

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 30, March/April 2020

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 a trip to Poland I took in 2000 for a vein treatment called CCSVI. It was supposed to help my MS progressing. Did it? The second feature looks at the launch of a new charity promoting HSCT (Haematopoietic Stem Cell Therapy) for MSers. See page 10.

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Spinimod (Mayzent) decision on UK availability for prog-MS expected in Spring or Summer

NICE has begun an appraisal of siponimod for secondary progressive MS to decide whether it should be prescribed by the NHS in England and Wales. The decision is due to be published in May. The Scottish Medicines Consortium has also scheduled an appraisal with the decision due to be published in July.

The European Commission recently approved Novartis's Mayzent (siponimod) as the first oral treatment for adults with active secondary progressive multiple sclerosis (SPMS) and now things have moved to a national level.

Active SPMS is defined by the presence of evident relapses or the detection of inflammatory activity in brain lesions on imaging scans.

"As the only indicated oral therapy proven for people living with SPMS with active disease, we are pleased that the European approval of Mayzent will help change the conversation about progressing MS and expand possibilities for patients and their caregivers," Max Bricchi, Novartis Pharmaceuticals's global head of neuroscience franchise, said in a press release.

Mayzent belongs to the same therapy class as Novartis's Gilenya (fingolimod).The therapy works by binding to two sphingosine-1-phosphate (S1P) receptors on the cell surface of immune cells, leading to the internalization and degradation of the receptors. This prevents immune cells in the lymph nodes from reaching the brain and spinal cord, thus reducing the inflammatory processes that promote MS development and progression. Siponimod is taken as a tablet, once daily

A phase III trial on siponimod called EXPAND in 2018 looked at 1651 people with secondary progressive MS diagnosed with MS for approximately 17 years, and had had SPMS for about 4 years. Just over half needed walking assistance. Participants took either siponimod (1105) or placebo (546) daily for up to 3 years.

Researchers found that 32% of those taking placebo experienced a 3 month confirmed increase in disability during the study, compared to 26% of those taking siponimod so the improvement, though welcome should not be overstated.

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Masitinib Slows Disability Progression in PPMS and Non-active SPMS, Phase 2/3 Trial Reports

Bio-Pharma company AB Science's new drug masitinib significantly slowed disability progression in people with primary progressive MS (PPMS) and non-active secondary progressive MS (SPMS) results from a Phase 2b/3 clinical trial show.

Masitinib, formerly known as AB1010, is taken as a tablet, twice daily and inhibits the activity of cells in the innate immune system, specifically mast cells, microglia, and macrophages. In doing so, the therapy is believed to limit the inflammatory processes that cause damage to the nervous system in MS.

"People with primary progressive (PPMS) and non-active secondary progressive (nSPMS) forms of multiple sclerosis account for half of all MS patients," Patrick Vermersch, PhD, a professor at University of Lille in France and a trial investigator, said in an AB Science press release.

PPMS is estimated to affect about 15% of all MS patients, while non-active SPMS (nSPMS) affects about 30% to 35%.

In the AB07002 Phase 2b/3 clinical trial (NCT01433497), a group consisting of 301 MS patients were enrolled, with 200 given 4.5 mg/kg of masitinib daily, and 101 a placebo. Results showed the 'primary endpoint' was met, in other words there were significantly lower increases in EDSS seen in the masitinib-treated group than the placebo group. This treatment effect was maintained for both the PPMS and non-active SPMS subpopulations. (Higher EDSS score represent worsening disability levels.)

Treatment also significantly delayed disease progression, as measured by the time to reach an EDSS score of 7.0 — functionally, this 7.0 score means a person requires the use of a wheelchair.

Further details of Masitinib research will be given at an upcoming scientific conference this year – hopefully either ACTRIMS or ECTRIMS . The company also announced a new patent filing for masitinib based on AB07002 trial results, and said it will be in contact with regulatory authorities to discuss further development of masitinib as a treatment for progressive forms of MS.

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Rhythmic Sound Clinical Trial to test improved MS walking

A pilot clinical trial to assess the safety and efficacy of a product that uses rhythmic sounds to improve walking abilities in people with progressive MS is planned in the USA.

The randomized and controlled trial, fully support by a grant from the Consortium of Multiple Sclerosis Centers (CMSC), will be conducted at the Cleveland Clinic USA. The product being tested is called MR-004 and is the brainchild of MedRhythms a digital therapeutics company exploring the use of sensors, software, and music to aid in walking rehabilitation.

MedRhythms states on its website that rhythmic auditory stimulation directly stimulates the brain to activate a mechanism known as "entrainment" — a neurologic process in which the brain's auditory and motor regions are coupled. Entrainment can enhance neuroplasticity (the brain's ability to strengthen pre-existing neural connections, allowing a person to acquire skills over time)

The company believes music induces neurological connections needed for the positive re-wiring of the brain. MR-004 is the company's pipeline product, based on rhythmic auditory stimulation, being developed for walking rehabilitation in MS.

More than 50 clinical research studies have reported improvements in movement based on the use of rhythmic auditory stimulation through music, the company reports. These studies were conducted in people with diseases or conditions affecting the brain, including MS, Parkinson's disease, cerebral palsy, and stroke.

"I've conducted many trials on interventions to improve walking in those living with MS, including the compelling impacts of rhythmic cueing in this population," Francois Bethoux, MD, a paid advisory member to MedRhythms who will lead the trial, said in the press release.

"I look forward to undertaking the role of principal investigator in this study, and to learn more about this investigational therapy and its potential impact on mobility and quality of life in patients with MS," Bethoux added. MedRhythms also announced the creation of Scientific Advisory Boards (SABs) to help direct the company's clinical and research activities in MS. **For details of all news stories go to page 13**



Looking back on my trip to Poland for CCSVI in 2000

Exactly ten years ago I travelled to a snowy Katowice in Poland to receive a radical new treatment for my SPMS. The treatment was based on a theory that MS is caused by the blockage of veins taking blood from the brain.

The theory, known as CCSVI (chronic cerebrospinal venous insufficiency), had been proposed by an Italian vascular surgeon, Paolo Zamboni in a 2008 paper published in the Journal of Neurology, Neurosurgery and Psychiatry.

In the paper Zamboni proposed that vein blockages can cause pressure in the brain, decreasing blood flow from it and leading to inflammation, ultimately resulting in MS and its progression. His paper claimed these vein blockages (CCSVI) were found in a group of people with MS but not in a group of people without MS. Moreover, relapsing-remitting and secondary progressive MS (SPMS) were associated with CCSVI patterns significantly different from those of primary progressive MS. To say the paper shook the foundations of the MS world would be an understatement.

The reason for this was that as well as solving the riddle of MS's cause, Zamboni appeared also to have a solution. Zamboni proposed surgical repair or unblocking of veins in the neck to treat CCSVI vein abnormalities.

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Continued from page 5. This was done mainly using "balloons" which were temporarily inserted into the veins and then inflated to increase the flow of blood, before being removed. In a minority of cases stents -tubes made of metal meshes – were inserted into veins and left in place

Within a year of Zamboni's first paper being published, private clinics in Eastern Europe, Mexico and the Caribbean were offering CCSVI testing and treatment in the form of vein balloons and stenting called the "liberation therapy". It is not known exactly how many patients were treated worldwide but the figure is believed to run into the thousands and in January 2010 I was one of the first to be treated.

So has my MS stabilised or even improved in the past ten years? Well, it certainly has not improved. I can walk less than I could in 2010 and I now self-catheterise three times a day. I didn't self-cath at all in 2010.

Unsurprisingly the past ten years have seen a growing scepticism about the CCSVI theory and not just because of the practical problems associated with the liberation procedure and stents. The vein problem hasn't been found exclusively in MSers, undermining the basis of the theory. The largest study into CCSVI conducted in 2013, involving 1,767 subjects, found zero correlation between vein blockage and MS. Another smaller study also in 2013 involving 177 again found no correlation at all. These two studies seemed to signal the scientific death of the CCSVI veins and MS hypothesis.

It has been known for 150 years that veins are connected with MS. In fact it was proposed that MS was due to a vascular defect as early as 1863 when a German pathologist Eduard von Rindfleisch noted a blood vessel in the centre of each MS plaque. Many would say Rindfleisch's connection between blood vessels and MS has never received the attention it deserves. And, sadly Zamboni's efforts to make veins the centre of MS research probably has set back rather than advanced the efforts of Rindfleisch and others to provide a vascular theory of MS*.* " **For further details go to page 13**

Mesenchymal Stem Cell Transplant is Safe and May Delay MS Progression

Transplanting patients' own mesenchymal stem cells (MSCs) is safe and can delay disease progression in people with multiple sclerosis (MS), a review of nine studies says. The review also showed that cells transplanted to the spinal cord (intrathecal injection) were associated with significantly slower disease progression rates, compared to cells delivered into the bloodstream.

Titled "Autologous Mesenchymal Stem Cell Transplantation in Multiple Sclerosis: A Meta-Analysis" the review was published in the journal Stem Cells International.

MSCs are found in several parts of the body, including the bone marrow, skin, and fat tissue. Autologous MSCs transplant involves collecting a patient's MSCs and expanding their numbers in the lab. Cells are then infused back into the patient's blood (intravenous injection), or into the fluid surrounding the spinal cord (intrathecal injection).

In the review, researchers reviewed nine studies (eight open-label, and one randomized study) encompassing 133 MS patients, including those with primary progressive and secondary progressive MS to assess the effectiveness and safety of autologous MSCs transplant in MS..

Regarding the treatment's effectiveness, results showed that 72% of patients reached the status of no evidence of disease activity (NEDA) — meaning no disability progression, no clinical relapse, or no new MRI lesions — at six months, and 62% after one year. The team also found that transplant by intrathecal injection was associated with significantly lower six-month and one-year progression rates compared to intravenous injection. No significant differences between age, EDSS, and MS duration were found in the groups meaning it worked just as well in patients with more advanced disability and longer disease duration.

Overall, in "this meta-analysis, we demonstrate the safety of aMSCs [autologous MSCs] for the treatment of MS," researchers wrote, "with the largest benefit profile obtained in patients with aMSCs intrathecal injection. All in all, comprehensive consideration of results indicate that aMSC transplantation is safe, and to better evaluate the efficacy more studies need to be investigated in the future," the team stated.

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Cognitive Decline in MS May Not Be Inevitable or Progressive, 10-year Study Suggests

Progressive cognitive decline in MS patients may not be as inevitable as previously thought, a study suggests. The study "A longitudinal study of cognitive function in multiple sclerosis: is decline inevitable?" was published in the Journal of Neurology.

Statistics indicate that some kind of cognitive impairment affects up to two-thirds of all MS patients, including memory deficits or problems processing information. Once a patient starts showing signs of cognitive decline, it is often assumed symptoms will inevitably worsen as MS progresses. However, findings from a new study carried out by researchers in Greece are challenging this scenario. Investigators reviewed data from 59 patients over a decade. Analyses revealed roughly a 10% increase in measures of overall cognitive impairment over the course of 10 years in the MS group analysed.

A more detailed analysis of five separate cognitive "domains" assessed in the test (verbal memory, visual/spatial memory, working memory, processing speed, and cognitive flexibility) suggested this rise was mainly driven by a decline in verbal memory. Cognitive impairment at 10 years was not associated with the occurrence or number of relapses in the intervening time, nor with disability (as measured by the Expanded Disability Status Scale) at any time point.

In general, patients with normal memory-related scores at the first assessment were more likely to be impaired in this domain 10 years later. Those with normal information processing speed, however, rarely showed a decline a decade later. Some with impairments in working memory and/or verbal fluency at the start of the research even experienced significant improvements in cognitive abilities 10 years on, often to the point of no longer being considered impaired.

"This 'bouncing-back' of cognitive function in impaired-at-baseline patients is an intriguing phenomenon that may reflect the [damage] compensation capabilities of the brain in MS patients," the researchers wrote.

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Incontinence in MS Affects Walking Ability, and Negatively Affects Patients' Quality of Life, Study Finds

Urinary incontinence, associated with poor muscle control in the pelvic area, negatively affects walking and quality of life in people with MS, a study shows.

Adding pelvic floor muscle training to an MS treatment programme may help to improve overall function, the researchers suggest, which could improve patient performance of daily life activities.

The study, "Pelvic floor dysfunction negatively impacts general functional performance in patients with multiple sclerosis," was published in the journal Neurology and Urodynamics. In the study a total of 43 MS patients — 24 women and 19 men; average age of 50.3 years were included. The researchers took into consideration that giving birth can stretch the muscles of the pelvic floor, noting that 11 (25.6%) of the women included in the study had never given birth.

To assess the participants' pelvic floor muscles, the researchers took into account each individual's urinary incontinence (UI), faecal incontinence, and constipation history. The team also assessed the patients' general functional performance and gait. The results showed that urinary incontinence had a significant and negative impact on the patients' quality of life and general functional performance.

One test suggested that MS patients with urinary incontinence had more trouble walking. Importantly, these patients also were the ones who were more dependent on others — rated as moderate-to-severe dependence — for daily activities. The participants with greater constipation also had lower quality of life scores, the data showed. In addition, those with more severe faecal incontinence presented a higher degree of urinary incontinence and constipation. Those findings suggest a relation between the variables of pelvic floor function, the researchers said.

The data suggests that MS patients' dependence on others for carrying out day-to-day activities is linked with the improper workings of the pelvic floor muscles, emphasizing the importance of this muscle group in the activities of daily life.

Based on these results, the team suggested that "it could be relevant to add pelvic floor muscle training to interventions aimed at improving overall functionality in patients with MS." **For further information on news stories go to page 13**



One year on, HSCT is still centre stage for prog-MSers

Just over one year ago I attended a black tie fundraising ball at Villa Park, Birmingham, launching a new charity promoting HSCT (Haematopoietic Stem Cell Therapy) for MS.

The new charity, AIMS (Auto Immune & Multiple Sclerosis), was set up to help people with auto-immune illnesses, particularly MS, to access HSCT treatment. HSCT is where an MS patient's immune system is replaced or "re-booted" and as a result the myelin coating of nerves in the brain and spinal cord no longer suffer the auto-immune attacks that characterise MS.

HSCT uses high dose chemotherapy which wipe out the body's existing immune system. The immune system is then rebuilt using stem cells which have been "harvested" from the patient's blood before chemotherapy and are then re-introduced afterwards. The newly rebooted immune system suffers no further auto-immune attacks, thus preventing further damage.

At the AIMS launch I met a number of MS patients including Becky White (pictured above) who had received HSCT. So how are they doing one year on? One of the people I spoke to at length was Damien Scott who was diagnosed with relapsing remitting MS in 2004. Damien travelled to Moscow in 2017 for treatment at the A.A. Maximov Haematology and Cell Therapy Department of the National Pirogov Medical Surgical Centre. At the Villa Park event Damien gave me some background information about his trip to Moscow:**Continued on page 11**

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"My decision was made easily. Whilst my disease has been very stable. My treatment experience was nothing short of amazing, life changing. The hospital care was second to none."

Last year Damien said he had noticed a real improvement in his MS symptoms, so have those improvements been sustained over the past year ? I asked him. He said: "I'm doing well, I have no disease progression or relapses. I have zero regrets about going to Russia for HSCT and would repeat it without a seconds thought."

Another person who is doing well following HSCT treatment is Becky White (pictured on previous page) who was treated with HSCT for her MS at Hammersmith hospital in 2018. She said " Since having HSCT I have experienced a number of improvements to the MS symptoms. The burning in my thighs, fatigue, weakness in my legs and l'hermittes sign have gone. Other difficulties have reduced, like the optic neuritis.

" I have had two MRI scans since I had HSCT and both scans not only show no new lesions, they show that existing lesions have reduced in size and some have disappeared. Although since 2018 I have been diagnosed with Graves Disease (overactive thyroid) , but am really not finding this difficult to manage.

Overall the HSCT patient reports one year after the Villa Park event are highly positive and the AIMS charity which organised the event goes from strength to strength. All looks well for HSCT as a new MS treatment. All credit to AIMS

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Gold Nanocrystals in Phase 2 Testing Show 'Robust' Remyelination Potential in Animal Models of MS

A revolutionary remyelination therapy, CNM-Au8, has shown a "robust" ability to stimulate the production of new myelin and increase the number of myelin-wrapped nerve fibres in the brain and spinal cord of mice with a demyelinating disease, allowing them to recover motor skills, a study reports.

Such data supports the effectiveness of Clene Nanomedicine's potential treatment, now being tested in clinical trials with MS patients. The early findings have been reported in the study "Nanocatalytic activity of clean-surfaced, faceted nanocrystalline gold enhances remyelination in animal models of multiple sclerosis," published in the journal Nature Scientific Reports.

Most approved MS therapies dampen the immune system's activity to prevent further myelin damage. However, they cannot undo existing damage or replace the myelin sheaths that have been lost. CNM-Au8 is a solution of gold nanoparticles with a patented crystal structure.

According to Clene Nanomedicine these nanocrystals have properties that make them "highly biologically active," allowing them to facilitate certain energy-related reactions within cells.

In the brain, both neurons and supporting cells, including oligodendrocytes that produce myelin, need substantial amounts of energy to work. In fact, the brain consumes more than 25% of the body's metabolic resources in order to sustain the efficient flux of information through its vast network of nerve fibres. CNM-Au8 is believed to enhance key metabolic reactions in neurons and oligodendrocytes so to increase energy reserves within these cells.

This process, which Clene calls nanocatalysis, is thought to improve the survival and function of neurons, and to support the ability of oligodendrocytes to create new myelin.

Researchers found that oral delivery of CNM-Au8 to mice and rat models of demyelination led to "robust remyelination activity" in the brain and spinal cord, leading to higher numbers of myelin-wrapped axons. Study data also showed that CNM-Au8 resulted in a greater migration of oligodendrocytes to lesion sites, and increased myelin production.

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Page 10-11 HSCT for MS feature

For further details on AIMS go to https://www.aimscharity.org/#:~:text=AIMS%20is%20the%20UK's%20first,with%20an%20emphasis%20on%20HSCT.&text=Our%20aims%20are%20to%3A,primarily%20those%20with%20Multiple%20Sclerosis.

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