The International Multiple Sclerosis Clinic –
A Virtual Tour of Best Practice Multiple Sclerosis Nursing

Proceedings of the International MS Nurse Symposium held on 21–22 September 2012 in Barcelona, Spain

Martin Duddy,[1] Tomas Olsson,[2] Jaume Sastre-Garriga,[3] Marion R Munk,[4] Del Thomas,[5] Andrea Gertz[6] and Stephen McGarvey[7]

1. Consultant Neurologist, Neurology Department, Royal Victoria Infirmary, Newcastle-upon-Tyne, UK; 2. Professor of Neurology, Karolinska Institute, Stockholm, Sweden; 3. Neurologist and Deputy Director, Multiple Sclerosis Centre of Catalonia, Vall d'Hebron University Hospital, Barcelona, Spain; 4. Lecturer and Ophthalmologist, Department of Ophthalmology and Optometry, Medical University of Vienna, Austria; 5. MS Specialist Nurse, Multiple Sclerosis Specialist Nursing Service, Wye Valley NHS Trust, Gaol Street Health Clinic, Hereford, UK; 6. MS Nurse Consultant, Neuro-Service GmbH, Langgöns, Germany; 7. Solutions in Mind, Richmond Hill, Canada

Abstract

Multiple sclerosis (MS), a progressive inflammatory and neurodegenerative disease of the central nervous system, is one of the most common causes of neurological disability in adults. The efficacy of disease-modifying therapies is improving and more oral medications are becoming available. These treatments have effects that include limiting chronic inflammatory damage, reducing the frequency of relapses, delaying disease progression and controlling symptoms. Most of these medications, however, can only delay disease progression and some have side effects that increase the burden of disease. The need for close monitoring varies between drugs and in the treatment-decision process, it is important to discuss the benefit–risk profile with the patient and to take account of the long-term nature of this disease. MS nurses have a pivotal role in the patient management and are important in ensuring compliance with treatment. The 2012 'MS International Clinic' at Barcelona gathered MS nursing professionals from 26 countries and offered a singular opportunity to review the pathophysiology of the disease and discuss the benefits and limitations of current treatment options. The MS International Clinic also aimed to strengthen the role of the MS nurse in symptom management and patient support and to share best nursing practices.

Pathogenesis and Management of Multiple Sclerosis –
An Update for the Multiple Sclerosis Nurse

Bernd Kieseier, Dusseldorf, Germany

The Pathogenesis of Multiple Sclerosis

Since the clinical presentation of multiple sclerosis (MS) with the typical plaques in the brain was first correlated in 1868,[1] much has been learned about this immune-mediated disease, which is characterised by chronic inflammation, demyelination, axonal damage, white matter lesions, brain and spinal cord atrophy and astrocytosis.[2] Within white matter lesions that are visible on magnetic resonance imaging (MRI) scans from an early stage,[3] macrophages strip and engulf the myelin sheath leading to nerve conduction block and neurological deficit.[2] A relapse is usually followed by a recovery period, in which remyelination can occur,[4] but continued inflammation eventually leads to axonal loss and brain atrophy.[5]

Figure 1: Pathophysiology of Multiple Sclerosis
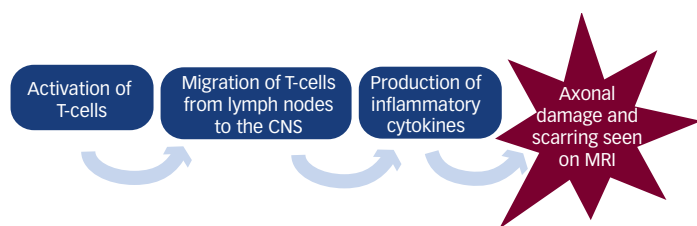
CNS = central nervous system; MRI = magnetic resonance imaging.

Figure 2: Multiple Sclerosis Clinical Course

CIS = clinically isolated syndrome; MRI = magnetic resonance imaging; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Figure 3: Therapeutic Dimensions in the Multiple Sclerosis Treatment Decision-making Process

Nearly all risk genes identified for MS (currently about 100) are associated with immune function[5] and therapies that alter lymphocyte function and migration[6] are effective in MS, suggesting an immune aetiology. Some variants o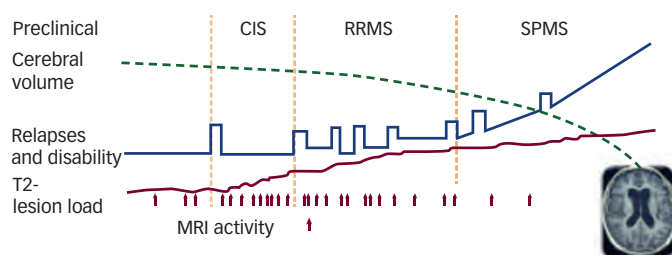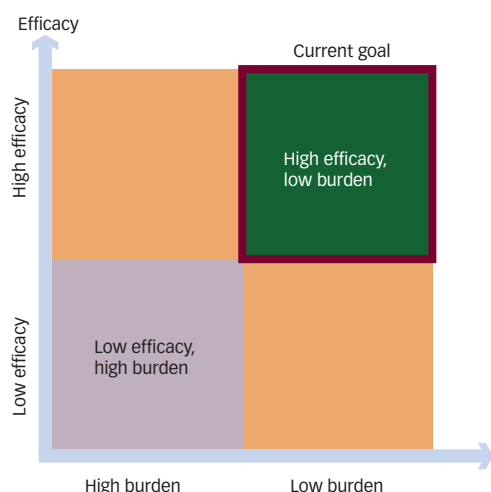f the human leucocyte antigen (HLA) complex and the major histocompatibility complex (MHC) have been associated with MS,[7,8] but the risk they confer to a carrier for developing MS is too small to be predictive of disease. These genes, however, are likely to be valuable in determining a clearer understanding of MS pathogenesis.

In the brains of patients with MS there appears to be an imbalance between the competing pro-inflammatory and anti-inflammatory processes.[9] Genetic and environmental factors may assist the movement of autoreactive T cells and antibodies through a damaged blood–brain barrier (BBB) and into the central nervous system (CNS). Once inside brain tissue, pro-inflammatory cytokines, such as interferon gamma (IFNγ), tumour necrosis factor alpha (TNF-α) and interleukin (IL)-2, -15, -17 and -23 are released by activated T-cells. These increase the expression

of cell-surface molecules on lymphocytes and antigen-presenting cells (astrocytes, microglia and macrophages), triggering an immune response. In addition, the release of certain anti-inflammatory cytokines (IL-1, -4 and -10) from T-cells stimulates production of antibodies by B cells, which damage host tissue (see *Figure 1*).[10,11]

Disease Course

MS has an unpredictable and variable course (see *Figure 2*).[12] The disease first manifests with a neurological sign or symptom such as loss of vision, bladder and bowel dysfunction, ataxia or sensory disturbances (e.g. clinically isolated syndrome [CIS]). After this, most patients spend years alternating between periods of relapse and remission (relapsing-remitting multiple sclerosis [RRMS]), but approximately 50 % will have progressed to a chronic advanced stage within 10 years (secondary progressive MS [SPMS]).[12] At this stage there is clear cerebral volume reduction with increased lesion load visible in MRI.[10] Most patients show impaired walking within 15 years and are wheelchair bound after 25 years. Up to 65 % of patients show cognitive deficits that may significantly impair work and daily activities.[13]

Medications in Current Multiple Sclerosis Management

In MS, disease-modifying therapies (DMTs), although not a cure, help modify and slow down this course and delay progression.[12] For almost 20 years the beta interferons (IFNβs) and glatiramer acetate (GA) have been administered to achieve some limitation of damage to the CNS, to delay disease progression and to provide a degree of long-term improvement in symptoms and quality of life (QoL). Regrettably, the latter two goals are only partially achieved with these drugs. Antispastic drugs, analgesics and antidepressants are also used for short-term symptomatic relief and temporarily improve QoL, but have no disease-modifying effect.[14,15]

In 1993 the first IFNβ therapy for MS was introduced, followed by GA in 2001, mitoxantrone in 2002 and natalizumab in 2006. Fingolimod, a reversible spingosin-1-phosphate (S1P) receptor antagonist and the first oral DMT in MS treatment, was approved for the treatment of RRMS by the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) in 2010 and 2011, respectively. Teriflunomide was approved by the FDA in for RRMS in 2012 and by the EMEA in 2013 and dimethyl fumarate (BG-12) was approved by the FDA for RRMS in 2013; several other agents are in development (e.g. laquinimod, alemtuzumab, daclizumab, ocrelizumab and pegylated IFNβ).[16]

The DMTs are associated with various safety and adherence concerns, particularly flu-like symptoms seen with the IFNβs and administration-site reactions in the treatments given by subcutaneous injection. Therefore, the decision-making process in MS treatment choice should consider two major dimensions: efficacy and burden (see *Figure 3*).[17] The ideal treatment for MS would have a high efficacy and low burden, but the commercially available DMTs fall short of this target.

German MS guidelines recommend IFNβ therapy and steroids as first-line therapy. The injectable agents, IFNβ and GA, are used in CIS, with the possibility of escalating therapy with fingolimod or natalizumab, as first choice, and possibly mitoxantrone, as a second option, for patients with RRMS. On progression, IFNβs, or less commonly, mitoxantrone are used.[18] The Canadian Multiple Sclerosis Working Group (CMSWG) updated its recommendations to address suboptimal responses, switching or escalating treatments and the levels of concern required to justify changing treatment.[19]

Table 1: Comparative Efficacy of the Interferon Betas and Glatiramer Acetate in Placebo-controlled and Head-to-head Clinical Trials as Disease-modifying Treatments Commencing During Relapsing-Remitting Multiple Sclerosis or Clinically Isolated Syndrome

Study/Analysis Reference	Major Endpoints	Treatments Compared	Results
Analysis of clinical studies in RRMS: Warnke et al.[20]	Relapse rate reduction	IFNβ-1a sc	34 % (p<0.0001 versus placebo)
	Relapse rate reduction	IFNβ-1b sc	32 % (p=0.005 versus placebo)
	Relapse rate reduction	Glatiramer acetate sc	29 % (p=0.007 versus placebo)
Early treatment start of MS – during CIS: Comi et al.[23,24] (PreCISe), Jacobs et al.[26] (CHAMPS), Kappos et al.[27] (BENEFIT)	Proportion developing CDMS	IFNβ-1a versus placebo sc	34 % versus 45 % (p=0.047 versus placebo)
	Risk reduction of CDMS	Glatiramer acetate sc	45 % (p=0.0005 versus placebo)
	Risk reduction of CDMS	IFNβ-1a im	44 % (p=0.002 versus placebo)
	Risk reduction of CDMS	IFNβ-1b sc (after 7 years' follow up)	37 % (p=0.003 for early versus delayed treatment)
Head to head comparison: Wolansky et al.[22] (BECOME)	Mean combined active lesion count over 1-year period	IFNβ-1b sc versus glatiramer acetate sc	p=0.67 (for IFNβ-1b versus glatiramer acetate)
Head to head comparison: Mikol et al.[21] (REGARD)	Time-to-first relapse for both agents	IFNβ-1a sc versus glatiramer acetate sc	495 days (for IFNβ-1b) 432 days (for glatiramer acetate); (HR = 0.94, 95 % CI 0.74–1.21; p=0.643 for IFNβ-1a versus glatiramer acetate)
Head to head comparison: O'Connor et al.[29] (BEYOND)	Risk of relapse in RRMS	IFNβ-1b sc (250 μg or 500 μg) versus glatiramer acetate	No difference

BECOME = Betaseron® vs. Copaxone® in multiple sclerosis with triple-dose gadolinium and 3-T MRI Endpoints study; BENEFIT = Betaferon®/Betaseron® in Newly Emerging Multiple Sclerosis for Initial Treatment study; BEYOND = Betaferon Efficacy Yielding Outcomes of a New Dose study; CHAMPS = Controlled High Risk Avonex Multiple Sclerosis Study; PreCISe = Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis [CDMS] of Subjects Presenting With Clinically Isolated Syndrome; REGARD = REbif vs. Glatiramer Acetate in Relapsing MS Disease study. CI = confidence interval; CIS = clinically isolated syndrome; HR = hazard ratio; IFN = interferon; im = intramuscular; RRMS = relapsing-remitting multiple sclerosis; sc = subcutaneous.

In various placebo-controlled and head-to-head clinical studies little difference has been shown between the interferons and GA in terms of efficacy for treating RRMS (see *Table 1*). Parameters such as relapse rate reduction,[20] time-to-first-relapse[21] and combined active lesion scores[22] show similar improvements compared either directly in the same study or indirectly between studies. Some long-term studies have shown that the initiation of treatment when CIS is first reported significantly delays time to clinically diagnosed MS and subsequent disease progression, but all appear to provide similar improvements in this respect.[23–29]

A review of clinical studies that were conducted during the past 2 decades found 60 % to 76 % of MS patients adhered to IFNβ or GA treatment for 2 to 5 years.[30] A common cause of stopping these treatments was lack of efficacy (relapses) accounting for 14 % to 51 % of discontinuations and adverse events (including injection site reactions, flu-like symptoms, depression, headache and fatigue) accounting for 30 % to 57 % of discontinuations.[30] These tolerability matters, however, are not substantial and the data place injectable DMTs in the 'low efficacy–low burden' category on the graph in *Figure 3*.

Natalizumab is a monoclonal antibody against α-4 integrin that blocks leukocyte trafficking across the BBB and is a highly effective treatment for MS. In the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) trial, in patients with RRMS, the reduction in annualised relapse rate (ARR) versus placebo after 1 year was 68 % (p<0.001) and this rate was maintained after 2 years.[31] Natalizumab, however, increases the risk of progressive multifocal leukoencephalopathy (PML) due to opportunistic infection by John Cunningham virus (JCV), which is frequently fatal or results in severe disability.[32] Risk-management strategies include: testing for presence of anti-JCV antibodies before or during treatment, MRI scans taken within 3 months prior to treatment initiation and repeated periodically with regular follow up.[32] After 2 years the treatment should be reviewed since the risk of PML increases with the number of natalizumab infusions: 0.04/1,000 for 1–12 months of treatment and 1.99/1,000 for 37–48 months. Prior immunosuppressant therapy also affects risk of PML.[33] Altogether, these data suggest that natalizumab should be placed in the 'high-efficacy–high burden' category in *Figure 3*.

Mitoxantrone was developed as an anticancer agent and inhibits DNA synthesis and repair in both healthy and diseased cells, it has substantial immunosuppressant properties and is effective in MS treatment. Its use in MS, however, is uncommon being limited mostly due to its association with cardiotoxicity and bone marrow effects in some patients.[34]

One head-to-head study has compared the ARRs of the oral DMT, fingolimod (FTY720) with more mature DMTs in patients with RRMS. The Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) showed a reduction in relapse rate of 52 % after 1 year for fingolimod versus IFNβ-1a intramuscular (p<0.001).[35] The reduction in relapse rate was 61 % (p<0.001) for patients with highly active disease despite treatment with IFNβ.[35,36] A recent integrated analysis of safety data from the Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis (FREEDOMS) , FREEDOMS II and TRANSFORMS studies showed that among patients receiving the approved fingolimod dose of 0.5 mg/day, 1.0 % had bradycardia, 0.1 % had second-degree atrioventricular (AV) block and 0.1 % had 2:1 AV block during treatment.[37] The TRANSFORMS trial also showed that after 1 month of treatment there was no evidence of an effect on AV conduction. The incidence of AV block during the 6-hour observation period following the first dose was 4.7 % (versus 1.5 % for placebo) for first-degree AV block, 0.2 % for second-degree type 1, 0.1 % for second-degree type 2 and 0 % for third-degree (one confirmed case in the post-marketing setting).[35]

The safety profiles of current immune-modifying agents, therefore, determine adherence to therapy and ultimately efficacy. The likely burden of therapy together with burden of disease should contribute to treatment decision-making.

Phase III clinical trial results have recently been reported for two new oral MS agents. In the Determination of the Efficacy and safety of oral Fumarate IN rElapsing-remitting multiple sclerosis (DEFINE) study, a twice-daily dosage of 240 mg dimethyl fumarate (BG-12) showed a

reduction in ARR of 53 % (p<0.001) versus placebo.[38] In the efficacy and safety study of oral BG-12 with active reference in RRMS Comparator and an Oral Fumarate iN Relapsing-remitting Multiple sclerosis (CONFIRM) study, a 240 mg BG-12 regimen reduced ARR by 44 % versus placebo (p<0.001).[39] Teriflunomide, a drug which inhibits a key enzyme required for pyrimidine synthesis, was recently been approved for use in RRMS in the US and Europe and has also been reported to reduce ARR but to a lesser extent. In the TEriflunomide Multiple Sclerosis Oral (TEMSO) and the Teriflunomide Oral in people With relapsing MS (TOWER) studies a 14 mg dose of teriflunomide yielded: 32 % (p<0.001) and 36 % (p<0.001) reductions in ARR, respectively.[40,41] Alemtuzumab, a monoclonal antibody to lymphocyte CD52 antigens, has an advantageous dosing regimen being administered as an intravenous infusion on 5 consecutive days and then on 3 consecutive days 12 months later. Licence applications for this drug have been filed with the FDA and EMEA following two phase III trials. The Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) I trial followed 581 patients with RRMS

for 2 years and showed a reduction of 55 % (p<0.0001) in ARR with alemtuzumab compared with IFNβ-1a.[42] The drug was generally well tolerated, and the most common side effects were infusion-associated reactions (90 %), infections of the upper respiratory and urinary tracts (77 %) and autoimmune thyroid disease (16 %).[43]

It is clear from clinical experience that additional highly effective agents with minimal toxicities are needed. The goal is to improve efficacy outcomes over conventional therapies, i.e. IFNβ and GA, which show modest reductions in ARR in a narrow range of efficacy (30 %),[44] enabling a substantial proportion of patients to live free of disease activity and recover from relapses. MS drug treatments are received by patients over many years and tolerability profiles need to be improved, with reduction of risk of high-impact events such as PML (for natalizumab) and cardiotoxicity (for mitoxantrone). A minimal therapy burden will favourably affect the overall health status and QoL of patients of MS, but the burden of the disease itself must not be overlooked. ■

Individualising Patient Support – Preventing and Managing Non-concordance

Andrea Gertz, Langgöns, Germany

According to the Medical Advisory Board of the German MS Society, approximately half of MS patients do not comply with therapy, and up to a quarter discontinue their IFNβ regimens during the first 6 months due to side effects. After 5 years, as many as one-third discontinue therapy because of disease progression. Non-compliance and non-adherence result in loss of efficacy of DMTs and subsequent increase in relapse rates. It can also cause worsening of symptoms, disability progression, decreased in QoL and can necessitate dose escalation, which may exacerbate side effects and increase costs.[45]

Concordance is an overarching term that comprises compliance, adherence and persistence and often reflects the relationship between the patient and the healthcare team.[46] The causes of non-concordance are complex and multi-factorial resulting mostly from lack of information

about the side effects of the drugs. MS nurses have an important role in promoting concordance to the therapeutic plan due to the privileged relationship they have with patients. Solutions for improving concordance include better management of patient expectations, education on side effects and guidance on improved injection techniques.[47] The ultimate goals of MS nurse involvement are to motivate the patient to take the medication properly, to adhere to the prescribed schedule and to keep follow-up appointments. Other support strategies include sending reminders (text messages, emails), providing information that the patient can consult after the appointment (e.g. patient education websites, interactive applications), helping the patient understand the importance of adherence by using plain language, listening to individual concerns and needs and offering encouragement and praise for a 'job well done'.[48,49] ■

Case Consults and Participant Responses

Led by Martin Duddy, Newcastle, UK

Case 1 – A Patient with Rapidly Progressing Relapsing-Remitting Multiple Sclerosis

A 32-year-old female was diagnosed with RRMS 7 years ago at the age of 25. She has been taking IFNβ-1a 30 µg intramuscular weekly for the last 7 years. She had an episode of optic neuritis in January of this year and an episode of myelitis in June.

It is recommended that the MS nurse first establishes treatment adherence and confirms the history of relapse. A change of therapy may be considered. Depending on the designated role of the MS nurse at the MS centre or practice, the MS nurse may at this point order blood tests for neutralising antibodies, schedule an MRI and/or refer the patient to a neurologist.

A recent MRI scan shows 20 new lesions compared with a previous MRI performed in January 2011, and six gadolinium-enhancing lesions. A decision is made to switch the patient to fingolimod. The patient attends the clinic to discuss the new therapy with her MS nurse.

When faced with a change in DMT, patients often react with concern over progression of disease and the efficacy and side effects of a new drug. There may even be resistance to switching despite the clear loss of efficacy of the current drug. It is extremely important to explain the benefits and risks of a new therapy to the patient, addressing both misconceptions and rational concerns while continuing to provide support. The clinical trial results showing improved relapse reduction on fingolimod compared to IFNβ-1a should be reinforced. The tests required before and after starting

the drug will need to be explained. The MS nurse should also manage expectations, stressing that all DMTs are targeted at averting future relapses and disability and are not expected to improve long-standing existing symptoms. The MS nurse has a crucial role before and during observation following administration of the first dose of fingolimod by ensuring that the patient has been screened appropriately (history of heart disease and diabetes, concomitant medication and history of ophthalmic diseases, e.g. uveitis and cystoid macular oedema). The MS nurse should ensure that the patient knows where and how the treatment is taking place. During the 6-hour treatment, the MS nurse could meet the patient and answer any questions. This observation period is an excellent opportunity to counsel the patient and implement long-term adherence strategies.

The patient attended the clinic for her first dose observation. She returns after 3 months of therapy with fingolimod. She seems disappointed and although she is free from relapses, she complains that her vision has not returned to normal and that a Lhermitte's sign from her myelitis in July has not disappeared. She has missed her scheduled follow-up appointment with the ophthalmologist and is reluctant to attend the clinic for further routine follow up as scheduled.

Following fingolimod dosing, patients should be followed up at regular intervals according to the schedule given in *Figure 4*. The MS nurse should reinforce the message that any infection occurring during treatment or up to 2 months after interruption should be reported. The nurse should also explain the need for ophthalmological evaluation 3 to 4 months after initiating treatment and regular blood work. Therapy goals should be redefined. If necessary, the patient can be referred to a pain expert or a psychotherapist.

Case 2 – Identifying/Managing Relapse in a Relapsing-Remitting Multiple Sclerosis Patient

A 29-year-old man was diagnosed with RRMS at the age of 21, but did not start interferon therapy (IFNβ-1b 250 µg every other day) until the age of 27 (2 years ago). He has some sequelae from previous episodes, including an unstable gait, although he is ambulatory. He had an attack last year (optic neuritis), which resolved. He has been able to continue full-time employment.

For the last 2 years, he has attended a clinic every 6 months. Now, 2 years after starting DMT he has relocated to a new area and has attended one appointment at a new clinic.

In first appointment, it is important to take the clinical history and establish a connection with the patient in order to ensure adherence. Given the impact of loss of mobility on QoL, gait instability needs to be addressed.

Four months later, the patient calls your office as he is concerned that he is suffering another attack. He has muscle spasms and weakness in his left leg with blurred vision and painful eye movements. He says he is not sleeping well and feels there is no point in going out with friends.

Figure 4: Recommended Patient Management and Follow Up During Fingolimod Treatment
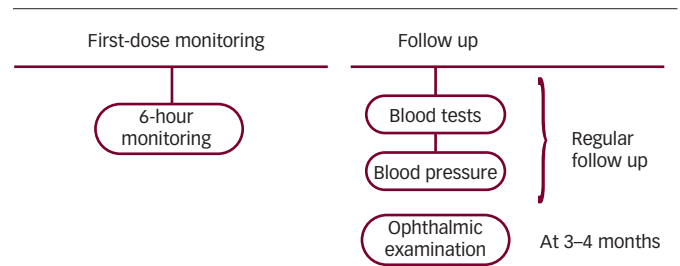
Source: Novartis.[36]

A patient who has missed the 3-month follow-up appointment and seeks help when relapsing needs to be informed about the onset of relapses and potential triggers. Emotional factors also need to be addressed as they can significantly influence clinical outcomes. The patient seems to be disconnected with the disease and treatment and is under stress due to his mobility problems and loss of sleep; he may also be depressed (loss of social connections). It is important that the MS nurse enquires about the patient's life and does not focus on the disease/symptoms. If possible, the MS nurse should discuss life goals with the patient. The patient should nevertheless be referred to a neurologist for evaluation.

It is decided that the patient should be admitted to the neurology unit where he receives methylprednisolone for 3 days.

Methylprednisolone therapy aims to relieve symptoms by speeding recovery from a recent attack. However, it is important that the patient is aware of the side effects of the drug (aseptic femoral necrosis, mood and sleep disturbance, metallic taste, constipation, oedema). In rare cases of an infusion reaction, which is not always due to hypersensitivity to the drug, dexamethasone can be used instead and/or antihistamines can be administered. On discharge, the patient should be advised to drink lots of liquids and avoid excessive salt and sugar, and information on the available support services should be provided.

The patient was discharged after 3 days of steroid therapy and his symptoms improved. Six weeks later he attends a follow-up appointment. He has some residual effects on his gait (dragging) and has experienced a fall. He asks if the interferon therapy is 'still working' and whether alternatives are available.

This patient needs to be referred to the neurologist to discuss treatment options. An MRI scan may be requested and switching therapy will depend on patient's preferences and other factors (e.g. local reimbursement). Frustration with the disease, treatment and healthcare team are common and the patient should be offered alternatives, but it is important to emphasise the importance of remaining on treatment. The clinical cases presented highlight the importance of monitoring adherence and providing support in order to ensure the efficacy of DMTs. The MS nurse has undoubtedly an essential role in educating the patient on disease progression and side effects of the currently available drugs. ■

Profiling Patient Types to Build Better Practice

Andrea Gertz, Langgöns, Germany

MS patients present distinct typologies that reflect personality traits and determine treatment outcomes (see *Table 2*). The 'pragmatic patient' is by nature reflective, accepts the diagnosis and has faith in treatment.

This patient is usually in contact with other patients with MS, 'lives for the present' and does not think about comorbidities, but has specific goals in life and tries to experience everything before the disease takes its toll.

Table 2: Motivation Tools for Different Multiple Sclerosis Patient Types

The Pragmatic Patient	The Consistent Patient	The Hungry Patient	The Visionless Patient	The Unconcerned Patient
• Needs a conversational partner • Enjoys being involved in activities • Seeks financial, social and legal information • Has an attitude "How can I make the best out of the rest?"	• Exchanges information with other patients • Seeks tips for coping with everyday life • Needs 'quick and dirty' information • Browses the internet for informational material and participates in online communities	• Expects high-quality and in-depth informational material • Seeks independent and scientific information • Keeps abreast of new and relevant information • Likes to be in contact with the experts	• Needs coping strategies • Seeks motivation for treatment • Requires help defining goals and changing perspective	• Needs to be motivated and help defining goals • Requires psychological support and a 'life coach' • Needs reassurance about treatment success and detailed information about similar patient cases • Needs hand-on support for coping with everyday life (occupation, nutrition, exercise)

The second type, the 'consistent patient', also accepts the diagnosis and lives life to the fullest, but does not want to know what will happen in the future. This type of patient usually has a stable family situation, a job and may network with other patients in the same circumstances. The 'hungry patient', on the other hand, is a 'seeker' and constantly looks for new information about treatment and interacts with experts. The ultimate goal of this patient is to overcome the burden imposed by the disease. The fourth type is the 'visionless patient', who is generally pessimistic about life and treatment. This patient does not seek information about the disease, is anxious about everything and has no hope for the future. Finally, the 'unconcerned patient' does not wish to be involved in treatment and usually ignores the disease. This patient does not seek information nor wants any kind of contact with other patients and may even reject treatment and resist medical advice.

The most common type observed in the clinical practice of the audience is the hungry patient, followed by the consistent and pragmatic types. However, patient typologies are dynamic and change according to life events, disease stage and treatment outcomes; communication strategies have to be adapted to these different typologies. The MS nurse should be able to identify patient types in order to optimise MS nurse–patient communication and management.

Patient classification can be achieved with specific questioning techniques. Closed questions allow the MS nurse to assess the patient's understanding of the diagnosis or side effects of a drug, for example. Open ended questions, which cannot simply be answered with yes or no, can reveal patient motivation and attitude towards the disease and treatment.

Circular questions may involve role playing. The patient is questioned via a third person, e.g. a carer or family member ("Considering that you have so many relapses, what does your partner say about the fact that you are ignoring basic treatment?") The answer is not the opinion of this third person, but reflects the attitude of that individual. Circular questions help overcome 'blockades' in communication and are most useful for the pragmatic, consistent and visionless types.

Scale and developmental questions allow patients to categorise themselves, to actively show their 'true feelings' ("On a scale of 1 to 6, where do you see yourself in terms of the necessary treatment compliance?") Once a patient describes a tendency, the MS nurse should then ask open questions to trigger a reflective process on motivation and cooperation ("How did you come up with this value? What is your goal?") In this way, the patient is able to express management objectives and plans, which should prompt the MS nurse to enquire about the kind of support needed to achieve these goals. All types of patients, especially the pragmatic patient, benefit from these questions.

Finally, the 'miracle questions' enable the patient to imagine scenarios ("What would happen if you woke up tomorrow and all your limitations had disappeared?") These questions elicit hidden motivations and are important for sustaining treatment, withstanding side effects or willingness to continue treatment. These types of questions can provide insight ("There is something out there worth living for!") and can be used with all types of patients, but in particular the visionless patient.

Patient typologies also help to understand and predict treatment discontinuation. Consistent patients show the lowest discontinuation, while the unconcerned patient more frequently interrupts treatment. Several factors, such as disease progression, drug side effects, injection fatigue, loss of a job or a partner, financial problems and even 'feeling healthier', can change the patient type and influence discontinuation. The visionless patient and, unexpectedly, the consistent patient are more likely to discontinue treatment due to sudden events that negatively impact their lives and these types should be the most closely monitored.

The MS nurse needs to constantly re-examine and observe how patients are progressing. However, there may be mixed types and the MS nurse will have to identify which traits predominate in order to identify the primary behavioural patterns and act accordingly. It is critical to recognise events that may cause patients to transition from a steady state of treatment compliance to a state of discouragement and take action to modify their attitudes promptly. ■

Communication Excellence – Optimising the Interaction with Patients

Stephen McGarvey, Richmond Hill, Canada

Effective MS nurse–patient communication helps patients control symptoms and comply with treatment. However, MS nurses need adequate training in order to align the impact of their messages with intention and reduce frustration caused

by misunderstandings and effectively manage patient stress and anxiety.

In modifying a patient's behaviour there is a hierarchy of change (see *Figure 5*), which comprises, at the unconscious level, identity, beliefs, values and capabilities. The patient's self-perception, beliefs, capabilities and attitudes can change naturally throughout the different stages of disease and treatment. The key to implementing desired changes in behaviour (e.g. convincing the patient to take the medication as prescribed), is ignoring excuses and shifting the focus to management of perceptions. The ultimate goal is to identify the patient's thinking pattern (unconscious) that is causing the undesirable outcome so that both behaviour and environment can be positively changed (conscious).

Asking the right questions is essential. If a patient says "I am tired of this treatment, I am feeling depressed", the MS nurse should not ask why, but should ask instead "How would you like to feel? What would help you feel that way? Why would it make you feel that way?" Here, the MS nurse is guiding the patient's imagination and changing the focus from negative to positive thoughts. Positive statements should always be used: "It is important to remember to take your medication" (not "you must try not to forget to take your medication"). Recognising

Figure 5: The Hierarchy of Change Within the Human Brain
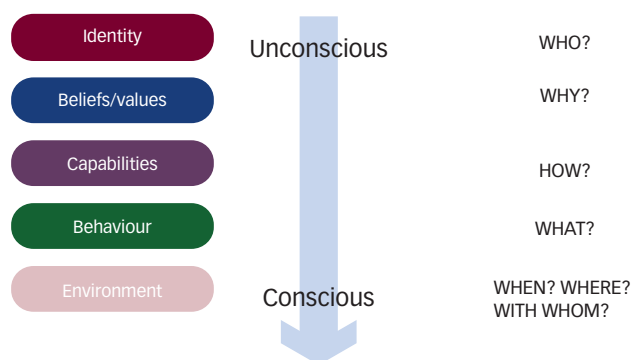
Source: This hierarchy of change was adapted from Robert Dilts' Logical Levels. Dilts, 1990.[50]

the fact that most patients do forget to take their medication is the first step in finding solutions to the problem.

When the MS nurse provides clear and direct actions for the patient to take and links those actions to a desired emotion or state, permanent behavioural changes can be attained. ■

The Role of the Multiple Sclerosis Nurse – Based on Participant Feedback

Led by Del Thomas, Hereford, UK

Across Europe and the Middle East, the MS nurse assumes distinct roles in patient diagnosis and treatment. Main responsibilities include helping newly diagnosed patients understand the disease, explaining risk and benefits of DMTs, managing symptoms and adverse events and providing injection training. This was illustrated in audience feedback as shown in *Table 3*.

An important aspect of the MS nurse scope of practice in the context of MS is monitoring and encouraging concordance with therapy, but the support of the MS nurse specialist is not always recognised.

MS nurses are often the first point of contact with patients, who are mostly interested in learning about impact of DMTs on QoL, relapse rates and side effects. Patients complain most frequently about fatigue, mobility impairment and urinary incontinence/frequency, but the majority of the MS nurses can only recommend drugs to relieve these symptoms.

There is clearly room for the continuum of care provided by MS nurses to expand, and provide an important link between the patient and the multidisciplinary healthcare team.

Overview of Posters Presented at the Multiple Sclerosis International Clinic
A total of 18 posters were presented at the MS clinic – an overview is given in *Table 4*. These reported studies ranging in size from individual case reports to a description of a department currently treating 1,085 patients with MS. They all highlighted the multiple varied ways MS nurses improve treatment practice, QoL and outcomes for their patients and that their role is critical is ensuring patient education, communication, personal support, monitoring and compliance. They also emphasised that MS nurses are a vital link between the patient and the rest of the multi-disciplinary team. In addition, they showed that MS nurses frequently initiate valuable programmes that improve patient activity, coping abilities and overall wellbeing. ■

Table 3: The Role of the Multiple Sclerosis Nurse – Feedback from the Audience

Responsibilities of the Multiple Sclerosis Nurse	Do Not But Would Like To	Do Not And Do Not Want To
I help newly diagnosed patients understand their disease	Greece, France (some)	
I explain mechanisms of action, benefits and risks of disease-modifying therapies	Poland, Lebanon, Kuwait, France (some)	
I manage adverse events of disease-modifying therapies	France	
I undertake injection training	Finland, Austria	UK (some)
I am the primary point of contact for patients suffering a relapse	Poland, Austria, France (some)	
I am involved in symptom management	Lebanon, Poland	
I monitor concordance with therapy	Austria, France (some)	
I schedule routine follow up	France	Germany

Table 4: Overview of Poster Presentations at the MS International Clinic (Barcelona)

Author/Affiliation	Poster Title	Aims of Study	Findings
Single Case Reports and Case Series			
Huber et al., Neuro-Service, Langgöns, Germany	An interesting case	Management aimed to enable 21-year-old multiple sclerosis (MS) patient to walk, improve QoL, complete education, live normal life	Rehabilitation plan including increasing activity levels and management of bladder/bowel problems to improve the patient's status. Study highlighted that patient-management methods have improved substantially over past 15 years
Schwarze et al.	QoL after PML or PML – and now?	A report MS nurse intervention on a single case of a patient (male aged 40 years) with MS for 14 years who developed PML (JCV-positive) after receiving natalizumab during a 4-year period after relapsing on IFNβ-1b	Several MS nurses held an expert discussion, researched similar experiences and agreed interventions with drug therapy, symptomatic therapy, adaptation of living conditions, need for nursing care and liaison with other agencies (social services, etc.) Patient felt more positive and able to cope with negative consequences of therapy
Slic FB, Medical University of Warsaw, Poland	The patients I see: A review of five consecutive patients	To review the MS cases admitted on one day in a seven-bed MS ward in Warsaw	5 patients (1 male; 4 female, aged 31–54 years) all mobile but had varying problems to deal with. Findings show it is important to have time to listen to patients
Nursing Roles in Multiple Sclerosis Clinics/Departments			
Bocwinska D, University Hospital, Krakow, Poland	Supporting MS patients – examples from my practice	To demonstrate the benefits of activities such as yoga, Nordic walking and aqua-aerobics on patient wellbeing and fitness	Drug treatment in MS can be significantly complemented by patient activities. Activities, e.g. aqua-aerobics, provide patient satisfaction and improved physical and emotional condition
Bruns M et al., Berlin, Germany	Encouraging concordance with injection therapy: my role	To achieve and maintain adherence/ compliance and QoL and establish cooperation between doctors and patients	Three MS nurses' experience shows that finding out the patient's motivation is important and it is vital to keep the patient on treatment to maintain good health
Gomes T, Centro Hospitaler do Porto, Portugal	Supporting patients with MS: an example of my practice	To evaluate the value of phone line support in a 6-month study including 136 patients	Calls (n=136) help patient management. They were more common among patients living remotely from the clinic. Most calls were about worsening symptoms, medication requests, medical appointments and complementary diagnoses
Noc AP, University Medical Center, Ljubljana, Slovenia	My department: an overview and my role	To present the activity in an MS centre in Ljubljana with emphasis on the role of the MS nurse	Currently treating 1,085 patients (75 % female). The key for an MS centre is close cooperation between the neurologist and other staff (including MS nurses). Staff should be constantly aware of individual MS patient needs
Pamula A, No 10 Military Hospital, Bydgoszcz, Poland	My department: an overview and my role	To examine the MS nurse's role in treatment monitoring and its importance for patient wellbeing and outcomes	Proper treatment/monitoring of MS patients prolongs physical ability and improves status. Providing accurate information to the physician enables improved QoL and outcomes
Improving Compliance, Quality of Life and Adaptation			
Augusto B and Melo A, Hospitals da Universidade de Coimbra, Portugal	Life in me: Therapy report in patients with MS	To provide information tailored to the needs of the MS patient	Study is ongoing. Forming partnerships between healthcare providers and patients and cleaving information is likely to improve QoL and help patient problem-solving abilities
Brunet I, Rennes University Hospital, France	Benefits of therapeutic education following loss of ambulation in patients with multiple sclerosis	To determine whether TPE programs can help patients with declining ambulation to modify perception of disease and disability and find autonomy	Patients who participated in TPE (n=6) had less-negative perceptions of disease and disability and develop better adaptation skills that patients not in TPE (n=6). This was a small study needing confirmation with a larger population
Cardosa H et al., Hospital Egas Moniz, Lisbon, Portugal	Nursing interventions on compliance in patients with MS	To analyse 5-years of patient data by gender and change of treatment	80 % of patients (n=61) starting new treatment were female. MS nurses established a good and supportive relationship with MS patients and this unique position helps ensure compliance
Mokadym H et al., Franch-Comte University Besacon, France	Evaluation of the quality of life of patients affected by MS according to their own perception and the perception of their relatives	To assess QoL in MS as rated by patients and relatives using the PERSE3P scale and compare	The perceptions of patients and relatives using the PERSE3P scale in MS patients (n=21) were similar – thus relatives could be used to assess QoL when the patient is unable to respond
Stadmuller A, Aschaffenburg, Germany	Encouraging concordance with therapy: my role	To identify patient motivation ("brightness in the eyes") – identify patient goals and improve QoL	Patients must be well informed about treatment, side effects, control examination and risks. Patients who trust their doctor are more likely to be compliant and have better QoL; isolated patients less likely
Zimmer et al, University Hospital Basel, Switzerland	Empowering patients and MS nurses new services and practices inspired by a new treatment	To develop new services led by an MS nurse to assess and treat patients and enable them to self-manage	The new services enabled better patient education and transferred evidence-based knowledge and supported patients in self-treatment and improved supervision and management
Improving Disease-modifying Therapy Self-administration			
Moreira F et al., Centro Hospitalar Alto Ave, Guimaraes, Portugal	Efficacy of nursing intervention on self-administration of immunomodulatory therapy	To identify and correct self-administration errors among 104 patients. Develop more assertive approaches with patients and evaluate changes between first and later visits	In 104 MS patients, MS nurses improved patient practice. Findings showed MS nurses should be assertive, autonomy in patients, correct errors and encourage compliance

Table 4: Cont.

Author/Affiliation	Poster Title	Aims of Study	Findings
Teixeira C, Hospital Distrital de Santarem, Portugal	Use of IFNβ-1b with EXTAVIJECT injection: the experience with the patients at the Hospital Distrital de Santarem (Portugal)	To evaluate factors influencing adherence to treatment with IFNβ-1b including: self-perceived skill levels, anxiety and pain on drug injection and side effects	In MS patients (n=24), self-perceived higher skills in drug preparation/injection were not associated with long duration of MS. Anxiety and pain on drug administration was higher in patients with MS >10 years. Common side effects were, local pain redness oedema, flu-like symptoms and headache
Patient Monitoring after Fingolimod Administration			
Cordeiro C, Hospital de Santa Maria, Lisbon, Portugal	Nursing care during the first dose monitoring of fingolimod	Summarise experience during monitoring of patients after fingolimod first dose (heart rate especially) and address nursing interventions	In a group of 22 patients there was an asymptomatic decline in heart rate during 6-hour period with no need for additional intervention
Rodrigues C and Branco C, Centro Hospitalar de Setubal, Portugal	Selection of fingolimod patients and nursing care in the first dose	Discuss therapeutic decisions for patients receiving fingolimod and evaluate first 6 hours after first dose	In four MS patients there were no significant changes in heart rate and only moderate blood pressure increases seen during 6 hours after first fingolimod dose

IFNβ = interferon beta; JCV = John Cunningham virus; PERSE3P = Perception of MS and Relapses According to Relatives; PML = progressive multifocal leukoencephalopathy; QoL = quality of life; TPE = therapeutic patient education.

Conclusions

Despite recent advances in DMTs, the long-term management of MS presents challenges for both patients and healthcare providers. Building trust, promoting autonomy and educating patients about the burden of therapy have the greatest impact on treatment adherence. Newly diagnosed MS patients go through several successive and contradictory emotional states, including denial, anger, depression and acceptance. The MS nurse has to navigate through these stages and provide support to patients, families and caregivers. Identifying patients at risk and providing access to support resources, including mental health services if necessary, are critical skills. Despite the poor prognosis associated with MS, an adequate management of disease, with the help of the MS nurse, can enable patients to come to terms with their diagnosis and live rewarding and productive lives within their capabilities. Effective communication is therefore vital to successful disease-management programmes and high-quality care. ■

1. Murray TJ, *Multiple Sclerosis: The History of a Disease*, New York: Demos Medica Publishing, 2005.
2. Compston A, Coles A, Multiple sclerosis, *Lancet*, 2008;372:1502–17.
3. Reynolds R, Roncaroli F, Nicholas R, et al., The neuropathological basis of clinical progression in multiple sclerosis, *Acta Neuropathol,* 2011;122:155–70.
4. Patrikios P, Stadelmann C, Kutzelnigg A, et al., Remyelination is extensive in a subset of multiple sclerosis patients, *Brain*, 2006;129:3165–72.
5. Gourraud PA, Harbo HF, Hauser SL, et al., The genetics of multiple sclerosis: an up-to-date review, *Immunol Rev*, 2012;248:87–103.
6. Weber MS, Menge T, Lehmann-Horn K, et al., Current treatment strategies for multiple sclerosis - efficacy versus neurological adverse effects, *Curr Pharm Des*, 2012;18:209–19.
7. Compston DA, Batchelor JR, McDonald WI, B-lymphocyte alloantigens associated with multiple sclerosis, *Lancet*, 1976;2:1261–5.
8. Terasaki PI, Park MS, Opelz G, et al., Multiple sclerosis and high incidence of a B lymphocyte antigen, *Science*, 1976;193:1245–7.
9. Zeis T, Graumann U, Reynolds R, et al., Normal-appearing white matter in multiple sclerosis is in a subtle balance between inflammation and neuroprotection, *Brain*, 2008;131:288–303.
10. Barten LJ, Allington DR, Procacci KA, et al., New approaches in the management of multiple sclerosis, *Drug Des Devel Ther*, 2010;4:343–66.
11. Borazanci AP, Harris MK, Schwendimann RN, et al., Multiple sclerosis: clinical features, pathophysiology, neuroimaging and future therapies, *Future Neurol*, 2009;4:18.
12. Hauser SL, Goodin DS (eds), Multiple sclerosis and other demyelinating disorders. In: *Harrison's Principles of Internal Medicine*. 16th ed., New York: McGraw Hill Medical Publishing, 2005;2461–71.
13. Weinshenker BG, The natural history of multiple sclerosis, *Neurol Clin*, 1995;13:119–46.
14. Murray TJ, Diagnosis and treatment of multiple sclerosis, *BMJ*, 2006;332:525–7.
15. Niino M, Sasaki H, Update on the treatment options for multiple sclerosis, *Expert Rev Clin Immunol*, 2010;6:77–88.
16. Marta M, Giovannoni G, Disease modifying drugs in multiple sclerosis: mechanisms of action and new drugs in the horizon, *CNS Neurol Disord Drug Targets*, 2012;11:610–23.
17. Saidha S, Eckstein C, Calabresi PA, New and emerging disease modifying therapies for multiple sclerosis, *Ann N Y Acad Sci*, 2012;1247:117–37.
18. Henze T, Rieckmann P, Toyka KV, et al., Symptomatic treatment of multiple sclerosis. Multiple Sclerosis Therapy Consensus Group (MSTCG) of the German Multiple Sclerosis Society, *Eur Neurol*, 2006;56:78–105.
19. Freedman MS, Selchen D, Arnold DL, et al., Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations, *Can J Neurol Sci*, 2013;40:307–23.
20. Warnke C, Leussink VI, Kieseier BC, et al., [Interferon beta for multiple sclerosis. How much is good enough?], *Nervenarzt*, 2010;81:1476–82.
21. Mikol DD, Barkhof F, Chang P, et al., Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial, *Lancet Neurol*, 2008;7:903–14.
22. Wolansky LJ, Cook SD, Sheynzon V, et al., Betaseron® vs. Copaxone® in multiple sclerosis with triple-dose gadolinium and 3-T MRI Endpoints (BECOME): efficacy of the optimised MRI protocol and announcement of primary study outcome, *Mult Scler*, 2006;12:S98.
23. Comi G, Filippi M, Barkhof F, et al., Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study, *Lancet*, 2001;357:1576–82.
24. Comi G, Martinelli V, Rodegher M, et al., Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial, *Lancet*, 2009;374:1503–11.
25. Hartung HP, Early treatment and dose optimisation BENEFIT and BEYOND, *J Neurol*, 2005;252(Suppl. 3):iii44-iii50.
26. Jacobs LD, Beck RW, Simon JH, et al., Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group, *N Engl J Med*, 2000;343:898–904.
27. Kappos L, Freedman MS, Polman CH, et al., Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial, *Lancet Neurol*, 2009;8:987–97.
28. Kappos L, Traboulsee A, Constantinescu C, et al., Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS, *Neurology*, 2006;67:944–53.
29. O'Connor P, Filippi M, Arnason B, et al., 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study, *Lancet Neurol*, 2009;8:889–97.
30. Costello K, Kennedy P, Scanzillo J, Recognizing non-adherence in patients with multiple sclerosis and maintaining treatment adherence in the long term, *Medscape J Med*, 2008;10:225.
31. Polman CH, O'Connor PW, Havrdova E, et al., A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis, *N Engl J Med*, 2006;354:899–910.
32. Hunt D, Giovannoni G, Natalizumab-associated progressive multifocal leucoencephalopathy: a practical approach to risk profiling and monitoring, *Pract Neurol*, 2012;12:25–35.
33. Bloomgren G, Richman S, Hotermans C, et al., Risk of natalizumab-associated progressive multifocal leukoencephalopathy, *N Engl J Med*, 2012;366:1870–80.
34. Le Page E, Leray E, Edan G, et al., Long-term safety profile of mitoxantrone in a French cohort of 802 multiple sclerosis patients: a 5-year prospective study, *Mult Scler*, 2011;17:867–75.
35. Cohen JA, Barkhof F, Comi G, et al., Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis, *N Engl J Med*, 2010;362:402–15.
36. Novartis, Gilenya summary of product characteristics 2013. Available at: http://www.medicines.org.uk/emc/medicine/24443/SPC/Gilenya+0.5mg+hard+capsules/ (accessed 20 May 2013).
37. Cohen JA, O'Connor P, Caliolio T, et al., Long-term safety of fingolimod in relapsing multiple sclerosis: update to integrated analyses of phase 2 and 3 studies and extension phases, 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Lyon, France, 10–13 October 2012.
38. Gold R, Kappos L, Arnold DL, et al., Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis, *N Engl J Med,* 2012;367:1098–107.
39. Fox RJ, Miller DH, Phillips JT, et al., Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis, *N Engl J Med,* 2012;367:1087–97.
40. Kappos L, Comi G, Confavreux C, The efficacy and safety of teriflunomide in patients with relapsing MS: results from TOWER, a phase III, placebo-controlled study, 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Lyon, France, 10–13 October 2012.
41. O'Connor P, Wolinsky JS, Confavreux C, et al., Randomized trial of oral teriflunomide for relapsing multiple sclerosis, *N Engl J Med*, 2011;365:1293–303.
42. Cohen JA, Coles AJ, Arnold DL, et al., Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial, *Lancet*, 2012;380:1819–28.
43. Coles AJ, Twyman CL, Arnold DL, et al., Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial, *Lancet*, 2012;380:1829–39.
44. Mendes A, Sa MJ, Classical immunomodulatory therapy in multiple sclerosis: how it acts, how it works, *Arq Neuropsiquiatr*, 2011;69:536–43.
45. Kobelt G, Berg J, Lindgren P, et al., Costs and quality of life of patients with multiple sclerosis in Europe, *J Neurol Neurosurg Psychiatry*, 2006;77:918–26.
46. Bloom LF, Lapierre NM, Wilson KG, et al., Concordance in goal setting between patients with multiple sclerosis and their rehabilitation team, *Am J Phys Med Rehabil*, 2006;85:807–13.
47. Saunders C, Caon C, Smrtka J, et al., Factors that influence adherence and strategies to maintain adherence to injected therapies for patients with multiple sclerosis, *J Neurosci Nurs*, 2010;42:S10–18.
48. Bruce JM, Lynch SG, Multiple sclerosis: MS treatment adherence–how to keep patients on medication?, *Nat Rev Neurol*, 2011;7:421–2.
49. Haynes RB, Ackloo E, Sahota N, et al., Interventions for enhancing medication adherence, *Cochrane Database Syst Rev*, 2008;CD000011.
50. Dilts R, *Changing Belief Systems with NLP*, Cupertino, California: Meta Publications, 1990.