

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 40, November/December 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 ageing and the question of whether MS leads to premature ageing . There's also a feature on exercise, physiotherapy and exoskeletons . See page 10 for details.

IN THIS ISSUE



Does prog-MS cause premature ageing?
See page 5

Malaria drug leads to small improvement in PPMS – page 3

Stem cell transplant may better treat SPMS than drugs, p7

News

ATA188 Benefits in SPMS and PPMS - Hint at Remyelination

An investigational infusion treatment for progressive MS could reverse disability and improve exercise capacity, Bio-pharma Atara Biotherapeutics reported in an update on a Phase 1 trial and a long-term extension study. Findings into the treatment called ATA 188 also suggest gains may be tied to remyelination.

Trial results extending up to 39 months, were presented as an e-poster at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) which took place virtually in October, the drug's developer Atara Biotherapeutics reported in a press release, The e-poster was titled, "Updated open-label extension clinical data and new magnetization transfer ratio imaging data from a Phase I study of ATA188, an off-the-shelf, allogeneic Epstein-Barr virus-targeted T-cell immunotherapy for progressive multiple sclerosis."

"At ECTRIMS, we were presenting new imaging data suggestive of remyelination that provide a potential biologic basis for the clinical EDSS [a score measuring patient disability] improvements observed with ATA188 treatment in the Phase 1 and OLE (Open Label Extension) studies," AJ Joshi, chief medical officer at Atara, said in the release.

Evidence suggests that the Epstein-Barr virus (EBV), a common type of herpes virus, infects immune B-cells causing them to wrongly produce antibodies that attack the myelin sheath. Damage to myelin disrupts electric signals traveling along the nerve fibres connecting the brain and body, resulting in disabling MS symptoms.

Administered by infusion into the bloodstream, ATA188 is a treatment composed of immune T-cells modified to target and kill B-cells and antibody-producing plasma cells that are infected with EBV. ATA188 is therapy with T-cells collected from healthy donors instead of patients. It has a novel mechanism of action, and our clinical programme is generating new insights into how the targeting of EBV-infected B cells and plasma cells can potentially benefit people living with progressive multiple sclerosis," Joshi added.

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

Malaria drug linked to treating COVID leads to improvement in primary progressive MS

The malaria drug hydroxychloroquine which was once considered as a treatment for COVID-19 appears to slow disability progression in primary-progressive MS (PPMS) according to the results of a study published on September 30 by the journal "Annals of Neurology".

In the phase 2 clinical trial, only 8 of 35 participants treated with the drug — which has been used for years to treat malaria, a mosquito-borne disease, and is also used to treat some autoimmune inflammatory rheumatoid diseases, including rheumatoid arthritis and lupus — experienced clinically significant worsening of disability between 6 and 18 months after starting treatment, the study found. On the basis of prior study data, 10 were expected to show signs of worsening disability so the effect was only small but was "statistically significant" nevertheless.

As part of the study participants were given one 200 milligram (mg) tablet of the drug twice daily, and were evaluated using several standard measures for MS progression, including an Expanded Disability Status Scale (EDSS) score, contrast magnetic resonance imaging (MRI), timed 25-foot walk test, the Nine-Hole Peg Test, and the Symbol Digit Modalities Test, the researchers say. For the purposes of the study, those with a 20 percent or more decline in performance on the timed 25-foot walk test were considered to have worsening disability.

In addition to appearing to slow progression, hydroxychloroquine was generally safe, the study authors wrote. In all, 15 participants experienced drug-related side effects, with six reporting vivid dreams, three developing nausea, three indicating upset stomach, and three reporting tinnitus, or ringing in the ears. Six participants developed serious side effects, but none were linked with hydroxychloroquine, the researchers noted.

Although the drug was associated with less disability worsening in people with PPMS in the study, larger trials of the drug in people with the condition are needed to confirm the results, according to Jeffrey Cohen, MD, the director of the experimental therapeutics program at the Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research in Ohio.

"Further investigation would be reasonable, but these results are very preliminary and do not support use of hydroxychloroquine to treat PPMS outside of studies," he added

For details of all stories go to page 13

News

Fesoterodine Fumarate Can Ease MS Bladder Problems

Treatment with fesoterodine fumarate —an extended-release tablet that patients take by mouth — can reduce bladder pressure and improve quality of life in people with bladder impairments due to MS, new research shows.

“A three-month treatment with fesoterodine fumarate seems to have a critical impact on patients’ QoL [quality of life],” the investigators wrote, noting their study “revealed a significant increase in QoL in each group” of participants given the tablet. The findings were published in Neurourology and Urodynamics, in a study titled “Efficacy of fesoterodine fumarate (8 mg) in neurogenic detrusor overactivity due to spinal cord lesion or multiple sclerosis: A prospective study.”

Most people with MS — up to 75% — will experience bladder-related health problems at some point in their lives, research shows. In particular, people with MS and other forms of nerve damage may develop something called neurogenic overactive bladder or nOAB. This condition occurs when the bladder is overly active because of flawed activity in the nervous system. Specifically, nOAB in MS tends to develop because the detrusor — the muscle around the bladder — is “squeezing” too much. Such bladder-related problems can severely impact quality of life for patients, the researcher said.

Fesoterodine fumarate, marketed as a long-acting tablet under the brand name Toviaz, works to block the molecular signals that tell the detrusor to “squeeze.” It is approved to treat overactive bladder when the cause isn’t clear, but there are little published data on the use of this medicine in people with neurogenic overactive bladder, specifically. Now, researchers in Greece reported on 124 people with an overactive bladder due to nervous system problems who were treated with fesoterodine fumarate at a dose of 8 mg per day for three months. About one-quarter of these patients had MS; the rest had spinal cord damage. The total group included 68 males and 56 females.

The results of the study showed that three-month treatment led to statistically significant improvements in many measures of bladder function. For example, it markedly reduced the maximum detrusor pressure — which, as its name suggests, is the highest amount of force that the detrusor puts on the bladder. The treatment also increased the maximum amount the bladder could hold, and it significantly improved life quality.

For details of all stories go to page 13



Does MS lead to premature ageing?

As you get older you become increasingly aware of a sad but inevitable fact of life – your body is ageing. When I was at school my biology teacher told me ageing is essential for evolution to do its job properly. Even bacteria and fungi age, albeit at a different speed to humans.

One thing I learned after my MS diagnosis, is that the disease speeds up ageing, causing us to age more quickly than non-MSers. This is because the inflammation that is characteristic of relapsing remitting MS leads to white matter loss which in turn leads to brain shrinkage and less "cognitive reserve". There is a developing view that relapsing remitting MS as it changes into secondary progressive MS speeds this process up.

To get a bit technical here, ageing is all about the length of your chromosomes. As cells divide, the end of the chromosomes, called telomeres, shorten. Telomeres protect chromosome from damage, as well as help repair and avoid unnecessary recombination. This is a process by which pieces of DNA are broken and recombined to produce new combinations of genetic material. Telomeres are quite long when you're young and as you age they get shorter.

Telomeres and their length can be seen as a biological clock of ageing. Shorter telomeres that you often find in MS are linked with greater disability, lower brain volume, and all the sorts of things you associate with getting older. A recent review of seven studies of MS showed that MSers typically have shorter telomeres than controls; in other words, we are biologically older than healthy age-matched controls. So, being born in 1958 I might have a chronological age of 63 but my biological age could be far higher – say 73.

Interestingly one neurologist with quite a big media presence recently revealed he was seeing an increasing number of older people with MS, who are developing progressive worsening of their functioning after many years of being NEIDA (no evident inflammatory disease activity) even though they were on a DMD (Disease Modifying Drug) and stable physically. He was surprised. **Continued on page 6**

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Continued from page 5. When he did various tests clinically, radiologically with MRI and biochemically (spinal fluid analysis) he said he couldn't find any evidence of MS disease activity and concluded a large part of what he was seeing was age-related neurodegeneration occurring decades earlier than it should because MS has shredded these patients' brains and sapped their cognitive reserve. I think we are talking about shorter telomeres here.

The neurologist didn't really answer the question about what older people with long term MS should do, but focussed on things like the importance of early diagnosis and treatment upfront with the aim of protecting the reserve capacity of the nervous system so pwMS can age normally. Sadly, if true this is helpful to the young newly diagnosed but isn't much use to someone like me who was born too early and had too few relapses to benefit from each new Disease Modifying Drug as I watched them being released onto the market and whose disease is now progressive and not really suitable to be treated.

So, is there anything I can do about the premature ageing process? I suppose I could ask my neurologist if I am NEIDA (no evident inflammatory disease activity) I could even ask about my telomere length . However, I doubt whether I will get a helpful answer to either question if for no other reason than I think I have been consigned to the "no hopers" group of his patients, but in reality he probably doesn't know the answer to either and it would be too expensive and time consuming for him to find out.

More positively, however, I can ensure that I am doing everything I can from a health and wellness perspective. I am talking here about exercise diet and using my brain. In observational studies, higher levels of physical activity or exercise were related to longer telomere lengths in various populations, and studies show athletes tend to have longer telomere lengths than non-athletes.

A small pilot study in 2013 found that changes in diet, and exercise may result in longer telomeres. So I have started to make changes in both the above areas, and also started to learn a new language – Greek – as I have also read that learning a new language – may be a powerful anti ageing strategy, so until next time I will keep on eating healthily, exercise and finally let me wish you a good day or Να έχεις μια όμορφη μέρα, as they say in Greece.

. **More information on page 13.** **Page 5 Picture: K Mitch Hodge at Unsplash**

Stem Cell Transplant May Better Treat SPMS Than Drugs

A patient-derived stem cell transplant is more effective than available disease-modifying therapies (DMTs) at slowing disease progression in people with active secondary progressive multiple sclerosis (SPMS), according to a real-life study in Italy. Data highlight the potential benefits of this therapeutic approach in SPMS patients, and support its further evaluation in future, appropriately controlled clinical trials, researchers noted.

These findings were presented by Giacomo Boffa, MD, of the University of Genova, at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) The presentation was titled, “Autologous hematopoietic stem cell transplantation reduces disability progression in patients with secondary progressive multiple sclerosis: results from the Italian MS Register.”

The study included 69 SPMS patients who received AHSCT (AHSCT group) within the Italian Bone Marrow Transplantation Study Group, and 217 matched patients using DMTs (DMT group) and who were participating in the Italian MS Register. The mean age was about 38.

After a mean follow-up of 5.2 years, results showed that the stem cell transplant was associated with a significantly slower disease progression compared with approved DMTs. Particularly, the AHSCT group exhibited generally sable disability scores over time, “while patients treated with other DMTs had a continuous disability progression,” Boffa said. In addition, the stem cell transplant significantly delayed the time to confirmed disability progression relative to other DMTs, with 62% of AHSCT-treated patients remaining free of disability progression at five years.

Patients receiving AHSCT were also four times more likely to achieve confirmed disability improvement relative to those given DMTs. Notably, five years after the procedure, “20% of patients still maintained disability improvement, compared with only 4% of patients treated with other DMTs,” Boffa said. These finding suggest that stem cell transplant is superior to DMTs at slowing disability progression in people with active SPMS. The possibility to reduce disability and maintain this is a crucial need for patients with a progressive disease and it’s hardly obtained with standard anti-inflammatory drugs, Boffa added.

He noted, however, that these results may not be applicable to SPMS patients without signs of inflammatory activity (active disease). Still, they “reinforce the notion that ongoing inflammation during progressive MS requires adequate immunotherapy.” Future controlled clinical trials “are needed to confirm the efficacy of AHSCT in patients with active SPMS,” the researchers wrote.

For details of all news stories go to page 13

News

Cognitive Rehab is an 'effective, Low-risk' treatment for prog-MS

Cognitive rehabilitation is an effective therapy for cognitive problems brought on by MS progression, a review study highlights. "Clinicians should consider this low-cost, low-risk, yet effective treatment approach for their patients," its researchers wrote. The study, "Neurological update: cognitive rehabilitation in multiple sclerosis," was published in the Journal of Neurology.

For as many as two out of every three people with MS, cognitive impairment is a symptom of the disease. How this impairment manifests varies from person to person, but often involves problems with learning and memory, as well as difficulty or delays in processing new information.

Most medications approved to treat MS are not especially effective at addressing cognitive dysfunction. Cognitive rehabilitation is a non-pharmacological approach to managing such difficulties. It has two broad strategies, restorative and compensatory. Both involve doing activities or other work to ease cognitive symptoms.

In restorative cognitive rehabilitation, sometimes called cognitive remediation, the goal is to reinforce, strengthen, and restore cognitive skills that may be impaired. This type of rehabilitation commonly involves repetitive exercises that are done using a computer. By contrast, compensatory cognitive rehabilitation does not aim to help patients gain back lost cognitive skills. Instead, it focuses on creating strategies to help people handle their impairments, finding ways to make difficult things more manageable.

A trio of researchers at the Kessler Foundation and New Jersey Medical School at Rutgers University conducted a review of published scientific studies on the effects of both kinds of cognitive rehabilitation in people with MS. In total, the team assessed 81 studies, most of which were published in the last decade. Analysing these data collectively, the researchers found "evidence that cognitive rehabilitation programs (either restorative or compensatory) are efficacious in treating MS-related cognitive dysfunction".

"Cognitive rehabilitation should be part of a comprehensive treatment plan for people with MS who experience cognitive deficits. Given the lack of approved pharmacological treatments, behavioural approaches are the best treatment options that clinicians can currently offer," John DeLuca, PhD, a study co-author with the Kessler Foundation, said in a press release." "Furthermore, computer-based treatments can be easily delivered at home, making this low-cost effective intervention more convenient and accessible to individuals in need."**For details of all news stories go to page 13**

Covid boosters recommended in SPMS

Should those of us with SPMS – who tend to be older- have a booster COVID-19 vaccine or not. The answer is simple, YES. That's according to a study published in the influential New England Journal of Medicine (NEJM)

The study showed that in Israelis aged 60 or over those who had a booster or third dose of the Pfizer-BionTech RNA vaccine were 11.3 times less likely to be infected with SARS-CoV-2 compared to people who had been double vaccinated.

The more impressive finding is that severe COVID-19 was reduced by a factor of 19.5 in the boosted group compared to the non-boosted group.

The question is whether or not this study's findings are relevant to pwMS. Older people have immunosenescence which is a form of immunosuppression and hence if you have MS and are on immunosuppressive therapy you need to boost your immunity. The principles are very similar.

In the UK pwMS on immunosuppressive therapies are being called up for a third dose. You are advised to go ahead with the booster.

People on anti-CD20 therapy should be aware that if they have no B-cells in their peripheral blood they are unlikely to make an antibody response, but the booster should theoretically improve their anti-SARS-CoV-2 T-cell responses.

If they want to make an antibody response they can ask their team if they can delay their next infusion to allow some B-cell reconstitution before being vaccinated. The question is whether or not this is necessary is a moot point and the best thing is to seek expert advice.

For further information on news stories go to page 13



How I discovered exercise is good, despite disability

About six weeks ago I got a phone call from a local MS Society sponsored physiotherapist who was offering four free physio sessions in my own home.

I was a bit surprised at first but when I made enquiries I was reminded I had signed up several months ago to a local MS Society sponsored exercise rehabilitation scheme designed to help people like me who had struggled to exercise during the lockdown when gyms, swimming pools etc were often closed

Naturally, I took up the offer of free physio and the physio duly arrived at my house. On day one she got me to show her my present state of mobility or immobility and then set up a fairly ambitious programme of four weekly sessions, which involved activities which sounded a little daunting (including a 20 minute walk on my rollator) standing up against a wall for 5 minutes and squats.

When the physio left after the first session I promised I would follow the same routine each day until our next session – one week after the first. However, when she arrived, exactly one week later, I had the embarrassment of telling her I had not done anything since her first visit because last week's exercise had left me too exhausted to do virtually anything since. I made pathetic excuses of saying I was "too far gone" in terms of progression to exercise and we might as well abandon the whole project - which was clearly a and bad move on my part.

The physio was very understanding when confronted with my pathetic excuses did not leave, as I had secretly hoped, but rather suggested that we try to modify the exercises and make them less arduous so we could arrive at a routine which would enable me to exercise every day for a shorter period and carry out less exhausting routines involving fewer steps, basically spending less time on my feet. I listened to her ideas about why I was having such difficulties and the physio said it was her view that my problems were as much to do with being de-conditioned as being disabled and that we should give exercise another go. I must admit that I was a little sceptical at first but having nothing to lose I agreed I would to exercise again. **Continued on page 11**

Continued from page 10 Although shorter with less walking this second session was more successful than the first. I felt my movement was better, it was less tiring and my recovery time was far shorter, so much so that the following week , (week three) I was able to carry out a less arduous daily exercise routine which I have been able to stick to for the past month.

I am lucky as far as walking is concerned because I still have some basic mobility on which to build. But, I asked myself, would there be any advantage in taking up "walking" exercise for someone who was less mobile than myself and if so, how on earth would they do it? These are difficult questions but the answer probably lies in robotic "exoskeleton" assisted rehabilitation.

A robotic exoskeleton consists of an externally worn device that encases a user's hips, back, and legs during rehab, providing greater physical performance. Interestingly some research was published recently which showed that four weeks of robotic exoskeleton-assisted exercise rehabilitation, called REAER, worked better than conventional "gait training" in improving mobility in people with MS who had substantial walking difficulties. The study, "A pilot randomized controlled trial of robotic exoskeleton-assisted exercise rehabilitation in multiple sclerosis,"(REAER) was published in the journal Multiple Sclerosis and Related Disorders.

It involved 10 adults (mean age 49.9) with MS and significant disability. The participants were randomly assigned to undergo either a 30-45 minute session of REAER (six patients) or conventional gait training (four patients), twice a week for four weeks (about one month).REAER involved progressive walking training over-ground using Ekso Bionics's Ekso-GT, the first robotic exoskeleton cleared by the U.S. Food and Drug Administration for use in people with spinal cord injury or stroke.

Ekso-GT can provide adaptive amounts of power to either side of an individual's body, challenging the patient as he or she progresses through rehabilitation. It has been shown to mobilize patients earlier, more frequently, and with a greater number of high-intensity steps. In the group of patients receiving REAER intervention, the maximum allowable degree of robotic assistance was progressively reduced across the sessions.

The researchers assessed patients' functional mobility, walking endurance, cognitive processing speed, and brain connectivity. Every participant attended all eight sessions over the four-week period.

The results showed that patients undergoing REAER had large improvements in functional mobility, cognitive processing speed, and brain connectivity after the four-week intervention. Indeed, as an example, these patients took about 59% more steps during the last session compared with the first. In the conventional training group, meanwhile, the patients' outcomes remained stable or worsened after the intervention. The team behind the research plans to design a larger trial to further study the effects of robotic exoskeleton-assisted exercise rehabilitation. Bring it on, I say. **For details of all news and features go to page 13**

Spasticity biggest MS problem among those who suffer it

Spasticity is the most challenging symptom in MS for those who experience it. That's according to a study, the results of which were presented at the 2021 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) held October 25-28, 2021 in Orlando, Florida.

The objective of the study was to describe the most challenging symptoms patients with MS and spasticity experience and the priorities to manage them.

Researchers partnered with three US-based multiple sclerosis advocacy organizations to develop the Symptoms and Emotions Exploration Needed in Multiple Sclerosis Spasticity (SEEN-MSS) online survey and recruit the cohort, which comprised of 961 individuals (78% women mean age 56.6years). The individuals participated from February to April 2021.

Patients were on average between 10 and 16 years from diagnosis reported a range of 1 (mild disability) to 7 (severe disability).

The majority (more than 60%) of individuals reported at least 8 co-occurring symptoms. Seventeen percent of individuals reported that spasticity was the most challenging symptom. It was among the top 5 most challenging for 72% of the individuals. The other top 5 symptoms that were reported as most challenging were fatigue (59%), difficulty walking (45%), and pain (40%).

"This survey highlights the substantial burden of symptoms for pwMSS [people with MS and spasticity], including spasticity, and the importance of symptom management on a day-to-day basis," the researchers said. "These results emphasize the importance of proactive communication regarding the constellation of symptoms associated with spasticity and addressing the individual needs and treatment goals of pwMSS."

For further details of all features go to page 13

References contact details etc

Page 2 ATA-188 story

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Page 3 Hydroxychloroquine story

https://www.everydayhealth.com/multiple-sclerosis/hydroxychloroquine-may-slow-ppms-progression-study-shows/

Page 4 Fesoterodine story

https://multiplesclerosisnewstoday.com/news-posts/2021/09/21/oral-fesoterodine-fumarate-can-ease-bladder-problems-ms-patients/

Page 5-6 Ageing and MS

For more info on the academic research on this go to Bühring et al. Systematic Review of Studies on Telomere Length in Patients with Multiple Sclerosis. Aging Dis. 2021 Aug 1;12(5):1272-1286.

Page 7 Stem cells story

https://multiplesclerosisnewstoday.com/news-posts/2021/10/15/ectrims2021-stem-cell-transplant-superior-dmts-treating-spms-study/

Page 8 Cog-rehab story

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Page 9 Covid boosters story

Bar-On et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. NEJM September 15, 2021 DOI: 10.1056/NEJMoa2114255

pages 10-12 Exercise feature

For research on exoskeletons see https://multiplesclerosisnewstoday.com/news-posts/2021/06/08/robotic-exoskeleton-rehabilitation-ms-improves-motor-cognitive-function/Picture: Pat-kwon-unsplash

Page 13 Spasticity story

https://www.neurologyadvisor.com/topics/multiple-sclerosis/spasticity-among-top-most-challenging-symptoms-in-multiple-sclerosis-with-spasticity/

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