

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 22, November/December 2018

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 eight pages of important prog-MS news stories plus two features about issues that matter to prog-MSers. In the first feature (page 5) I "celebrate" the 25th anniversary of my diagnosis and ask how much has changed in the MS world in a quarter of a century.

The second feature looks at my experiences of taking high dose simvastatin – a drug that is currently being trialled in secondary progressive MS. For me the drug came with problems but did its benefits outweigh those problems? See page 10 for further details.

IN THIS ISSUE



My MS silver jubilee – 25 years since diagnosis. See page 5

UK and Ireland Simvastatin trial locations revealed – page 2

Siponimod moves step closer to SPMS treatment – page 3

Simvastatin in SPMS - trial locations revealed

A list of 26 hospitals carrying out the trial of Simvastatin in secondary progressive MS in UK and Ireland (MS-STAT2) has been published.

Nine hospitals currently recruiting are: Addenbrooke's Hospital, Cambridge; The Anne Rowling Regenerative Neurology Clinic, Edinburgh; Royal Devon and Exeter Hospital, Exeter; Leeds General Infirmary; University College London Hospital; Salford Royal Hospital, Manchester; Poole Hospital; Royal Hallamshire Hospital Sheffield; Morriston & Neath Port Talbot Hospitals (Abertawe Bro Morgannwg University Local Health Board) Swansea.

The 17 hospitals not yet recruiting are: St Vincent's University Hospital Dublin; Belfast City Hospital, Belfast; Royal Sussex County Hospital Brighton; University Hospital of Wales, Cardiff; The Queen Elizabeth University Hospital, Glasgow; The Leeds Teaching Hospital, Leeds; The Walton Centre NHS Foundation Trust Liverpool; Queen's Hospital, Barking; Havering and Redbridge University Hospitals; King's College Hospital London; Charing Cross Hospital, London; Royal Victoria Infirmary, Newcastle Upon Tyne; Nottingham Teaching Hospitals, Nottingham; Queen's Medical Centre, Nottingham; John Radcliffe Hospital, Oxford; Derriford Hospital Plymouth, and University Hospital of North Staffordshire Stoke-on-Trent,

The trial is due to end in 2023 and is placebo controlled. This means that some trial participants will not receive simvastatin but receive a dummy pill for the three years of the trial. For a list of exclusion criteria and contacts see the website below.

https://clinicaltrials.gov/ct2/show/NCT03387670#contactlocation

For details of sources for all news stories go to page 14

EMA to Review siponimod as SPMS treatment

Approval is being sought from the European Medicines Agency (EMA) for siponimod as a treatment for adults with secondary progressive MS (SPMS). The EMA is expected to make a final decision on siponimod by late 2019.

Siponimod, formerly known as BAF312, belongs to the same class of drugs as Gilenya (fimgolimod) . It acts on certain types of white blood cells (lymphocytes) which are involved in the autoimmune attack on myelin seen in MS and binds to special locations (or receptors) on the surface of the lymphocytes, called sphingosine-1-phosphate receptors (S1P-R). This causes a larger proportion of lymphocytes to be retained in the lymph glands. The number of activated lymphocytes reaching the brain is decreased, resulting in reduced immune attack on nerve cells in the brain and spinal cord.

The application to the EMA was backed up with clinical data from the EXPAND Phase 3 clinical trial (NCT01665144), which included1,651 SPMS patients with moderate to severe disability across 31 countries. Participants were randomized to receive either a 2 mg siponimod tablet or a placebo once a day.

Clinical trial data showed that siponimod could lower disability progression in non-relapsing patients by 14 to 20 percent at three months, and by 29 to 33 percent at six months compared to placebo. It also improved cognitive processing speed in patients who had relapses within two years and in those who did not.

Siponimod could also significantly reduce blood levels of neurofilament light chain — a biomarker of nerve cell damage — meaning the therapy can effectively protect nerve cells.

For details of sources for all news stories go to page 14

Asthma drug Ibudilast shows major effect in slowing brain shrinkage in progressive MS

Ibudilast, a drug used in Japan and Korea to treat asthma and some complications of stroke, has been shown to slow brain shrinkage by 48% in progressive MS patients in a phase 2 trial. The trial's lead researcher says the finding is 'remarkable'.

Progressive multiple sclerosis patients — with primary or secondary progressive disease — treated with high doses of oral ibudilast in the Phase 2 clinical trial showed a 48 percent slowing in the progression of brain atrophy, or shrinkage, relative to those given a placebo, study data show.

What this decline might mean in terms of daily disability or other clinical benefits for patients is still difficult to say, said Robert Fox, MD, the trial's principal investigator. Fox is vice-chair for research at the Cleveland Clinic's Neurological Institute.

With treatment options for progressive MS patients "very limited" and primarily targeting "younger patients with more active inflammation," Fox said, a 48% improvement in a measure that might translate to lesser disability and greater quality of life compares favourably with what we see with other therapies approved or being tested for progressive patients.

Fox added "I think the data set provided here is robust enough to justify going to a Phase 3 trial." MediciNova, the pharmaceutical company that is developing ibudilast and helped fund the Phase 2 work, would need to sponsor a Phase 3 trial alone or in collaboration with others. To date, it expressed an intention to do just that.

"With a convenient oral administration, a very favourable safety and tolerability profile, and the potential for better efficacy than other drugs for progressive MS, we believe ibudilast could become the best-in-disease drug," Yuichi Iwaki, MD, MediciNova's president and CEO, said in a press release.

Fox remains hopeful a pivotal Phase 3 study will be underway soon. Ibudilast is taken as a tablet twice daily.

For details of all news stories go to page 14



My personal MS Silver jubilee

I am celebrating a silver jubilee this year. It's 25 years since I was diagnosed with MS.

However, for me 1993 (25 years ago) wasn't the beginning of my MS "journey". I had suffered classic MS symptoms like double vision and urinary problems years before diagnosis and had already seen a neurologist in 1986 aged 28. The consultant had muttered something about myelin and said I could have a myelogram test if I really wanted but I didn't know what he was talking about so we agreed to "wait and see".

Seven years later in 1993 after another episode of double vision I did some online research at the local library – internet access was in its infancy by this time - and armed with a little information I decided that I should ask my GP about myelograms, myelin, and specifically whether he thought I had MS which I had discovered was a disease involving myelin. The GP dodged all questions, instead referring me to see another neurologist who told me rather bluntly that I obviously had MS and probably had been showing symptoms when I had first seen a neurologist, seven years earlier.

He ordered a lumbar puncture just to be sure and when the results came back positive for MS I was sent home and that was it. It would be more than ten years before I saw a neurologist again. Nobody seemed remotely interested.

At the time of my 1993 diagnosis there were no disease modifying drugs, no MS nurses and once you were diagnosed you were on your own. "Diagnose and adios" I think is how the Americans put it. As my MS seemed to be fairly inactive I didn't do much about it and in a sense there was very little I could do. The ABC drugs (avonex, betaferon and copaxone) were only just being introduced and there were strict rules about prescribing them. I didn't meet the criteria anyway so I put up and shut up as they say.

continued on page 6



Continued from page 5

Of course I still had MS but if there was one thing that gave me hope it was reading we were close to finding a cure. I remember reading a magazine article in the mid-90s promising that a cure for MS was ten years away and I reckoned my MS would be cured by round 2005 and I would, in a few years, look back on a brief and mildly unpleasant episode in my life that lasted around 10 years.

Then, shortly after the millennium, I had a couple more relapses and in 2005 I noticed a more worrying problem. After the second relapse I was unable to walk more than 200 metres or so. The words "progressive MS" sprang to mind, and when the neurologist wrote these very words at the top of my case notes I realised I has just joined a group with little hope of a cure

Of course life had to go on and in 2005 I took voluntary redundancy from my job in London where I had been working at the BBC . I left the capital and moved back to the town where I was born and where I still had lots of friends including my ex-wife who had agreed to help me with things like my shopping and cleaning. I also moved back into my former job as a freelance print journalist initially working for a newspaper then picking up whatever work I could. At first this proved quite lucrative but as I could no longer walk very well, or drive long distances, going out to meet people and "selling myself" became a growing problem and work proved increasingly less rewarding.

I am by nature a positive person, but even my natural optimism is sometimes hard to sustain when I realise that promise of a cure in ten years made in the mid-1990s has not happened 20 year later. It could be argued that we are no nearer to finding the cause of MS than we were 25 years ago.

In August I was 60 and there was much to celebrate in what has been a happy and fulfilled working life. But there was also an element of sadness about an illness that has cast a shadow over more than half of it. As I look forward to the future there will doubtless be new causes of concern – not least something I read from the University of Utah which said that following diagnosis an average MSer has a life span of 25 to 35 year. As I mark the 25th anniversary since diagnosis I just hope I am the exception and have more than ten years left. I hope I have a lot more living left to do.

For further details go to page 14

DMTs Slow Down Disability Progression in SPMS Patients with Relapses

Treatment with disease-modifying therapies (DMTs) may slow disability progression in patients with secondary progressive multiple sclerosis (SPMS) who are actively experiencing relapses, a new analysis of an MS patient registry shows.

The study, "Determinants of disability accumulation in secondary-progressive multiple sclerosis" was presented at the 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Berlin, Germany. The presentation was given by Nathaniel Lizak, from the Clinical Outcomes Research Unit at The University of Melbourne in Australia.

Over time, SPMS can be either active (with relapses and/or evidence of new MRI activity) or not active, as well as with progression (disease worsening) or without progression. To investigate these factors, researchers conducted a retrospective study to evaluate which variables affect the rate of disability progression during SPMS, including the use of DMTs.

For those with SPMS who had relapses, the use of a DMT was linked with a lower disability slope, regardless of the class of DMT used. Also, among patients with ongoing relapses, those who were older and took longer to convert to SPMS were found to be associated with a slower disability progression. In contrast, the rate by which disability accumulated did not seem to be influenced by the same factors in SPMS patients without relapses.

For details of sources for all news stories go to page 14

Anti-retroviral drug shows neuroprotection in progressive MS trial

Positive Phase 2b Trial results presented at the recent ECTRIMS (European Committee for Treatment and Research on Multiple Sclerosis) demonstrate the neuroprotective effect of the anti-retroviral drug GNbAC1 and suggest it could be used as a single agent on progressive MS populations who don't have active inflammation.

GNbAC1 is a selective monoclonal antibody, being developed by Swiss pharmaceutical company GeNeuro and is believed to work on the MS- associated retrovirus (MSRV) a virus that is commonly present, but inactive in the genome. MSRV has been identified at high levels in the blood of MS patients compared to healthy individuals.

The randomized, double-blind, placebo-controlled CHANGE-MS Phase 2b trial (NCT02782858) included 270 MS patients (ages 18 to 55) across 50 clinical centres in 12 European countries. The study was conducted for six months, with an extension period of up to one year.

"At week 48, GNbAC1 18 mg/kg showed robust evidence of efficacy across MRI-based, paraclinical measures of neurodegeneration, potentially predictive of a benefit on disability progression in late-phase MS studies," the researchers wrote.

"The CHANGE-MS, Phase 2b study showed consistent neuroprotective benefits with GNbAC1," Hans-Peter Hartung, the trial's principal investigator, said in a press release. "Importantly, these benefits were prominent in the inactive sub-population of patients in this study, precisely the group of MS patients that are sub-optimally treated with currently available therapies. These results appear to be the outcome of a completely new mechanism of action targeting a cause of MS progression."

Jesús Martin-Garcia, GeNeuro CEO, added: "These positive Phase 2b results demonstrating the neuroprotective effect of GNbAC1 suggest that it could be used as a single agent on progressive MS populations without active inflammation as well as with existing anti-inflammation MS drugs."

For details of all news stories go to page 14

New study finds older MSers have less depression than young

A recent brief report by MS researchers at the Kessler Foundation has provided preliminary evidence that older individuals with multiple sclerosis (MS) report lower levels of depression and higher quality of life than their younger counterparts.

These findings are consistent with the trend toward improvement in wellbeing with age in the general population. The article, "Subjective well-being differs with age in multiple sclerosis: A brief report", was published in Rehabilitation Psychology.

Fifty-seven individuals with MS, aged 35 to 65 participated in the study. They were divided into three age groups: 35-44, 45-54, and 55-65. Researchers measured depression and quality of life in each of the groups. They found a significant difference between-groups for both measures. The oldest group reported the lowest levels of depressive symptoms and the highest levels of physical quality of life.

"These results were unexpected," said Dr. Strober, senior research scientist at Kessler Foundation, "given the functional limitations, disease progression, and neurological lesions seen in the aging MS population. Contrary to our hypothesis, the trend by age paralleled that of the general population."

"These findings suggest that younger individuals with MS are at greater risk for depression and poor quality of life," summarised Dr. Strober. "If this trend is confirmed in future studies, targeted screening for depression by age may be warranted in this population."

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For further information on news stories go to page 14



My experience of taking high dose simvastatin for two years

Anyone who has followed the news about the upcoming phase III trial of the drug Simvastatin in progressive MS (see recruitment details of MS-STAT 2 on page 2) may be interested in the following personal story about my experience of taking it.

Simvastatin belongs to a group of drugs called statins. Statins are widely prescribed to lower the level of "bad" cholesterol in the blood and reduce the risk of diseases affecting the heart and circulation. Simvastatin has been shown to be of use in treating secondary progressive MS (SPMS). In 2014 a phase II trial in SPMS (MS-STAT 1) showed it reduced the loss of brain tissue and slowed down progression.

The thinking behind the MS-STAT project comes from research by neurologist Prof. Jeremy Chattaway. A small clinical trial (MS-STAT 1) of 70 SPMS patients took 80 mg simvastatin daily for two years. This group was then compared with a group of 70 patients who took a placebo. The simvastatin group did far better than the placebo group with lower rates of brain shrinkage.

It is not known how simvastatin might be doing this, but there has been evidence that statins reduce inflammation and have neuroprotective effects. It is also recognised that cardiovascular problems are linked to greater disability in MS, so the benefits of simvastatin seen in SPMS could be a direct result of lower cholesterol and improvement in cardiovascular health. Crucially the research paper said that simvastatin was "well tolerated".

My own interest in simvastatin and this trial is not just professional but also a highly personal one because from early 2016 to early 2018, my neurologist let me take 80 mg simvastatin daily for my secondary progressive MS (SPMS) essentially shadowing the earlier trial into statins and SPMS - MS-STAT 1.

Continued on page 11



Continued from page 10

I would love to report that my experience was totally positive. It had been reported in the MS-STAT 1 trial that the drug was "well tolerated". Sadly that was not the case for me. Initially, from early 2016 until the beginning of 2018, everything went well.

Then in January 2018 things changed. I suffered excruciating pain between my heel and calf muscle which made walking impossible. I put the problem down to one of those strange events that happen in MS. The problem (tendonitis) went away, then, a few months later, I started to suffer another strange problem in one of my big toes which was incredibly sore when I put any pressure on it. I decided to look up the side effects of statins which are more severe the higher the dose – and 80mg daily is a high dose.

I found that unexplained muscle pain, tenderness, and weakness were high up the "contraindications" or side effects list. Then in the Summer of 2018 I started to suffer from hives. Following two sleepless nights of intense itching I decided to give simvastatin a break and the hives promptly disappeared. I went to see my GP armed with the list of simvastatin's side effects which listed muscle tenderness and hives, asking for his advice.

My GP said the problems were probably caused by my body reacting to two years of high dose simvastatin and I had better come off the drug. He said he understood the theory about statins and progressive MS and suggested a more tolerable statin might be atorvastatin and taken at a lower dose. So, for the past six months, I have been taking atorvastatin at 40mg daily. I am not sure whether it will have the same disease modifying effect as the high dose simvastatin but I can at least be sure of one thing – I am unlikely to suffer from excruciating muscle pain, tenderness or hives again and I haven't. That small mercy is a blessed relief, believe me.

For further reading see page 14

Health watchdog NICE Rules Against NHS Ocrevus for Primary Progressive MS

NICE (The National Institute for Health and Care Excellence) has issued a final decision meaning Ocrevus (ocrelizumab) will not be offered as a treatment for primary progressive MS (PPMS) in England and Wales.

The agency's "final appraisal," which mirrors its draft June ruling, is based on the cost-effectiveness of the drug — its price versus its benefits as a PPMS treatment for NHS patients.

"The most plausible cost-effectiveness estimates for ocrelizumab compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources," the final appraisal states. "Because of this, ocrelizumab cannot be recommended for treating early primary progressive multiple sclerosis in adults."

Ocrevus is approved across the EU and in the U.S. to treat both relapsing-remitting MS (RRMS) and PPMS, but is costly. Ocrevus, administered as a total 600 mg intravenous infusion every six months, sells in the U.S. at an estimated annual list price of $65,000.

Despite being turned down in England and Wales for PPMS the drug has been approved to treat people with certain types of relapsing MS.

NICE acknowledge that its decision leaves PPMS patients without easy access to any disease-modifying treatment, and that a pivotal study in these patients — especially those with early stage disease — showed benefit in terms of slower disability worsening. But the agency added, "the size and duration of this effect are uncertain."

For further details of all news stories go to page 14

Blocking molecule linked to nerve cell damage in mouse-MS could lead to treatment for SPMS, study reports

Blocking a molecule linked to nerve cell damage in animals eased inflammation, demyelination, and neurodegeneration in mouse models of secondary progressive MS (SPMS).

This is the finding of a study "Inhibiting repulsive guidance molecule (RGMa) suppresses secondary progression in mouse models of multiple sclerosis" published in the journal Cell Death & Disease.

Studies done in mouse models of MS have shown that RGMa contributes to progression of MS-like disease. The latest study found that treating these animal MS models with an antibody that blocks RGMa eased signs of the disease.

A team of researchers at Osaka University, in Japan, showed that humanized anti-RGMa antibody decreased the expression of RGMa in the spinal cord of the mice, and reduced the proportion of mice with disease progression. Microscopic analysis of spinal cord tissue also showed that anti-RGMa suppressed inflammation, reducing the infiltration and activation of immune cells, and prevented the loss of myelin (demyelination) and death of nerve cells.

According to the researchers, RGMa is implicated in not only inflammation, but also neurodegeneration and neuroregeneration in MS. It is hoped a humanized anti-RGMa antibody is an effective treatment for SPMS.

For details of all news stories go to page 14

References contact details etc

Page 2

Simvastatin trials story

Source: https://clinicaltrials.gov/ct2/show/NCT03387670#contactlocation

Page 3

Siponimod story

Source: https://multiplesclerosisnewstoday.com/2018/10/10/fda-ema-accept-to-review-siponimod-as-treatment-for-spms

Page 4 Ibudilast story

Source: https://multiplesclerosisnewstoday.com/2018/09/18/ibudilast-slows-brain-atrophy-progressive-ms-finding-remarkable/

page 7 DMTs may slow progression in secondary progressives with relapses

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page 8 Anti-retrovirals story

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Page 9 Wellbeing story

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pages 10-11

Simvastatin feature

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page 12 Ocrevus story

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Page 13 mouse MS model story

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