Multiple Sclerosis Management – A Changing Landscape 2013

Proceedings of the Meeting: Multiple Sclerosis Management – A Changing Landscape 2013, held on 26–27 April 2013 in Vienna, Austria

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Abstract

The aims of this educational meeting, held in Vienna, Austria, were to explore the significant advances that have occurred in multiple sclerosis (MS) management over the past two decades, to highlight modern-day perspectives and challenges and to consider the impact of the new oral first-line treatments expected to enter the MS market shortly. The meeting was attended by 372 delegates with neurological interests from 30 countries and was opened by Per Soelberg Sørensen (Copenhagen, Denmark).

Keywords

Multiple sclerosis, magnetic resonance imaging, pathophysiology, role of injectable agents, oral agents, individualised therapy

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Multiple Sclerosis Management 2013

The keynote lecture was given by Fred D Lublin (New York, New York, US), who outlined present and future challenges in the treatment of multiple sclerosis (MS). His theme was: where are we with current MS treatments and at what stage should patients be treated?

There are now 10 marketed disease-modifying agents with seven different modes of action (all anti-inflammatory) for MS treatment and more have been submitted for regulatory approval.[1–4] Most of these treatments focus on clinically isolated syndrome (CIS) and relapsing remitting MS (RRMS).[5]

The biggest challenge in MS treatment is progressive disease: the majority of current treatments are approved for RRMS and are much less effective in progressive disease.[6] Consequently, many patients with secondary progressive MS (SPMS) feel abandoned. The most valid treatment strategy currently is to treat early and delay or prevent SPMS.[7] There is considerable research effort in progress to address the progressive stage of the disease, but repairing damaged or lost axons is challenging. Therefore, despite the ongoing emergence of new agents, there remain many unmet treatment needs in MS therapy.[8]

An important question in MS is which patients should be treated and when? Some studies have suggested that certain immunophenotypes and pathophenotypes predispose MS.[9,10] The change in the Macdonald criteria, including dissemination of MRI lesions in time and space, has increased diagnostic sensitivity and specificity[11] and this has helped determine which patients are at risk and need to start treatment to inhibit or prevent accumulating neurological damage.

In clinical terms, MS progresses in steps of incomplete recovery leading to gradual worsening. In pathological terms, neuronal inflammatory disease leads to degeneration. This progression is driven by exacerbations[12] and reducing their incidence through disease-modifying treatment (DMT) has advantageous long-term consequences.

To better reduce relapses and inhibit progression, some investigators have tried concomitant use of first-line DMTs in MS. The CombiRX study was an example of this approach. Sponsored by the US National Institutes of Health (NIH), the CombiRx study, a phase III, three-year-long study included 1,008 patients with RRMS and combined both glatiramer acetate (GA) treatment and interferon beta-1a (IFNβ-1a) compared with these agents given separately.[13,14] In all of the three different definitions of exacerbations used in the CombiRx trial, GA monotherapy showed a significantly greater reduction on relapse rate compared with IFNβ-1a treatment. In the efficacy head-to-head trial arm, GA monotherapy was superior to IFNβ-1a in reducing the risk of exacerbation. The combination did show advantages

in MRI metrics and, intriguingly, patients with an expanded disability status scale (EDSS) of 0 were three to five times more likely to progress than those with an EDSS >0.

A problem in MS is how to assess the treatment efficacy. Better measures are needed in clinical trials to define exacerbations and relapses, which vary between trials.[15] The ultimate goal in MS treatment is reducing disability progression, however, there is disagreement and inconsistency over disability outcomes measures (EDSS is not sensitive enough) and time to clinically definite MS (CDMS) is variable.[16] There is also no agreement over diagnostic approaches including: biomarkers, genomics, gene expression models, epigenomics, proteomics, advanced magnetic resonance imaging (MRI) metrics and clinical MRI biomarker profiles.[17–20]

The recent approval of several effective treatments in MS (including oral agents) and the imminent approval of more have increased the exciting potential of personalised medicine in MS in the near future.[17,21] With the entry of a number of first-line oral treatments for RRMS expected to enter the market, there is a need for a structured approach. The next steps in the development of such an approach are to: determine who will respond to which agent and, after starting treatment, identify responders and non-responders. It will also be necessary to create an updated MS classification paradigm (radiologically isolated syndrome [RIS], CIS, RRMS), whether there is full or stepwise recovery from relapse and the change in annualised relapse rates (ARR) over time.

There are, however, challenges for the evaluation of future treatments in MS. Disease progression is not inevitable and up to a third of patients do not worsen, which is a problem when evaluating the effectiveness of new treatments in clinical trials.[22] Other concerns include the design of the trial (head-to-head versus observational studies), choice of therapies, dosing frequencies, parameters of the disease to monitor, how to compare groups (what statistical inferences to use), identifying and controlling bias and ensuring sufficient statistical power.[23,24] In such trials, the criteria for choosing therapies and monitoring response should include MRI lesion load, disease activity and increasing use of biomarkers e.g. immune factors such as interleukin (IL)-17, IL-21 and genetic/genomic markers.

With an increasing choice of effective drugs becoming available and treatments starting earlier, the 'disease-free' concept in MS in which patients have no relapses, progression or gadolinium (Gd)-enhancing lesions, is now becoming a usable measure in assessing therapies.[25] Future studies may increasingly measure this as a pre-planned endpoint.

Overall, MS is, to some extent, treatable. The therapies given in MS have manifold objectives in aiming to: reduce relapse rates, slow disability progressions, modify the disease, treat acute exacerbations, provide enhanced recovery and function, treat symptoms, provide neuroprotection, enable repair and improve quality of life. The current DMTs do not achieve all these goals but they do alleviate symptoms or enhance function and delay progression. Some therapies are also becoming available that enhance repair. The prognosis for the newly diagnosed patient with MS therefore has substantially improved in recent years and the release of new treatments will make further improvements possible.

Twenty Years of Progress in Multiple Sclerosis

Second-line Options for Multiple Sclerosis Following First-line Treatment Failure

Bernd C Kieseier (Dusseldorf, Germany) outlined the lack of good evidence and guidelines in circulation considering second-line therapies after first-line treatment failure in MS and stressed the need to critically reassess the practice of monitoring disease progression and activity in MS patients.

When first-line treatment is apparently ineffective, it is important to determine whether the failure is transient or permanent. To assess this, it is necessary to have a robust definition of failure (such as increase of 1 point on EDSS scale): currently not available. In addition, there is no consensus to guide treatment of patients with first-line treatment failure.[26–29]

There is also a general lack of class 1 evidence supporting the use of alternatives, such as fingolimod, mitoxantrone and natalizumab. It is not possible to decide whether these are more effective than 'platform therapy' (IFNβ or GA). The pivotal studies for the assessment of fingolimod, mitoxantrone and natalizumab in MS (FREEDOMS, MIMS and AFFIRM studies) used patients with highly active disease, not those who had experienced treatment failure[30–32] and, as a result, it is not possible to determine how well these treatments function when switching to second-line therapy.

As a result of cost constraints, current treatment algorithms in MS are driven by medical authorities, not by patients, and this restricts treatments that can be offered, especially when a switch is needed to more-effective treatment. In second-line therapy it would be valuable to identify which patients are potential responders to target treatment and avoid giving inappropriate medications.

Second-line therapy has shown superior efficacy over first line. An example is the TRANSFORMS study (1,292 patients) with RRMS who were treated with 1.25 mg or 0.5 mg fingolimod/day or 30 µg IFNβ-1a intramuscular/week.[33] There was a significant reduction in ARR for both fingolimod doses ($p>0.001$) and improvements in MRI findings. In an extension study, switching patients previously treated with IFNβ-1a to fingolimod produced significant efficacy improvements. There are, however, safety concerns with second-line drugs. Both binding and neutralising antibodies (NAbs) have been reported,[34] which can reduce long-term efficacy. Serious adverse events (SAEs), particularly progressive multifocal leukoencephalopathy (PML), are well known with natalizumab and to be anticipated.[35] The risk of John Cunningham (JC) virus infection with natalizumab can be stratified since the virus is present in 50–60 % of population.[36] Adverse events (AEs) associated with fingolimod (cardiac effects, infection and macular oedema[37]) and with mitoxantrone (amenorrhoea, nausea and vomiting, alopecia and urinary tract infections[38]) are difficult to predict and long-term safety data is limited. Some potential markers for fingolimod efficacy have been proposed, in particular, L-selectin (CD62L) (Schwab et al. in press), but there is a lack of surrogate markers in MS and a lack of prognostic factors. There is, therefore, an urgent clinical need to further investigate escalating therapy in MS. Switching to alternative medications may reduce disease activity but patient-specific factors and the risk–benefit profile of the new drug must be considered. Neurologists have traditionally been slow to switch treatments in MS patients, but this is improving.

Benefit–Risk of Injectable Multiple Sclerosis Therapies

The injectable therapies in MS have been available for 20 years and much experience on their efficacy and safety has been gained during that time. Franz Fazekas (Graz, Austria) provided his impressions and thoughts on these treatments, noting that their efficacy ranges from modest to good when started early. Overall, ARR from a systematic review of multiple clinical trials using IFNβ-1a intramuscular or subcutaneous, IFNβ-1b subcutaneous and GA range from 1.43–1.93 versus 2.32 for placebo.[39] Similar reductions are seen in assessments of disability.

Axonal loss is a major pathological process that is responsible for irreversible neurological disability in patients with MS[40] – surrogate markers are needed to monitor this loss and early therapy should be initiated before it has become extensive. Several large studies have emphasised the importance of the early commencement of various treatments. These include the CHAMPS study for IFNβ-1a intramuscular, the long-running BENEFIT study for IFNβ-1a[41] and the PreCISE trial for GA.[42]

Injectable IFNβ-1a therapies are associated with flu-like symptoms in 50 % of patients, skin reactions in 26 % and administration site reactions in 10 %,[43] but these tend to diminish with time and generally, early treatment does not compromise well-being.[44] Injectable IFNβ-1a treatments can also result in Nabs that reduce efficacy in some cases. Screening for these should be integrated with routine clinical and imaging indicators to guide treatment decisions.

The long-term use of injectable therapy has proved effective and safe.[41,45] The optimum duration of injectable therapy, however, is unclear. It has demonstrated effectiveness over many years but after 10 years or more the therapy should be stopped if the patient requests it. In many cases, the efficacy range of injectable therapy is too limited and treatment escalation to a more effective medication is necessary. When side effects occur, treatments should either be stopped or de-escalated.[46,47]

Various head-to-head studies have compared the relative efficacies of injectable treatments. A comparison of IFNβ-1a intramuscular 30 µg versus IFNβ-1a subcutaneous 44 µg in the EVIDENCE trial showed fewer relapses with IFNβ-1a subcutaneous.[48] The INCOMIN trial compared IFNβ1-a intramuscular 30 µg with IFNβ-1a subcutaneous 8 MIU and showed similar efficacy in both.[49] A comparison of IFNβ-1b intramuscular 30 µg versus 60 µg showed that there was no efficacy difference between doses of this weekly intramuscular therapy.[50] More recently, the CombiRx study (discussed above) showed that a combination of both IFNβ-1a intramuscular 30 µg and GA 20 mg showed no clinical benefit but that GA alone was superior to IFNβ alone in reducing exacerbation risk.[13] In addition, the REGARD trial, a head-to-head clinical trial of GA mg and IFNβ-1a 44 µg found no significant difference in relapse rates in response to these treatments (hazard ratio 0.943; p=0.643 for the difference in time-to-first relapse).[51]

Injectable MS therapies are a valuable option in RRMS. Their long-term use is safe despite some inconveniences and associated AEs. It is likely that these therapies will remain in use for a long time; neurologists understand how they work and how to use them. New oral and other agents may eventually replace the current injectables but safety profiles must be considered first.

Understanding and Communicating Risks and Benefits in Chronic Diseases

Angela Fagerlin (Ann Arbor, Michigan, US) delivered the guest lecture that explored problems in communicating risks and benefits of treatments to patients with MS. She stressed that in terms of patient communication it is not what you say but the way you say it. In MS and many other diseases it is important that the patient is given all the information and that decision-making is shared as preference-sensitive decision-making brings significant health benefits.[52] When discussing treatments with patients, it is important to consider literacy and numeracy.

Graphical formats are useful in changing patient perception but the appropriate type of graph has to be selected; creating educational materials (e.g. decision aids) or using decision-coaching methods can improve patient decision-making. Overall, physicians should avoid giving too much information to patients at any one time and follow the principle that 'less is more'.

Emerging Insights into Disease Pathophysiology from Studies of Primary Progressive, Secondary Progressive and Progressive Relapsing Multiple Sclerosis

The state of knowledge around the more progressive forms of MS was considered by Hans Lassmann (Vienna, Austria), who reminded the audience that there are two established views of MS pathology: the plaque-centred view,[53] which is over 100 years old, and the immunological view,[54] which is based on encephalomyelitis models. MS is an inflammatory disease but it is different from that seen in the autoimmune encephalitis models;[55] in progressive disease patient response differs to that during relapsing disease.

The pathological features of MS change over the course of the disease. In the early stages there are predominantly focal lesions in the white matter but in progressive stages there is more cortical and diffuse white matter injury.[56] Inflammatory processes are more pronounced in acute and relapsing stages and in the progressive stage. However, it is not clear why these not seen on MRI and why treatments are less effective in progressive disease. In progressive forms the inflammation is increasingly trapped within the central nervous system and drugs have to pass the blood–brain barrier (BBB) and are less effective.

Insights and Challenges for Modern Multiple Sclerosis Management

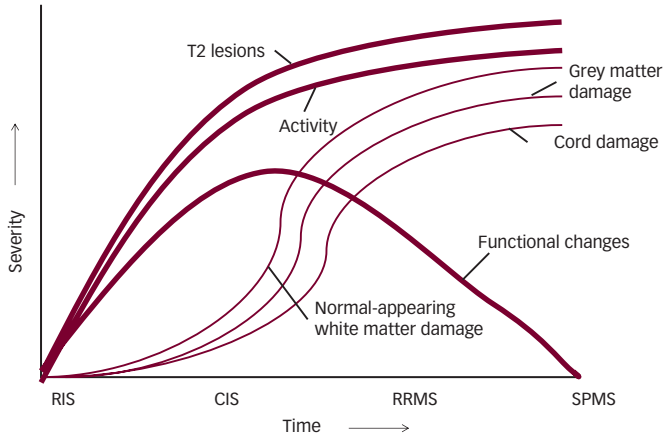
Assessing Disease Progression – Physician and Patient Perspectives

Alan Thompson (London, UK) described the current focus on progressive disease as "very key". Of the MS patient population, 55–60 % have progressive disease[57] and feel neglected; they sense that as most drug treatments are for RRMS and not for progressive disease. In progressive MS, 44 % of patients want disease stabilisation; 18 % want recovery.

Progressive MS presents several challenges. First, there is no agreed definition: in clinical terms it is accumulation of disability; in MRI terms it is increased number of lesions; and in pathological terms it is abundant axonal damage and atrophy. It can be assessed from patient and physician perspectives, both of which can be measured scientifically using Short Form (SF)-36[58] and other scales. Measuring disease is another factor: measures range from the medical model to the psychosocial model (the US Food and Drug Administration [FDA] recommends that patient-related outcomes should be increasingly used in clinical trials). There is a need to identify the concept and the framework of what is being measured, but a stronger underpinning of outcomes in progressive MS is required. Measuring the impact and influence of interactions is problematic: measures need to be robust and responsive (many current measures are not). Patient-reported outcomes need to be valid and should be qualitative and quantitative, such as the Fatigue Impact Scale.[59] Therefore, a clearer understanding of which variables are progressing and responder analyses are needed to properly assess progression.

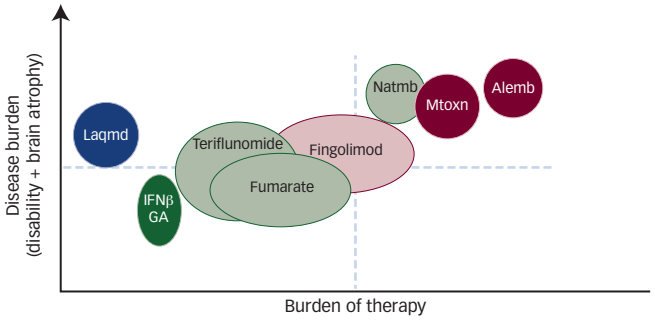
The MS Outcomes Assessment Consortium (MSOAC) is developing new clinical outcome measures of indicating disability in MS, using seven clinical trial datasets. This includes the Critical Path Institute ('C-Path') who operate under the auspices of the FDA.[60] The Progressive MS

Figure 1: Timescale of Magnetic Resonance Imaging-detected Pathological Processes in Multiple Sclerosis



CIS = clinically isolated syndrome; RIS = radiologically isolated syndrome; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Figure 2: Therapeutic Options in Multiple Sclerosis – Disease Activity versus Treatment Burden



Alemb = alemtuzumab; GA = glatiramer acetate; IFNβ = interferon beta; Laqmd = laquinimod; Mtoxn = mitoxantrone; Natmb = natalizumab.

Table 1: The Magnitude of Activity of Four Oral Multiple Sclerosis Treatments at Central Nervous System and Peripheral Sites

Agent	Activity	
	Central Nervous System	Peripheral
Fingolimod	Low	High
Teriflunomide	–	High
Laquinimod	High	Low
BG-12	Low	High

Table 2: Comparative Effects of Fingolimod and Interferon IFNβ-1a on Magnetic Resonance Imaging Parameters in the FREEDOMS and REFORMS Studies

Parameter	Study and Treatment	
	FREEDOMS Fingolimod	REFORMS IFNβ-1a
T2 lesion count	–74 %	–35 %
Gd-enhancing lesions	–82 %	–55 %
Brain volume	–38 %	–40 %

Gd = gadolinium; IFNβ = interferon beta.

Collaborative aims to expedite treatments for progressive MS and has identified five roadblocks to treatment.

Advanced Magnetic Resonance Imaging Techniques

Recent advances in MRI techniques and their implications on understanding the pathology of MS were discussed by Massimo Filippi (Milan, Italy). Over the course of MS the pathological profile changes (see *Figure 1*).[61–63] In progression, there is an increased heterogeneity in white matter lesions and more centrifugal and centripetal lesions.[64,65] In addition, cortical lesions[66,67] are strongly predictive of disease status and tend to be more apparent later in the disease course. Diffuse grey matter damage has been shown to correlate with EDSS increase (69 %) and cognitive deterioration (97 %).[68,69]

Multiparametric MRI approaches have shown that the brain can compensate for damage in MS using cognitive reserves;[70–72] patients with higher brain or cognitive reserves fare better. Functional MRI approaches have revealed spinal cord changes in MS that are different in PPMS compared with SPMS;[73] they have also revealed cortical reorganisation[74] and general disorganisation that is related to cognition.[75]

MS involves a complex balance between tissue damage, repair and cortical reorganisation accompanied by increasing structural destruction in the brain and spinal cord. Newer MRI techniques have enabled the specific detection of different pathologies in MS and these show better correlation with disease course than conventional MRI.

The Advent of Oral Multiple Sclerosis Agents

Mechanism of Action of Oral Agents for Multiple Sclerosis

Wolfgang Brück (Gottingen, Germany) assessed the recently introduced and emerging oral agents for MS that are significantly changing the treatment landscape. Most oral drugs are small molecules that can cross the BBB into the CNS. Drugs that are effective once they enter CNS, however, are currently lacking. The first approved oral agent in MS, fingolimod, is a modulator of sphingosine-1 phosphate (S1P) receptors that are expressed at various sites in the CNS (including neurons and glia).[76,77] This action prevents lymphocytes from exiting lymph nodes and thus inhibits inflammatory processes. Fingolimod also suppresses peripheral lymphocyte activity. The cuprizone experimental model has shown that S1P receptors are involved in controlling response to injury and that fingolimod may contribute to this.[78]

Another approved oral agent for use in RRMS, teriflunomide, is the active metabolite of the prodrug leflunomide that inhibits nucleotide synthesis by blocking dihydroorotate dehydrogenase. It is not a selective agent and affects all rapidly proliferating cells. Teriflunomide is believed to have the potential advantage of not increasing the risk of infection (as with other MS agents) due to its limited effects on the immune system.[79] BG-12 dimethyl fumarate was also recently approved for use in RRMS, it is believed to cause glutathione depletion leading to induction of the anti-inflammatory stress protein HO-1 and increased secretion of nuclear factor (Nrf2) followed by an antioxidant response. These effects induce type II dendritic cells and anti-proliferative effects.[80,81] Recent data suggest that BG-12 also acts as an antioxidant and improves mitochondrial function in diseased brain tissue.[82]

Laquinimod, quinolone 3-carboxamide, is in late-stage development and is believed to act against MS by inhibiting both Th1 and Th17 responses[83] and switching a pro-inflammatory to an anti-inflammatory response. It also prevents T-cells from entering the CNS. Laquinimod affects antigen presentation, decreases IL-17 production but increases

levels of protective proteins in the brain. This drug reduces activation of astrogliosis and inhibits *NFKB* gene transcription resulting in reduced demyelination and axonal damage. Laquinimod has a clear effect on both peripheral and CNS immune cells that is dose-dependent.

The magnitude of the effect of these four oral agents in the CNS and peripherally varies, as shown in *Table 1*. Dr Brück raised the intriguing possibility that these new oral drugs increase the possibility of polytherapy in MS. A medication that has a peripheral effect may be combined with one that has a neuroprotective effect in the CNS to create a combination that has complementary properties and possibly greater efficacy.

Recent Clinical Investigations with New Oral Agents for Multiple Sclerosis

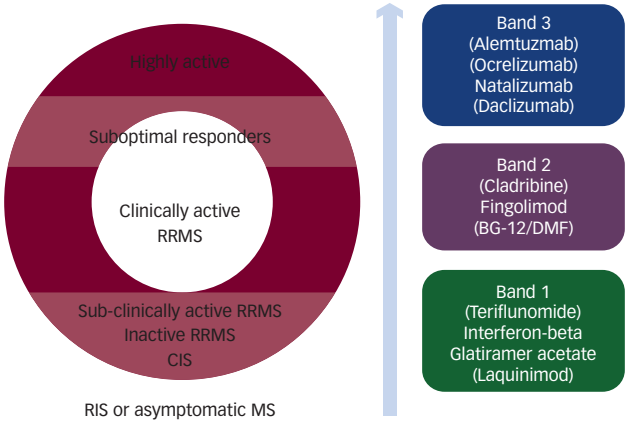
The clinical trial data supporting fingolimod, BG-12, teriflunomide and laquinimod were outlined by Giancarlo Comi (Milan, Italy). Fingolimod has shown notable efficacy advantages in recent clinical trials. In the FREEDOMS trial, fingolimod (0.5 mg versus 1.25 mg versus placebo in 1,272 patients with RRMS) significantly reduced the ARR versus placebo (p<0.001) and significantly reduced the risk of disability progression (p=0.02) over the 24-month period.[84] Over 2 years of treatment, fingolimod significantly reduced the overall rate of brain atrophy by 36 % compared with placebo (–0.84 % versus –1.31 %).[85,86] In this study, fingolimod also showed greater reductions in T2 lesion numbers and Gd-enhancing lesions but similar reductions in brain volume compared with IFNβ-1a as previously used in the REFORMS trial (see *Table 2*). In the FREEDOMS II trial (fingolimod 0.5 mg and 1.25 mg versus placebo in 1,083 patients with RRMS), fingolimod reduced long-term ARR by approximately 50 % compared with placebo but had little effect on disability.[87] AEs associated with fingolimod include: bradycardia, macular oedema, elevated blood pressure (BP), liver enzyme increase, risks to pregnancy and infection (should vaccinate against varicella zoster virus [VZV]).

BG-12 has also shown impressive efficacy performance in pivotal clinical trials. The DEFINE study showed that the ARR was reduced by approximately 50 % with BG-12 versus placebo and produced a large reduction in MRI activity.[88] The CONFIRM study showed ARR reductions of 44 % and 50.5 % for BID and TID for BG-12 but 28.6 % for the comparator, GA. It also showed improved times to disability progression (21 %, 24 % and 7 %) and new or enlarging T2 lesions (71 %, 73 % and 54 %).[89] Common AEs with BG-12 include flushing, diarrhoea, nausea, upper respiratory tract infection (URTI), abdominal pain and proteinuria. In addition a few cases of PML have also been reported.

Teriflunomide has been evaluated in various clinical trials (TEMSO, TOWER, TENERE, TOPIC, TERACLES). The TEMSO study showed that teriflunomide 7 mg or 14 mg/day produced 31.2 % and 31.5 % ARR relative risk reductions versus placebo (p<0.001 for both).[90] This study also showed that teriflunomide significantly reduced disability progression (at the higher dose), and MRI evidence of disease activity compared with placebo. In the TOWER study there were 36.3 % (p<0.0001) and 22.3 % (p=0.02) reductions in ARR for the 14 mg and 7 mg/day doses of teriflunomide, respectively.[91] AEs included: diarrhoea, nausea, hair thinning, elevated liver enzymes and serious infections. Teriflunomide should not be used in pregnancy.[90–92] Using the higher dose in the TENERE study (teriflunomide 14 mg and 7 mg versus IFNβ-1a subcutaneous 44 µg) has shown no effect on disability.[93]

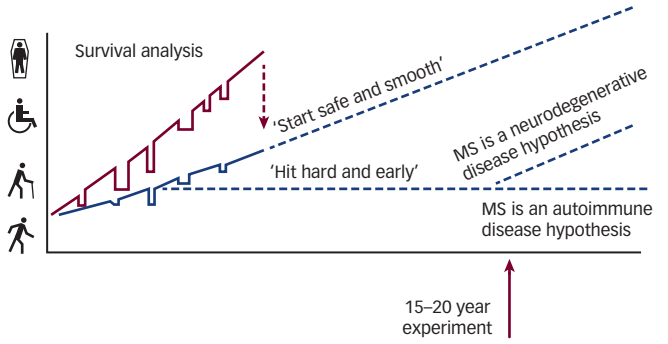
Professor Comi described laquinimod as having an unusual mode of action with manifold pharmacodynamic activities in MS and has been evaluated in a series of clinical trials (ALLEGRO, BRAVO and CONCERTO). Pooled analyses of ARR from ALLEGRO and BRAVO showed that laquinimod reduced the relapse rate by 21.4 % (p=0.0005).[94] These analyses also showed that the risk of confirmed disability progression sustained for 3 months was significantly reduced with laquinimod compared with placebo, 34.2 % (p=0.0017) and was 46 % in 6 months (p<0.0001). Such reductions have only been previously seen with alemtuzumab.[94] MRI findings in these trials showed a 30 % reduction in Gd-enhancing lesions and 30 % reduction in brain volume loss for laquinimod versus placebo. The data suggest that laquinimod

Figure 3: UK Payers or NHS – The Multiple Sclerosis Treatment Doughnut



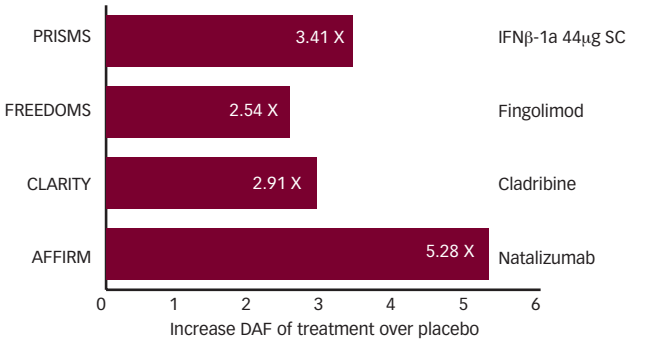
CIS = clinically isolated syndrome; DMF = dimethyl fumarate; RIS = radiologically isolated syndrome; RRMS = relapsing remitting multiple sclerosis.

Figure 4: What is your Treatment Philosophy? Maintenance Escalation versus Induction



MS = multiple sclerosis.

Figure 5: Increase in Disease Activity-free Patients with Active Treatment Compared with Placebo



DAF = disease-activity-free; IFNβ = interferon beta; SC = subcutaneous.

Table 3: Aspects of Multiple Sclerosis and Associated Treatments

Subject	Presenter	Aspects of Multiple Sclerosis and Associated Treatments
Symptomatic Treatment		
Options for the treatment of spasticity in MS	Mauro Zaffaroni Gallarate, Italy	In MS, spasticity is common and disabling with peculiar pathophysiological mechanisms More accurate methods are needed to measure spasticity and to describe different patterns in MS Spasticity in MS has specific clinical implications with marked negative impact on well-being and quality of life Established and newer pharmacological and other strategies are available to treat spasticity in MS at different stages
Management of tremor in MS	Julian Benito-León, Madrid, Spain	Tremor is one of the most prevalent and disabling features of MS The predominant type in MS is large amplitude, postural and kinetic tremor affecting the arms. The head, neck and vocal cords can also be involved The link between MS and tremor is poorly understood but clinical and experimental studies show it involves the cerebellum Current medication is often unsuccessful in treating tremor – surgical treatment can be satisfactory Further work is required but robotic exoskeleton and neurostimulation may be valuable in future treatment
Sleep disorders and fatigue in MS	Lauren B Strober Newark, New Jersey, US	In MS sleep disorders are prevalent with particular characteristics and aetiologies Sleep disorders can have a significant effect on other MS symptoms (e.g. fatigue, cognition) Fatigue in MS is distinct from sleep and sleepiness – there are many hurdles in assessment Practitioners should better assess sleep problems and fatigue in clinical practice on a routine basis
Management of Special Populations		
Treating MS during pregnancy	Maria Houtchens, Boston, Massachusetts, US	MS affects women in unique ways over the length of the reproductive and life cycles Pregnancy does not negatively impact outcomes in women with MS It is important to ensure disease stability for at least one year prior to attempting conception DMTs for MS have risks for pregnancy and lactation that need to be understood by neurologists Exclusive breastfeeding is not disadvantageous and may be beneficial in post-partum period In pregnant women with MS stopping treatment for 9 months or longer is undesirable for disease control The injectable therapies (IFNβ and particularly GA) have been shown to have few safety concerns for the pregnant women or on foetal development whereas the oral therapies (e.g. teriflunomide) have serious safety concerns and are contraindicated in pregnancy. The use of GA and IFNβ may therefore continue to grow in this indication and in other vulnerable groups of patients with MS
Management of MS in paediatric patients	Marc Tardieu, Paris, France	MS in children is not identical to MS in adults (particularly in under-12-year-old children) New definitions of MS and related diseases in children have been published The International Paediatric MS Study Group recommends that all children with MS should receive IFNβ or GA but are no formal trial or pharmacokinetic data to support this Nearly 40 % of paediatric patients with MS discontinue treatment due to intolerance, toxicity, persistent relapses or non-adherence
Treatment Concerns		
Haematopoietic stem cell therapy for MS	Gianluigi Mancardi, Genoa, Italy	Clinical outcomes and toxicity of AHSCT are diverse Intense immunosuppression followed by AHSCT can produce 1. sustained suppression of MS progression in aggressive disease unresponsive to other therapies and 2. sustained clinical improvement particularly in RRMS A phase II randomised trial showed AHSCT was 80 % more effective than mitoxantrone in terms of MRI lesions but failed to stop demyelination and was similar to mitoxantrone in terms of disability progression – a larger clinical trial of AHSCT is planned for aggressive disease
Clinical experience with new oral agents	Giancarlo Comi, Milan, Italy	The new oral agents for MS treatment, BG-12, fingolimod, laquinimod and teriflunomide have various mechanisms of action These agents have shown similar or better efficacy to injectable therapies but have been associated with some serious adverse events and these need to be evaluated in clinical practice The oral agents increase the prospects for individualised therapy in MS The improved efficacy and low burden particularly of laquinimod relative to the established injectable therapies make the new drugs attractive options for use in MS Laquinimod inhibits Th1 and Th17 responses and has multiple other actions which give it considerable potential in MS treatment The oral agents will also increase the options for combinations of MS therapies consisting of complementary drugs that act in the CNS and the periphery The doses and safety of combination therapies in MS will need evaluation but they may increase efficacy and improve outcomes
Management of optic neuritis attacks	Raj Kapoor, London, UK	Optic neuritis has a relatively well-defined clinical presentation and natural history and shares a similar pathology with MS and this has therapeutic implications Corticosteroids continue to have a role in the management of optic neuritis attacks, despite a relatively weak evidence base of efficacy Treatments are emerging for neuroprotection and repair after attacks of optic neuritis

Table 3 (cont.): Aspects of Multiple Sclerosis and Associated Treatments

Subject	Presenter	Aspects of Multiple Sclerosis and Associated Treatments
Pathology		
Pathology-imaging correlations in MS	Hans Lassmann, Vienna, Austria	White matter lesions are accurately visualised by MRI but this has limited power to detect lesions in the grey matter or diffuse brain damage Contrast enhancement reflects damage to the blood–brain barrier when new waves of inflammatory cells enter the CNS. This technique is non-sensitive and does show mild disturbances of cerebrovascular permeability, which are also present in inactive lesions and normal-appearing white matter Absence of contrast enhancement does not equal absence of inflammation Ultra-high-field MRI offers new possibilities to identify previously unrecognised pathologies in the MS brain New MRI and magnetic resonance spectroscopy techniques provide additional insights into the pathophysiology of brain lesions in MS patients
Cortical demyelination and correlation with cognitive decline in MS	Michael Khalil, Graz, Austria	Cognitive deficits are frequent in MS and are already present in patients with clinically isolated syndrome Cognitive dysfunction in MS often shows subtle domain-specific deficits rather than global cognitive decline Cortical pathology is significantly associated with the extent of cognitive impairment Conventional MRI techniques are not sufficiently sensitive to cortical pathology Non-conventional advanced MRI techniques including high-field-strength MRI, provide significant information on the correlations of cognitive impairment with focal and widespread cortical pathology in MS

AHSCT = autologous haematopoietic stem cell transplantation; CNS = central nervous system; DMT = disease-modifying treatment; GA = glatiramer acetate; IFNβ = interferon beta; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; Th = T helper cell.

offers unique advantages in MS, with a favourable safety profile (only elevations in liver enzymes reported as AEs), and good efficacy in terms of brain atrophy and disability progression (see *Figure 2*). Overall, the new oral agents in MS have shown encouraging efficacy in clinical trials, but there remains a need for a structured approach to determine their use in the in regular clinical setting.

Prospects for Individualised Therapy for Multiple Sclerosis

The introduction of several new oral agents and the impending introduction of several more have increased the choice of MS therapies available to neurologists. Patients respond differently to MS therapies and the drugs are suited to different disease phases of the disease and/or patient status. Gavin Giovannoni (London, UK) wondered whether it is time to consider individualised therapy in MS. A major aspect of this is who should decide whether to treat early and actively? To answer this, a series of questions were put to patients with MS at St Bartholomews Hospital, London, UK to assess their attitudes to treatment:

- Would you choose aggressive first-line treatment over safer first-line treatments? yes: 63 %, maybe: 25 %, no: 11 %.
- Who should make the decision on accessibility of treatments to early-phase patients? Regulators: 5 %, payers (governments, insurance companies): 0 %, neurologists: 44 %, patients: 41 %, other: 11 %.
- What chance of a serious life-threatening AE would you accept as a complication of early aggressive treatment? Risk of 0.01 %: 20 %; risk of 0.1 %: 33 %; risk of 1 %: 20 %.

It is now well-recognised that delaying active treatment can hasten disease progression compared with early intervention, but such a strategy is not always provided in many territories. The UK NHS 'doughnut' model of treatment shows that more aggressive treatments are reserved for more active disease and this is decided on an institutional or health authority basis (see *Figure 3*). Dr Giovannoni suggested that all treatments should be available from the start and the patients, guided by neurologists, should decide which was appropriate for their individual needs. Experience from recent alemtuzumab trials shows that this therapy is more effective when started early[95,96] (see *Figure 4*) and that alemtuzumab decreases relapse rates and decreases disability progression to a greater extent than

Table 4: Comparative Efficacy, Safety and Tolerability of Injectable and Oral Drugs

Injectable and Oral Drugs in the Treatment of Multiple Sclerosis				
	Agent	Efficacy	Safety	Tolerability
Injectables	IFNβ-1b subcutaneous	+	++	+
	IFNβ-1a subcutaneous	+	++	+
	IFNβ-1a intramuscular	+	++	+
	GA	+	++	+
Orals	Fingolimod	++	+(+)	++
	Teriflunomide	+	+(+)	++
	BG-12	++	++	++
	Laquinimod	+(+)	+(+)	++

GA = glatiramer acetate; IFNβ = interferon beta.

IFNβ-1a. This raises the question: is it fair or ethical to make MS patients wait 20 years for the outcome of an experiment?

Studies have shown that relapses,[97,98] MRI activity,[99,100] and disease progression[101,102] are all significant and are predictive of greater disease activity. Treatment with DMTs decreases disease activity and improves outcomes. With greater treatment success, an acceptable definition of a cure in MS is needed. The terms 'no evidence of detectable disease' (NEDD), 'treat-to-target' (T2T) and 'disease-activity-free' (DAF) are entering the lexicon. With improved diagnostic methods and an increasing selection of drug therapies, Dr Giovannoni left the audience with the question: 'have we finally entered the era of individualised therapy for MS?'

Workshop Sessions

A series of 10 workshops tackled various aspects of MS and treatment. These were divided into the themes of symptomatic treatment, management of special populations, treatment concerns and pathology. An overview of the sessions and main points is given in *Table 3*.

Debate – With the Introduction of Oral Agents, Injectables Will Have No Place in the Modern Management of Multiple Sclerosis

The meeting finished with a timely debate about whether new oral treatments would oust the pre-existing injectable therapies in MS management. Óscar Fernandez (Malaga, Spain) argued in favour.

Argument in Favour

Over the past 20 years DMTs have had variable success in MS. However, the new orals have improved efficacy and safety and their introduction has started a new era in MS management. The timeline of MS treatments shows that the 1990s saw the introduction of IFNβ-1b, IFNβ-1a, the 2000s saw the introduction of GA, mitoxantrone and natalizumab and the 2010s are seeing the introduction of oral agents: fingolimod, teriflunomide, BG-12 and laquinimod. Other new treatments are likely to follow.

The efficacy of current first-line injectables is about 30 %.[14,84] The efficacy, safety and tolerability of the oral agents compare well with those of the injectables or improve on it (see *Table 4*). Safety concerns of injectables include injection site reactions, flu-like symptoms (IFNβ), subcutaneous lipoatrophy, myalgia, depression and chest tightness (GA). In clinical studies, up to 40 % of patients discontinue within 2 years and 32 % of patients will have ≥1 injection-related reaction.[103] In addition, one-third of the reasons for missing doses was the injection itself and only 4 % had a medication possession ratio >85 % (time a patient has access to medication), in a range of 72–76 %.[104]

Despite the availability of automatic injection devices that make administration easier and less traumatic, among patients who had received 5 years of treatment, 100 % said they would prefer an oral treatment. Oral therapies increase the possibility of personalised treatment and treatment combinations. Dr Fernandez conceded that despite the obvious advantages of oral therapy, injectable treatments were likely to remain in use for some time.

Argument Against

Per Soelberg Sørensen (Copenhagen, Denmark) countered these arguments and suggested that there was life left in injectable therapies in MS for the foreseeable future. There are currently two types of injectables (IFNβ and GA) and there will soon be four types of oral agents. Some patients have an excellent response to injectable therapies and there is consequently no need to transfer them to less well-known treatments. With the existing injectable treatments, 30 % show an excellent response, 40 % have a moderate response and only 30 % have an unsatisfactory response. Future treatment approaches may differ between patients who are established on a therapy and those who have not been treated; switching them may not be justified if they are well controlled.

The advantage of injectable therapies in MS was demonstrated by the increases in disease activity-free patients being better for IFNβ-1a and natalizumab in the PRISMS and AFFIRM studies than for fingolimod and cladribine in the FREEDOMS and CLARITY studies (see *Figure 5*).[100,105,106] IFNβ has been used in MS for over 20 years and there are millions of years of patient observation and experience supporting its use. Flu-like symptoms and injection site reactions decrease with time and few are severe. There is only a modest increase in liver enzymes and some NAbs. Furthermore, the efficacy of IFNβs can be increased with add-on therapies and PEGylation.

GA has been used for 22 years and AEs are rare: it is not associated with NAbs, or drug–drug interactions and there are no long-term safety signals.[107] Safety concerns associated with some oral agents, however, need to be considered when selecting an appropriate therapy.[108] Fingolimod has a risk of cardiovascular events, macular oedema, potential teratogenicity, influenza and herpes infections, gastroenteritis and bronchitis.[37] With BG-12 a few cases of PML have been reported, and it is associated with flushing and gastrointestinal events.[89,109] Teriflunomide increases the incidence of diarrhoea, nausea, hair thinning and raises levels of alanine transaminase (ALT)[90] and laquinimod is associated with ALT elevations.[110]

Many patients will likely remain on injectables, but, in future, new patients may be given oral agents as first-line therapy. There is a general lack of experience with oral agents so some neurologists may be unwilling to use them immediately. Injectables, therefore, will not disappear but will become part of the mix. Neurologists, however, must take account of their patients' opinions when choosing MS therapies.

The audience was asked if they agreed with the statement before and after hearing the arguments. It was therefore generally believed that injectables will continue to have a place in MS management.

	Before Debate	After Debate
Agree	17 %	23 %
Disagree	83 %	77 %

Conclusion

Per Soelberg Sørensen concluded the meeting. He asserted that this is an exciting time in MS, the treatment landscape is changing rapidly with many new therapies and diagnostic improvements arriving in quick succession. The overall prognosis for the patient newly diagnosed with MS is better now that it was 20 years ago when DMTs first became available. It is now possible to limit the numbers of patients developing the secondary progressive disease phase, the importance of early therapy is now recognised and more patients are receiving DMTs. Intensive effort is being directed towards effective therapies in SPMS for which treatment is much more challenging and there continues to be fewer options available. The new orals appear to offer equivalent or improved efficacy than the IFNβs with greater convenience, but experience with side effects could change the picture. They also raise the possibility of combination therapy, which could increase efficacy if complementary drugs are used. At the same time, however, the use of injectable therapies in MS continues to grow so those are unlikely to disappear anytime soon. Clinical experience will determine which of the new orals provide genuine new benefits in MS treatment and which have positive effects on long-term patient outcomes. ■

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Definitions of Multiple Sclerosis Treatment Study Names

AFFIRM: Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis; **ALLEGRO**: Oral Laquinimod in Preventing Progression in Multiple Sclerosis; **BENEFIT**: Betaferon®/Betaseron® in Newly Emerging Multiple Sclerosis for Initial Treatment Study; **BEYOND**: Betaferon Efficacy Yielding Outcomes of a New Dose study; **BRAVO**: Laquinimod Double Blind Placebo Controlled Study in RRMS Patients With a Rater Blinded Reference Arm of Interferon β-1a (Avonex®); **CHAMPS**: Controlled High Risk Avonex Multiple Sclerosis Study; **CLARITY**: Cladribine Tablets Treating Multiple Sclerosis Orally; **CombiRx**: Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; **CONCERTO**: Efficacy and Safety and Tolerability of Laquinimod in Subjects With Relapsing Remitting Multiple Sclerosis; **CONFIRM**: Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis; **DEFINE**: Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis; **EVIDENCE**: EVidence of Interferon Dose-response: European North American Comparative Efficacy; **FREEDOMS**: Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis; **INCOMIN**: Every-other-day Interferon Beta-1b Versus Once-weekly Interferon Beta-1a for Multiple Sclerosis; **MIMS**: Mitoxantrone in Multiple Sclerosis; **PreCISe**: Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis of Subjects Presenting With Clinically Isolated Syndrome; **PRISMS**: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; **REFORM**: Tolerability of Rebif (New Formulation) (IFN Beta-1a) and Betaseron (IFN Beta-1b) in IFN-naive Subjects With Relapsing Remitting Multiple Sclerosis; **REGARD**: Rebif vs. Glatiramer Acetate in Relapsing MS Disease Study; **TEMSO**: Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients With Multiple Sclerosis; **TENERE**: Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis; **TERACLES**: Efficacy and Safety of Teriflunomide in Patients with Relapsing Multiple Sclerosis and Treated with Interferon-beta; **TOPIC**: Phase III Study With Teriflunomide Versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis; **TOWER**: Efficacy Study of Teriflunomide in Patients With Relapsing Multiple Sclerosis; **TRANSFORMS**: Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis.