

My prog-MS ezine

For people with progressive MS and those interested in it

Issue number 18, March/ April 2018

Welcome to issue 18 of my ezine about progressive MS and MS progression. My name is Ian Cook. I'm a secondary progressive MSer from Birmingham, UK.

In this issue are six pages of news plus two features about issues that matter to prog-MSers. In news there's a story about an early stage US stem cell trial which has shown impressive results for us progressives and a story about an asthma drug which reduces disability progression by a remarkable 26%.

There are two features. One on pages 4-5 looks at my experiences trying out disabled cycling – it was a lot of fun. The other feature on pages 8 and 9 is more serious and looks at myelin, cholesterol, the use of statins in treating MS related nerve damage and how they might be in some way be related.

Finally, if there is any story you would like me to follow then I'm at iancookjournalist@yahoo.co.uk

IN THIS ISSUE



Feature

Spring forward into cycling - on a trike!

Pages 4-5

US Stem cell trial's big benefits in prog-MS – p2

Asthma drug reduces disability progression by 26% – p3



Stem cells benefit three-quarters of prog-MS patients in phase 1 trial

A stem cell treatment at the Tisch MS Research Lab in New York improved neurological symptoms among three quarters of progressive MS patients treated in a phase 1 trial. The results have led researchers to fast-track a phase 2 trial.

Results of the treatment "Phase I Trial of Intrathecal Mesenchymal Stem Cell-Derived Neural Progenitors in Progressive Multiple Sclerosis," were published in the journal EBioMedicine. The treatment involved injecting mesenchymal stem cell-derived nerve cell progenitors (cells which mature into nerve cells) directly into the spinal canal.

Three injections of stem cells derived from 20 patients were given three months apart. Researchers used fresh cells delivered within 30 minutes of harvesting rather than cells preserved by refrigeration. This may have contributed to the good results, researchers said. Among the trial group 16 of the 20 patients had secondary progressive MS. Half were unable to walk at the beginning of the study, and had EDSS (Expanded Disability Status Scale) scores of 7 or higher. Eight required assistance to walk, and had EDSS scores of 6 to 6.5. Two were able to walk without assistance, with EDSS scores between 3.5 and 5.5.

The stem cell treatment led to improvements in 15 of the 20 patients' neurological symptoms. The disease of two worsened, and the condition of three remained the same. Fourteen of the patients had better muscle strength after the treatment, mainly in the lower limbs. Four of the 10 patients who were able to walk when the trial began improved their scores on a measure of exercise capacity — the timed 25-foot walk test — by 20 percent or more. And two patients who had been unable to walk when the study began were able to complete the walk test with assistive devices. Other improvements included better bladder function in half of the patients. Some were able to stop taking their bladder medications. Patients who responded to the treatment improved their disability scores by 0.5 to 2.0 EDSS points**. (Photo: thanks to Wheelchair Kamikaze) Details of all stories on p12**

Prog-MS drug ibudilast's 26% reduction in disability progression

Biopharma company MediciNova has announced additional positive data from a phase 2b trial of ibudilast, a drug already used to treat asthma and stroke patients which is being trialled in progressive MS.

In the Phase 2b trial ibudilast demonstrated a 26% reduction in the risk of confirmed disability progression for people with progressive MS compared to a placebo, as measured by Expanded Disability Status Scale (EDSS). Based on the strong trends in reducing confirmed disability progression in this Phase 2b trial, MediciNova has determined that a Phase 3 trial of MN-166 that enrols approximately 700 people will be sufficient to show the drug works to reduce disability progression in primary and secondary progressive MS.

Ibudilast, also known as MN-166 has been marketed in Japan and Korea since 1989 to treat post-stroke complications and bronchial asthma. MediciNova is developing the drug for progressive MS and other neurological conditions such as amyotrophic lateral sclerosis (ALS), a form of motor-neuron disease whose sufferers include Prof. Stephen Hawking.

The drug works by inhibiting the enzyme phosphodiesterase. It reduces inflammation and acts on a number of biochemical processes associated with nerve damage and myelin repair. Previous studies suggest it may have a neuroprotective effect. It is a tablet taken twice daily. As a next step, MediciNova plans to get feedback from the US Food and Drugs Administration (FDA) in order to get the drug licensed for prog-MS as fast as possible.

Masitinib trial in progressive MS looks promising

A Phase 3 clinical trial of an experimental drug masitinib as a treatment for primary progressive and relapse-free secondary progressive MS can continue without having to add patients, an independent review board has decided. The decision is significant because it suggests the effect of the drug is already clear to researchers and there is no need to add extra patients to the study.

Masitinib blocks a number of biochemical processes involved in inflammation and immune responses. It targets mast cells, a type of cell involved in allergic reactions. In an earlier small study of Masitinib, MS disease activity improved from month 3 of the study for those treated, and worsened in those taking placebo or dummy drug. This difference was maintained for the course of the study. Masitinib is taken as a tablet, twice daily.

The company behind Masitinib AB Science said the probability of the therapy being successful is above 80 percent. Final results of the study are expected in the second quarter of 2019.
For further details of all news stories go to page 12.



On yer trike – yes, you can cycle with balance problems

When I was in my early twenties in the 1980s I worked as a local newspaper reporter and cycled five miles to work every day. I would often take my cycle out with me to report on the various stories I wrote about. I clocked up more than 100 miles a week on my bike.

Of course my cycling habits changed when MS arrived in the early 1990s and then again when my disease became progressive around 2005. In that year I had a relapse involving an MS related eye problem called nystagmus which severely affects your balance, and selling my bike seemed like my only option. So, for more than 10 years I have not been in the saddle, and to be honest I have missed cycling.

Over the 10 years that I have been without a cycle it seems everyone else has been collectively getting on their bikes. With innovations like Boris bikes, cycle lanes, the Tour De France coming to Britain, Team Sky and Bradley Wiggins, cycling has become increasingly fashionable, even cool. I feel as though I have missed out.

But it's not just a cool and sporty activity I have lost out on. There's the exercise and more importantly I have lost a way of getting from "a" to "b" that doesn't require a driving licence. I now have to apply for a driving licence every three years and if I get turned down, which is always a possibility, then a bike or a trike might enable me to make short journeys.

So, it was with a sense of excitement that I read about the Wheels for All charity - a nationally recognised cycling programme for people with additional needs and disabilities that helps people like me get into the saddle. There's a national network of 50 plus centres with specially adapted cycles, and trained leaders with the knowledge and confidence to help disabled adults and children enjoy cycling safely and confidently.

Continued on page 5



Continued from page 4.

And, better still, I discovered a Wheels For All centre two miles from where I live, tucked away in one of Birmingham's inner city suburbs at a council run "wellbeing centre" which has an athletics track where the cycling sessions take place. The first person I met on arrival was the local Wheels For All co-ordinator who asked me about my cycling experience and my disability.

Then we discussed what I might reasonably expect to achieve on my first session and looked at my various options. As well as conventional two wheelers there were three wheelers (trikes) four wheelers, rucumbents (where you cycle almost lying down with your legs in front of you) , and upright hand-cranked cycles and trikes where you also power yourself using your hands rather than your legs. There were several other cycles adapted for other requirements.

The co-ordinator, called Chris, pointed out that given my balance and mobility problems the obvious thing would be to start me off on a cycle with more than two wheels which would give me far greater stability. I could choose between a trike (three-wheeler) and a rather exotic four wheeler. I chose the three wheeler and armed with cycle safety helmet I pedalled away, slowly at first but gradually gaining confidence and speed.

I did my first circuit and the feeling was exhilarating. Cycling at 20 miles per hour gave me the sort of thrill that I hadn't experienced in years and I had to fight the temptation to go as fast as possible, reminding myself that there were others on the track and I didn't want to cause any injuries. At the end of half hour of pedalling I felt a real sense of achievement.

I am not suggesting that cycling is a cure or a treatment for MS but I do know that exercise in general improves cardiovascular fitness and being fit should mean I am less likely to suffer from other illnesses that will make my MS worse. My ambition is to eventually get back on a two wheeler which will help me improve my balance and give me much needed exercise. However, I would happily settle for a three wheeler if that was the safest option.

But cycling is about more than just physical improvements. I have read of MSers who say it gives them back their independence and confidence. So there are lots of reasons for giving cycling a go. You may be pleasantly surprised at what you can achieve. I read somewhere that aerobic activity not only keeps you fit but also encourages the brain to release chemicals which make you feel good called endorphins. Keeping healthy and feeling good are two very good reasons for cycling which is why I intend to carry on pedalling away. **For more details of all news and features go to page 12**

New drug a “potential game changer” for progressive MS

Australian researchers are set to conduct a large study into a drug that may help halt the progression of MS.

The drug, a small molecule called DITPA (Diiodothyropropionic acid), may offer protection to nerve fibres damaged by the disease in the brain, spinal cord and optic nerves, as well as enhancing their repair.

Its effects, and the mechanism that allows it to work, were found by a team led by Dr Petratos of Monash University in Melbourne during research into a group of molecules affecting the development of oligodendrocytes. These are brain cells which play an important role in making myelin.

DITPA has been approved by the US Food and Drug Administration (FDA) for use in clinical trials to treat a rare disorder called Allan-Herndon-Dudley syndrome (AHDS), which severely affects movement, and DITPA has been used in larger trials for cardiac problems which means it is already passed significant milestones on the drug development pathway.

DITPA also has the advantage of being able to cross the blood-brain barrier to target affected cells in the brain, a limitation of many existing treatments.

The study, was given the go-ahead after MS Research Australia announced a $70,000 grant to support it. If successful, clinical trials will follow. Dr Petratos said: “The drug that we’ve identified may have a significant benefit in changing the course of MS progression primarily from the aspect of protection of the central nervous system as well as enhancing repair. This is a potential game-changer for MS patients in the future,” he added

Ocrevus granted EU licence for early stage primary progressive MS

The European Commission (EC) has granted a licence for the use of ocrelizumab, also known as Ocrevus, in people with early primary progressive MS (PPMS).

The licence for ocrelizumab is based on data from the ORATORIO study where ocrelizumab was shown to be the first and only treatment in a study of this size to slow disability progression and reduce signs of disease activity in the brain (MRI lesions) within this patient population, compared with placebo, with a median follow-up of three years.

More details of all news stories on page 12

Antidepressant drug has potential to treat progressive MS

An early study of an antidepressant drug called clomipramine shows "outstanding" potential to treat people with progressive MS by protecting nerves from various processes thought to underlie progression, researchers believe.

In the research study, which focused on already-approved generic drugs, titled "Systematic screening of generic drugs for progressive multiple sclerosis" and published in the journal Nature Communications, clomipramine was identified as a "highly promising" progressive MS drug.

Researchers screened 1,040 generic, orally available medications (ie: pills or tablets) available at the U.S. Drug Collection. They studied drugs that were already approved for other conditions , which ensured their safety for human use.

From the initial pool, researchers identified 249 well-tolerated therapies able to cross the blood-brain barrier. Of the 249 medicines selected, 35 prevented iron-induced damage to nerve cells in lab tests (iron is released due to cell damage, damaging nerve cells in turn). To narrow further their selection, these 35 medicines were tested for their potential to protect mitochondria (the powerhouse or energy providing parts of cells), as well as the drugs' capacity to reduce the immune attacks T-cells mount against nerve cells in MS.

The screening first identified several antipsychotics and antidepressants as capable of strongly reducing T-cell proliferation and damage to mitochondria. From this screen, the antidepressant clomipramine, sold under the brand name Anafranil, showed "outstanding effects" the researchers wrote.

The team next tested the therapeutic effects of clomipramine in mouse models of human MS, so-called experimental autoimmune encephalomyelitis (EAE) mice. They used different models, one of acute and two others of chronic "mouse-MS". In the acute EAE model, early treatment with clomipramine completely suppressed clinical signs of the disease, with the therapy reducing inflammation and microglial activation (the activation of specific immune cells in the central nervous system), and preserving nerve cells.

In the two mouse models of chronic EAE, the MOG-EAE and the immunized Biozzi ABH mouse (known to resemble more closely human secondary progressive MS), researchers found that clomipramine given at symptom onset also led to a significant reduction of clinical severity, namely in the degree of paralysis. No EAE model fully captures all aspects of progressive MS, however, so the therapy needs further testing in humans. As clomipramine is approved there is ample clinical experience regarding potential side effects, meaning the researchers can start clinical trials to assess its efficacy in MS more quickly, skipping the Phase 1 trials in healthy volunteers essential to determining a potential therapy's tolerance.

For further details of all news stories go to page 12



Myelin, cholesterol and the use of statins in treating MS related nerve damage

Regenerating myelin is vital in recovering the use of MS affected nerves. But regeneration is a massive problem in secondary progressive MS (SPMS) as the body has endured a decade of relapsing remitting MS when myelin has already been lost as well as the further myelin damage endured as the illness progresses.

This may account for the failure of many drugs tried out on secondary progressive MS. However, there is some hope of moving things forward in the shape of research from a team led by Prof. Mikael Simons from the Technical University of Munich.

Prof. Simons has published a study in the journal Science explaining why nerves can't remyelinate after long periods of demyelination such as happens in SPMS.

His analysis goes something like this. Fat coming from myelin, which is destroyed in the auto-immune attacks that characterise MS, is not carried away rapidly enough by phagocytes, the body's debris removing cells.

This accumulation of debris triggers chronic inflammation that in turn hinders remyelination. To make matters worse cholesterol, which is present in large quantities in myelin, crystalizes after it is lost in demyelination and these cholesterol crystals trigger more inflammation. **Continued on p9**

Continued from page 8 : "Myelin contains a very high amount of cholesterol," explains Prof. Simons. “When myelin is destroyed, the cholesterol released has to be removed from the tissue. This is performed by microglia and macrophages, also referred to as phagocytes (Debris removing cells). They take up the damaged myelin, digest it and transport the non-digestible remainder, such as cholesterol, out of the cell by transport molecules. However, if too much cholesterol accumulates in the cell, cholesterol can form needle-shaped crystals, which cause damage to the cell.”

Using a mouse model, Simons and his team showed the devastating impact of the crystalline cholesterol: It activates the so-called inflammasome in phagocytes (debris removing cells) which results in the release of even more immune cells. "Very similar problems occur in atherosclerosis, -the thickening and hardening of the walls of the arteries which often occurs as we grow older. However this problem occurs not in the brain tissue, but in blood vessels," says Simons.

And this is where the role of Simvastatin, a drug currently being trialled in secondary progressive possibly comes in. It has been known for some time that taking a statin like Simvastatin for a year or longer can shrink plaques that cause atherosclerosis. This reversal of atherosclerosis surprised many experts who believed it couldn’t be done. Completely reversing it isn't possible yet. But taking a statin can reduce the risk of complications from atherosclerosis. It decreases inflammation, which stabilizes the plaque. For this reason, statins are often key to treating the condition.

Could it be that Simvastatin, which can cross the blood brain barrier, is doing exactly the same thing in the brain of MSers, clearing up the myelin debris and, if not in itself remyelinating then clearing away the cholesterol rich rubbish that has accumulated after demyelination takes place, and creating an environment where remyelination might be able to happen?

Interestingly in his MS blog Prof. Gavin Giovannoni asks the question “how do statins work in secondary progressive MS?” and comes up with ten possible explanations. The final one “Block the production of oxidised cholesterols (oxysterols),” was in his own words “where I would suggest an activity could be occurring.” I think Prof Giovannoni’s analysis is not a million miles away from the analysis of Prof. Simons and although I am no scientist I think this is probably how statins work. They are not in themselves the cure (remyelination) but they may slow down or even halt the progression of our MS by clearing up the inflammatory cholesterol crystals released by the break -up of myelin which in turn may allow remyelination to take place.

For details of all news stories and features go to page 12

glatiramer acetate to be tested for PPMS

A trial of glatiramer acetate in Primary Progressive MS (PPMS) is taking place in Israel, organised by Israeli drugs company Mapi Pharma. The first PPMS patient has already been recruited.

In the U.S. Copaxone (glatiramer acetate injection,) which is marketed by Teva Pharmaceutical) is injected daily in 20 mg or thrice-weekly 40 mg dosage. Mapi Pharma's "GA Depot"" contains glatiramer acetate in a long-acting "depot formulation" injection given once every four weeks.

The trial (NCT03362294) will look at GA Depot's safety and efficacy in slowing the progression of disability in PPMS patients. All patients will be given GA Depot through intramuscular injection once every four weeks for 52 weeks.

The company anticipates enrolling from 12 to 24 PPMS patients who are not receiving a disease modifying treatment. After the GA Depot treatment period, four weeks of follow-up will be conducted in a total of 17 medical visits. The study's estimated completion date is December 2019. Patient recruitment is currently underway in Israel.

A healthy diet can reduce MS disabilities

People with MS can improve their lives by eating well, exercising, and maintaining a healthy lifestyle. That's the conclusion of a recently published study in Neurology, the journal of the American Academy of Neurology.

Almost 7,000 people living with MS participated in the study which looked at the association between diet quality and intake of specific foods with regards to disability and symptom severity. Specific diets — such as paleo, the Wahls protocol, weight loss plans, and other programmes — were included, as well as activity levels and whether or not the participant smoked.

Researchers said people with the healthiest diet were 20 percent less likely to have severe disabilities compared to those with a less healthy diet. Even after making adjustments to variables such as age and length of the disease, researchers found study participants to be more likely to have fewer disabilities. Participants with an overall healthy lifestyle were nearly 50 percent less likely to have depression, 30 percent less likely to have severe fatigue, and more than 40 percent less likely to have pain.

Participants with the best diet ate an average of 1.7 servings of whole grains per day and 3.3 servings of fresh fruit, vegetables, and legumes. That was about two times that of the least healthy participants. **For details of all news stories go to page 12**

Fampra helps improve cognition and use of arms and hands

Fampyra (fampridine), a drug approved to treat walking difficulties in MS, also improves cognition and movement in the arms and hands.

These are the findings of a research paper titled “Extremities and Cognition: Fampridine Effect” presented to the 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2018.

The research, carried out at Dokuz Eylul University in Turkey, looked at the effectiveness of fampridine (Fampyra/Ampyra) on MS symptoms in 134 walking-impaired patients who were treated with the drug. These results were compared to 77 healthy individuals.

At six months of treatment, MS patients showed significant improvements in both physical and cognitive assessments. The researchers concluded “fampridine has positive effects on cognitive, upper and lower extremity functions” in MS patients with impaired walking. In addition, these results demonstrated that cognitive function is “associated with both upper and lower extremity functions,” they wrote, and “this association was more prominent in information processing speed.”

Fampyra, which was approved in 2010 by the U.S. Food and Drug Administration (FDA) and is marketed by Acorda Therapeutics, is sold in the US under the brand name Ampyra (dalfampridine).

Study on sun, vitamin D and prog-MS gives mixed picture

Vitamin D levels appear to have no impact on fatigue and disability among patients with secondary progressive MS but longer exposure to the sun is linked to lower levels of fatigue and lower disability in primary progressive MS patients.

That’s the conclusion of a study — “Dietary intakes of vitamin D, sunshine exposure, EDSS and fatigue scale in Multiple Sclerosis: Are there any correlations?” — presented at the ACTRIMS 2017 Forum in Orlando, Florida in February.

The researchers also found spending more time in the sun could make people with MS feel more energetic, though dietary vitamin D intake’s effect is mixed, depending on what particular type of MS a particular patient has.

The study, by the Kashani Hospital of Isfahan University of Medical Sciences, suggests that more research is needed to examine the effects of sun exposure on these parameters across different subtypes of MS. Their study included 126 patients, of whom 84 had relapsing MS and 21 each had primary or secondary progressive disease.

For details of all news stories go to page 12

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Page 2

Stem cells story

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Pages 4-5 cycling feature

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Page 11 sun exposure and vitamin D story

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In the next (May June) edition **Should the right to end our MS be in our own hands?**	

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