Transcription of the audio file for the Belinda Weller Distinguished Lecture
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[Prof David Hunt, University of Edinburgh] Well, thank you, everyone. Thank you very much. It is really wonderful to see so many of you here today. Can I extend the warmest welcome to all of you for this very special lecture in memory of a very special person?

Belinda Weller was the heart and the soul of the Edinburgh MS community for many years. It is wonderful to see so many of you here, so many friends, family, colleagues, people with MS, here to celebrate her. I'd like to extend a particularly warm welcome to Belinda's family. Professor David Weller, Belinda's husband, Phoebe, who is joining online from Australia. I think it's about 3:00 A.M. In Sydney at the moment. Maddie and Tristan. Welcome. It's really great to see you here today.

As an MS team in Edinburgh, we had thought long and hard about how we could best remember and honour Belinda's legacy. At the heart of what we wanted to do was to do something that, like Belinda, brought people together in celebration with a focus on improving outcomes for those affected by multiple sclerosis and neuro-inflammatory conditions.
We're delighted to bring you this Distinguished Lecture and it's great to see such a brilliant turnout both here and online. This is also a wonderful opportunity for us to remember Belinda and her professional legacy as a doctor, a researcher, and a teacher. Belinda was the kindest and most skilled of doctors. Her deep understanding of medicine with dual training in both medicine and physiotherapy informed her unique holistic approach. Her warmth and compassion shone through everything that she did. Belinda was an outstanding clinical leader.
She established and led the MS service in Edinburgh from scratch, developing a highly skilled expert team of specialist nurses, consultants, radiologists, researchers, pharmacists, and rehabilitation teams. But don't take my word for it. There is a website called "I want great care.com," which is feared by many, many doctors. In fact, I can see a few people breaking out in a cold sweat. But even in this, the most unforgiving of forums, there is nothing but universal praise for Belinda. In the words of one former patient, there are no words complimentary enough to describe the fantastic Dr Weller.

Belinda's creation and leadership of the MS team was the foundation of the exciting and dynamic environment for MS care and research in Edinburgh. And she ensured that this was grounded and focused in the needs of people affected by these conditions. Belinda made pivotal contributions to multiple sclerosis research in Edinburgh. She established early on when she arrived here, much needed clinical trial infrastructure in Edinburgh, first through the Wellcome Trust Clinical Research facility, and latterly through the Anne Rowling Clinic.

Informed by her own excellence in team sports. She was an outstanding netball player, and I think that there's a netball competition in Malawi that is named after her. But informed by her own excellence in team sports, she was known widely in the UK and the international MS community as a team player who contributed to very many pivotal academic and industry studies which have shaped and developed the revolution in care which we have seen over the past two decades in multiple sclerosis and neuro immunological disease. As well as being a team player, Belinda was also a research leader.

Her farsighted leadership of the Scottish MS Register has led to the creation of a unique resource and map of multiple sclerosis in Scotland, which has informed epidemiology, driven up Scottish MS standards of care, helped keep MS patients safe during the pandemic and will be at the forefront of future efforts to eradicate multiple sclerosis. The register reflected Belinda's approach. It was rigorous, common sense, and patient focused. Belinda was also a brilliant teacher, not just of medical students, but of us, of those who worked and trained alongside her. She trained a generation of clinicians, of specialist nurses, of researchers, pharmacists, and healthcare professionals.

Working alongside Belinda in clinic as a registrar and a consultant was a uniquely fun experience. She brought an infectious sense of warmth and enthusiasm to even the most challenging of clinics. As a colleague, she was supportive, decisive, and kind, and we miss her. Belinda's professional legacy lives in us. It lives in all of us, in our clinics, in our research, and our education, and it's this which we celebrate today.

We thought long and hard as a team about who to invite to give this Distinguished Lecture and we're delighted that Professor Jackie Palace accepted our invitation.

Jackie is a Professor of Neurology at Oxford University where she's played a key role in leading both clinical services and research in both multiple sclerosis and related neuroimmunological disorders, often at the interface of the two.

Jackie is an internationally renowned researcher who has made seminal contributions to the field, and recently delivered the highly prestigious ECTRIMS plenary lecture. But Jackie, Belinda told me and many others on many occasions what a great inspiration you were to her, and how much she admired your work and leadership both as a neurologist and as a researcher. We can think of no one better to deliver the Belinda Weller Distinguished Lecture. Thank you, Jackie. Thank you.

[Prof Jacqueline Palace, University of Oxford] It's a deep honour and a delight to be invited to give the inaugural Distinguished Belinda Weller Lecture.

Although I didn't work directly with Belinda and I lived far away, we were great friends and colleagues at many meetings and conferences, including ECTRIMS, the ABN, and the MS Debating Society, which she beat me up, by the way. I also miss her.
As you say, David, she was very warm, she was immense fun. She was kind and she was full of energy and I have very happy memories of our time together.

Today, I've been asked to cover a disease like multiple sclerosis in that it's CNS autoimmune disease against myelin, but it's caused by antibodies to MOG. About two decades ago, many of the diseases that I'm going to mention, but mainly MOGAD were incorporated in MS as forme frustes.

About 20 years ago and since then, patients with Aquaporin-4 antibody associated NMOSD have been pulled out and identified. A larger group of patients with myelin, oligodendrocyte, glycoprotein, antibody associated disease have now been identified. And I think that there will be other diseases that will be pulled out in the future. This will make MS itself clearer and more homogeneous to be able to study.

I'm going to briefly talk about the history, then challenges of the diagnostic MOG antibody assay because I think this is really important in our clinical practice. Some diagnostic features, treatment lessons, and the distinction from MS.

Starting with the history. So, MOGAD can present in many different ways. It's huge. How did we miss it? You can have long transverse or short transverse myelitis. You can have unilateral or bilateral optic neuritis. In children acute disseminated encephalomyelitis, or brain attacks, brain stem attacks in adults. And a rarer, but very distinct picture, of cortical encephalitis with seizures, and any combination of these. I think one reason why we missed it is because these patients present either to paediatric neurologists or paediatricians, or to ophthalmologists or to neurologists. They're just all over the place, and it was very difficult to actually identify them. If you look back in history, then it was quite a long time ago in the 1830s, when people started to realise there was a link between amaurosis and diseases of the eyes and the spinal cord. Although there were many NMO cases going back even in the 1700s that were described, it's very difficult to be sure which were Aquaporin-4 positive, which might have been MOG positive. But I reckon this case by Pescetto of a 42-year-old male presented with acute bilateral amaurosis and a severe cervical myelitis, that had complete recovery, is very likely to have MOGAD and not Aquaporin-4 disease.

Allbutt, who was credited with being one of the first people to describe Devic's disease but wasn't, hypothesised that the link between the spinal cord syndrome and the eye syndrome was related to the sympathetic nervous system links of spreading meningeal irritation. Just over 25 years

later, Katz correctly suggested that there was something circulating in the blood. Bogaert described the first case I can find in the literature of relapsing ADEM, and the reason this is important is because we know that the majority of people with relapsing ADEM will have MOG antibodies. But over the decades, and years after this, the MS community still didn't really accept that many of these patients that looked a bit different really had something different. This is from the 1930s in Brain's chapter on MS, when he was discussing relapsing ADEM, and he also discussed NMO. There was a 4-year-old child who had recurrent attacks of ADEM, one with visual impairment, and this is very typical of MOGAD. He said, well, look, they look clinically different, their pathologically look different, but there's no reason to suggest there's a different cause. Even in 2008, the MS criteria panel did not accept that there was something called multiphasic ADEM and they suggested these patients probably had MS. The issue has always been that it's been difficult to actually detect the antibodies.

What is MOG? MOG is clearly found on myelin and you can see in this picture, layers one to two are on the oligodendrocyte, two on the outside, and layers three to six coming from the inside to the outside on the tightly packed myelin sheath. And you can see that MOG is found mainly on the exterior, on the surface of the myelin sheath rather than on the oligodendrocyte. It's a minor component, in fact, of myelin, less than 0.1%. But it's really important for the structural integrity. It's exclusively expressed in the CNS and it's accessible to antibodies. Therefore, antibodies against it are likely to be pathogenic. Now we come on to the bit that I think is most challenging and that's the diagnostic antibody assay. And I'm really grateful to Paddy Waters for lending me his slides. The antigenic structure is important in assays, and here, and don't worry that they look different. These are two monomers, two MOG monomers.
This is the extracellular portion, the transmembrane portion, and the cytoplasmic portion, and really these weren't thought to be important. The extracellular portion is what the antibody binds with, so it wasn't really thought to be that important. But in fact, we now know that the intracellular portion actually brings these two monomers together and allows antibodies to bind bivalently. Well, you can see if you're doing an assay in solution or out of the membrane, you're going to lose your quaternary structure, and therefore, in ELISA or immune precipitation techniques, any antibodies you pick up are not going to be the same as the antibodies that are occurring in-vivo. The other thing to mention is that with ELISA in fact patient sera is sticky and it often sticks non-specifically to the plates, to the blocking solutions. You need a lot of controls to do them properly. If you're running them down Western blots, which is how most of the old data was testing for MOG antibodies because you've got to put the antigen in solution to run it down the gel, you denature it totally either into polypeptide chains or peptides, and therefore, any antibodies that bind against this are not going to recognise it in its conformational form, so they're not going to be the relevant pathogenic antibodies. And, MOG was a protein of interest in MS for decades. We all know the EAE models.

This was from a review in 2006 when they were revising what the pathological features of MS

and which is the most suitable EAE model, and the only antigen that was actually mentioned in this were MOG peptides. So it was thought that this was relevant to MS. Using Western blotting techniques, people were reporting antibodies in MS to MOG as well as mining basic protein. In this study, 100% of MS patients of all types had these antibodies. There was a neat study looking at people with clinically isolated syndrome and who went on to relapse time to relapse. Those that had these antibodies to denatured MOG, as well as MBP were more likely to go on to get MS than those who didn't. Now this makes sense. They're not pathogenic antibodies. If you've got ongoing disease activity and you've got tissue destruction, then you're going to release the peptides from inside the cell before they've actually formed the MOG on the cell surface and you're going to get a secondary antibody response, so it's a biomarker rather than causing pathogenic problems. Then there was this spontaneous double transgenic MOG mouse model reported. Using T cell receptors against MOG, and producing MOG antibodies. To their surprise, it didn't produce an MS like pathology, it produced Devic's disease. By Devic's disease, they meant there was pathology in the optic nerve and the spinal cord. But in contrast to Devic's disease, there was no complement activation and they didn't see the destructive necrotic pathology you'd expect. Of course, we now know this is typical of MOGAD. Then the real breakthrough came when Kevin O'Connor described a way of detecting antibodies to conformational MOG.

Now in this assay, it was just the extracellular portion of MOG as in a radio immunoassay. But what again, they noted, and it was a surprise, was they found antibodies to this in a subset of patients with ADEM, and it was rare in MS. And since that, over the next 10 to 15 years, people have been improving the MOG diagnostic assay. This is what we use in our lab in Oxford. Paddy Waters in our group. He expresses full length MOG on HEK cells, and then you overlay with patient serum. If they have antibodies, they'll bind. Then you bring in a secondary anti human antibody tagged with green fluorescent protein, and you look down the microscope and you can see the green binding to the cells, and it's a qualitative assay, you score it 1-4. Depending how strong the binding is. What Paddy has found is if you use the full length MOG on the cell line rather than the short length MOG, it's much more sensitive and that makes sense now because we know then you can get these bivalent binding antibodies. But he also found it wasn't very specific because the off-the-shelf anti human IgG was binding IgM and in CNS disease, virtually all or nearly all pathogenic antibodies are IgG. He now uses an anti-human IgG one and we have a very good sensitive, fairly good specific antibody assay. We've made it. We've got a diagnostic antibody assay, so we can just go out there and test everybody, problem solved, or is it?

Well, there is a long way to go. There are problems. This is from an international validation study because many countries looking at different assays, but using the same sera. These are all positive samples, they should all be red. These are all control samples. They should all be black. You can see first of all, that ELISA is no good. These are all live assays, so one to seven in different labs, they do slightly different techniques, but amazingly good reproducibility in these.

Then number eight is the fixed cell-based assay using a dead cell, it's not a live cell in the commercial lab. You can see it's got the highest false negative rate at nearly 13%. The only false positive, it was very low, 2.5%. There have been further studies looking at MS patients. The fixed cell-based assay again in the best lab was picking up 2% of MS patients as being false positives. The live cell-based assay at Oxford and in the Mayo 0% or 0.4%. Overall, the ELISA assays are no good, the cell-based assays are the best, the live seems more accurate than the fixed. Now, we've seen how the fixed cell-based assay performs in the commercial lab. How does it perform in the real world when you send a kit out? Now, this is an extreme example. This is published data, it's done in a hospital lab, academic unit. What you can see here is that the fixed cell-based assay, bears no resemblance to the results on the live-cell based assay. So, these are really the issues with the MOG antibody assay. In contrast to Aquaporin-4 IgG, the MOG IgG assay, there is no clear cut-off between controls and disease. You've got to decide whether you want a few false positives or a few false negatives. And 20% of patients will become sero-negative at follow up, so that won't be a false negative if you test them down the line. You haven't tested them during the acute attack. The cell based assay is the only reliable assay. As I've said, the live assay is reproducible if it's clear positive, but not if low positive. The fixed assay in the best lab picks up 2% of false positives in MS. The low titre is not specific, but it performs much worse in the real world and it's very variable. In a recent study from John Hopkins, they found that it had a 46% sensitivity compared to the live cell-based assay. The warning I just wanted to mention is that many NHS labs are using this commercial assay. Coming on to the diagnostic features. There are different presentations depending whether you're looking at adults or children. Adults, about half the patients will present with optic neuritis, they will go into the ophthalmologist. Then next we'd see transverse myelitis and then you'd get the brain attacks and the classic Devic's disease, optic neuritis and transverse myelitis. But in children, most of the children will present with ADEM or brain attacks, followed by optic neuritis. The majority of relapses in adults are optic neuritis, about 80%, but the majority of relapses in children will be optic neuritis or ADEM. It's got a slight increase predominance of females, but nothing like in Aquaporin-4 disease or MS, there's no racial predominance, but you do get oligoclonal bands in the CSF in the minority.

What do we find on the MRI scan? I've mentioned that most adults won't present with brain attacks, but nearly half of them will have changes on their MRI scan and the appearances are really typical of ADEM. They have these fluffy poorly demarcated lesions around on the brain MRI, often multiple enhancing lesions, and just to show you the difference, these are the lesions in MS and they're much better demarcated. Bilateral cerebellar peduncle lesions here are quite common. If you have a cortical encephalitis, then you may see cortical high signal and swelling, sometimes with overlying meningeal enhancement. I've tried to show you the difference in brain stem lesions between MOGAD and MS here. And it isn't the number of mid-brain lesions, pontine lesions, medullary lesions. It's the percentage of patients with diffuse lesions in all those areas are much higher in MOGAD than in MS, here if you look down these columns, and also a much greater likelihood of a complete resolution in MOGAD, 67% versus 16%. Coming on to the spinal

cord imaging, we have spinal cord involvement in adults in about 30%. The classic is a long spinal cord lesion, longitudinally extensive TM, which is at least three vertebral segments long. If you do axial cuts, it will be central. You need to do axial cuts in these patients. I think anyone with spinal cord lesions should have axial cuts. But you can get short transverse myelitis on their own or in combination in about 25%. Conus lesions are pretty common in MOGAD and they are very rare in MS. This is on an axial cut, something that's quite classic of MOGAD. You do see it in just under 10% of Aquaporin-4 patients. It's called the H sign. There's high signal in the grey matter, that looks like an H. And if it's a long lesion and you cut through the centre, you get this linear sagittal hyperintensity that's quite typical. Then when it comes to optic neuritis, as I said, the majority will have optic neuritis, long optic nerve lesions more than 50%. It's also quite typical to have bilateral optic neuritis at the same time simultaneous, that's a clue, and often it's anterior and you often get optic disc swelling shown here. You can even see optic nerve head swelling on the MRI in this case.

A few years ago, we described a series of patients presented with migraine and what we found was that there was increased signal outside of the optic nerve itself, so the inflammation spread outside into the periotic nerve regions. And perineural sheath enhancement shown here. I don't know if you can see, but in the middle here, you've got the optic nerve and then round the outside, you can see the optic nerve sheath enhancing. On a longitudinal cut, you can see down the side. This was all put together in 2023 in the MOGAD diagnostic criteria.

Basically, it said, first of all, if you have optic neuritis or a myelitis or a brain attack or a brainstem attack or a cerebellar attack, or you have one of those cortical encephalitides then you need to start to think about what the MOG antibody test is telling you. If it's a live cell-based assay, just needs to be clear positive, and not borderline. If it's a fixed cell-based assay, it's got to be high titre, at least 100 and then you don't need anything more. But if it's low positive, you don't know the titre, it's negative, but it's positive in the CSF, then you need to check the Aquaporin-4 antibodies and you need more features. Really what I've just told you, if it's an optic neuritis, they've got to either have bilateral disease, a long lesion, the perineural, sheath enhancement or optic disc oedema. If they've got a myelitis, it's got to be a long lesion, a central cord lesion, or an H sign or a conus lesion, If it's a brain or brainstem attack, they've got to be fluffy, lesions, deep grey matter lesions like in ADEM or have the cerebral cortical changes if they've got a cortical encephalitis. You can see how it all fits together, and they must look more like MS. But you can't go out there and you can't test everybody for MOG antibodies because you get false positives. You've got to work out when you're screening, and like with any medical screening, the prevalence of MOGAD in the cohort you're screening, the positive predictive value.

If you look at MS to MOGAD, it's very different the ratio in adults and children. In adults, the MS to MOGAD ratio is 100 to 3 and in paediatrics, it's pretty similar, 2 to 3 and in children under 12 in prepubescent children, it's the other way around, it's 1 to 4, MOGAD is more common. So in

the criteria, they were very keen to guide people as to who to screen, basically saying that in children, because more antibodies are common in inflammatory demyelinating conditions, you should screen them. In adults with standard optic neuritis, because the chances of them having MOG antibodies is only 5%, you've got to be cautious. In those with severe optic disc oedema, you will pick it up in 40%, but then you'd miss a lot of MOGAD cases. So, they suggested screening all your bilateral optic neuritis, long optic neuritis, and perineuritis, and a big do not screen adults with MS because you'll get probably more false positives than true positives. Now, we often get into the situation where we have low MOG antibodies and we're not sure if people have MS or MOGAD there are extra imaging clues. The percentage of lesion resolution is high in MOGAD and it's low in Aquaporin-4 disease and in MS. And new lesions outside of relapse, which is typical in untreated MS in its characteristic, is really rare in the antibody conditions. You can see in MOGAD with high lesion resolution, no new lesions, they're going to have a low lesion burden over time compared to an MS and so follow up imaging is then useful when the diagnosis is unclear.

Coming on to some treatment lessons now. The first thing to say is that MOGAD can be monophasic or relapsing. I've taken two incident cohort studies. One is from our group in the UK and one is from France. I've actually aligned the axes to be the same just to show that they've got very similar results. The early relapses are common and they appear to flatten off later. About 45% of patients will relapse over two to three years. You don't want to treat everybody from the word go with long term immune suppressants. When we're coming on to treatment strategy, if we start with treating acute relapses.

This is a study from a French group where they looked at patients recovering from their onset attack. So green is complete recovery, red is no recovery. These are the MOGAD patients compared to Aquaporin-4 and double sero-negative patients. Yes, the MOGAD patients do much better, but the one thing you've got to note is only 30% of patients actually have full recovery. The majority of patients are left with residual impairment just after their onset attack, so we need to prevent that. We need to treat it better.

One thing I really wanted to highlight is that MOGAD patients often recover amazingly well from being paraplegic to walking around really well. But what we noted, was that they were left with quite marked sphincter and sexual dysfunction. In our cohort of patients, we noted 28% of our whole cohort were left with really quite significant bladder dysfunction, 17% using catheters, and three quarters of our males with a TM onset were having problems. Bowel dysfunction, really significant bowel dysfunction in a fifth. And erectile dysfunction in a fifth of our males and nearly half of those with TM onset. So, when you see your patient doing incredibly well from a motor point of view, I don't think people should be sending them home with catheters and saying, I think it will get better. I think they need to go on to the next stage of treatment to try and get back their function. And this is the acute attack treatment algorithm, giving high dose IV methyl pred

urgently. I tend to start now with five days of a gramme. If there's an incomplete response or significant disability, we're already teeing up plasma exchange, IVIG, if we can't get hold of it and sometimes holding them with another course of IV methyl pred. If you don't know the antibody result, it doesn't matter then because you can hold them on prednisolone awaiting it. Because optic neuritis is the most common, there's better data on the effects of not giving treatment promptly. This is from a French cohort. This is a ten-day delay or more versus less. What they showed was a patient's visual outcome was worse if you delayed more than ten days and their retinal nerve fibre layer was thinner. This was an Israeli study where they mixed Aquaporin-4 and MOGAD patients, but the disease status did not affect the model and they did a seven-day delay less or more, and they also showed that vision impairment, permanent vision impairment was more likely than those with delay. But they also looked to see what was the critical time to treat and it was four days. If you delayed more than four days, the odds ratio was over 8 of failing to recover 20/20 vision.

This is another study of plasma exchange from the Mayo Clinic, they had nearly 400 patients. No, there were about 100 with NMO, about 100 with MOGAD, and about 100 with MS, and nearly 100 with idiopathic disease. So, it doesn't really matter what the diagnosis is. They clearly had bad visual impairment and for every week that the plasma exchange was delayed, the chances of complete recovery went down. And don't worry about the detail here. What they did was they modelled their patients' outcome and matched them to the optic neuritis treatment study. What they were able to show was even delay in the PLEX though by a month would pull back about 50% of your patients to 20/40 vision or better. So, it is worth going on a month downstream. In fact, now we've treated maybe 3 patients at three months with really poor vision and had really quite reasonable recoveries. Then I'm talking about rebound prevention and what I really mean here is just preventing those early relapses. So here is a study we published about eight years ago now, where we looked at if you gave a course of prednisolone after onset, did it make a difference to prevent them having relapses? What we found was if they had a course of 3 to 6 months or more than 6 months. When you took them off, this is when they came off the steroid, so they're not on it, they're not covered by the steroids now. They were less likely to relapse than if they had a shorter course.

Since then, more recently, this is an Australian study, this is a Chinese study. They've both shown that at least 3 months or more of prednisolone actually reduces the relapse risk. Most people now will follow on treatment with a short course of prednisolone to reduce those early relapses. I don't think it will necessarily prevent long term relapses. Relapse prevention, I only really use this in people who've got relapsing disease outside. If you look at where we could actually treat people, we can give them those broad oral immune suppressants that hit the T-cells, and B-cells, our old-fashioned drugs maybe. You can get those like anti-CD20s or anti-CD19s that hit the B-cell maturation pathway, those that actually attack the antibodies, and those that will hit IL-6. Two studies and there are more. This is from France, this is from our UK group, looking at relapsing

patients who were put on azathioprine, mycophenolate, or Ritux, versus those on no treatment, and it reduced their chances of relapse by hazard ratio of 0.4. We showed the same with a hazard ratio of 0.5. Immune therapies such as AZA, prednisolone, Ritux, mycophenolate seem to work. But for some reason, rituximab doesn't work as well in MOGAD, and it's an IgG-1 disease really, as well as it works in Aquaporin-4 disease. This is neatly shown in this report from France. They had 29 Aquaporin-4 patients, and 16 MOGAD patients. They had a 24% relapse rate in 38 months in the Aquaporin-4 patients. Then they had 38% that relapsed in half the time in the MOGAD group, so much higher relapse risk. But what was more interesting, was the majority over 90% of the Aquaporin-4 patients only relapsed when their B-cells recovered. So, when the Ritux was no longer working, whereas that wasn't the case in MOGAD, the majority relapsed when their B-cells were still suppressed.
So, they're definitely different mechanisms of action. Then I've chosen these two studies just to demonstrate two points. In the literature in paediatrics, IVIG has been used quite a lot and before relapse rate to on treatment is much lower with IVIG, and in a Mayo Clinic retrospective analysis, a small group of patients, none of their IVIG treated patients relapsed. Now, in contrast, the MS drugs, again, this is in the adult group, all their patients put on first line MS DMTs all relapsed. In the children, there was no reduction in annualised relapse rates, you would expect a small reduction due to regression towards the mean. We think that anti-IL-6 receptor agents should work in MOGAD because IL-6 is elevated in the CSF during acute attacks in MOGAD and Aquaporin-4 disease, but not in MS and we know that these drugs work in Aquaporin-4 disease and are licenced for it. There are some retrospective studies. Here's one before Tocilizumab and then on Tocilizumab just a small number of patients showing a reduction.

This is a recent study of four very resistant MOGAD patients. These arrows are relapses and this is before they're given Tocilizumab and they've been on the grey is IVIG, it hasn't worked. The green is mycophenolate, that hasn't worked. Then they go on Tocilizumab and it seems to suppress the relapses. There's now a randomised double-blind study of Satralizumab, which is the drug that's licenced in Aquaporin-4 disease. We heard about this earlier, didn't we this morning? The potential for the neonatal FC receptor drugs that block this. The Fc receptor showed as this little red flower pot. Your normal way of recycling your IgG is it gets taken up into the cell and at the acid pH, it will bind automatically to your FC receptor. This then recycles it back to the surface and in the neutral pH just automatically unbinds. If you block this, then your antibodies will be broken down. It's just like plasma exchange in a drug. There's now randomised controlled trial by UCB in MOGAD patients.

Then stopping treatment. Can you stop treatment?

Well, this is a report I've already mentioned how the relapses tail off anyway, but this is the first four years risk in the solid bars and the hatched bars are the second four years. You can see that in MOGAD the first four years there's a decent relapse risk, but in the second four years, it flattens

out. You don't see that Aquaporin-4 disease, the risk of relapse continues. This is the treatment algorithm, urgent, aggressive, acute relapse treatment. If people have had a single attack, we would treat people with 10mgs of prednisolone for three to six months and I would only use the higher dose for the first four weeks. Then if they relapse, then you use your immune suppressants, prednisolone, low dose, mycophenolate, IVIG, not MS drugs, not complement inhibitors, haven't gone into why. The only time I put somebody on long term immune suppressants, if they're monophasic, is if they've lost vision or had really bad outcomes in one eye. Because even if you say you've only got a 10% risk of relapse and we know it's higher, that's too high to lose the vision in your good eye in my view. And then if it fails, Rituximab or Tocilizumab.

Then if they've remained relapse free over a few years, consider stopping the treatment because you know the relapse risk may have gone down and always consider entering them into a randomised controlled trial. We're recruiting currently, so happy to take anybody's patients, and distinction from MS. This is a recent publication from a German cohort. The only reason I picked this out is because this is their MOGAD patients showing all the different treatments they're on and this light grey area is MS drugs. Until ten years ago, their MOGAD patients were all being treated with MS drugs, about a third of them. That means about a third of their patients probably misdiagnosed as MS because it can be quite tricky clinically to sometimes differentiate, and of course, the treatment isn't optimal.

So, MS has relapses, so does MOGAD, but they are more dramatic in MOGAD and they recover less well. However, MOGAD can be monophasic, which clearly MS is a longer-term disease, but it can be relapsing. As I mentioned, the brain MRI in MS is active in between the relapses, but not in MOGAD. But in MOGAD the lesions resolve much better, so you get a low lesion volume over time and you don't get the progressive phase that you see in MS in the antibody conditions. This is a summary slide and just running through very briefly because I've mentioned all of this, in MOGAD compared to MS, yes, we know its antibody mediated against myelin. We have a very broad clinical phenotype, monophasic, relapsing, but not progressive. It affects children and all ages, whereas we know MS tends to have a peak in early adulthood. There is no racial bias or place of birth effect that you see in MS and you can get oligoclonal bands, although in a minority. I've already described the MRI features, and if you're not sure, you can follow them up and look for lesion resolution and silent lesion activity. You treat them urgently and aggressively, follow it on with prednisolone, I think, and then if they relapse, you've got the immune suppressants, IVIG, but not the MS treatments. We can see cases that were clearly MOGAD. going back at least 100 years. EAE, MOG EAE, though was put down to be an MS model. Antibodies to denatured MOG were found in MS, and then until we had this double transgenic MOG mouse model which made people wonder.

Then we had the first assay in 2007, where then it was much clearer that the antibodies to a conformational MOG was describing a different disease. This assay has now been optimised and has allowed us to see the full extent of the clinical phenotype and how it responds to treatment. We now have MOGAD criteria and already have two randomised controlled trials.

So, I think it's fitting to dedicate the MOGAD story to Belinda because she has many or she had very many overlapping features that made it a success. So, it's been a long journey, and I don't think Belinda was afraid of long journey. She came all the way from Australia to settle in the UK to the benefit of UK neurology, the MS world, and patients with MS.

It was a journey of resilience and no-one could have shown more resilience and strength and positivity than Belinda in her illness. I think also it takes some resilience to leave the Australian climate to come to ours. It would never have been successful without collaboration and teamwork across the globe. Belinda was a great collaborator and team player.

Belinda wasn't about herself. She wasn't driven by her ego. She was there to work with people to get results to improve things for MS patients. And the MOGAD story led to a distinct disease being differentiated with its own way of being treated that was distinct from MS and even Aquaporin-4 disease. This has led to better outcomes in patients and Belinda has always been about improving her patients' lives. David and Maddie and Tristan and Phoebe, I hope you will agree that if Belinda was here now with me, she'd be celebrating the MOGAD story as well. Thank you.

[Prof David Hunt, University of Edinburgh] Thank you so much, Jackie. That was a wonderful story and a great lesson in measuring something well, and all of the things that has led to an improvement in patient care that has occurred with that. Now, can I open to some questions?

[Questions from the Lecture attendees] *Colin.* Jackie, over the years, one of the great mysteries in MS is how infrequently we see multiple sclerosis in kids. I guess about 30 years ago, we worked out that when we did see MS in kids, it was a bit different because it was often a real encephalitic type presentation, and there was often a very dramatic cellular response in the cerebrospinal fluid. Is that because it wasn't MS at all? It's always been MOGAD?
So, paediatric MS, especially in the younger children, I think nearly always was MOGAD. I remember sitting in the audience about to give a MOGAD story or just after a paediatric neurologist who they didn't have the MOG assay at that stage in their centre. Telling everybody that MS in children was very different and producing all the features. I'm sitting there thinking, they've all got MOGAD and that's absolutely true. You see the same in different races for Aquaporin-4 disease when a lot of MS like optico-spinal Asian MS is in fact Aquaporin-4 disease. In certain populations, it wasn't ever MS, it's been another disease. Yeah.
Peter, why doesn't Rituximab work? Its antibody mediated. Sure, it should work.

Why doesn't what? Rituximab work? Well, that's a very good question. We're not really sure. Firstly, you could have long lived antibodies. That's one possibility that because you're only hitting out you're you're not hitting out the plasma cells. Maybe they have long lived plasma cells. But the other thing is it is felt because it's not complement mediated, that maybe there's a lot of T-cell derived pathology and so maybe just hitting the antibodies is not going to work. If that's the case, the anti-Fc receptor drugs may not work so well. Thank you.

Any other questions, *Katie?* Jackie, that was great. Stopping treatment, I always find challenging in MOGAD. We try and do it after three or so years, but the graph you showed about the high incidence of relapses initially in the relapsing population and then plateauing off, say after four years. If you've had people on treatment, are you coming out since that point anyway, or do you have a almost a rebound flurry?

So that graph of the four year one, they were all untreated. Untreated, those ones were. They were a small number. There doesn't appear to be a flurry, but of course, it's always a risk. But it's a matter of putting somebody on decades of immune suppressants versus trying it and then treating really aggressively if they have a relapse. But I remember Romain Marignier from Léon telling me how he did this in one person and they ended up, which is unusual, with a devastating transverse myelitis which they couldn't recover from. But I don't know the majority of people we've tried it on have done well, but it needs a proper study really. We should be doing it in a perspective way and seeing what the outcomes are rather than randomly as we are. Thank you.

Yes. Any other questions? Jackie, I've got a question, sorry, *Charles*. Thank you very much for that. You made the point that MS, you get this progressive decline, whereas in MOGAD it wasn't such a feature. Did I understand that correctly? That's correct. Yes. I'm not a neurologist. But to what extent is that a reflection of the different age groups of the two populations?

Um, yeah. No, it's not related to age. You just in between the relapses, it's absolutely flat, which is why if you prevent the relapses, you can keep them stable. But if you had a population of MOGAD patients who were in their 50s, 60s, 70s, would they still be stable? Yeah, I haven't seen progression in any age group. We've got about 350 people of all ages from childhood. And sometimes I've seen somebody say in their 70s and they had an ADEM attack. I mean, this is my longest gap. But they had an ADEM attack when they were four, and then they've come back age 70. I'm sure that actually that was MOGAD. You can see very long gaps. I've not seen anyone with a progressive story ever. You can go back in their history. We'd be seeing people who had a history of MOGAD say ten years ago if they had relapses and they might be coming now. I've not seen it. Yeah. Thank you.

Anna Williams. Sorry. Thank you, Jackie. I'm now thinking that our EAE model that we're using to model MS with MOG, at least, is not modelling MS and effectively it's just modelling MOGAD.

Do you think that's why we're not translating therapies from MOG EAE into patients because we've got the wrong disease?
I think it might be, so I'm not an expert in animal models, and I think some of the spontaneous models. But yes, I think probably that is one reason is that we were looking in many cases at the wrong disease. Yeah. But I don't know about your specific model and I wouldn't like to give an opinion.

Jackie, how many other auto antibodies that are going to be as useful as MOG and Aquaporin-4 do you think are out there? I don't know. I would have to ask an immunologist. I think that as you probably know, it's quite difficult to discover an auto antibody until you know what the target is. So, it is quite difficult. Then we do discover antibodies that are biomarkers rather than actually pathogenic. But I do think there will be other antibodies out there. But personally, I think there'll probably be a smaller proportion. Thank you, Jackie. I think I can say on behalf of us all, that was a really fantastic lecture.

[Prof David Hunt, University of Edinburgh] I'd like to say, firstly, thank you very much to Jackie, but I know that David is also going to come up and say a few words as well. I'm going to move over here. Thank you, David. Thank Thank you.

[Prof David Weller] Thanks, Jackie. The family and I would really like to express our heartfelt gratitude for that inspiring lecture and to you, David, and the organising team for this meeting. It's a loss, losing Belinda is a loss we feel deeply every day, but it means a lot to us that she's so fondly remembered by colleagues and patients and a reminder, I guess, that her impact endures not just in memory, but in every life that she touched with, whether that was a colleague, a medical student or a patient. Neurology and the wonderful colleagues that Belinda shared her career with here in Edinburgh played a huge role in her life.

It was an environment where she could be intellectually challenged, something which she really needed, but also where she was allowed, as we've heard, to design a health service for patients who had quite complex needs. She was really embraced by so many people in this room and that's something that we'll always be grateful for.

The neurological community also embraced the family. We had these wonderful events in those early years called Neuro Bonding, an odd name, but we used to head up to these country hotels and Colin Mumford would often organise treks or cycling adventures, generally accompanied by quite a lot of food and beverages, but there was also a lot of singing in the DCN community, particularly back in those days and particularly at Christmas time. I'm not sure how much the children really enjoyed that, but Belinda and I loved it and it was really special for us.

I think this welcoming community that Belinda and I experienced here would play a major role in

us staying on in Edinburgh rather than going back to a warmer and sunnier place on the other side of the world. Belinda really loved mixing with the wider neurological community, people such as Jackie at meetings such as ECTRIMS and SANS and the ABN and of course, the MS debating meetings. She was always so enthused by these meetings and came back just buzzing, full of ideas and stories.

It's probably fair to say she invested equal enthusiasm in the social side of these meetings and sometimes took her colleagues to a level of revelry that they later regretted. But it was a wonderful clinical and academic community and one which she completely embraced. Belinda as I said, found inspiration in her colleagues here and around the UK and around the world. She really deeply valued the team that she worked with and with a particular nod to Matt and Nicola, who are long term members of that team.

It was a multidisciplinary team and I think that she loved that. It reflected her own multidisciplinary background. She was also, as you've heard, passionate about teaching and training and gave a lot of her time to mentoring others. But above all, I think she drew inspiration from her patients, often individuals who were facing challenges of a relentless illness with remarkable courage and dignity. She listened with empathy and understood their struggles and was continually moved by their resilience and the compassion that she saw in both her patients, their careers, and the people that looked after them. Um, so thank you, Jackie. That was an inspiring lecture. I guess as a humble GP, I understood a good part of it. I lost you there somewhere around the optimised MOG antibody assays, but came in again at the end. That was good. But the work that you're doing in the lives that you're changing are really inspirational. It's been great to hear. about some of that work today.

The wonderful gesture of devoting this lecture to Belinda's memory, for our family isn't just a tribute, but it's a reminder that Belinda isn't forgotten. Her work still matters and the love and respect she inspired lives on. I'd like to call on my trusty colleagues, Maddie and Tristan, who are going to present a small very Scottish gift to you.

[Maddie Weller] Hello. I think it's fitting that this inaugural Belinda Weller Distinguished Lecture is taking place so close to International Women's Day. Mum was a massive inspiration in my own medical career, showing me that it was possible to be an amazing mum, a friend, but also to be strong, intelligent, and to be outstanding in your field. It's been incredible to hear from you, Jackie today, from another amazing woman. And so, what we'd like to do is present to you a Scottish Quaich, an apology for the pronunciation! Which is a cup of friendship and thanks for your speech. Thanks very much.

[Prof David Hunt] Thank you very much indeed. It just simply falls to me not to offer you any cycling adventures, but there is definitely going to be food and drink and good humour and

bringing people together in a way that only really Belinda could. So, there's food and wine and drink outside. So, thank you all for coming.
Thank you, Jackie, and thank you to Belinda's family as well. Thank you.

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