

My prog-MS ezine

For people with progressive MS and other interested people

Issue 63, November-December 2025

Hello and welcome to the 63rd edition of my ezine about progressive Multiple Sclerosis and MS progression in general. My name is Ian Cook. I'm a non-active secondary progressive MSer from Birmingham, UK. My EDSS is now 6.5, sadly up from 6.0, and my age is 67.

The ezine is now in its 11th year and reading the contents made me think that at last there is progress in the world of progressive MS research, although still sadly still no cure. In issue 63 there are eight pages of prog-MS news stories. There are also two features. One feature, on page 5, looks at my recent unexpected brush with shingles, not once but three times! Is shingles related to MS and its progression? Read p5, you may be surprised.

There's another feature on page 10 looking at whether it makes sense, biologically speakin. to talk about relapsing and progressive MS as being different. A new analysis questions this, which has implications for us prog-MSrs, such as whether all drugs could treat all types of the illness. Huge implications for us here if true.

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News

Tolebrutinib gets UAE approval for progressive MS, a world first

The United Arab Emirates has become the first country to approve tolebrutinib, clearing the drug to treat adults with non-relapsing secondary progressive MS.

Tolebrutinib Sanofi's oral BTK inhibitor, is the first approved therapy that directly addresses the chronic inflammation that contributes to disability progression independent of relapses.

The U.S. Food and Drug Administration (FDA) is reviewing tolebrutinib for the same indication, and as a potential treatment to slow disability progression independent of relapse activity in adults with MS. A regulatory decision is expected in December.

Tolebrutinib works by blocking the activity of Bruton tyrosine kinase (BTK). This enzyme is needed to activate several immune cells, including B-cells and microglia, that play a central role in MS.

While some approved MS therapies can delay disability progression that occurs as a result of poor recovery from relapses, none have been shown to slow the progression that takes place independent of relapses.

However, recent data from three Phase 3 clinical trials have suggested that tolebrutinib may do just that. Results from the HERCULES trial (NCT04411641), which enrolled 1,131 adults with nonrelapsing SPMS, showed that about 2.5 years of tolebrutinib treatment led to a 31% lower risk of disability progression compared with a placebo.

Over the course of the trial, 22.6% of patients given tolebrutinib and 30.7% of those on the placebo experienced six-month confirmed disability progression, defined as an increase in EDSS scores that is sustained for at least six months. This difference was 'statistically significant'.

Similar results were seen in the GEMINI 1 (NCT04410978) and GEMINI 2 (NCT04410991) trials, which enrolled 1,873 adults with relapsing forms of MS and randomly assigned them to receive tolebrutinib or Aubagio (teriflunomide).While tolebrutinib failed to outperform Aubagio at reducing relapse rates, the proportion of patients who experienced six-month confirmed disability worsening was significantly lower with tolebrutinib (8.3% vs. 11.3%), reflecting a 29% reduced risk of disability worsening**.**

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

CART-cell therapy shows big improvement in progressive MS

A woman with secondary progressive MS (SPMS) and an EDSS score of 6.0 saw her EDSS drop to 4.0 after 24 weeks treatment with KYV-101, a B cell depleting therapy called CAR T cell therapy that has shown success in treating cancer.

The case study was in one of the most interesting posters (presentations) at the recent ECTRIMS conference in Barcelona and was contained in a Phase 1 study on the treatment called CAR T-cell therapy and its use in patients with 'treatment-refractory' (difficult to treat} progressive MS.

The investigational CAR T-cell therapy by Kyverna Therapeutics called KYV-101 is designed to treat progressive MS by eliminating B-cells through CAR (Chimeric Antigen Receptor) T-cell therapy. This involves genetically modifying a patient's own T-cells (a type of immune cell) in a lab to make the cells better at recognizing and killing rogue cells which cause auto-immunity, then infusing the T-cells back into the patient. The therapy has shown success in treating cancer. Early clinical trials have shown KYV-101 to be safe and well-tolerated in patients with progressive MS and to have preliminary signs of efficacy. The data presented at ECTRIMS focused on the first two participants in the Phase 1 trial.:

The first participant: A 51-year-old woman with secondary progressive MS (SPMS) and an EDSS score of 6.0 received the therapy. The treatment was well-tolerated, with the patient experiencing the side effect of 'grade 1 cytokine release syndrome' (CRS) but no immune effector cell-associated neurotoxicity syndrome (ICANS). CAR T-cells were detected in the cerebrospinal fluid (CSF) by day 14, confirming penetration into the central nervous system (CNS). This was accompanied by a sustained clearance of oligoclonal bands (OCBs)—a key marker of CNS inflammation—at the 24-week mark. While peripheral B cells began to return, they were primarily antigen-naive cells. The patient showed a notable clinical improvement, with her EDSS score decreasing from 6.0 to 4.0 by week 24.

Second Participant: A 63-year-old woman with an EDSS of 4.5 also received the therapy and experienced a similar manageable safety profile, with Grade 1 CRS and no ICANS. Additionally, there was a separate case report on the use of KYV-101 in a 61-year-old patient with refractory neuromyelitis optica spectrum disorder (NMOSD), a related neuroinflammatory condition. The patient experienced manageable CRS and ICANS, with her neurological condition showing slow but continued improvement**.**

For details of all news stories go to page 14

Tolebrutinib could cost between $3,000 and $6000 a year in US

Tolebrutinib, the new drug treatment for non-active secondary progressive MS, (naSPMS) from bio-pharma Sanofi will probably be available privately at a price of between $3,250 and $5,900 per year in the US once the drug passes all its regulatory hurdles.

That's according to a report compiled by The Institute for Clinical and Economic Review (ICER) an independent, non-profit research institute that conducts evidence-based reviews of prescription drugs, other treatments, and diagnostic tests.

This Summer ICER assessed and voted on the evidence for the net health benefit of tolebrutinib in adults with naSPMS. A majority of the panellists (12-1) found that current evidence is not adequate to demonstrate a net health benefit of tolebrutinib when compared to best 'supportive care'.

ICER's assessment of value informs critical decisions that stakeholders across the US health system need to make around pricing and coverage. Following the voting session, a policy roundtable of experts — including clinical experts, patients and patient advocates, the manufacturer, and representatives from US payers — convened to discuss the pricing implications and recommendations to ensure fair access. Key recommendations stemming from the roundtable discussion included:

Trial inclusion criteria are a reasonable starting point for developing coverage policies for tolebrutinib to identify patients with SPMS. Payers should engage clinical experts and patient representatives in considering how to address coverage requests for which there is limited or no evidence at the current time.

US prescription drug prices are significantly higher than those in the UK, - sometimes as high as 2-3 times more expensive. This disparity is primarily due to the fact the NHS buys in bulk and gets a discount. Also the UK's National Institute for Health and Care Excellence (NICE) negotiate prices and limits spending on drugs, unlike the fragmented US system where private insurers and pharmacy benefit managers (PBMs) negotiate prices, resulting in higher costs for brand-name drugs,

Following passing FDA regulatory hurdles in the US, Tolebrutinib will still have to be approved by the EMA (European Medicines Agency) the UK's Medicines and Healthcare products Regulatory Agency and for NHS patients NICE (National Institute and NICE (The National Institute for Health and Care Excellence)

Tolebrutinib is a tablet taken once daily. The main side effects reported in the phase II and III clinical trials were: respiratory infections (in particular, Covid-19, the common cold and flu) urinary tract infections and headache. .**For details of all news stories go to page 14**



If you have an itch, don't scratch it

For the past month I have suffered from shingles, not once, not twice but an amazing three times. When I use the term 'suffering' I mean it. Anyone who has had shingles will know it is characterised by intense itching which is very distressing. Ouch!

You may be wondering why I am talking about my shingles (pictured above left) The reason is because I have been asking myself whether my shingles may be in any way connected to my MS. I know that shingles is associated with age, and being in my sixties I can't discount the possibility that my problem is age related, but is there anything else? A connection with MS perhaps? After some study of academic journals the short answer, rather surprisingly, is "yes." Shingles may have quite a lot to do with MS.

Before we go any further it is perhaps a good idea to explain what shingles actually is. Shingles is a red itchy skin rash caused by the re-activation of the varicella zoster virus (VZV) the same virus that causes chickenpox in children. The Varicella Zoster virus (VZV) is a member of the herpes family of viruses. Its scientific name is HHV-3 and in this family of viruses its nearest relative is the Epstein Barr virus (HHV-4) which, in 2023 US researchers identified as 'a leading cause of MS'.

But is there a closer connection with shingles and MS than the two viruses (EBV and VZV) merely being members of the same virus family and close relatives, cousins, so to speak? Correlation we are always told does not mean causation. The fact that shingles is closely related to EBV may mean just that, and no more. However, there is some evidence that shingles may be more than an innocent bystander, more than an observer, in what they call the 'pathogenesis' of MS or the MS disease process.

To begin with, there is evidence that an MS diagnosis often follows an episode of shingles. A study published in the Journal of Infectious Diseases in 2011 found a significantly higher risk of an MS diagnosis within one year of a shingles episode. For me this is very interesting because my current brush with shingles is not my first. Back in my twenties while at journalism college I had an episode of shingles. It was not as bad as my current attack but it still led to a visit to the GP who gave some anti-viral pills and calamine lotion which you can put on the affected body parts and is quite successful in taking the heat out of the inflamed area

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Continued from page 5 . I remember the GP's surprise that someone in their twenties would turn up with shingles as it is a disease which tends to mainly affect older people.

More or less one year after my first brush with shingles I started to have episodes of double vision and other problems like loss of the use of my hand, things which then led to my first visit to see a neurologist in my late 20s and a subsequent MS diagnosis. One might almost say that for me the road which would ultimately lead to MS started with an episode of shingles, just like the 2011 paper said it could.

The second interesting thing about shingles is to do with the search for the cause of MS. The 2023 'landmark' study published in the journal 'Nature' identified EBV as 'a leading cause' of MS, and the term 'leading cause' suggests that there are other causes. I have often read about the 'dual virus hypothesis'. This is the idea that while EBV may indeed be the leading cause of MS there may be another virus involved. Researchers have looked at the rather exotically named 'human endogenous retroviruses' (HERVs) and their possible although unproven role in MS. While HERVs have been extensively studied it is quite legitimate to ask whether this other virus in the dual virus hypothesis might lie closer to home.

A 2020 paper published in the journal 'Viruses' titled 'Role of Viruses in the Pathogenesis of Multiple Sclerosis' explored a whole range of viruses in causing MS and while most of the paper looked at EBV there was also some discussion of its less studied relative VZV and its role in MS. The authors acknowledged that VZV has a potential role in MS. They said: 'A history of VZV and an increased antibody response to it is more common in MS patients than the general population'.

Of course, like everything else in the world of MS, I know that correlation does not mean causation, but if it ever becomes generally accepted that EBV is the cause of MS it would not be surprising that another virus, particularly one so closely related to EBV is also involved in the MS disease process. After my original brush with shingles at journalism college, I joined a local newspaper and spent several years reporting crime and court cases. Sitting in court day after day I observed that most crimes are the work of more than one criminal, usually a pair. In burglary cases there would always be the burglar and a 'look-out'. In the dock the wrong doers would always blame each other. Sentencing the criminals the judge would frequently say the criminals 'were in it together'. To use this analogy, you do wonder whether EBV and its close relative VZV are 'in it together' when it comes to causing MS.

As I lying here on my sick bed this will be something to think about, while desperately trying not to scratch that itch.

Photo p1 and p5 are pictures of my shingles, taken by me! For further details of sources for feature see page 14

FDA fast tracks DNA therapy for MS-related bladder issues

The U.S. Food and Drug Administration (FDA) has granted 'fast track designation' to EG110A, a DNA-based therapy from bio-pharma EG 427 to treat neurogenic detrusor overactivity (NDO) — a bladder disorder that can arise in MS

The FDA gives fast track status to experimental treatments that have the potential to address serious conditions where there are limited 'therapeutic options'. The designation is intended to speed the development and regulatory review of a therapy, providing benefits such as more frequent FDA interactions and potential eligibility for priority review once a marketing application is submitted.

"The FDA's decision to grant 'Fast Track designation' to EG110A demonstrates the urgent need for more effective therapies for individuals living with neurogenic detrusor overactivity," Philippe Chambon, MD, PhD, CEO at EG 427, said in a company press release.

NDO occurs when nerve damage, such as that caused by MS, disrupts signals that control bladder function, causing the detrusor muscle around the bladder to contract uncontrollably. This increases pressure inside the bladder and reduces the amount of urine it can hold, leading to urinary urgency, frequent urination, and urine leakage — symptoms that can significantly affect physical comfort, social engagement, and psychological well-being. Over time, it can also increase the risk of urinary tract infections and kidney damage.

While several medications can help decrease detrusor muscle activation, these are usually limited by tolerability issues or short-term benefits. EG110A is designed to address those limitations by targeting the sensory neurons that detect bladder filling and send signals to the spinal cord to initiate bladder muscle contractions.

The new treatment uses a harmless form of the herpes simplex virus type 1 (HSV-1) to deliver DNA instructions to these neurons that enable them to produce a modified fragment of botulinum toxin type F. This toxin blocks the release of chemical messengers by nerve cells that drive muscle contraction.

The therapy's safety and early efficacy are being evaluated in a Phase 1b/2a clinical trial (NCT06596291). Early 'top-line data' from the first patients who received the lowest dose showed that EG110A reduced urinary incontinence episodes by more than 88% after 12 weeks, with improvements seen as early as week 4. The therapy was well tolerated, with no treatment-related safety concerns.

For further details of all news and features go to page 14

New BTK inhibitor in Phase 3 trials for progressive MS

Zenas Biopharma is to develop the BTK inhibitor orelabrutinib to treat both primary progressive and secondary progressive MS. The news follows the success of another BTK inhibitor tolebrutinib in non-active SPMS.

A phase 3 clinical trial (NCT07067463) to test orelabrutinib in people with primary progressive MS (PPMS) is expected to enrol about 705 adults, ages 18 to 60, who will be randomly assigned to take a daily, 80 mg dose of orelabrutinib or a placebo for up to 120 weeks, or nearly 2.5 years.

The trial's main goal is to determine whether the therapy can delay 12-week confirmed disability progression, or an increase in disability levels sustained for at least 12 weeks. Other measures of progression will be assessed as secondary goals. A second Phase 3 trial to test the therapy against a placebo in people with secondary progressive disease (SPMS) is expected to start early next year.

MS is marked by inflammation that damages healthy cells in the brain and spinal cord. Bruton's tyrosine kinase (BTK) is an enzyme that's integral to the inflammatory activity of certain immune cells, including B-cells and microglia, that play key roles in driving MS. By blocking BTK, orelabrutinib aims to damp down disease-driving inflammation, including the chronic brain inflammation that's thought to contribute to the gradual progression of disability seen in people with progressive MS.

An earlier Phase 2 trial (NCT04711148) tested orelabrutinib against a placebo in more than 150 people with relapsing-remitting MS (RRMS), and results indicated the therapy was highly effective in reducing signs of disease activity on MRI scans.

"Given the statistically significant and clinically meaningful data from the Phase 2 trial … orelabrutinib has the potential to transform the treatment paradigm for this devastating disease", a Zenas spokesperson said**.**

For details of all news stories go to page 14.

UK nrSPMS Frexalimab trials after success in RRMS

Frexalimab, a therapy that bio-pharma Sanofi is developing for relapsing remitting MS, is now being tested in UK trials for non-relapsing Secondary Progressive MS (nrSPMS) patients.

A total of 900 adults with non-relapsing secondary progressive MS are being invited to take part in the clinical trial called FREVIVA (NCT06141486). There are several UK trial locations including Inverness, Liverpool, Blaenau Gwent, Cardiff, Exeter, London, Newcastle upon Tyne, Canterbury, Manchester, Oxford and Swansea.

For further details about this trial see https://clinicaltrials.gov/study/NCT06141486

The UK trials follow on from the recent ECTRIMS conference where new data from a Phase 2 clinical trial (NCT04879628) showed that rates of new or enlarging lesions and of lesions with active inflammation remained low through 120 weeks, or about 2.5 years in Frexalimab treated patients with Relapsing Remitting MS. Relapse rates were also low — with 88% of participants on a high dose of frexalimab remaining relapse-free — and disability scores remained stable throughout the studies, the data showed. The data was revealed at this year's European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress, held Sept. 24-26, in Barcelona, Spain.

Frexalimab is a second-generation antibody that blocks the CD40/CD40L pathway, which drives the activation of multiple immune cells involved in MS inflammation. By targeting the CD40L protein and preventing its interaction with the CD40 receptor, the therapy aims to dampen inflammatory responses without broadly depleting white blood cells, or lymphocytes. Lymphocyte depletion is the goal of many approved MS treatments, but it can raise the risk of infections and serious side effects.

Another key feature of frexalimab is its dual action on both arms of the immune system. It targets adaptive immune cells like T-cells and B-cells — which drive the inflammatory attacks behind MS relapses and active lesions — as well as innate immune cells, such as macrophages, microglia, and dendritic cells. These innate immune cells are thought to drive the chronic inflammation that contributes to gradual disability progression in MS.

Frexalimab is given as an injection under the skin.

For further information go to page 14



Is MS just one disease? And are terms like SPMS, PPMS etc therefore meaningless?

For decades MS has been 'sliced up' into different subtypes (relapsing remitting, primary progressive, secondary progressive etc). Subdividing MS specifies what treatments we are eligible for, or in the case of my MS– non-active secondary progressive MS, what treatments I am not eligible for - all of them.

However, for years neurologist Prof. Gavin Giovannoni of London's Barts Hospital has floated the idea that 'slicing up' MS into several disease subtypes is not supported by the science, and that MS is actually just one disease. Basically, it's all MS.

Now an academic paper published in the prestigious journal 'Nature Medicine' agrees with Prof. Giovannoni. And if the findings of this new paper are accepted by the MS 'establishment' – that MS is one disease, and that the 'sub-divisions' are arbitrary- then there could be major implications for us prog-MSers. The most important one being that drugs used to treat one 'sub-type' of MS, relapsing remitting for example, could be used on other types of MS like my own non-active SPMS.

So, back to the new paper. It's written by a group of researchers who look at mountains of MS research, what's called 'big data' through the prism of AI (Artificial Intelligence). They say: 'Traditional classification of MS into distinct subtypes poorly reflects its pathobiology and has limited value for prognosticating disease evolution and treatment response, thereby hampering drug discovery.'

The researchers analysed a large clinical trial database (approximately 8,000 patients, 118,000 patient visits and more than 35,000 magnetic resonance imaging scans) using 'probabilistic machine learning' (I think this means AI). The researchers say: 'Our findings support viewing MS as a disease "continuum". We propose a streamlined disease classification to offer a unifying understanding of the disease.' In plain English, this means MS is just one disease and it gets worse the longer you have it and the older you get. The continuum bit is the idea that we are all on the same bus travelling on 'route MS', but some of us have travelled for a bit longer (we are older) than others trvelled at a greater speed.

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Continued from p10 The notion that MS is one disease has been round for a few years and has been well articulated by Prof. Giovannoni who tends to talk of a disease 'spectrum' rather than a disease 'continuum' but basically is saying the same thing as the authors of the new research. In an academic paper appropriately titled: 'Multiple Sclerosis is One Disease' published in 2022 in the journal 'Therapeutic Advances in Neurological Disorders' Giovannoni reminds us that the origin of categories like relapsing and progressive stem from the introduction of the first MS drugs (the ABC drugs) back in the 1990s.

Then, in an attempt to gain 'orphan drug status', it was advantageous for drugs companies to carve up the large number of total MS patients into several small groups, and say that the first MS drugs (mainly beta interferons) would be appropriate for just one group – those with 'relapsing remitting' MS and in this way get the new drugs approved.

Prof. Giovannoni says we should ditch the disease sub-divisions, which are based on these commercial considerations not the biology of the disease. Neurologists should instead consider how active a patient's disease is (active inflammation). In an article titled 'A Smouldering Process: A New Way of Thinking about Multiple Sclerosis' the French drugs company Sanofi explores an idea central to Giovannoni's thinking – the idea that in all MS there is an ongoing, low-level inflammation and damage in the brain and spinal cord even during periods of remission or when there are no visible new lesions on MRI scans. It is argued this process, is the significant driver of long-term disability progression in MS. This, it is argued by other commentators, is 'the real MS'

So, if the 'real MS' is a smouldering condition, slowly progressing and just one disease, is there any hard evidence that treatments for one type, relapsing remitting for example, would work on another type – progressive disease? Well, yes there is. In 2018 a clinical trial looked at the relapsing MS drug natalizumab (Tysabri) and whether it would work in progressive MS. The two year trial which had a six month extension failed to show an improvement in patients' walking (their long limbs) but it did show improvement in patients' shorter upper limbs (arms and hands). In this there was an improvement in the 9 hole peg test where patients use their hands to put pegs in holes.

It was suggested at the time that this discrepancy was because the shorter limbs (arms)would respond more quickly than the longer lower limbs (legs) because MS is a length-dependent 'axonopathy', meaning longer central nervous system (CNS) axonal pathways (legs) are more susceptible to damage and dysfunction then shorter pathways (arms). If true this means that the disease modifiers will work for all of us, even us progressives, if they are given long enough for them to work. It's something you might point out to your neurologist at your next appointment. **For details of all features go to page 14.** **Photo Kristine Wook on Unsplash.**

News

Blood test for measuring MS progression being developed

Bio-pharma Octave Bioscience is developing a 'biomarker blood test' to detect disease progression in MS. The test will be of particular use for those of us with progressive MS where disease progression is faster, more noticeable and easily measured.

Octave Bioscience's MS Disease Progression test, or MSDP, objectively measures MS progression based on the levels of certain blood proteins. To date, assessing progression in MS has been subjective, with tests that often don't detect its bio-marker signs. Octave's work on the MSDP follows the successful development and commercialization of the company's MS Disease Activity (MSDA) test — the first blood test to assess disease activity in MS.

With funds from a new grant, Octave will conduct studies to identify individual proteins that may serve as biomarkers of progression, and will then develop an artificial intelligence-based model that analyses several blood biomarkers to provide a progression score. These studies will help advance the MSDP test toward commercial viability as a complementary solution to MSDA, according to the company.

MS is highly 'heterogeneous', meaning its activity and progression can vary significantly among individuals. Octave's test will measure several biomarkers and use artificial intelligence-driven algorithms to combine the results into an objective score. This will help clinicians track MS progression and make earlier and more informed adjustments to treatment plans whenever necessary, according to the developer.

The test will be delivered as a simple blood test, and is being developed to assess MS progression across all disease types. The company will collaborate with academic partners worldwide to study proteins associated with MS progression in patients, and the findings will be published in a leading MS journal.

The company's MSDA test was developed to assess disease activity and help guide decisions on MS care. It is commercially available in the U.S., and measures 18 proteins involved in four underlying biological processes. The results are combined into a numeric score that helps rank disease activity as low, moderate, or high.

For details of all stories go to page 14

News

Oestrogen hormones could treat progressive MS

Treatment with oestrogen hormones such as oestradiol may help reduce inflammation and nerve damage in progressive MS, particularly in cases where the disease is triggered or worsened by viral infections, according to new research.

A team of US researchers investigated the role of sex hormones in a mouse model of MS. They found that mice treated with oestrogen hormones, especially oestradiol, experienced fewer or less severe symptoms six months after a viral infection compared with untreated mice. Oestradiol also appeared to reduce damage to the myelin sheath — the protective coating around nerve fibres that is damaged in MS.

Women are diagnosed with MS more often than men, and in females the point at which MS becomes progressive often coincides with menopause. This may be linked to changes in sex hormone levels, as the body stops producing significant amounts of oestradiol after menopause. In contrast, hormone changes during pregnancy or the use of hormonal contraceptives have been linked to an easing of MS symptoms.

In the study, female mice were infected with Theiler's murine encephalomyelitis virus (TMEV), which causes inflammation and myelin damage similar to that seen in MS. Some mice were left uninfected as controls. Fifteen weeks later, all mice had their ovaries removed to stop natural hormone production. They were then given slow-release hormone pellets containing oestradiol, estriol (an oestrogen that increases during pregnancy), or a placebo.

Over time, mice receiving oestradiol or estriol showed fewer or less severe symptoms than those given the placebo, with oestradiol having the strongest effect. When the researchers examined the mice's spinal cords at the end of the study, they found that both hormones reduced inflammation, but only oestradiol also reduced damage to the myelin sheath.

These findings suggest that while both hormones may help reduce inflammation, oestradiol could offer stronger protection against myelin loss, potentially helping to slow progression in virus-related forms of MS. The researchers believe this could be explored further as a possible treatment option for progressive MS in humans.

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Page 13: Oestrogen may help protect against MS nerve damage

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