BRAIN HEALTH: TRANSLATING SCIENTIFIC EVIDENCE INTO CLINICAL PRACTICE IN MULTIPLE SCLEROSIS

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MEETING SUMMARY

Brain volume loss (BVL) progresses more rapidly in patients with multiple sclerosis (MS) than in healthy individuals, and brain atrophy begins early in the course of the disease. The objective of this symposium was to emphasise the importance of care and preservation of the brain within treatment protocols for MS so that early and appropriate management can be initiated to preserve brain volume and function.

Prof Per Solberg Sørensen chaired the symposium and welcomed the speakers. Prof Heinz Wiendl gave a presentation on BVL in MS and described its underlying pathophysiology. Dr Andreas Lysandropoulos illustrated how information on BVL is clinically relevant and can be taken from clinical studies to assist clinical practice and decision-making. The final presentation was given by Prof Andrew Chan who highlighted the important role of brain atrophy in decision-making for early treatment and presented recent data for two treatments for MS: teriflunomide and the monoclonal antibody alemtuzumab. The symposium was concluded by a short question and answer session.

Brain Volume Loss in Multiple Sclerosis: Underlying Pathophysiology

Professor Heinz Wiendl

MS has traditionally been regarded as a white matter disease and identifying lesions using conventional magnetic resonance imaging (MRI) has become essential in the early diagnosis and management of the disease.[1] More recently, grey matter disease has emerged as an important component of MS and has been suggested to correlate better with specific disability outcomes.[1] Healthy individuals lose between 0.1% and 0.3% of brain volume per year.[2] BVL in people with MS, however, is typically 3-times this rate throughout the course of the disease.[3] The rate of grey matter volume loss increases with the stage of the disease, from 3.4-fold in relapsing-remitting MS (RRMS) to 14-fold in secondary progressive MS.[3]

The application of different technologies can be useful in identifying loss of white and grey matter. Cortical extrinsic curvature (CEC) is a novel measure of white matter loss and is a more sensitive indicator of 'pure' white matter loss than conventional MRI methods.[4] Based on CEC measures, white matter atrophy appears to occur early in MS and may occur as early as clinically isolated syndrome (CIS). An increase in CEC in patients with MS correlates significantly with loss of white matter integrity in the corpus callosum as assessed by fractional anisotropy, supporting the validity of CEC.[4] There is increasing interest in nuclear regions of the brain such as the thalamus, which are affected early in the course of MS. A recent study evaluating early thalamic atrophy in patients with CIS and RRMS demonstrated that loss of relative thalamic volume correlated significantly with disease duration.[5] Patients with RRMS and CIS with disease duration ≤24 months already had a reduced relative thalamic volume versus healthy controls. The alterations in white matter in these patients could not be explained by the distribution of white matter lesions and it was concluded that early thalamic atrophy is mainly due to silent microstructural thalamic alterations.[5]

Pathological processes that underlie BVL include demyelination, gliosis, and axon loss. Focal loss of myelin tissue, particularly within overt white matter lesions, is a contributing factor of brain atrophy.[6] Demyelination is facilitated, at least in part, by autoreactive antibodies via several well-defined mechanisms including complement activation, phagocytosis by macrophages, and recruitment of autoreactive T cells.[7,8] Remyelination is not uncommon in early lesions, although it fails in later stages of MS.[9] Other mechanisms that may contribute to demyelination include the activities of cytotoxic $CD8^+$ T lymphocytes and activated macrophages, hypoxia-like injury leading to oligodendrocyte apoptosis, and primary oligodendrocyte degeneration.[8] As an MS plaque progresses from acute to chronic, early inflammation and oedema resolve and astrocytes produce a glial scar.[10] Gliosis may confound assessments of BVL in multiple ways including maintenance of volume in the event of axonal injury[9] and contraction of astrocyte volume as the lesion matures.[11] The volume of astrocytes is reduced, which represents a physical and chemical barrier to axon regeneration.[12] Perhaps the most destructive mechanism of MS is axonal loss/neurodegeneration. Axonal loss has been demonstrated in both acute (new active) and chronic active (older reactivated) lesions in MS patients with disease duration from 2 weeks to 27 years.[13] Axonal density is reduced up to 80% in chronic plaques.[10] Axonal pathology has been demonstrated in normal-appearing white matter as well as demyelinated lesions, indicating that factors other than inflammation can contribute to neurodegeneration.[10,14] Potential mechanisms include Wallerian degeneration as well as retrograde and anterograde transneuronal degeneration.[9,14] Different mechanisms contribute to this degeneration, including cytotoxic $CD8^+$ T cells, which may directly destroy axons,[14,15] possibly via granule-mediated death.

Recent *in vivo* microscopy studies evaluating the dynamics of neuronal reaction in response to an inflammatory trigger demonstrate that acute axonal transection is an early indicator of neurodegeneration in MS.[15-17] Neuronal reactions can occur in the absence of visible demyelination in which acute neuroinflammation induces a pervasive state of reversible axonal dysfunction.[16] Ultrastructural axonal damage may occur with or without demyelination and may recover spontaneously.[17] Transition from RRMS to secondary progressive MS occurs when the central nervous system (CNS) can no longer compensate for neuronal loss, resulting in progressive disability.[15] This important information demonstrates that any type of inflammatory mechanism

could eventually lead to neuronal dysfunction. This has also been demonstrated in studies in which it was shown that chronically demyelinated axons lacking Na^+/K^+ ATPase are incapable of nerve transmission.[18] Thus, demyelination is one possibility for axonal destruction or dysfunction but it is not the only one. Chronic CNS inflammation therefore involves several different pathological mechanisms that lead to neuroaxonal damage by apoptosis and necrosis. These mechanisms include reactive oxygen and nitrogen species, hypoxia, cytokines, and glutamate, which trigger mechanisms that include oxidative stress, mitochondrial damage and dysfunction, Ca^{2+} influx, and demyelination.[19]

Other adaptive immune cells involved in inflammation in MS include $CD3^+$ T cells. Numerous studies have shown that T cells, in addition to being directly destructive, act as orchestrators for other immune cells. Antibodies contribute to demyelination via opsonisation and complement deposition, and dendritic cells serve as antigen-presenting cells to autoreactive T cells during the inflammatory phase.[7,20] Pro-inflammatory cytokines released by autoreactive T cells, such as interferon (IFN)-γ, interleukin (IL)-23, IL-17, and tumour necrosis factor alpha, further activate immune cells to ultimately contribute to demyelination and CNS damage.[7] Over the past few years, it has emerged that cells of the innate immune system are also involved in neurodegeneration. Cells that form a normal part of the CNS glial cell population, such as macrophages, can cause injury by releasing proteases and reactive oxygen species.[20] Mast cells release enzymes that can lead to demyelination and destruction of oligodendrocytes and neurons.[7] Initial activation of the adaptive immune response triggers an inflammatory response that may decrease over time; however, it may be the activation of the innate immune response that results in the sustained inflammation of MS.

To summarise, BVL in MS is a combination of inflammatory and neurodegenerative events, with pathological correlates that include demyelination, axonal loss, and gliosis. Inflammation involves both the adaptive and the innate immune system, from outside and within the CNS. These events work together to result in the focal or diffuse brain atrophy of MS.

Lost in Translation? Brain Atrophy from Clinical Studies to Clinical Practice

Doctor Andreas Lysandropoulos

Evidence has shown that BVL is correlated with, and is predictive of, disability worsening in MS.[21] Popescu et al.[21] showed that early BVL is strongly correlated to clinical outcomes 10 years later. Interestingly, in RRMS, the correlation is stronger for central (periventricular) atrophy; whereas in primary progressive MS, whole brain volume and grey matter volume are better correlated with Expanded Disability Status Scale (EDSS) and MS Severity Scale scores.[21] In a 20-year longitudinal study, Fisniku et al.[22] showed that grey matter volume loss is significantly correlated with disability measures. In a meta-analysis of 13 randomised controlled trials of disease-modifying treatment of 2-year duration, Sormani et al.[23] showed that there was a significant correlation between treatment effects on BVL and disability progression, demonstrating that the effect of a drug on disability is also related to its effect on BVL. Cognition is a central issue in MS as more than half the patients will have serious cognitive disability. Studies have shown that cognitive impairment is correlated with parenchymal volume loss (but not T1 and T2 lesions)[24] either with whole or grey matter loss.[25] Brain atrophy is related to quality of life (QoL) through physical and cognitive disability and other outcomes such as emotional well-being and fatigue, which are correlated to grey matter, white matter, and parenchymal volume.[26]

Assessment of brain volume changes is important for measuring the efficacy of a disease-modifying treatment and may reflect neuroprotective effects. Brain volume can be reliably measured using MRI-based methods.[2] Several different approaches have been developed to assess BVL including direct segmentation or indirect registration techniques.[27] Segmentation defines brain tissue based on variation in signal intensity, whereas registration defines brain tissue based on edge displacement at two time points.[27] Accuracy in the techniques assessing changes in brain volume is important because atrophy is a slow process, with corresponding small volume changes.[27] MRI acquisitions should also be performed at the same imaging site using the same equipment and conditions for accurate longitudinal follow-up.[27] The phenomenon of pseudoatrophy during the first year on treatment is also a consideration as it may be associated with anti-inflammatory

treatments and may be more apparent in white matter than grey matter.[11]

Different clinical trials cannot be directly compared due to differences in patient demographics, disease stage, mechanism of drug action, and probably MRI techniques. However, if we accept that brain volume is a reflection of neurodegeneration, we can rely on clinical trial data to indicate the effect of a disease-modifying treatment on brain volume.

Case Study

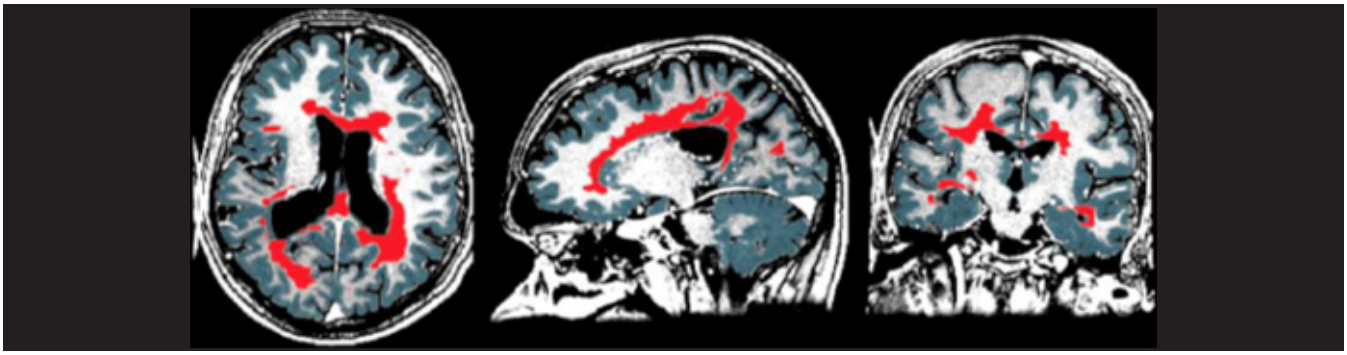
A young patient who had been on first-line disease-modifying treatment for 2 years presented a mild relapse with double vision, a new T2 gadolinium-enhancing lesion on MRI, and an EDSS of 2.0 during the relapse. The patient had recovered completely from his relapse.

As the EDSS, relapse rate, and lesion load were low, it was unclear whether or not second-line treatment should be commenced.

1. QC

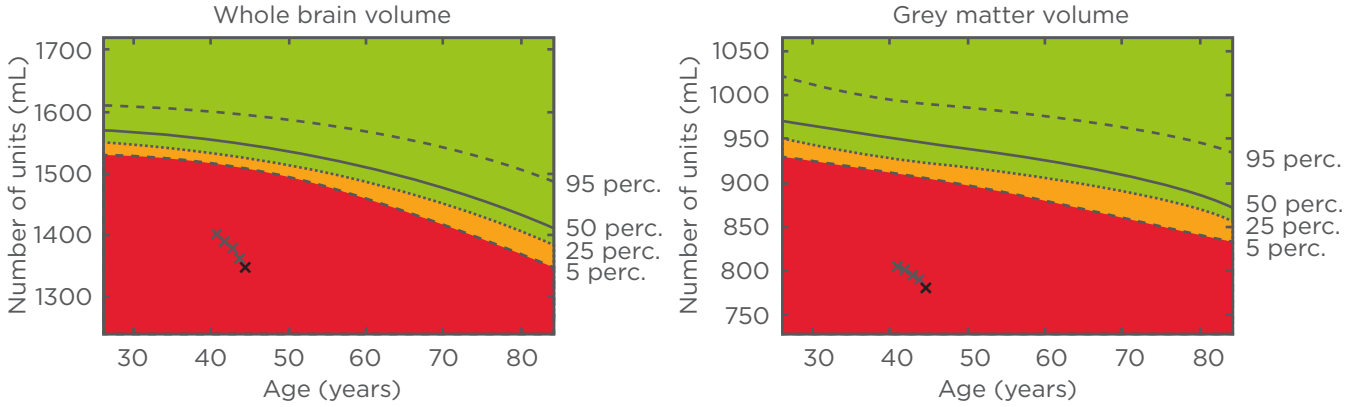
QC status	Remarks
Approved	No remarks

2. Visual results



3. Brain volumes

Brain structure	Volume (mL*) (current MRI)	Normal range (5th and 95th perc)	Normative perc	Atrophy (compared to previous MRI)
Whole brain volume	1345.8 mL*	1505-1591 mL*	<1	-0.97%
Grey matter volume	780.3 mL*	906-990 mL*	<1	-1.15%



*Displayed brain volumes are normalised for head size. The normalisation factor for this patient equals 0.87.

4. Lesion load

Type	Lesion volume (mL) (current MRI)	Lesion volume change (mL) (compared to previous MRI)
FLAIR lesions	74.45 mL	1.70 mL
Gd enhanced lesions	0.07 mL	-0.04 mL

Figure 1: Case study showing reductions in whole brain and grey matter volume in a young patient.
Visual representation of T2 lesion load is shown as red areas (visual results, upper section of figure). Volume reduction over time (age of patient) in whole brain and grey matter is indicated by crosses (brain volumes, lower section of figure).
QC: quality control; MRI: magnetic resonance imaging; Gd: gadollinium; perc: percentile; FLAIR: fluid attenuated inversion recovery.

However, measurements of brain volume (whole brain and grey matter volume) identified an ongoing important degenerative process. Measurements indicated that whole brain volume and grey matter volume were far below normal for a patient of this age (Figure 1), providing an indication for the need of immediate escalation to second-line treatment.

To summarise, measurement of BVL correlates with physical and cognitive disability as well as QoL in patients with MS, and slowing BVL is an emerging goal of therapy. Although not routinely used in clinical practice, the potential impact of disease-modifying treatment on BVL should be considered and incorporated into clinical decision-making.

The Role of Brain Atrophy in Decision-Making for Early Treatment

Professor Andrew Chan

Early treatment of MS is important to slow disease progression and improve prognosis. Several agents are now available, each demonstrating different mechanisms of action and efficacy and safety profiles. Teriflunomide and alemtuzumab, two available treatments for MS, demonstrate different efficacy and tolerability profiles which can allow treatment to be somewhat individualised according to disease risk and patient considerations.

Teriflunomide is a selective and reversible inhibitor of dihydroorotate dehydrogenase which reduces proliferation of activated T cells and B cells, while leaving resting and slowly-dividing cells relatively untouched,[28-31] allowing lymphocytes to remain available for immune surveillance.[32] Teriflunomide tablet once-daily has been investigated across the spectrum of relapsing MS, in patients with early MS and those with chronic progressive disease.[33-36] The Teriflunomide Multiple Sclerosis Oral (TEMSO) and Teriflunomide in Patients With Relapsing Multiple Sclerosis (TOWER) randomised Phase III trials evaluated the safety and efficacy of teriflunomide versus placebo in patients with relapsing MS.[35,37]

In a *post hoc* analysis of TEMSO, teriflunomide 14 mg reduced relapses by 30.6% versus placebo (p=0.0001) at 2-year follow-up.[38] Subgroup analysis of TEMSO according to baseline disease activity demonstrated significant effects with teriflunomide in reducing BVL versus placebo in patients with both high and low disease activity at baseline.[39] Similar results were observed in another *post hoc* analysis of the same trial performed according to confirmed disability progression (CDP; defined as an increase from baseline of ≥1.0 point on EDSS [or ≥0.5 points for patients with a baseline EDSS score >5.5] that persisted for at least 12 weeks). Teriflunomide slowed BVL in patients with 12-week CDP (43.9% reduction, p=0.0043) and without 12-week CDP (23% reduction, p=0.0129) versus placebo at 2 years.[40] These results demonstrate the clinical utility of teriflunomide early in treatment, before CDP is observed. Both of the Phase III trials for teriflunomide have shown consistent benefit on disability worsening.[35,37] The long-term extension of TEMSO (currently at 9-year follow-up) has shown that assessments of disability scores have remained relatively stable throughout.[41] In a pooled analysis of four placebo-controlled trials, the most common adverse events included hair thinning (13.5% for teriflunomide 14 mg versus 5.0% for placebo), diarrhoea (13.6% versus 7.5%), alanine aminotransferase increase (15.0% versus 8.9%), and nausea (10.7% versus 7.2%),[42] with no increased risk of serious infections.[43] In extensions studies with up to 13 years follow-up, no new safety signals have been identified.[42-45]

Alemtuzumab is a monoclonal antibody specific for CD52, a protein that is expressed on the surface of B and T lymphocytes and other immune cells.[46] Binding of the antibody to CD52 results in a depletion of CD52-expressing cells. However, within weeks of treatment, a distinct pattern of repopulation occurs that is believed to rebalance the immune system to a more anti-inflammatory state.[46,47]

Two Phase III trials have evaluated the safety and efficacy of alemtuzumab versus subcutaneous IFN-β1a in patients with RRMS; CARE-MS I, conducted in treatment-naïve patients[48] and CARE-MS II, conducted in patients who had relapsed after first-line treatment.[49] In both CARE-MS I and CARE-MS II, patients receiving alemtuzumab were treated at baseline with 12 mg of antibody daily for 5 consecutive days, followed by 12 mg of antibody daily for 3 consecutive days 12 months later. In CARE-MS I, alemtuzumab produced a 42% slowing in BVL versus subcutaneous IFN-β1a at 2 years (Figure 2).[50]

In CARE-MS II, alemtuzumab produced a 24% slowing in BVL versus subcutaneous IFN-β1a at 2 years.[50] Following completion of CARE-MS I or CARE-MS II, patients were offered the

opportunity to enter extension studies.[50-52] In CARE-MS I, median rate of BVL decreased progressively over 4 years and remained low in Year 5 (Year 1: -0.59%, Year 2: -0.25%, Year 3: -0.19%, Year 4: -0.15%, Year 5: -0.20%). The median rate of BVL progressively slowed over 3 years in CARE-MS II and remained low in Years 4 and 5 (Year 1: -0.48%, Year 2: -0.22%, Year 3: -0.10%, Year 4: -0.19%, Year 5: -0.07%).[50] In an evaluation of BVL in patients who were switched from subcutaneous IFN-β1a to alemtuzumab upon entering the extension studies, BVL at 2 years (prior to switching) was -0.50% and -0.33% in CARE-MS I and CARE-MS II, respectively. After switching, median BVL at years 1, 2, and 3 was -0.07%, -0.13%, and -0.09% in CARE-MS I and 0.02%, -0.05%, and -0.14% in CARE-MS II, respectively.[52] Patients continued to show improvements in pre-existing disability, with 33% and 43% of patients with 6-month confirmed disability improvement at 5 years for CARE-MS I and CARE-MS II extensions, respectively.[53,54] Importantly, 68% and 60% of patients, respectively, did not receive re-treatment with alemtuzumab after the second course at Month 12.[53,54] Significant improvements in QoL were demonstrated for alemtuzumab versus IFN-β1a at 1-year and 2-year follow-up in CARE-MS II as measured by disease-specific (Functional Assessment of Multiple Sclerosis) and general (EQ visual analogue scale) measures.[55,56]

During the alemtuzumab clinical development programme, infections were predominantly mild-to-moderate and decreased over time to an incidence of 42% at 5 years (Genzyme, data on file). Immune thrombocytopaenic purpura developed in approximately 2% of patients, most of whom had a sustained and durable response to treatment with first-line therapy for immune thrombocytopaenic purpura.[57]

To conclude, teriflunomide has significant efficacy for BVL versus placebo, shows long-term benefits with continuous treatment, and has a well-established safety profile, with up to 13 years of data. The monoclonal antibody alemtuzumab has a consistent safety profile and has shown durable efficacy of >5 years in reduction of BVL that is associated with reductions in disability worsening and improvements in QoL.

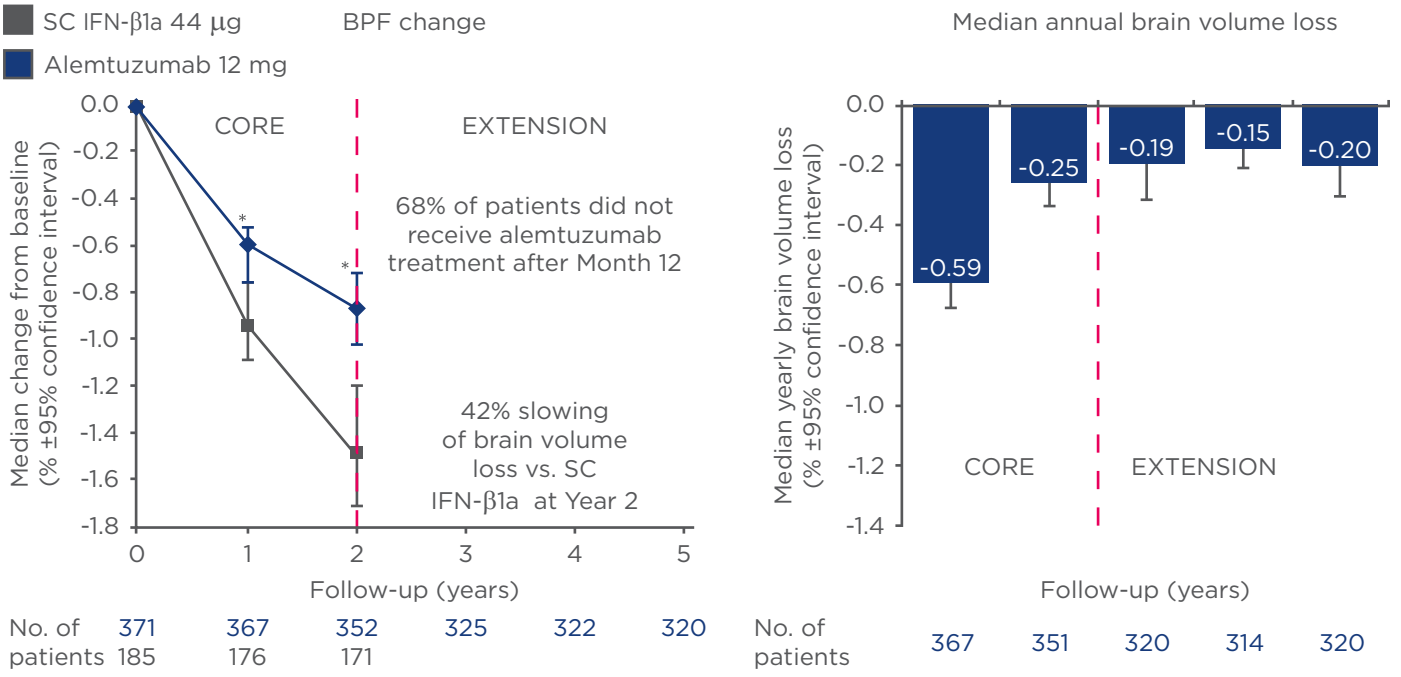


Figure 2: Slowing of brain volume loss over 5-year follow-up with alemtuzumab in treatment-naïve patients in CARE-MS I.[50]

Left: Change from baseline in BPF over time in the core study (0–2 years) for patients treated with alemtuzumab and SC IFN-β1a.

Right: Median annual change in brain volume in the core and extension studies for patients treated with alemtuzumab.

*p<0.0001 for alemtuzumab versus SC IFN-β1a.

SC: subcutaneous; IFN-β1a: interferon beta-1a; BPF: brain parenchymal fraction.

QUESTION AND ANSWER SESSION

Prof Sørensen noted that in RRMS, clear MRI parameters have been set to characterise activity and asked the panel whether MRI parameters should be defined to allow characterisation of disease worsening.

Prof Wiendl responded that there is a critical need for objective measures of disease worsening other than the 'clinical impression' that is currently used. Consensus criteria needs to be defined based on clinical studies with clear methodology that can be applied to a real-world setting.

Prof Sørensen noted the difficulties in measuring whole brain or grey matter atrophy and asked the panel if they thought alternative measurements, such as thalamic volume, would be more practical for use in clinical practice.

Dr Lysandropoulos thought that working together with radiologists and hospital directors to ensure that the same MRI machine is used under consistent conditions, together with the use of appropriate software, should allow accurate enough brain measurement.

Prof Sørensen mentioned the impressive data for alemtuzumab showing that 60–70% of patients did not require further treatment after the two courses for up to 5 years and asked whether patients could be re-treated with alemtuzumab if necessary.

Prof Chan responded that re-treatment appears to be safe and no new safety signals have been observed so far.

Prof Sørensen asked Dr Chan if it is safe to use any of the first-line treatments for MS, e.g. IFN, after treatment with alemtuzumab.

Prof Chan said that, theoretically, it would be safe, although clinical experience is limited. Most of the patients in the extension trials were re-treated with alemtuzumab; only 2–3% were re-treated with alternative medications.

A member of the audience asked the panel whether there were any data available on switching patients from rituximab to alemtuzumab.

The panel responded that there was not a lot of data but in principle, switching from rituximab to alemtuzumab would be possible. To date, only anecdotal evidence is available on the efficacy and safety of this sequence.

A member of the audience asked the panel if there was any anecdotal evidence of patients treated with alemtuzumab that did not need to be re-treated with any drug.

The panel responded that an important question for immunologists is 'what is the difference in the re-programmed immune system between patients that need another course of treatment and those that become stable without secondary autoimmunity'. There is no clear answer. Studies are underway to investigate the development of T cell receptor repertoire profiling to provide some insight.

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