He said he was not aware of an increased risk of falls at the beginning of FES use but he did urge caution particularly in the early days " We do know that the muscles that are being stimulated will fatigue more quickly in this period and advise people to build up the use of the stimulator over the first 2-3 weeks. In this time the muscles become stronger and more fatigue resistant."

He also said that following this initial period the main limiting factor in how far someone is able to walk is not fatigue in the muscles but general fatigue or weakness in the rest of their body.

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I took this to mean that he thought my "leg collapse" would be most likely caused by fatigue in the rest of my body particularly in the larger weight bearing leg muscles of the upper leg like the quadriceps (quads). He explained some more.

"The point is that when you use FES for correction of dropped foot, the muscles that are activated by FES are those below the knee. The quads above the knee are not stimulated so will not be affected by FES induced fatigue. But the quads will still be affected by normal exercise related fatigue."

There was another point. As well as not stimulating the quad muscles the FES only stimulates muscles below the knee intermittently. These muscles are stimulated when the foot is lifted and then rested when the foot is on the ground giving the muscles time to rest.

He concluded by saying he thought it was most likely MS progression had caused my leg collapse, not FES. Then about a week later my leg collapsed when I wasn't wearing the FES So, I thought perhaps he did have a point and I accepted FES is a walking aid for MS not a cure.

Then last year I gave back my FES to the hospital. I suppose I came to the conclusion that FES is useful while your MS is at a certain stage but beyond that it simply outlives its usefulness. And sadly that stage has arrived for me. I now use an elbow crutch. I have never had leg collapse while using that – which is a result of sorts.

http://www.odstockmedical.com/about-fes

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Mesenchymal Stem Cell Transplants Help Stop Prog-MS

Transplanting mesenchymal stem cells (MSCs) is safe and can delay disease progression in people with active, progressive MS according to results from a clinical trial conducted in Israel. Six months after the transplant a considerable proportion of patients showed no signs of disease activity.

The findings were shared at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held Sept. 11–13 in Stockholm, Sweden.

An MSC transplant (MSCT) involves collecting a patient's MSCs from bone marrow or blood, and expanding their numbers in the lab. Cells then are infused back into the blood (intravenous injection) or the fluid surrounding the spinal cord (intrathecal injection) of the patient.

A Phase 2 clinical trial assessing the safety and effectiveness of two protocols of MSC transplant in people with active, progressive MS was conducted at Hadassah University Hospital, Israel, and enrolled 48 patients with progressive MS (age 65 or younger), and moderate-to-severe disability (EDSS ranging from 3.0 to 6.5). All patients had failed previously to respond to at least one line of MS therapy.

Results showed that significantly fewer of the transplanted patients experienced a treatment fail (the study's primary goal), which was determined as either an increase in EDSS or deterioration in any functional system of this scale relative to when the study began.

The proportion of patients who experienced a disability worsening was 6.7% in the MSC-by intrathecal (injection into the spinal canal) group, 9.7% in the MSC-intravenous injection group, and 48.4% in the placebo group. Importantly, 58.6% of the patients transplanted by intrathecal injection, and 40.6% of those who were given MSC intravenous injections, reached no evidence of disease activity (NEDA, a measure that refers to a state with no relapses, no EDSS progression, and no new or active lesions on MRI), compared with 9.7% in the placebo group.

The researchers emphasized that a Phase 3 clinical trial is warranted to confirm these findings.

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Remyelinating drug Liothyronine may aid walking in progMS

Treating MS patients with a potential remyelinating agent called liothyronine is safe and well-tolerated according to the results of a Phase 1b trial. Preliminary results also suggest benefits in walking in progressive MS patients.

The study, "A Phase 1b, open-label study to evaluate the safety and tolerability of the putative remyelinating agent, liothyronine, in individuals with multiple sclerosis," was presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), by Scott D. Newsome, professor of neurology at John Hopkins University School of Medicine.

According to Newsome, thyroid hormones are critical for the development of the nervous system. These hormones may promote remyelination in the central nervous system (brain and spinal cord) by boosting the differentiation of oligodendrocyte precursor cells into mature oligodendrocytes. Those are the cell types that form myelin. Tri-iodothyronine (T3) is believed to play a central role in the most important actions of the thyroid hormones. Therefore, researchers believe that liothyronine — a synthetic form of T3 — may induce repair and limit neurodegeneration in people with MS.

A team from the US conducted a study in 20 adults — ages 18 to 58 — with relapsing and progressive MS. The study lasted 24 weeks. Participants had a mean age of 46.4 years, and included nine men and 11 women. Eight of the 20 patients had progressive MS. Their baseline mean EDSS score was 4.4. A score of 4.5 means the patient has some limitations or disability, and may require minimal assistance to walk.

Results showed that treatment with liothyronine was well-tolerated, with no serious treatment-related adverse events, nor evidence of disease activation or clinical worsening. In early analyses, T25FW (timed 25 foot walking) scores improved in the eight patients with progressive disease.

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NervGen planning trials of new drug to boost myelin repair

NervGen Pharma, a Canadian company that specialises in the treatment of nerve damage, is to start clinical trials evaluating the potential of its new drug NVG-291 to treat MS and spinal cord injury.

NVG-291 is an investigational peptide (short chain of amino acid) that has shown an ability to stimulate nerve regeneration following an injury in several animal models. It works by inhibiting the activity of the protein tyrosine phosphatase sigma (PTPσ), a neural receptor that blocks nerve regeneration following tissue damage.

NVG-291 is similar in structure, but slightly different in composition, to another PTPσ-targeting compound known as intracellular sigma peptide (ISP). Previous studies in MS mouse models found that ISP stimulates the production and migration of oligodendrocyte precursor cells (OPCs) — the precursors of cells that produce myelin (the fatty substance that protects nerve segments or axons) — to MS lesions. As a result, ISP promoted myelin repair in damaged nerves, lowered tissue inflammation, and helped animals recover some lost abilities.

NervGen is now planning to explore NVG-291's nerve regenerative properties and their ability to treat MS and spinal cord injury in people. Next steps include a Phase 1 trial of the compound in 40 to 75 healthy volunteers in early 2020.

Next comes an expansion of that Phase 1 trial to include a people with spinal cord injury; this extension is scheduled to start in the second half of 2020. A Phase 2 trial assessing the drug's safety and effectiveness in a group of MS patients is expected to start in early 2021.

"While we continue to evaluate the potential of our platform in additional indications, over the next 24 months we will focus on aggressively advancing the clinical programs for NVG-291 in spinal cord injury and multiple sclerosis," Ernest Wong, PhD, president and chief executive officer of NervGen, said in a press release.

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At 61 am I now too old for new MS treatments?

Age and eligibility for treatment was a subject raised recently by American blogger and MSer Ed Tobias. He wanted to know if, at 71, he was too old for an aggressive MS treatment that was doing the rounds.

According to Ed the question of age and treatment had originally been raised by the popular the Barts-MS blog https://multiple-sclerosis-research.org/ which Ed says "lit up his radar". The blog had apparently asked whether "elderly" people with MS should be treated differently to those who are younger and the question arose because a case of progressive multifocal leukoencephalopathy (PML), a serious brain disease, was recently reported in a 76-year-old patient.

According to Ed's blog, citing Roche Pharmaceuticals, the 76 year old man with PML had long had MS but wasn't treated with a disease-modifying therapy (DMT), in this case Ocrevus (ocrelizumab), until July 2017. His last dose was in February.

Ed is 71, 18 months past his second round of treatment with Lemtrada (alemtuzumab) and fits into the category of someone who's being treated with a medication that, like Ocrevus, has both high efficacy and potentially serious side effects**.**

In his blog, Ed says the Barts blog author wondered whether someone of Ed's age should be treated with an aggressive medication such as Ocrevus or Lemtrada.

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In fairness to those concerned about ageing Msers and aggressive medication there are medical factors associating with ageing and MS. Older people with MS are more likely to have illnesses in addition to their MS, immune systems that are deteriorating, and less biological reserve to deal with serious, life-threatening infections. But does that mean we ageing MSers shouldn't get the same level of access to new treatments as younger MSers? Ed asks.

He says that according to researchers at Brigham and Women's Hospital in Boston a group of 195 people with MS who were 65 or older were recently studied. The researchers reported that this group had a low rate of adverse reactions to the newer DMTs, and that most side effects were mild, suggesting it's safe for seniors to use high-efficacy DMTs.

Ed also says "We old folks may be living with several illnesses, as the Barts blog noted, and the biological reserve in our brains may be less than that of younger people. But don't count us out when it comes to prescribing the "big gun" DMTs."

He goes on: "We need more research on older people with MS. According to a 2015 article in the Journal of Neuroscience Nursing, 'approximately 90% of people with MS now in their 20s may live into their 70s,' and 'approximately a quarter of people with MS are mature adults over 65 years old.' So don't cast us aside."

As a 61 year old man I agree with everything that Ed says , and one personal bugbear of mine is research into new drugs for MS which often have an age cut- off that would in most cases rule out out Ed and in many cases rule out 61 year-old people like me from trying them out. I hate to use the word ageism but I often wonder if there is a medical reason for this age cut off. I ask the question because I am now old enough to be ineligible for several drugs trials which I guess means I may be ineligible for the drugs should they ever be licensed. A worrying thought.

Ed's blog is at www.themswire.com ***For further details of all news stories and features go to page 13***

News

Higher Vit D Levels May Boost 'Myelin Integrity' in Prog-MS

Higher levels of vitamin D in the blood may help protect the myelin sheath, slowing damage to nerve cells in people with progressive MS, a brain imaging study reports. The study, "Vitamin D and MRI measures in progressive multiple sclerosis," was published in the journal Multiple Sclerosis and Related Disorders.

Vitamin D deficiency has been proposed as a risk factor for MS, but most studies have been conducted in people with relapsing-remitting MS. What data exist for progressive disease suggest that vitamin D levels in these people are even lower than in RRMS patients, and may predict conversion to secondary progressive multiple sclerosis (SPMS).

Low vitamin D levels have been associated with greater lesion volume, brain atrophy (shrinkage), and disability over time, but the link between such levels and clinical progression on magnetic resonance imaging (MRI) scans in progressive MS remains unclear. A US team addressed this in people with primary progressive MS (PPMS) and SPMS taking part in the SPRINT-MS Phase 2b trial (NCT01982942) of ibudilast.

Among the 286 patients studied 137 patients had PPMS and 130 SPMS. Blood levels of 25-hydroxyvitamin, or 25(OH) vit D, were examined. Looking at its two components, the mean level for vitamin D2 was 43.8 ng/ml, and 40.7 ng/ml for vitamin D3. No differences were seen when comparing PPMS with SPMS patients, but older women with longer disease duration had higher vitamin 25(OH)D3 levels.

Grouping patients according to 25(OH)D3 blood levels — under 30, between 30–39 or 40–49, and over 50 ng/ml — continued to show no differences between groups regarding Expanded Disability Status Scale mean scores or in any conventional brain imaging measures, such as brain volume and active or inflammatory new lesions.

Levels of 25(OH)D3 were not associated with brain volume or lesional measures in progressive MS contrary to what has been described in RRMS. However, when researchers accounted for factors such as age, gender, and disease duration, a subsequent analysis showed that higher levels of 25(OH)D3 were significantly associated with greater scores in whole brain (WB) and in normal appearing grey matter (NAGM) using magnetization transfer ratio (MTR) — which assesses myelin content and nerve fibre density.

"The positive associations between vitamin 25(OH)D3 and WB/NAGM-MTR values suggest that vitamin D may have a protective role in progressive MS patients" in terms of "myelin integrity," the researchers said. Such benefits could be via immune modulation, and anti-inflammatory and antioxidant effects, they added. **For further details of all news stories go to page 13**

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To Contact me email iancookjournalist@yahoo.co.uk or via twitter@iancookMSer

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