Review of the novelties presented at the 27th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (II)

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Summary. The new insights presented at the 5th Joint Triennial Congress of the European and Americas Committees on Treatment and Research in Multiple Sclerosis (ECTRIMS and ACTRIMS) held in Amsterdam, the Netherlands, 19-22 October 2011, have been summarized at the fourth edition of Post-ECTRIMS meeting held in Madrid in November 2011. Regional grey-matter atrophy is more sensitive to cognitive impairment than global grey-matter atrophy measures. In patients with clinically isolated syndrome cognitive impairment does not predict conversion to multiple sclerosis (MS) after 5-years of follow-up. Focusing on central nervous system plasticity and functional reorganization in MS, an early intervention can improve clinical aspects and enhances brain plasticity. Preservation of a potential for plasticity provides a rationale for rehabilitation interventions even in later stages of disease. Therapeutical strategies have focused on stem cell-mediated remyelination and immunomodulation functions, on cellular infiltration into the brain, and on new ways for immunomodulation for the development of future therapies in MS. Encouraging findings from clinical trials with current and emerging disease-modifying therapy being developed was also a key theme at this edition. Positive results have been reported for rituximab, ocrelizumab, ofatumumab, daclizumab, alemtuzumab, teriflunomide, BG-12, and laquinimod, including a favorable safety profile. Since armamentarium for the treatment of MS is fast increasing, concerns exist about the risk of severe adverse events with their use. This aspect reinforces the importance of disease registries as a proactive tool for monitoring drug safety in the post-approval setting.

Key words. Cognition. ECTRIMS. Multiple sclerosis. Rehabilitation. Treatment.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international meeting on this pathology. The last Congress, held in October 2011, was attended by 7991 specialists in multiple sclerosis (MS) from 95 countries.

The Post-ECTRIMS experts' meeting, which has been held in Madrid each year for the last four years and enjoys the scientific backing of the Spanish Neurology Society, provides a setting where renowned national leading figures in this area can present the most significant data considered at ECTRIMS 2011.

Cognitive impairment in MS

Among the latest novelties and insights on how to address cognitive impairment in MS, some of the most notable are the works designed by the group led by DeLuca [1] to evaluate the effectiveness of a cognitive rehabilitation technique (the modified Story Memory Technique) in improving memory and learning in patients with MS. This is a compensatory technique consisting in a 10-session intervention that teaches patients to improve their learning by basing it on the context of the information and pictures. The neuropsychological results deriving from two randomised clinical trials at four weeks and at six months show that this cognitive

retention technique improves both short-term and long-term memory, as well as learning in general. These findings are more apparent in moderately and severely compromised patients, and agree with those from other work published on this topic. The results of magnetic resonance imaging (MRI) carried out in another randomised clinical trial showed that, at six months, this technique increased the cortical activation of areas traditionally involved in memory, such as the frontal, parietal, precuneus, corpus callosum, fornix and right inferior longitudinal fasciculus.

Benedict's group [2] evaluated a 3T MRI method to check whether there are any differences in the development of the regional grey matter atrophy between MS patients with and without cognitive dysfunction. Using the tensor-based morphometry (TBM) technique they analysed, both at baseline level and at 12 months, a total of 13 controls and 33 patients with MS. Cognitive performance was obtained by means of the neuropsychological battery MACFIMS and cognitive dysfunction was defined as an altered score in ≥ 2 tests. Both at the baseline level and at 12 months, patients were seen to have greater grey matter atrophy than controls, above all in those with cognitive dysfunction. Yet, the most interesting finding was the difference between the baseline level and at 12 months as regards the zones of regional grey matter atrophy, with greater involvement of the cerebral cortex in more advanced phases of the cognitive impairment and of the deep grey matter in the early phases.

From all this, it was concluded that the TBM 3T technique is a sensitive method for detecting longitudinal changes in regions of the grey matter, that regional grey matter atrophy is more sensitive to cognitive impairment than measures of global cerebral atrophy, and that cognitive impairment is associated to longitudinal changes in regions of the grey matter.

In view of recent evidence showing early cognitive impairment to be a risk factor for conversion to clinically defined MS in patients with isolated demyelinating syndrome, Montalban's group [3] designed a study to evaluate its value as a predictor of conversion to MS according to the McDonald criteria of 2005. A total of 53 patients were analysed by means of a full neuropsychological battery and MRI (data not available) at the baseline time, at 12 months and at five years. The neuropsychological aspects focused on areas that are normally affected in patients, such as memory, attention, processing speed and executive functions, and cognitive impairment was defined as the result of more than three altered tests. The analysis showed that 15.1% of patients with isolated demyelinating syndrome presented cognitive impairment and 60.4% converted to clinically defined MS at five years; in contrast, no significant differences were found between groups with cognitive deterioration (37.5%) or without cognitive deterioration (44.4%) or in the time taken to convert to MS. These findings point to a prevalence of cognitive impairment in patients with isolated demyelinating syndrome below the reported value, which reaches 30% in some of the studies published. In this cohort of patients, the presence of cognitive impairment in isolated demyelinating syndrome does not predict conversion to MS at five years.

Functional reorganisation and rehabilitation in MS

Calzá [4] drew a clear distinction between the 'cerebral' reserve, or the structural plasticity component, and the 'cognitive' reserve, or the functional component. Taking this as her starting point, the author set out from the premise that, in the presence of the same pathology of the central nervous system, the severity of the clinical manifestations may differ depending on the amount of cognitive and cerebral reserve. To find an answer to this, she referred to two classic conditions, stroke and Alzheimer's disease, as a prototypical acute disease and chronic neurodegenerative disease, respectively, and observed that the greater the cerebral reserve is, the better the patient's recovery will be following a stroke and the greater the delay before the clinical onset of a chronic neurodegenerative disease will be.

Cerebral plasticity is grounded on different mechanisms and levels that range from the molecular to the systemic. As possible targets, pathways or approaches of action, the question arises as to whether it is possible to protect or increase the cerebral reserve and improve plasticity, and whether this protection could affect the course of chronic neurodegenerative diseases.

To be able to answer this issue, Calzá used animal models of Alzheimer's disease and highlighted the fact that the most important thing is to look for the right moment to act upon the right target. As an example, it is a well-known fact that there is a poor clinicopathological correlation between amyloid plaques and cognitive impairment, and thus the amyloid starts the degenerative cascade but progresses independently. The clinical manifestations are therefore not going to be related to the amount of amyloid but to the number of other known events, such as neurofibrillary tangles and

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synaptic and neuronal disorders, among others. This accounts for the number of failures in clinical trials with drugs versus β-amyloid with apparent clinical signs and symptoms. In this respect, Calzá proposes prevention in asymptomatic phases, either by preventing the formation of plaques or the action of amyloid or by stemming the neurodegenerative cascade, which could involve increasing the reserve and enhancing the plasticity.

As an example of new targets and drugs in animal models, Calzá cited galanin, a neuropeptide that modulates the cholinergic function, which it could be possible to act upon by increasing the expression of one of its receptors in order to protect the cholinergic cells from death induced by β-amyloid. Another example she referred to was the drug CHF5074, a γ-secretase modulator, which prevents the formation of plaques. In relation to the action of CHF5074, the same author highlighted two studies conducted on models with transgenic mice, TG2576 [5] and hSwAPP [6].

In TG2576 mice, which express the mutant amyloid precursor protein, cognitive impairment appears earlier than the plaques. Moreover, it has been found that, in early phases before the formation of plaques, both learning and memory are fully recovered in mice treated with CHF5074. There is also an activation of the brain plasticity mechanisms reflected by a normalisation of the levels of synaptophysin, a marker of plasticity and of synaptic proteins, greater astroglial reaction with fewer microglia activated, and an increase in neuronal protection. Likewise, in the early stages of plaque formation, middle-aged hSwAPP mice with Alzheimer's disease show diminished neurogenesis and disabled neuronal maturation. On being treated with CHF5074, the potential for neurogenesis is restored in the subgranular zone of the hippocampal dentate gyrus, and clinically both learning and memory are improved. These results show that an early intervention can improve clinical aspects by somehow enhancing brain plasticity.

With regard to adaptive plasticity, the patterns of activation depend on the pathological substrate. Similar changes can be induced with learning or rehabilitation, and improvements are achieved with training; in contrast, interrupting the activation could damage the function. MRI studies have shown that plasticity is mediated via functional distribution networks in the brain and clinical recovery is facilitated by functional reorganisation. As an example of this, Louapre et al. [7] presented a study in which they described the appearance of early cognitive impairment as a consequence of a modification of the functional networks, with a mixed alteration that is both local (involving the connections of the cognitive functional networks in the cingulate) and diffuse, caused by damage to the microstructure of the white matter.

In reference to the patterns of brain activation in MS and based on a study conducted by Cifelli and Matthews [8], Matthews [9] suggested that they could vary due to both the lesion load and the clinical stage of the disease, so that the increase in lesion load would give rise to a fault in the plasticity mechanisms.

Later, and based on work by Rocca et al. [10], Matthews also referred to the relationship between the elements of plasticity and the clinical forms of MS, and proved that there is a topographical relationship in the motor activation response that is dependent on the different clinical forms of MS. Hence, in benign MS, the primary sensory-motor cortex was activated; in the early relapsing-remitting and secondary progressive forms, activation occurred in the secondary motor cortex; and in the progressive disease, the parietal cortex was activated.

Matthews then suggested that the patterns of brain activation in MS might vary with cognitive dysfunction and the progression of the disability. Along similar lines, the works by Mainero et al. [11] and Penner et al. [12] concluded that patients with relapsing-remitting MS and severe cognitive impairment have less activation than in mild cases. Similarly, He et al. [13] observed that the progression of disability in MS reduces the effectiveness of the functional neuronal networks. Hence, it could be suggested that the progression of disability in MS might be due to a fault in the plasticity mechanisms and, in relation to this possibility, Barkhof's group [14] put forward the following hypothesis concerning the progression of MS. In the first phase there would be minimal structural damage accompanied by an important response involving reorganisation and brain plasticity, with very low clinical disability and no cognitive impairment. The second phase would involve a peak in the functional reorganisation, in which there would still not be any important clinical repercussions, despite the greater structural involvement. And the third phase would include a decline in brain plasticity coinciding with greater structural damage, progression of disability and increasing cognitive impairment. This would mean that the adaptive plasticity must be very affected or annihilated in highly disabled patients. Nevertheless, Tomassini et al. [15] showed that, in relation to behaviour and visuomotor skills, plasticity is conserved at any level of disability in

patients with MS, as performance of these patients improves with long-term training. This finding challenges Barkhof's concept of disability as a fault in adaptive plasticity and leads us to conclude that preservation of a potential for plasticity provides a rationale for introducing neurorehabilitation interventions, even in advanced stages of the disease. Matthews concluded his dissertation by calling attention to the need to establish mechanisms that contribute to plasticity in order to optimise neurorehabilitation procedures.

How to measure clinical progression

To evaluate the effectiveness of a treatment in a clinical trial, it is necessary to find proxy (surrogate) variables that, despite not being prognostic factors, allow the progression of the disability to be predicted before it begins. Disability is the most important variable in a clinical trial and also the most difficult to calculate, since it progresses over many years (in contrast to the duration of the studies, which do not usually last more than two years), it is irreversible once it has begun and the scale that is used to measure it – the Expanded Disability Status Scale (EDSS) – has a low level of sensitivity, among other problems related to its application. As a result, we have to use surrogate markers to replace the EDSS which can be measured easily before the progression of the disability begins. Thus, for example, in phase II studies MRI active lesions are usually taken as the main variable, while in phase III studies, the rate of attacks is used.

The key question is whether the MRI active lesions and the rate of attacks are really valid as surrogate variables for disability, that is to say, if we show that a treatment is effective on these variables, can we predict that it will also be effective in delaying the progression of the disability? This question can be answered from two perspectives: that of clinical trials and the individual perspective for each patient.

From the perspective of clinical trials, a recent meta-analysis conducted by Sormani et al. [16] showed that over 70% of the effect of treatments on the EDSS can be explained by the effect of the treatment on the rate of attacks, and nearly 60% of the effect of treatments on the EDSS can be explained by the effect of the treatments on the active lesions. Likewise, when a 50% reduction in the rate of attacks occurs in a clinical trial, a 30% reduction in the relative risk of progression of the EDSS can be expected; and when a 50% reduction in MRI active lesions is produced, a 5% decrease in the risk of progression can be expected. From the individual point of view, to be able to validate a surrogate marker it must satisfy Prentice's four criteria, i.e. the treatment must have a significant effect on the surrogate marker and on the clinical variable, there must be a significant relation between the surrogate marker and the clinical variable, and the effect of the treatment on the clinical variable is mediated by the effect on the surrogate marker.

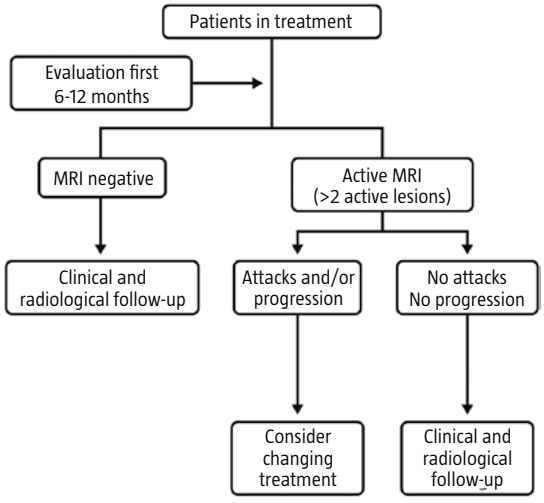
In a retrospective analysis included in the PRISMS study [17], in which the surrogate markers were the MRI active lesions and the rate of attacks and the clinical variable was the EDSS, all the Prentice criteria were fulfilled; in other words, in this study with subcutaneous interferon β-1a (and other similar treatments), MRI activity and the rate of attacks are surrogate variables for disability. It can be concluded that, in patients with relapsing-remitting MS, the effect of interferon on disability at two years is wholly (100%) due to the effect of interferon on the MRI active lesions and the rate of attacks during the first year of treatment. The short-term effect of treatment on the MRI and the rate of attacks predicts the effect on disability, also in the short term.

The practical consequences would be recruitment of fewer patients, together with a shorter duration of pivotal clinical trials with classic immunomodulators in the recurring forms, since the effect of treatment on the EDSS at two years can be replaced by the effect on the MRI active lesions and the rate of attacks in the first year. It should be noted that these conclusions cannot be extrapolated to the long term or to new pharmaceuticals – they are only valid in the short term. If the effect of treatment on disability in the long term can be proxied by short-term markers, and if this also happens with the new drugs, then another meta-analysis should be conducted.

The creation and validation of new disability scales will make it possible to study different dimensions of the disease and to measure progression with a higher degree of sensitivity, although interpreting the results may be a complicated affair, above all from the clinical point of view. As new ways of measuring the clinical progression, and in view of the limitations of the disability scales that are currently available, steps are being taken to improve and expand on already existing tools and to validate other new and more sensitive ones, both in the health care setting and in clinical trials.

Possible improvements to the EDSS are aimed towards the production of a composite scale that combines it with others which evaluate deficient fields, the simplification of the norms for scoring,

Figure 1. Decision algorithm in patients in treatment with disease-modifying agents.



and the determination of the functional systems with greater specific weight in order to rationalise their use. Proposals for improving the Multiple Sclerosis Functional Composite Scale include adding a visual test, replacing the PASAT by a cognitive test that is simpler to apply (Symbol Digit Modalities Test), changing the method of scoring, and using a walking test that calls for a greater effort from the patient than the 25-step test (T25WF).

Several studies have been carried out recently with the aim of validating the new tools for measuring progression. Thus, in patients with primary progressive MS and in treatment with rituximab, Zhang et al. [18] observed a moderate degree of correlation (70%) between the progression at 12 weeks, as defined by the EDSS scale, and the T25WF test. Applying the EDSS progression criteria or the progression criteria of the T25WF test increased the 'sensitivity' for detecting the progression of the disability, and greater 'precision' was achieved on applying the progression criteria of both tests. Moreover, in any of the cases the power to detect the effectiveness of the treatment was increased. In patients with primary progressive forms, it would be better to apply both scales jointly to detect the progression of disability, although they need to be validated before they can be applied in clinical trials and in clinical practice.

Miller et al. [19] have shown, in an observational study, how depression is related to the degree of disability. An increase in the score on the Patient Health Questionnaire-9 depression test was inversely related to walking speed (T25WF), regardless of age, sex, race, form of MS and the use of antidepressants. It could be tempting to establish a causal relationship and propose that a higher degree of depression diminishes walking speed, even though it is not possible, since this is an observational study and its results only allow us to claim that there is a certain relationship between them.

Finally, Bonzano et al. [20] presented the electric glove as a new quantitative and objective tool for evaluating dexterity in the hands, which are so often affected in patients with MS and which the EDSS does not quantify at all. After placing a set of electrodes on the fleshy parts of the fingers, the patient is asked to tap the tip of the thumb against the tips of the other fingers sequentially. A number of different variables can be quantified in this way, including the length of time they are in contact, the interval between taps, the speed in one hand, the difference between the speeds of the two hands, and so forth. In the studies that were conducted, the scores obtained with this test yielded a high degree of correlation with the EDSS, except in patients with low disability (EDSS < 3).

Identifying response to treatment

Tintoré [21] pointed out that the early identification of non-responder patients is important to be able to optimise the therapeutic response in MS. The work carried out by her group on a prospective cohort of patients revealed the presence of > 2 MRI active lesions at 12 months as the most important radiological measurement related to a response to treatment. On combining the clinical information and the radiological information as a measure with predictive value, she observed that patients who, at 12 months of treatment, presented clinical or radiological activity or progression in at least two of the three variables analysed (attacks, increased disability or MRI activity) had almost six times more risk of continuing to be active after three years and almost 13 times as much risk if they were positive for the three variables. Taking these results as her starting point, she proposed a decision algorithm for handling patients treated with disease-modifying agents (Fig. 1).

The Italian group led by Sormani, on the other hand, proposed that the RIO score should be modified by eliminating the clinical criterion of disability and applying only MRI criteria (0: absence of new

lesions; 1: presence of new lesions) and relapses (0: 0 relapses; 1: 1 relapse; 2: ≥ 2 relapses). In the same way, patients with a score of 2-3 at the end of 12 months presented a greater probability of progressing and suffering attacks during the follow-up.

In another context, Hillert [22] highlighted the importance of biological markers in MS. Among the biomarkers of treatment response that have been explored in recent years, some of the most significant he drew attention to were indicators of pathogenic inflammatory processes (CXCL13, osteopontin, lipid-specific IgM bands) and tissue damage (light neurofilaments), as well as pharmacodynamic response indicators.

Although in another line, the conclusions from the work carried out by Romeo et al. [23] to identify demographic, clinical and MRI baseline factors as response predictors, even before starting treatment, stressed the importance of early treatment in long-term response. The authors defined non-responder patients as those who have a progression of 1.5 points of confirmed disability at six months or those who have changed to a second-line drug; responders were taken to be those who did not present attacks and who had progressed < 1.5 points. In a cohort of 668 patients with a relapsing-remitting form of the disease, they identified 33% of responder patients versus 22% of non-responders. A comparison of the two groups showed that non-responder patients presented a more advanced disease status on beginning treatment, since they had a higher score on the EDSS, a greater probability of having multifocal onset and initially more Gd-enhancing lesions. Similarly, detecting more than two MRI active lesions in a scan carried out at 12 months was associated with a higher risk of disability progression after five years (odds ratio non-responders versus responders: 4; 95% confidence interval: 1.6-10; p = 0.003). From these findings the authors concluded that it can also be used as a tool to predict a lack of response.

As regards the potential predicting factors in isolated demyelinating syndromes, Meyniel et al. [24] presented the findings of the first multinational study to use a multivariate analysis model – demographic, clinical, MRI and cerebrospinal fluid (CSF) data – to establish the time to relapse. The most notable results validate the prognostic value of all the baseline radiological criteria in patients with isolated demyelinating syndrome for the independent prediction of the appearance of a second attack in clinical practice, more particularly Gd uptake and the total number of lesions in T_2 (≥ 3) with an infratentorial and juxtacortical location. The study stresses the importance of the value of early treatment to delay the appearance of a second attack in patients with isolated demyelinating syndrome.

Freedman et al. [25] reported the results from a sub-study of the BENEFIT study, which examined patients with isolated demyelinating syndrome in order to evaluate clinical/MRI/laboratory parameters as predictors of the activity of the disease prior to treatment and in the first year of treatment. To sum up, at baseline level both age and the number of lesions in T_2 predict conversion; in the first year of treatment, the presence of attacks, the progression of disability and the appearance of new lesions predict the clinical or radiological activity that appears during the follow-up.

New biomarkers of disease progression and response to treatment in MS

Baranzini's group presented the latest results of two studies that were the continuation of work that had already been published by the group related with the disease progression and response to treatment. The first [26] was aimed at identifying patterns of gene expression with microarrays in patients with isolated demyelinating syndrome; the main finding was the detection of a diminished expression of the *TOB1* gene (which encodes a transcription factor that regulates cell proliferation) in patients who converted to MS. The same group offered interesting data on the effect of suppressing the *TOB1* gene in experimental models with mice, both in the clinical course of the disease and in the patterns of cytokine secretion.

In the second work [27] several triplets were identified, mainly genes related to the apoptosis pathway, and type I interferon pathway regulators that were highly predictive of the response to interferon-β. In this regard, they presented some results from a gene expression sub-study from the clinical trial IMPROVE, which evaluates the effectiveness of a new formulation of subcutaneous interferon β-1a. After classifying patients according to clinical and radiological criteria, they identified combinations of two or three genes that were highly predictive of an optimal or sub-optimal response to interferon-β.

With regard to the process of identifying new biomarkers in CSF, Comabella [28] pointed out a first *discovery* phase, which is aimed at identifying candidate markers by means of non-biased and semi-quantitative approaches such as proteomics, and a second phase involving the validation and de-

velopment of a clinical trial, with more sensitive and more quantitative techniques. From all the proteomics studies on the CSF of MS patients, Comabella highlighted three candidates as biomarkers, i.e. fetuin-A, vitamin D binding protein and, especially, chitinase 3-like 1 (CHI3L1), which when present in high levels in the CSF are associated with conversion to relapsing-remitting MS. These findings were validated by ELISA (Fig. 2). An important validation study is currently being carried out on a large cohort of CSF samples from patients with first attacks and controls with other neurological diseases. Many European and national groups contribute to this study.

Taking as their starting point the well-established role of certain cytokines and receptors as risk factors for MS, Vandenbroeck et al. [29] genotyped 368 polymorphisms included in 55 genes, most of which were genes coding for interleukins and interleukin receptors. An initial genotyping in a cohort of 462 patients with MS and 470 controls living in Bilbao showed *SOCS1*, *IL28RA*, *OSMR* and *IL28-RA2* to be the genes that presented the greatest association with MS and they were selected for a later validation phase in five independent cohorts, in which only *SOCS1* was validated. It is interesting to note that by carrying out the staging according to clinical forms, it was found that the risk allele (T) of *SOCS1* was represented more in the relapsing-recurring and secondary progressive forms than primary progressive MS, and that this association was independent from another chr16 MS risk locus, CLEC16A. Presumably, *SOCS1* can play a role as a disease-modifying gene.

Matsushita et al. [30] also reported the results of their work, which simultaneously determines CSF levels of cytokines and chemokines in patients with neuromyelitis optica, MS and controls with other neurological diseases and their correlation with clinical and CSF parameters. Briefly, the levels of IL-17, IL-6, CXCL8 and CXCL10 were significantly higher in patients with neuromyelitis optica during the attack in comparison to relapsing-remitting MS in attacks and controls; patients with neuromyelitis optica presented higher levels of IL-6 and CXCL8 during the flare-up than when remitting. Furthermore, IL-6, CXCL-8 and G-CSF levels correlated positively with EDSS and the number of neutrophils in CSF. From the data it can be concluded that inflammation mediated by Th1/Th17 cells could be involved in the pathogenesis of neuromyelitis optica.

Finally, the group led by DeJager [31] has studied whether there are molecular subgroups of MS and their possible relationship to the course of the disease and response to treatment. Using microarrays in non-treated patients, they identified two subgroups of patients with a different pattern of gene expression and who presented different responses to treatment with immunomodulators.

Treatment of MS

Cell therapy

Therapeutic strategies with stem cells are based on immunomodulation and on favouring remyelination. From a theoretical point of view, this remyelination can be accomplished by mobilising endogenous stem cells or transplanting stem cells, although in practice axonal regeneration is difficult to achieve.

The places where remyelinating cells are synthesised include the subpopulations of oligodendrocyte precursor cells, the embryonic precursors of Schwann cells, neural crest cells and olfactory bulb cells.

The remyelination associated with transplanting oligodendrocyte precursor cells is correlated with clinical and neurophysiological recovery. Although oligodendrocyte precursor cells migrate and proliferate within the damaged tissue, they are unable to survive and proliferate within healthy brain tissue. This led Martino et al. [32] to suggest that it will be necessary to identify the lesions to be treated, which should be the most relevant ones, in clinical terms. Yet, obtaining large amounts of oligodendrocyte precursor cells is not such a simple task.

Some studies have indicated that human oligodendrocyte precursor cells require more time to remyelinate than murine precursors. To study the remyelinating potential of human stem cells from embryos that were induced to distinguish themselves as highly purified oligodendrocyte precursor cells (GRNOPC1), with a proven capacity for remyelination in murine experimental models, Kocsis et al. [33] developed an experimental model with non-human primates, which consisted in transplanting such cells into a spinal cord in which demyelination had previously been induced. The results showed that all the GRNOPC1 cells in the spinal cord survived in all cases, although remyelination was accomplished in only four of them at months 1.5, 4.5, 6 and 12, which was later than in the murine models. The results of the neurological examination were normal and no evidence of tumours or other pathologies was found. Therefore, GRNOPC1 cells are safe, in addition to active, and would be available for use in clinical trials.

Another line of research, which addressed the transplanting of haematopoietic stem cells in MS, was conducted by Abrahamsson et al. [34] in order to identify different immune reconstitution mechanisms following transplant, according to different previously developed myeloablative immunosuppression protocols. The results of the same study showed that conditioning regimens that use cyclophosphamide + alemtuzumab allow immune reconstitution mainly through an expansion of the memory T cells and an increase in the immunoregulatory populations. Reconstitution with cyclophosphamide + anti-thymocyte globulin, however, gives rise to an expansion of the naïve T cells and a reciprocal contraction of the memory cells, which suggests an immune reconstitution that is superior to that observed with regimens that include alemtuzumab.

Moreover, Tsakiri et al. [35] posited the hypothesis that TNFR2 signalling in non-haematopoietic cells is essential for regulatory T cell-mediated suppression to take place in experimental autoimmune encephalitis. To prove this, the researchers used TNFR2 knockout mice models and observed an exacerbation of experimental autoimmune encephalitis with no remission phase, which was associated to a smaller number of FoxP3+ regulatory T cells. Furthermore, the regulatory T cells of TNFR2 knockout mice displayed reduced suppression and proliferation functions. These data suggest that the expression of TNFR2 in non-haematopoietic cells is vital to maintain the immunosuppression mediated by FoxP3+ regulatory T cells in experimental autoimmune encephalitis. Thus, an alteration in the signalling pathway could be responsible for the failure of FoxP3+ regulatory T cells to prevent or control autoimmunity in MS and may account for the chronic recurring course of the disease.

New immunomodulation pathways in multiple sclerosis

The recent identification of several indices of early alteration to the blood-brain barrier opens up the way to search for new adhesion molecules involved in the selective recruitment of immune cells that are central nervous system-specific and which could nowadays be considered the basis for developing monoclonal antibodies that are somewhat more specific than those currently available [36].

As regards the activated leukocyte cell adhesion molecule (ALCAM), Prat [37] observed that, in experimental models of MS, the anti-ALCAM monoclonal antibody reduced infiltration of the lymphocytes CD4+, CD20+ and monocytes across the blood-brain barrier, thereby proving to be quite unspecific. In addition, the same author studied the MCAM or CD146, which is an adhesion molecule that is expressed above all in CD4+ and CD8+. These lymphocyte populations produce IL-17 and IL-23R (two cytokines that are closely linked in models of inflammation), are found at high levels in the blood of patients with MS in attacks and are present in active lesions. The anti-MCAM antibody made the experimental autoimmune encephalitis less aggressive, both in terms of prevention and as therapy.

Another line of study was molecular imaging and cell labelling proposed by Dousset [38] with the aim of obtaining a 'radiological' image. It is possible to label a specific function, cell or molecule and labelling was performed *in vitro* and the follow-up carried out *in vivo* in patients. The aim was to achieve a non-invasive way of tracking grafts, evaluating cell mobility, differentiation or viability *in vivo*, or studying the release of molecules or activation of genes, as well as assessing their usefulness in positron emission tomography studies and in the search for new contrast agents that are MS-specific. Related to this, Beckmann et al. [39] considered the use of USPIO (Ultrasmall Superparamagnetic Iron Oxide), which is made up of nano-particles of iron,

Figure 2. Levels of CHI3L1 in the cerebrospinal fluid of patients with isolated demyelinating syndrome and controls. Control group: patients with other neurological diseases (n = 20). Group 1: samples from patients with isolated demyelinating syndrome who do not convert to clinically defined multiple sclerosis (n = 36). Group 2: samples from patients with isolated demyelinating syndrome who convert to clinically defined multiple sclerosis (n = 48). [a] $p = 2.3 \times 10^{-5}$.

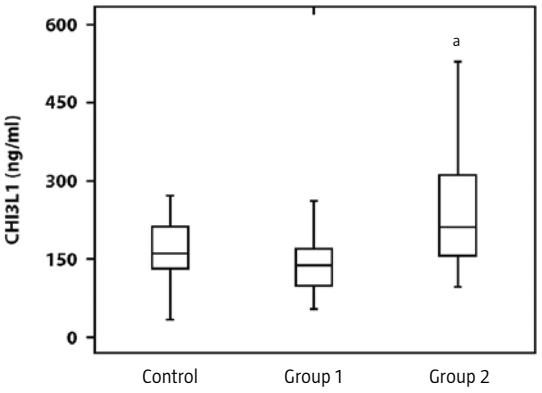
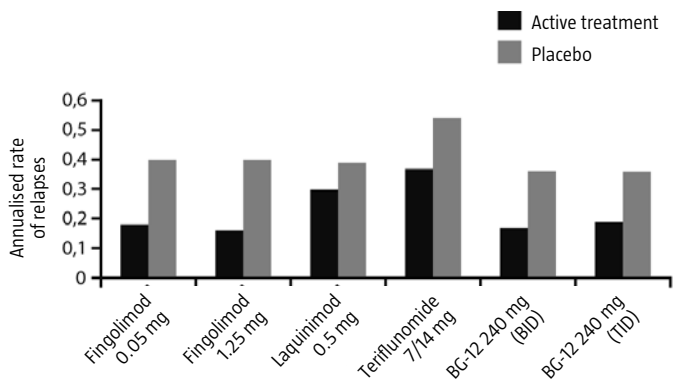


Figure 3. Annualised rate of relapses of the oral drugs versus placebo. Results of different clinical studies (FREEDOMS, ALLEGRO, TEMSO, DEFINE), so that no direct comparison can be carried out. BID, twice a day; TID, three times a day.



to be able to use MRI to view macrophage activation in the inflamed zones, since they phagocytise this compound. As a result, the sensitivity of MRI for capturing lesions increases tenfold with respect to Gd. In studies with humans, the authors found a discrepancy in the uptake of those contrast agents. Thus, while the T_1-weighted images showed a lesion that was not enhanced with Gd immediately after its administration, the same scan performed 24 hours after administering USPIO revealed uptake of this contrast medium in the peripheral area of the lesion. The authors suggested that tracking the macrophage infiltrate with USPIO could be a more powerful predictor of the development of MS than imaging a pathological increase in the permeability of the blood-brain barrier using Gd.

In an exceptional study conducted by Ajami et al. [40] the monocytes that infiltrate into the central nervous system were seen to induce experimental autoimmune encephalitis, but did not contribute to the pool of resident microglial cells. Using a murine model of experimental autoimmune encephalitis with parabiosis and ablation of the blood monocytes by means of irradiation, the same authors succeeded in replacing the circulating progenitor cells without affecting the resident microglia. Their results showed a strong relation between monocyte infiltration and progression of the disease, although this was only transitory, since the recruited monocytes undergo apoptosis. It is the resident microglia that becomes active and produces progression of the disease, despite the fact that the infiltrating monocyte is the one that induces the disease. Therefore the use of blood monocytes as a therapeutic target could be useful in the treatment of MS.

Disease-modifying therapy. New data

The different approaches to current and emerging disease-modifying therapies were a key topic in this edition of the congress (Table I; Fig. 3), together with the promising results from clinical trials that are currently being conducted.

Rituximab and ocrelizumab

Rituximab is a selective monoclonal antibody for CD20+ lymphocytes that is effective in lowering activity in MRI. Yet, when the clinical course is analysed, the HERMES study shows that, at weeks 24 and 48, the reduction in the rate of attacks compared to placebo is relatively small, though still a figure that must be taken into account. Furthermore, the authors also point out that rituximab is not effective in the primary progressive forms of the disease [41].

More interesting results have been obtained with ocrelizumab, an anti-CD20 antibody. The work shows an 80% reduction in the annualised rate of attacks versus placebo and 73% versus interferon β-1a [42].

Ofatumumab

This drug stands out for being of potential value in MS due to its having complement-dependent cytotoxicity as one of its therapeutic targets. The initial pilot study offers some very promising results as regards the reduction of active lesions.

Daclizumab

This is an anti-CD25 monoclonal antibody that has proved to have a favourable effect in MRI in relapsing-recurring forms. The CHOICE study [43], conducted on patients treated with interferon β who were randomly chosen to be given either high or low doses of daclizumab or interferon β and placebo, shows a significant difference as regards the number of lesions in favour of the high dose of daclizumab. The side effects were well tolerated and similar to those reported for all drugs that are selective for B cells, one of the most notable being the allergic reaction that occurs at the site of the injection after the second injection at 15 days.

The SELECT study [44], which is currently still being carried out, analyses the effectiveness and safety of two doses of daclizumab (150 mg, 300 mg) versus placebo in patients with relapsing-remitting MS and some parameter that reflects activity prior to being included in the study. Preliminary results

showed that both doses of daclizumab significantly reduce the rate of attacks by 50-55%, with around 80-81% of patients free from relapses versus placebo. On analysing the progression of the confirmed disability at three months, it was observed that the 150 mg dose yielded a significant 57% reduction in the progression, which was not achieved with the 300 mg dose. Both doses of daclizumab were effective in reducing active lesions in MRI, as well as in the presence of new lesions or lesions that were larger in T_2. The side effects were very similar in the three groups that were analysed, the most common being infections and events affecting the skin.

Table I. Reduction in the annualised rate of yearly relapse of the disease-modifying treatments.

Study	Treatment	Rate of attacks	Ref.
REGARD, BEYOND	IFN versus glatiramer acetate	No difference	[61,62]
AFFIRM	Natalizumab versus placebo	68%	[63]
	Rituximab versus placebo	20%	[41]
	Ocrelizumab (600 mg, 2000 mg) versus placebo	80-73%	[42]
CAMMS 223	Alemtuzumab versus subcutaneous IFN β-1a	74%	[45]
TRANSFORMS	Fingolimod versus intramuscular IFN β-1a	52%	[64]
TEMSO	Teriflunomide versus placebo	31%	[47]
DEFINE	BG-12 240 mg (twice a day, three times a day) versus placebo	53-48%	[48]
ALLEGRO	Laquinimod versus placebo	23%	[49]

Results of different clinical studies that do not allow direct comparison. IFN: interferon.

Alemtuzumab

In previous studies it displayed a very prolonged cytotoxic effect, generally lasting 1-3 years, with a reduction in T and B lymphocytes and monocytes. The CAMMS223 study [45] has shown that over three years alemtuzumab reduces the annualised rate of attacks by 74% versus subcutaneous interferon β-1a at doses of 44 µg three times a week, which are figures that are higher than those observed with natalizumab. Very similar data were observed in a three-year follow-up with respect to the EDSS, with a difference of 70% between alemtuzumab and interferon β-1a.

The CARE-MS-I study [46], which is currently being conducted, compares the effectiveness and safety of alemtuzumab with respect to interferon β-1a (Rebif®). The main variables are the rate of attacks and the time elapsed before the increase in confirmed disability at the sixth month. The study includes a total of 581 naïve patients with a history of relapsing-remitting MS ≤ 5 years, with an EDSS between 0-3, and at least one attack in the last year or at least two attacks in the last two years. Patients were chosen at random to receive alemtuzumab (five pulses/day – one year's rest – three pulses a day) or interferon β-1a at a proportion of 2 to 1. Alemtuzumab is seen to significantly reduce the annual rate of attacks in comparison to interferon β-1a from the first year onwards, but does not prove effective in the progression of the disability. Alemtuzumab was seen to have a significant effect on radiological parameters of activity and cerebral atrophy.

In terms of safety, the percentages of serious infections were kept to a minimum and were similar in both treatment arms. Thyroid pathologies were more frequent in the alemtuzumab group (18.1%) than in the interferon β-1a group (6.4%). Nevertheless, the percentage of patients with severe thyroid events was very low and most of the patients could be managed easily with conventional therapy. Cases of idiopathic thrombocytopenic purpura were few in number and similar in both arms: 0.8% in alemtuzumab and 0.5% in interferon β-1a. As occurs with severe thyroid events, patients were easily managed with conventional therapy without the need to perform a splenectomy in any of the cases.

Teriflunomide

The recently published TEMSO study [47] was conducted on 1088 patients with relapsing-remitting MS, an EDSS of up to 5.5, at least one relapse in the past year or at least two relapses in the two previous years, who were selected at random to receive 7 mg or 14 mg of teriflunomide or placebo. Results showed a significant difference in favour of teriflunomide both clinically and in the appearance of new lesions. More particularly, both doses of teriflunomide reduced the annual rate of relapses by 31-32% versus placebo and, to a greater extent, the number of Gd-enhancing lesions, with a 57.2% reduction with a dose of 7 mg and 80.4% in the case of the 14 mg dose versus placebo. Side effects were well tolerated.

BG-12

The DEFINE study [48] with BG-12 yields promising results, above all, at the anti-inflammatory level and to a lesser extent with regard to reducing the progression of the disability. BG-12 reduces the num-

ber of active lesions by 90% and 73% versus placebo in the groups with two or three times a day, respectively; likewise, BG-12 twice a day reduces the annualised rate of relapses by 53% and BG-12 three times a day does so by 48%. Side effects include febricula, headache, dermatological symptoms (transient rash), diarrhoea in 2% of patients, transitory increase in hepatic enzymes, lymphopenia and microalbuminuria.

Laquinimod

The ALLEGRO study [49] was carried out in patients with previously active relapsing-recurring forms to compare 0.6 mg/day of laquinimod versus placebo. A significant effect was observed in the reduction of the annualised rate of relapses (23%), as well as in the reduction of Gd^+ enhancing lesions (37%) and new lesions in T_2 (30%). It also reduces the risk of developing progression of disability by 36%, although with no significant differences compared to placebo. On analysing cerebral atrophy, a significant reduction of 33% was obtained versus placebo. The use of magnetisation transfer imaging, a non-conventional MRI measure of neuronal destruction, again showed the possible neuroprotector effect of laquinimod. The side effects were well tolerated and short-lived.

The BRAVO study [50], which is currently in progress, evaluates the rate of attacks by comparing 0.6 mg/day oral laquinimod versus placebo with a third comparison group of intramuscular interferon β-1a as the only reference arm. The study involved naïve patients with relapsing-remitting MS, with a certain degree of activity in the period prior to their being included. Laquinimod does not display any significant benefit on the rate of attacks or active lesions, but positive effects were found in new lesions in T_2. An analysis of the progression revealed that laquinimod significantly reduces confirmed progression at three months by up to 33.5% and this value rises to 40.6% at six months. Likewise, laquinimod is effective in significantly reducing parameters related to cerebral atrophy. Data concerning safety are very similar in the three groups, hepatic risk being the most worrying concern.

Natalizumab

The RESTORE study [51] aims to analyse the time elapsed until the disease is reactivated following the withdrawal of natalizumab over 24 weeks in asymptomatic patients and with no clinical or radiological activity. It also seeks to determine whether introducing other immunomodulator drugs is going to modify this reactivation. After the last dose of natalizumab, patients were randomly selected to continue with natalizumab, receive placebo, immunomodulators such as glatiramer acetate or intramuscular interferon β-1a immediately, or methylprednisolone at the twelfth week. It was observed that interrupting natalizumab was followed by an increase in disease activity that appears to begin as of the twelfth week, or at least it becomes more intense. The administration of corticoids from that moment on is not going to suppress activity and carrying out a periodic MRI scan as of the twelfth week could help to identify higher-risk patients. Presumably, introducing a conventional immunomodulator after withdrawing natalizumab would not modify the risk of reactivating the disease [52].

Risk management

The forthcoming availability of new drugs with different mechanisms of action and an assortment of risk-benefit profiles makes it more difficult to evaluate effectiveness and efficiency, to evaluate the risk of drugs used in combination or individually, as well as the treatment algorithms for MS. The risk-benefit concept of each drug changes over time so that post-authorisation studies and registries become fundamental and essential tools.

As part of personalised medicine, the detection of early markers would be useful for predicting possible risks for each individual patient. This aspect is reflected in Sandrock et al. [53], which deals with the staging of the risk of progressive multifocal leukoencephalopathy with natalizumab, and which is going to depend on the situation of anti-JVC antibodies in serum, on the time or the duration of the disease, on exposure to the drug and on the initial immunosuppression status. Jones et al. [54], referring to risk management with alemtuzumab, report that analysing samples from before immunosuppression to predict risks provides proof of the involvement of certain cytokines in the risk of autoimmunity. Thus, pre-treatment IL-21 increased the risk of autoimmune complications, IL-7 offered protection against autoimmune complications and CCL21 was associated to the risk of autoimmune complications. Finally, and as a classic example, there are the practical consequences deriving from taking into account neutralising antibody titres in the clinical response to interferon β-1a.

In short, there is a need for increasingly more precise markers that are capable of predicting the early response to treatments, and early markers that make it possible to predict the possible indi-

vidual risks of each patient. Future combined therapies are put forward with a strong preference for combinations between anti-inflammatory therapies or neuroprotector anti-inflammatory drugs in order to prevent long-term side effects.

The complexity of future therapy for MS makes patient registries even more important as a proactive tool for monitoring the safety of a drug after it has been authorised, since they allow the frequency of adverse events to be determined with greater accuracy among the highest number of patients exposed to the drug; they make it possible to detect long-term safety, the effects of combinations of drugs, changes in treatments, therapeutic failures, effectiveness and real benefit in daily clinical practice (like the progressive multifocal leukoencephalopathy with natalizumab; Table II); they provide information about factors that can give an individual risk of a patient's presenting an adverse event; they are useful to compare patients who received or did not receive other treatments; and they make it possible to compare different generations of drugs in terms of their effectiveness and their side effects. The challenge today, as something to be improved in the future, is to set up unified international registries, under the auspices of the regulatory agencies, scientific societies and pharmaceutical industry.

Table II. Safety profile of the new or emerging treatments for multiple sclerosis.

	Administración	Safety profile [a]
Teriflunomide	Oral	Gastrointestinal symptoms (nauseas, diarrhoea), moderate alopecia, transitory increase in hepatic enzymes
BG-12	Oral	Febricula, headache, dermatological symptoms (transient rash), diarrhoea, transitory increase in hepatic enzymes, lymphopenia, microalbuminuria, fatigue
Laquinimod	Oral	Abdominal pain, back pain, cough, transitory increase in hepatic enzymes
FTY720	Oral	Lymphopenia, exacerbation of herpes virus infection, macular oedema, adverse cardiovascular effects
Daclizumab	Subcutaneous	Infections and events affecting the skin
Alemtuzumab	Intravenous	Infections, thyroid pathology, idiopathic thrombocytopenic purpura (no case required a splenectomy)
Rituximab/ocrelizumab	Intravenous	Reactions to the infusion
Natalizumab	Intravenous	Progressive multifocal leukoencephalopathy

[a] The most relevant data from the latest studies conducted in a clinical setting.

Symptomatic treatment of MS

In recent years interest in the symptomatic treatment of MS has grown, as has the scientific evidence derived from controlled clinical trials. Because the clinical signs and symptoms of the disease could easily fill a second chapter, in the lines that follow we provide but a brief overview of the aspects addressed at the congress.

One novel treatment used to control spasticity that should be highlighted is Sativex ®, a combination of cannabinoid extracts that has been shown to offer small benefits in the reduction of spasticity according to several studies. It is generally well tolerated and presents some psychotropic effect, which probably depends on the dose, and points towards the possibility of a long-term cognitive effect. The study that contributed to its authorisation or reinforced its consideration as treatment has recently been published [55]. It was a randomised, double-blind, placebo-controlled multicentre study conducted in Europe, the results of which show that 47.5% of patients see improvements in their spasticity, spasms and sleep scores compared to placebo; the widespread placebo effect that was observed is a result that must also be highlighted.

The pharmacological treatment of gait control has focused on fampridine and more especially on the study published by Goodman et al. [56], the results of which show an improvement in gait with the sustained-release formulation, a response that is independent of the baseline characteristics of the patients and the previous immunomodulator treatment. The tolerability profile was similar to those of earlier studies, the most frequent events being urinary tract infections and falls.

Finally, in the management of ataxia and tremor, Thompson et al. [57] criticised the lack of sound scientific evidence on which to base themselves, due to the current use of drugs that were introduced decades ago, when the quality of the studies was considerably lower than that required by the regulations. They have shown how there are mismatches between the results from different studies with the same treatment, even when the same main variables are analysed.

Paediatric multiple sclerosis

Figures from epidemiological studies suggest that

Table III. Magnetic resonance predictors in the diagnosis of multiple sclerosis with respect to other demyelinating diseases.

Type of lesions	Relative risk	95% CI
T_1 hypointense	72.8	22.7-233.4
Periventricular	12.1	5.7-25.5
Contrast enhancement	11.9	6.5-21.8
Corpus callosum	7.3	4.3-12.3
White matter of the brain	5.1	2.9-9.3
Brain stem	2.7	1.6-4.6
Thalamus	0.39	0.2-0.9

95% CI: 95% confidence interval.

up to 5% of all cases of the disease have their onset before the age of 18, with a prevalence in childhood and adolescence (> 11 years) of around 0.40 and 1.35 per 100,000, respectively, and it is considered an underdiagnosed condition.

The environmental and genetic factors involved in the disease are the following: DRB1*1501 (relative risk, RR = 2.28), Epstein–Barr virus positive (RR = 2.55) and vitamin D deficiency (RR = 2.28) [58]. Clinically, paediatric MS is characterised by a predominance of remitting forms (90%) and a high rate of relapses from onset, with greater involvement of the brain and brain stem, although with complete recovery of the deficits. Cognitive alterations can be present in up to 30% of patients.

A study of the CSF shows lower-levels of oligoclonal bands and IgG in comparison to adolescents, thus suggesting greater compromise of innate immunity than acquired immunity. Data from RMI scans point to a higher number of lesions in T_2 and enhancing lesions (greater lesion load), as well as hypointense T_1 lesions from the onset that can be reversible [59]. As MR predictors in the diagnosis of MS with respect to other demyelinating diseases, Verhey et al. [59] highlight the presence of hypointense T_1 lesions from the onset, with an RR of 72.8% (Table III).

The data referring to the treatment come from non-controlled studies with small series, conducted with immunomodulators (interferons and glatiramer acetate) without varying the doses or adjusting the forms and frequencies of administration. First-line classic immunomodulators have proved to be effective and safe, with side effects that are similar to those described in adults; the first experiments with natalizumab have shown that it is also an effective and safe treatment in paediatric ages [60].

The recommendations put forward in this last edition have focused on the need for research aimed at the paediatric age, and the possibility of developing specific guidelines for the diagnosis and treatment of paediatric MS.

Conclusions

Regional grey matter atrophy is more sensitive to cognitive impairment than the measures of global cerebral atrophy. In patients with isolated demyelinating syndrome, cognitive impairment does not predict conversion to MS at five years.

Studies on brain plasticity and functional reorganisation show that early intervention can improve clinical aspects by somehow enhancing brain plasticity. The conservation of a potential plasticity provides a rationale for the introduction of neurorehabilitation interventions, even in advanced stages of the disease.

Advances in the identification of new biomarkers of disease progression and response to treatment open up the way to the introduction of proteomics as a suitable technique, although the results must always be validated with other standardised, more sensitive techniques. Gene expression studies show that a deficiency of the *TOB1* gene favours pro-inflammatory-type responses and could explain the higher risk of conversion to MS in patients with isolated demyelinating syndrome. On the other hand, the *SOCS1* gene could play a role in MS not only as a susceptibility gene, but also as a disease-modifying gene.

The therapeutic strategies focus on the dual role played by stem cells in immunomodulation and remyelination, and on the new immunomodulation pathways, with MCAM or CD16 being identified as a target to obtain a preventive or therapeutic benefit.

The latest data from clinical trials currently being carried out with disease-modifying drugs offer positive results for rituximab, ocrelizumab, ofatumumab, daclizumab, alemtuzumab, teriflunomide, BG-12 and laquinimod, including a favourable safety profile. The forthcoming availability of new drugs and the complexity of the MS therapy in the future make post-authorisation studies and registries even more important as a proactive tool for monitoring the safety of a drug following authorisation.

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Revisión de las novedades presentadas en el XXVII Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS) (II)

Resumen. Los datos más relevantes presentados en el V Congreso Trianual de los Comités Europeos y Americanos para el Tratamiento y la Investigación en Esclerosis Múltiple (ECTRIMS/ACTRIMS), celebrado en Ámsterdam del 19 al 22 de octubre de 2011, han sido resumidos en la cuarta edición de la reunión Post-ECTRIMS, celebrada en Madrid en noviembre de 2011. Las últimas aportaciones en torno al déficit cognitivo en la esclerosis múltiple han manifestado que la atrofia regional de la sustancia gris es más sensible al deterioro cognitivo que las medidas de la atrofia cerebral global, y en pacientes con síndrome clínicamente aislado el deterioro cognitivo no predice la conversión a esclerosis múltiple a los cinco años. El abordaje de la reorganización funcional ha demostrado que una intervención precoz puede mejorar aspectos clínicos y potenciar la plasticidad, de modo que la preservación de una plasticidad potencial ofrece una justificación para las intervenciones neurorrehabilitadoras, incluso en etapas avanzadas de la enfermedad. Las estrategias terapéuticas se han centrado en el doble papel de las células madre en inmunomodulación y remielinización, y en las nuevas vías de inmunomodulación para el desarrollo de futuras terapias en esclerosis múltiple. Los ensayos clínicos actualmente en curso muestran resultados positivos para rituximab, ocrelizumab, ofatumumab, daclizumab, alemtuzumab, teriflunomida, BG-12 y laquinimod, incluyendo un perfil de seguridad favorable. La inminente disponibilidad de nuevos fármacos y la complejidad de la futura terapia de la esclerosis múltiple refuerzan la importancia de los estudios y registros postautorización como herramienta proactiva para monitorizar la seguridad de un fármaco postautorización.

Palabras clave. Cognición. ECTRIMS. Esclerosis Múltiple. Rehabilitación. Tratamiento.