THE ROLE OF NURSE IN MEDICAL CARE OF PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS

UPDATE ON THE TREATMENT OPTIONS FOR MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a chronic, potentially disabling, immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). The pathophysiology of MS, though not fully understood, includes early inflammatory cell infiltration of the CNS affecting primarily the white matter, demyelination and axonal damage, resulting in permanent clinical disability, which occurs at an early stage of the disease [1]. Thus, focal CNS inflammation, demyelination and axonal loss are typical features although pathologically there is heterogeneity [1].

MS is a challenging disease to treat, not least because of its significant heterogeneity and unpredictable clinical course. Parameters of the early disease course such as brain magnetic resonance imaging (MRI) data and the number of clinical attacks in the first 2-10 years tend to predict long term outcome in MS patients [2, 3]. This evidence provides a rationale for early intervention with disease modifying therapies (DMTs), aiming to reduce relapses and resulting residual disabilities, and to prevent or delay the onset of progressive disability.

Conventional DMTs in multiple sclerosis

Immunomodulatory agents, which became available from the early 1990s, aim to prevent relapses, minimise disability and reduce disability progression (particularly relapse-related disability). The immunomodulatory agents interferon (IFN)-beta 1a, IFN-beta 1b and glatiramer acetate (GA) are first-line therapy in MS [4].

Pivotal phase III studies of IFN-beta and GA, conducted as 2-year, double-blinded, randomized, placebo-controlled, multicentre trials, have all demonstrated a significant reduction in relapse rate (by approximately 30%) and improvement in brain MRI measures of disease activity in relapsing-remitting (RR) MS patients [4]. Additionally, in these studies, treatment of MS with IFN-beta and GA produced a beneficial effect on MRI measures of disease severity such as T2 disease burden and modestly slowed sustained disability progression.

While both IFN-beta 1a and IFN-beta 1b demonstrated significant reductions of the attack rates and MRI burden of disease in secondary progressive (SP) MS patients [4], the European trial with IFN-beta 1b was the only study to show a significant reduction in the confirmed 1-point Expanded Disability Status Scale (EDSS) progression rate in this setting [5].

Some head-to-head trials and long-term follow-up data have since added to the evidence on DMTs in the RRMS setting. The results for standard doses of IFN-beta 1a im compared to IFN-beta 1a sc and IFN-beta 1b sc in the EVIDENCE [6] and INCOMIN trials [7], respectively, are believed to reflect a dose-response effect.

Trials comparing GA with IFN-beta 1b sc (BEYOND, BETAFERON Efficacy Yielding Outcomes of a New Dose [8]; BECOME, BETASERON versus COPAXONE in MS with triple-dose gadolinium and 3T MRI Endpoints [9]) and IFN-beta 1a sc (RE-

GARD, REBIF 44 μg versus GA in Relapsing MS Disease [10]) quite unexpectedly showed lower relapse rates than in the pivotal trials with these agents, but did not reveal clinically important differences in efficacy between the IFN-beta treatments and GA.

To determine whether early treatment with DMTs (IFN-beta or GA) following a clinically isolated syndrome (CIS), the first demyelinating clinical event suggestive of MS, can delay the second clinical event and therefore a diagnosis of clinically definite MS (CDMS), four large-scale placebo-controlled clinical trials were conducted [4, 11]. All these trials have shown a consistent reduction in the cumulative probability of developing CDMS in CIS patients receiving early treatment with these conventional DMTs, and extension studies and long-term follow up data have since demonstrated the long-term benefits in this setting as well [12,13].

Neither IFN-beta [14] nor GA [15] have shown efficacy in primary progressive MS.

Long-term adherence to disease-modifying therapy in RRMS is associated with improved patient outcomes, including a reduced risk of relapse and a better preserved quality of life. However, the unpredictable nature of the disease, even when it is being treated, may make it difficult to convince patients of the importance of treatment adherence. A number of studies have attempted to pinpoint factors that affect adherence. Nursing interventions that address some of these factors may improve adherence and, thus, the disease course for a variety of RRMS patients. Nursing interventions, including telephone counseling and motivational interview techniques, can improve adherence.

Second-line DMTs in multiple sclerosis

Despite notable advances in the understanding of MS and the availability of afore-mentioned several treatment options, there is a need for therapies that are more effective, safe, convenient, and well tolerated. Further development of DMT in MS has rapidly evolved over the last few years and continues to do so, leading to the additions to the treatment armamentarium, comprising recently introduced antibody natalizumab and more recently, the sphyngosin-1-phosphate receptor modulator fingolimod. Because data on these new therapies continue to emerge, nurses will play a pivotal role in educating patients regarding the benefits and risks of potential treatments and in monitoring patients for response, safety, tolerability, and adherence.

Natalizumab (TYSABRI®) is a recombinant, humanized monoclonal antibody directed against the α4-integrin, a component of Very Late Antigen (VLA)-4 on the surface of lymphocytes. Natalizumab blocks the interaction of VLA-4 with its ligand vascular-cell adhesion molecule 1 (VCAM-1) on the surface of vascular endothelial cells in brain and spinal cord blood vessels, thus reducing the adhesion and migration of lymphocytes into the brain and thereby reducing inflammation [16].

The safety and efficacy of natalizumab in the treatment of RRMS was evaluated in two phase III studies. The first study compared natalizumab vs. placebo (AFFIRM) and the second natalizumab plus interferon-beta 1a (Avonex) vs. placebo plus Avonex (SENTINEL) [17, 18]. In the AFFIRM study, natalizumab (300 mg in intravenous infusion, once every 4 weeks) reduced the rate of clinical relapse at 1 year by 68% and the risk of 24 week sustained progression of disability by 54% over 2 years [17]. The accumulation of new or enlarging hyperintense lesions over two years, as detected by T2-weighted MRI, was reduced by 83% for natalizumab versus placebo [17]. In the 2-year SENTINEL study, add-on natalizumab resulted in a 24% reduction in the relative risk of sustained disability progression compared to IFN-beta 1a alone, a reduction in annualized relapse rates of 54% and 55%, respectively, at 1 and 2 years, and an 83% reduction in new or enlarging lesions on T2-weighted MRI. Natalizumab effects were sustained with low annualised relapse rates and stable disability scores confirmed in the open-label STRATA extension study evaluating the long-term safety of natalizumab in participants of these and other controlled studies.

Convincing data on relapse rate reduction after one year in the AFFIRM study resulted in accelerated approval of the agent in the US at the end of 2004. Only three months later, in 2005, natalizumab was withdrawn from the market when two fatal cases of progressive multifocal leucoencephalopathy (PML), were reported in patients receiving natalizumab and IFN-β in the SENTINEL trial [19,20]. A subsequent safety evaluation of the drug estimated the risk of PML to

be 1 in 1000 (0.1%) over an 18-month treatment period [21]. Following this report, natalizumab was re-approved as monotherapy for active relapsing MS in 2006 by the EMEA with a number of restrictions [4]. The approval label currently represents a compromise between the expected benefit of natalizumab in active relapsing disease and the potential risk of this therapy with emphasis on the greatest possible patient safety. Up to November 2010, there were on the whole 75 confirmed natalizumab-associated PML cases [22].

Finally, it is assumed now that beneficial effects outweigh the risk of developing PML, as supported by a recent risk-benefit analysis [23]. Therefore, according to the current scientific information, natalizumab is indicated as a "disease-modifying monotherapy of highly active relapsing MS" for the following patient groups [4]: 1) patients showing high levels of disease activity despite treatment with an IFN- beta preparation, or 2) untreated/treatment-naïve patients with rapidly progressing RRMS (at least two serious relapses per year). The Multiple Sclerosis Therapy Consensus Group (MSTCG) recommends that patients with RRMS not responding to immunosuppressive drugs can be switched to natalizumab after considering the risk-benefit ratio and only after at least a 3-month drug-free interval following azathioprine-equivalent drugs and after a longer interval (up to 6 months) following MX (expert opinion) [4]. However, no definitive data are available yet on the safe time intervals.

Fingolimod, a synthetic analogue of the immunosuppressive fungal metabolite myriocin [24], is a sphingosin-1-phosphate (S1P) receptor modulator for once daily oral administration. Fingolimod binding to S1P receptors on lymphocytes prevents their egress from lymph nodes, resulting in a dose-related reduction in the number of circulating lymphocytes and a reduced infiltration of autoaggressive lymphocytes into the central nervous system.

For the 24-month phase III FREEDOMS study, RRMS patients were randomized to receive oral fingolimod at doses of 0.5 mg or 1.25 mg daily or placebo [25]. The annualized relapse rate was significantly lower with both 0.5 mg and 1.25 mg fingolimod (0.18 and 0.16, respectively) than with placebo (0.40); this relative reduction of about 58% for fingolimod groups was seen in both treatment-naïve patients and patients previously treated with DMTs. Compared to placebo, patients on fingolimod also showed a reduced risk of disability progression and a benefit in MRI-related efficacy end points, with no significant differences in efficacy between the two fingolimod doses.

In the recently completed 12-month, phase III controlled trial (TRANSFORMS), a total of 1292 patients with active RRMS were randomized to 0.5 mg or 1.25 mg daily oral Fingolimod or 30 μg once-weekly intramuscular IFN-beta 1a (AVONEX) [26]. Fingolimod significantly reduced annualized relapse rates (52% for 0.5 mg and 38% for 1.25 mg, both p < 0.0001) and MRI measures of inflammation compared with AVONEX. Safety data showed that the drug was generally well-tolerated, although there was an increased rate of localised skin malignancies and two fatalities from severe herpes infection. Other side-effects were a transient bradycardia and infrequent atrioventricular conduction blocks after the first dose of fingolimod, minor increases in blood pressure persisting on therapy, and asymptomatic liver enzyme elevations. Macular oedema, mostly reversible within 1 to 6 months after discontinuation of therapy [27], occurred in 3 patients on fingolimod.

Based on the results for the 0.5 mg dose in the FREEDOMS and TRANSFORMS trials, fingolimod (Gilenya®) was recently approved by the FDA for the treatment of patients with RRMS, and the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for European countries.

Conclusion

A number of DMTs became available during the past 15 years which significantly changed the therapeutic approach in multiple sclerosis (MS). These conventional DMTs with broad experience - interferon-beta 1b, interferon-beta 1a, and glatiramer acetate are still partially effective and are not free from adverse effects. Therefore, further development of DMT in MS has rapidly evolved over the last few years and continues to do so, leading to the additions to the treatment armamentarium, comprising immunosuppressive drug mitoxantrone, recently introduced antibody natalizumab and more recently, the sphyngosin-1-phosphate receptor modulator fingolimod.

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