Review of the novelties presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (III)

Óscar Fernández, Carmen Arnal-García, Rafael Arroyo-González, Lluís Brieva, M. Carmen Calles-Hernández, Bonaventura Casanova-Estruch, Manuel Comabella, Virginia de las Heras, Juan A. García-Merino, Miguel A. Hernández-Pérez, Guillermo Izquierdo, Elisabet Matas, José E. Meca-Lallana, María del Mar Mendibe-Bilbao, Delicias Muñoz-García, Javier Olascoaga, Celia Oreja-Guevara, José M. Prieto, Lluís Ramió-Torrentà, Alfredo Rodríguez-Antigüedad, Albert Saiz, Nieves Téllez, Luisa M. Villar, Mar Tintoré; Post-ECTRIMS Group

Summary. The most significant data presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in France in October 2012, have been summarised in the fifth edition of the Post-ECTRIMS Experts Meeting, held in Madrid in October 2012. This led to the drafting of this review, which has been published in three parts. This third part of the Post-ECTRIMS review presents the findings from the latest studies conducted with disease-modifying treatments, more specifically with glatiramer acetate, laquinimod, ponesimod, BG-12, teriflunomide, daclizumab, natalizumab and secukinumab (AIN457). Likewise, we also address the reasons that justify the search for innovative treatments for multiple sclerosis, with antigen-specific therapy, cell therapy and therapy aimed at promoting remyelination being highlighted among other future therapeutic strategies. Access to new pharmacological agents and the complexity of the therapy of multiple sclerosis in the future will require new design strategies and directions in clinical trials, including the use of surrogate markers, new statistical applications, superiority, inferiority or equivalence clinical trials and adaptable designs.

Key words. Cannabinoids. Cell therapy. Glatiramer acetate. Laquinimod. Multiple sclerosis.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international conference on this disease. At its most recent meeting, held in October 2012, ECTRIMS brought together 7,500 specialists in multiple sclerosis (MS) from 96 countries.

For the fifth consecutive year, the Post-ECTRIMS Expert Meeting was held in Madrid. This annual meeting, which brings together renowned national leaders to present the most relevant data discussed at the Congress of ECTRIMS, has the scientific backing of the Spanish Society of Neurology.

This paper is the third part of a full review, to be published in three parts, of the latest developments in basic and clinical research presented at the ECTRIMS conference, the largest international conference devoted to the understanding and treatment of MS.

From the natural history of MS to its treatment history

The natural history of MS refers to the course of the disease in the absence of treatment. Natural history studies, which have greatly advanced our knowledge of the disease, rely on the existence of large cohorts of untreated MS patients, databases, modern statistical techniques, and up-to-date cooperative records, such as EDMUS, which involves 283 centres in 41 countries, and MSBase, in which 65 countries participate.

In discussing the natural history of MS, it is important to define the boundaries of the subject. Confavreux [1] focused primarily on the assessment of the progression of the disease and the concepts of irreversible disability and onset date. Setting the exact onset date of MS is difficult given that transient temporary improvements typically occur in the course of the disease and that attacks with stable sequelae may occur followed by a true clini-

Hospital Regional Universitario Carlos Haya; Málaga (O. Fernández). Hospital Virgen de las Nieves; Granada (C. Arnal-García). Hospital Clínico San Carlos; Madrid (R. Arroyo-González, C. Oreja-Guevara). Hospital Arnau de Vilanova; Lleida (Ll. Brieva). Hospital Universitario Son Espases; Palma de Mallorca (M.C. Calles-Hernández). Hospital La Fe; Valencia (B. Casanova-Estruch). Hospital Universitari Vall d'Hebron; Barcelona (M. Comabella, M. Tintoré). Hospital Infanta Sofía; Madrid (V. de las Heras). Hospital Universitario Puerta de Hierro; Madrid (J.A. García-Merino). Hospital Universitario Nuestra Señora de la Candelaria; Santa Cruz de Tenerife (M.A. Hernández-Pérez). Hospital Universitario Virgen Macarena; Sevilla (G. Izquierdo). Hospital Universitari de Bellvitge; L'Hospitalet de Llobregat, Barcelona (E. Matas). Hospital Universitario Virgen de la Arrixaca; Murcia (J.E. Meca-Lallana). Hospital de Cruces; Bilbao (M.M. Mendibe-Bilbao). Hospital Xeral-Cíes; Vigo, Pontevedra (D. Muñoz-García). Hospital Universitario Donostia; San Sebastián (J. Olascoaga). Complejo Hospitalario Universitario; Santiago de Compostela, A Coruña (J.M. Prieto). Hospital Universitari Josep Trueta; Institut d'Investigació Biomèdica de Girona; Girona (Ll. Ramió-Torrentà). Hospital Universitario de Basurto; Bilbao (A. Rodríguez-Antigüedad). Hospital Clínic; Barcelona (A. Saiz). Hospital Clínico Universitario; Valladolid (N. Téllez). Hospital Universitario Ramón y Cajal; Madrid (L.M. Villar).

Corresponding author:
Dr. Óscar Fernández Fernández. Director del Instituto de Neurociencias Clínicas. Hospital Regional Universitario Carlos Haya. Avda. Carlos Haya, s/n. E-29010 Málaga.

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Fax:
+34 951 291 157.

E-mail:
oscar.fernandez.sspa@juntadeandalucia.es

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cal progression. To consider a patient as showing irreversible disability, there must be a constant worsening of signs and symptoms over a period of 6 to 12 months [2]. Levels 4-7 of the Expanded Disability Status Scale (EDSS) are the most relevant to the assessment of disease progression.

Population analyses have shown that clinical relapses contribute minimally to irreversible disability associated with MS. In fact, the cumulative rate of disability and the age at which it is achieved are similar in progressive and relapsing forms of the disease [3-6]. This characteristic suggests that the presence or absence of a preceding relapsing-remitting phase is not decisive for disability, nor are superimposed attacks in progressive forms of the disease [3]. Irreversible disability is largely oblivious to medical history, i.e., assessable clinical variables influence the time span over which patients reach a disability threshold but not the subsequent accumulation of irreversible disability, although this depends to some extent on the age of the patient. The median chronological age at which disability is reached has been found to be 44 years for EDSS 4, 55 years for EDSS 6, and 63 years for EDSS 7 and has been found to be independent of the presence of an initial course with attacks or the progressive form of the disease [5,7,8]. The initial course of attacks or occurrence of the progressive form of the disease is clearly related to the patient's age (29 years for onset of the relapsing-remitting form and 39 years for onset of the progressive form), and the risk of conversion to progressive forms of the disease is more closely associated with age than with attack phase duration, with a critical age of approximately 45 years [9]. Patients who first manifest the disease at a later age may have better progression; such patients often remain free of disease longer and reach irreversible disability at an older age.

All of these results are based on population analyses and do not exclude interindividual variability. In clinical practice, there is wide variation in the age at which a particular disability is reached [4,5,8], ranging from almost asymptomatic cases to malignant and rapidly fatal cases. Thus, predicting the prognosis of a given patient is virtually impossible.

Confavreux [1] recognised two distinct clinical stages of MS, one associated with no irreversible disability and another associated with irreversible disability. These stages were recognised based on data from magnetic resonance imaging (MRI) and brain atrophy studies, which confirmed diffuse neurodegeneration from the onset. The presence of two distinct stages of the disease suggests a clear dissociation between the possibilities for treatment with current anti-inflammatory drugs and the clinical course of the disease. Given this therapeutic limitation, it becomes necessary to optimise the information that can be obtained from epidemiological studies by using new statistical techniques and associations with health and socioeconomic networks to assess novel treatment regimens, to investigate new drugs with different mechanisms of action, and to improve long-term safety with the aim of improving the balance of efficacy, safety, and cost of novel treatments.

Future directions and strategies in the design of clinical trials

Monitoring the progression of MS and understanding the effects of new drugs on the course of the disease is undoubtedly a challenge. This is due both to the high variability in the manifestations of MS and the difficulty of measuring the clinical endpoints of attacks due to the lack of available biomarkers. It is problematic to rely on the EDSS scale as a metric because it is not reproducible nor sensitive to change. Coupled with the fact that patients usually become less active as the disease progresses and with the ethical problems associated with placebo studies [10], this raises the need for new design strategies. One example of such problems is illustrated by the study of Garattini et al. [11], which examined the results of pivotal trials of new drugs in patients who were responders to interferon and glatiramer acetate. In that study, it was estimated that approximately 30% of MS attacks would have been prevented if patients had been treated with either of these drugs as the control arm.

The use of surrogate markers as measures of authentic clinical targets is growing in acceptance, in part because the use of such markers can reduce the necessary sample size or trial duration. However, validating a surrogate marker is a complex process; it requires demonstrating that the treatment is effective both on the surrogate and on the actual target. In addition, the surrogate and the clinical target should be significantly correlated, and most importantly, the effect of treatment on the final target must disappear when adjusting for the surrogate. Surrogates are considered specific for a given treatment and cannot be inferred for other drugs with different mechanisms of action. As surrogates for immunomodulation and neuroprotection, Wolinsky [12] discussed monthly serial MRI and its well-established role in phase II trials. However, MRI has modest short-term and invalid long-term correlations as a surrogate marker of disability [13].

New MRI techniques, such as subtraction MRI, have the ability to detect a greater number of active lesions and show good agreement between observed and predicted disability progression in the longer term [14]. As measures of neuroprotection, only measures of atrophy and the evaluation of lesions that evolve into permanent 'black holes' have established validity.

New designs for future drugs include active drug-controlled trials of superiority for very effective drugs and of non-inferiority or equivalence for drugs that have good safety profiles but are less effective [15]. There is also the possibility of using MRI surrogates as primary endpoints in phase III clinical trials. In the latter case, the design should be resized to the surrogate and assessment should not rely solely on clinical significance but should include a precise analysis of the predictor effect. As a simple alternative to placebo-controlled clinical trials, the variable 'time it takes to reach the targets' can be used. This offers the advantage of allowing patients to change to the active arm of the trial after presenting the event or of staying in the placebo arm only if the course of their disease is stable, thus eliminating the ethical problem.

The use of new customisable designs would allow the characteristics of a clinical trial to be modified based on the information obtained during the trial, enabling a rapid impact of the agent under study without changing the trial's validity. Randomisation would be customisable, allowing patients to be transferred to the active group as information is obtained, and validated MRI surrogate markers could be useful as targets in this situation. Such a design, therefore, provides a model that could consolidate both new clinical trial design and surrogate validation.

Regarding the subgroups of patients who are often created in clinical studies based on certain characteristics of the participants, Sormani [16] claimed that it is wrong to reanalyse each subgroup and *p* values for each of them because such results may be misleading. Interaction tests should be applied to establish whether the results of the analysis can be considered homogeneous or heterogeneous for all subgroups. If interaction tests are not significant, the results can be considered applicable to all subgroups.

According to Lublin [17], future clinical trials could be directed to compound targets of clinical and radiological parameters. An example of such a compound target would be the concept 'disease-free'; however, this would not actually represent a defined concept because it would depend on the procedures used in the study, the frequency of their implementation and the follow-up time. In fact, it is a dichotomous concept, with the possible loss of other measures, such as cognitive status, quality of life, atrophy and white matter changes. Moreover, the components that make up the concept have different sensitivities. The solution would be to standardise measures to establish reliable comparisons.

Another developing idea raises the possibility of validating new statistical applications that can be used to compare data efficacy between nonrandomised cohorts. As an example, the study of Spelman et al. uses the propensity-matched registry application to compare the therapeutic efficacy of natalizumab with that of interferon/glatiramer acetate, as revealed by the TOP-MSCOMET studies [18], in which the patient populations differ in their baseline characteristics. The propensity-matched registry application permits estimation of the likelihood that a patient would fall into a given therapeutic arm based on his or her baseline characteristics, enabling the selection and matching of patients with similar scores and thus the homogenisation of the database, permitting a significant reduction in the number of patients. This technique clearly reduces selection bias, allows the pseudo-randomisation of samples, and is applicable in clinical practice studies; however, it requires a very large sample size because it results in a significant elimination of patients.

Modifying treatments for MS: results of recent studies

Glatiramer acetate

Among new studies of glatiramer acetate, an open, retrospective study conducted under routine clinical practice conditions involved the evaluation of the effect of glatiramer acetate, low-dose interferon-β and high-dose interferon-β on brain volume after five years of treatment in patients with relapsing-remitting MS compared to a control group consisting of patients who remained untreated for 8-24 months [19]. All of the treated patients showed a lower level of atrophy than the control patients. The change in brain volume was significantly lower for glatiramer acetate-treated patients (–2.27%) compared to patients treated with a low dose of interferon-β (–2.62%; $p < 0.0036$) or with a high dose of interferon-β (–3.21%; $p < 0.0001$).

The CombiRx study [20] is a multicentre, double-blind randomised trial that compared the combined use of interferon-β-1a and glatiramer acetate with the isolated use of each agent in patients with

relapsing-remitting MS and at least two attacks in the last three years. The annualised relapse rate was not lower in the group of patients treated with a combination of the two drugs than in either isolated treatment group at the first, second and third years of follow-up. The results failed to demonstrate the enhancing effect that was expected from the combined use of both drugs based on their different mechanisms of action.

The GALA study [21] is a double-blind, randomised, placebo-controlled trial involving patients with relapsing-remitting MS, EDSS ≤ 5.5, who were attack-free ≤ 30 days. It was designed to assess the efficacy of the administration of glatiramer acetate at doses of 40 mg 3 times per week for a year followed by an extension phase. The novel dosing regimen tested in the study reduced the annualised relapse rate by 34% compared to placebo ($p < 0.0001$), similar to observations made in the pilot study. MRI findings show that this dosing schedule reduced the number of T_2 lesions by 37.1% versus placebo ($p < 0.0001$) and that it reduced the number of gadolinium-enhancing lesions by 44.8% ($p < 0.0001$). The use of glatiramer acetate at 40 mg 3 times per week is being evaluated by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA).

Laquinimod

Recent studies of the use of laquinimod show a dual effect of this drug on the peripheral immune system and on the resident non-neuronal cells of the central nervous system (astrocytes, microglia and oligodendrocytes) that would be expected to result in a reduction in demyelination and axonal destruction [22].

The clinical development of laquinimod has been quite important, with phase II studies at doses of 0.3 mg/day and 0.6 mg/day and two phase III studies (ALLEGRO [23] and BRAVO). The latest findings regarding laquinimod are derived from the combined analysis of both studies. The patient populations of these studies are quite similar, and together, they represent a total of 2,437 patients (Table). The primary target was the annualised relapse rate, while the secondary targets were progression of disability and markers of inflammation on MRI. The results show that laquinimod reduced the annualised relapse rate by 21%, reduced gadolinium-enhancing lesions by 30% and reduced T_2 lesions by 24.2%. In terms of disability, laquinimod reduced the confirmed progression of the disease by 34% at three months and by 46% at six months. These findings are consistent with the results of previous studies that demonstrated a distinct profile for this drug compared to that of interferons and glatiramer acetate, with laquinimod having a more obvious effect on disability than on the attacks. In addition, the advantages of early use of the drug in terms of progression of disability should be noted. The MRI data confirm the clinical findings, showing a reduction in brain volume loss of 30% compared to placebo ($p < 0.0001$). Similar results were obtained in the isolated ALLEGRO and BRAVO studies, with reductions in brain volume loss of 33% and 27%, respectively, compared to placebo. This effect did not occur with the active comparison drug interferon-β-1a. The neuroprotective effect of laquinimod was revealed in a substudy of ALLEGRO that showed a 33% reduction in thalamic atrophy during the first two years.

The upcoming launch of the CONCERTO study will evaluate two doses of laquinimod (0.6 mg/day and 1.2 mg/day) versus placebo in a total of 1,800 patients with relapsing-remitting MS. This study is intended to provide details of the dose-response effect of this drug with the central nervous system as a therapeutic target and to determine whether it can complement currently available drugs.

BG-12

BG-12 significantly reduced the annualised relapse rate and the percentage of patients with relapsing-remitting MS who relapsed over periods longer than two years in two phase III studies, DEFINE [24] and CONFIRM [25]. Combined analysis of the clinical efficacy data obtained in these two studies confirms these results for BG-12 administered twice a day and three times a day, with reduced clinical relapses of 49% in both cases and significant reduction in the progression of disability (29% and 32%, respectively, compared to placebo). In addition, the number of gadolinium-enhancing lesions was significantly reduced by 82.7% and 69.8%, respectively. The main adverse events were flushing and gastrointestinal tolerability problems in patients taking 2-3 pills a day, features that could lead to compliance problems. BF-12 represents a potential future oral treatment that has a good safety profile in patients with relapsing-remitting MS.

Teriflunomide

The TOWER study [26] is the second pivotal phase III placebo-controlled trial of the teriflunomide clinical program. The findings of this study confirm the results of the TEMSO study [27], establish the manageable safety profile of teriflunomide, and support its therapeutic potential in the treatment of MS with attacks. The duration of the TOWER

Table. Summary of the results of recent clinical studies of the use of glatiramer acetate (GA) and laquinimod in patients with MS.

		Treatment	Key efficacy results
Glatiramer acetate (GA)	CombiRx study (n = 1,008)	GA + interferon-β-1a, GA + placebo, interferon-β-1a + placebo	Annualised relapse rate in the three years of study: combination: 0.12, GA: 0.11 (p = 0.27 vs. combination); interferon-β-1a: 0.16 (p = 0.02 vs. combination)
			Proportion of patients who relapsed during the three years of follow-up: combination: 23.1%, GA: 20.5% (p = 0.21 vs. combination); interferon-β-1a: 26% (p = 0.19 versus combination)
			Percentage of patients free of disease: combination: 33%; GA: 19.4% (p < 0.01 versus combination); interferon-β-1a: 21.2% (p < 0.01 vs. combination)
	GALA study (n = 1,404)	GA 40 mg 3 times/week, placebo	Annualised relapse rate: ↓ 34.4% (0.33 GA 40 mg vs. 0.5 placebo; p < 0.0001)
			Number of T_2 lesions: ↓ 34.7% (3.65 GA 40 mg vs. 5.59 placebo; p < 0.0001)
			Number of gadolinium-enhancing lesions on T_1: ↓ 44.78% (0.9 GA 40 mg vs. 1.63 placebo; p < 0.0001)
Laquinimod	ALLEGRO and BRAVO combined analysis (n = 2,437)	Laquinimod 0.6 mg, placebo	Annualised relapse rate: ↓ 21% (0.3 laquinimod vs. 0.38 placebo; p < 0.0005)
			Disability risk: ↓ 34.2% at three months; ↓ 46% at six months
			Number of gadolinium-enhancing lesions on T_1 at month 12 and 24: ↓ 30% (1.46 laquinimod vs. 2.08 placebo; p < 0.0001)
			Number of new T_2 lesions at 12 and 24 months: ↓ 24.2% (6.79 laquinimod vs. 8.95 placebo; p < 0.0001)
			Loss of brain volume from baseline to 24 months: ↓ 30% (0.83 laquinimod vs. 1.18 placebo; p < 0.0001)

study was 48 weeks. Unlike the TEMSO study, its results in terms of reducing attacks were similar for both doses (14 and 7 mg). Patients treated with 14 mg teriflunomide showed a reduction of 36.3% versus placebo in the annualised relapse rate; reduction was 22.3% for the 7 mg dose. In addition, 14 mg teriflunomide reduces the risk of sustained progression of disability at 12 weeks by 31.5%; findings were similar for the 7 mg dosage. The safety profile was similar for both doses, consistent with the results of previous studies of this drug.

Daclizumab

The SELECTION clinical trial [28] is the open-extension phase of the SELECT study; it tests two doses of daclizumab versus placebo. In this study, 92% of the patients who completed treatment at week 52 participated. Patients who received placebo in the SELECT study were randomised to receive 150 mg or 300 mg of daclizumab, while those who had received daclizumab in SELECT were randomised to continue treatment with the original dose of the drug either immediately or after a washout period of 24 weeks. Because the efficacy data for both doses were very similar, the results for the two dosage groups were combined. The annualised relapse rate was reduced by 59% compared to the previous year (0.18 vs. 0.43; p < 0.001); the percentage of patients with confirmed progression after three months was also reduced (5% versus 10%; p < 0.033). The MRI data showed a reduction of 74% in new or enlarged lesions and a reduction of 86% in enhancing lesions. Combination of data from patients who continued with daclizumab in the second year and comparison of these patients with patients in the SELECT study who were assigned to placebo during the first year shows that the reduction in attack rate is maintained after two years. With regard to confirmed disability at two years, 83% of patients treated with 150 mg daclizumab and 88% of those treated with 300 mg daclizumab were progression-free. The authors did not consider that there would be a disease relapse among the subjects assigned to discontinuation of treatment, considering the average of gadolinium-

enhancing lesions in baseline pretreatment (1.6) compared to the average at the end of the washout period (1.1). The safety data indicate one death by autoimmune hepatitis in the group with discontinuation of 300 mg daclizumab, although there was a low incidence of serious infections in both studies. Elevation of ALT/AST (> ×5) was less frequent in the SELECTION study and was not observed in the group of patients who remained in continuous treatment in the group at low doses during the second year of treatment. These results confirm those of previous SELECT studies and show that the efficacy of daclizumab is maintained in the second year of treatment, with no relapse of disease activity after 24 weeks of washout. The risks associated with daclizumab appear to be similar in the first and second years of treatment.

Ponesimod

Ponesimod is a selective and reversible agonist of the sphingosine-1 phosphate receptor-1 (S1P1R), which blocks the exit of lymphocytes from lymph nodes, thereby reducing the number of circulating lymphocytes and preventing the infiltration of lymphocytes into target tissues. Its role in the pathogenesis of MS has been evaluated in a phase IIb [29] multicentre double-blind dose-response study in a total of 464 patients with relapsing-remitting MS who were randomised in a 1:1:1:1 ratio to receive placebo or 10, 20 or 40 mg of ponesimod. The primary target, reduction in the number of new active lesions, was fulfilled for all doses versus placebo, although improvement was most pronounced at doses of 20 (83%) and 40 mg (77%). A significant 50% reduction in the annualised relapse rate was observed at the 40 mg dose. Lymphocyte counts decreased rapidly with all three doses, and this decrease was maintained throughout the treatment period, only to recover within 2 to 3 weeks after cessation of treatment. The rapid reversibility of ponesimod gives it a clear advantage over fingolimod. The safety data show that ponesimod is generally well tolerated.

Secukinumab (AIN457)

Secukinumab is a humanised anti-IL-17 monoclonal antibody that has shown significant efficacy and a favourable safety and tolerability profile in studies on psoriasis, rheumatoid arthritis, and uveitis. There is an ongoing multicentre study [30] of patients with relapsing-remitting MS who were randomised 1:1 to receive 10 mg/kg of AIN457 or placebo intravenously for 20 weeks and MRI every four weeks until week 36. The primary target is a composite measure of active lesions, and this target was significant from week 12. There was a significant reduction (67%) in the number of new T1 gadolinium-enhancing lesions and a trend towards reduction in the annualised relapse rate. Adverse events were rated as mild to moderate, with a higher dropout rate in the placebo group.

Natalizumab

In patients with secondary progressive forms (n = 12) and primary progressive forms (n = 12) of MS, Romme-Christensen et al. [31] evaluated the levels of markers for inflammation (osteopontin, CXCL13 and MMP-9) and for axonal damage and demyelination –neurofilament and myelin basic protein (MBP) levels– in the cerebrospinal fluid after 60 weeks of treatment with natalizumab. The results show that natalizumab reduces measures of inflammation, axonal damage and demyelination in the cerebrospinal fluid of patients with progressive forms of the disease and that it is associated with favourable changes in clinical and MRI results. Natalizumab also improves the parameters of the magnetisation transfer ratio, suggesting that it may protect against tissue damage. No safety problems were reported for this drug.

The RESTORE phase II clinical trial [32] analysed whether interruption of natalizumab treatment for 24 weeks in asymptomatic patients is sufficient to restore immune function and reduce disease activity and whether other immunomodulatory treatments help control disease activity after natalizumab withdrawal. Following the last dose of natalizumab, patients were randomised to continue with natalizumab, to receive placebo, glatiramer acetate or interferon-β immediately, or to receive methylprednisolone at week 12. The results show recurrence of the disease 12 weeks after the discontinuation of natalizumab; this was unchanged by methylprednisolone administration or by the introduction of immunomodulators. The use of periodic MRI from week 12 could help identify patients at risk.

In contrast, preliminary analysis of the TYSEDMUS observational study [33], which assesses disease activity in patients treated with natalizumab 12 months after cessation of treatment, shows no rebound effect with regard to attacks. The severity of disability is under evaluation.

Antigen-specific immunotherapy and cell therapy in MS

Current therapies for MS are aimed at mitigating or modulating the overall function of the immune sys-

tem. These treatments do not discriminate between harmful autoreactive cells and cells that ensure immune homeostasis. As a result, current treatments reduce the attack rate and disease progression at the expense of affecting the immune system. Antigen-specific immunotherapy is a form of immunosuppression that is capable of selectively blocking the deleterious action of a specific autoreactive cell function [34] without affecting the balance of the immune system. Other factors that make the search for innovative treatments in MS necessary include the incomplete control of inflammatory activity in relapsing-remitting forms of the disease, the lack of treatments that can prevent irreversible axonal damage and promote repair of the central nervous system, and the lack of an approved treatment for primary progressive forms of the disease. For these reasons, there is an increasing interest in cell therapy as an anti-inflammatory and reparative strategy in MS. (See Table I of the second part of the review [35]).

Antigen-specific immunotherapy

The MBP (82-98) myelin peptide represents the dominant epitope against which B and T cells in HLA-DR2 patients are directed. Its administration results in long-term suppression of the levels of anti-MBP autoantibodies in the cerebrospinal fluid of patients with progressive MS. A phase II clinical trial evaluated the clinical efficacy of MBP (82-98) administration in a cohort of patients who were grouped based on the expression of HLA-class II haplotypes; the results showed less disease progression in the HLA-DR2 and HLA-DR4 subgroups than in placebo-treated patients [36]. These findings show that antigenic tolerance can occur in a very personalised and targeted selection of patients, although a subsequent phase III study in patients of the HLA-DR2 and HLA-DR4 haplotypes with secondary progressive MS showed no clinical benefit of the administration of MBP (82-98) compared to placebo [37]. In addition, the oral administration of myelin, which, in animal models, prevents the development of experimental autoimmune encephalomyelitis, had no demonstrable effect on the number of attacks in a phase III clinical trial involving a total of 515 patients.

Another MBP antigen, an altered peptide ligand, has been shown in a phase II study to decrease the volume of gadolinium-enhancing lesions at doses of 5 mg and to increase the incidence of attacks, as well as MRI activity, at a dose of 50 mg. Another method used in antigen-specific immunotherapy utilises a DNA plasmid that encodes MBP. In a phase II study, the use of this plasmid as a DNA vaccine to control the total length of MBP that is expressed under cytomegalovirus control reduced the number of new MRI brain lesions in MS patients and reduced the Th1 response against myelin antigens. There was also a significant reduction in autoantibody levels in the cerebrospinal fluid of patients treated with the plasmid.

Cell therapy

According to Uccelli [38], the administration of mesenchymal stem cells (MSC) is a promising therapeutic modality because of its *in vitro* plasticity and expandability and because such cells can be administered safely *in vivo* by the intravenous route. In MS, the function of stem cell therapy of this type is essentially anti-inflammatory, conferring the ability to inhibit T cell proliferation and to modulate the immune response. Stem cell therapy could also potentially exert a protective function and promote central nervous system repair. Experimental data in mice with experimental autoimmune encephalomyelitis show that administration of MSC significantly attenuates the disease, inhibits demyelination and preserves axons.

The use of autologous stem cells is safer and poses less risk of infection than the use of allogeneic cells. Although useful *in vitro*, allogeneic MSC can promote *in vivo* rejection, resulting in decreased effectiveness. The route of administration is quite controversial. When similar doses are compared, the intrathecal route is the most likely to have an effect but carries an increased risk of direct release of the cells into the central nervous system, with a reported case of encephalopathy. The possibilities for indirect action of stem cells administered by the intravenous route, along with similar efficacy compared to the intrathecal route with regard to clinical and histological parameters in the animal model of experimental autoimmune encephalomyelitis, have led to its being considered preferable. Most preclinical studies in murine models have used a single dose of 1×10^6 MSC. In evaluating the effects of MSC therapy on various stages of the disease, studies have focused on subjects with progressive disease or on subjects who are active disease non-responders to available treatments, as well as on finding neuroprotective effects.

In terms of safety, no serious adverse events of MSC therapy for MS have been reported except for the previously mentioned case of encephalopathy. Other adverse events include some cases of meningeal irritation and a case of rash secondary to intravenous infusion. With regard to efficiency, only preliminary data are available from phase I studies;

based on MRI, evoked potentials and immunological measures, the data suggest that the treatment is effective. The MESEMS multicentre phase II clinical trial will offer efficacy and safety data on the intravenous administration of MSC in MS patients who present with attacks.

In addition to the foregoing, the immunological properties of haematopoietic stem cells, as well as their immunomodulatory effects and their potential usefulness in the reconstitution of the immune system with the goal of controlling autoimmunity, justify their use in MS. There are numerous clinical trials in progress in which a total of at least 500 MS patients are undergoing autologous transplant of haematopoietic stem cells. A review of the clinical experience derived from these studies has been provided by Karussis [39]. In 75% of cases, the protocols involved the use of cyclophosphamide and granulocyte colony stimulating factor; BEAM was used for conditioning in 50% of the cases. Mortality related to the procedure ranged from 2-5%, and mortality rates were clearly associated with the experience of each centre; a mortality rate of approximately 1% has been reported in experienced centres. The overall survival rate was 90% after 10 years. All studies have shown complete or almost complete disappearance of inflammatory activity on MRI that is maintained over time and is accompanied by a lessening of disability and a large reduction in the annualised relapse rate. Progression-free survival was 60-80% at three years, approximately 65% at 10 years in secondary progressive forms, and 40% in primary progressive forms. Patients with severe inflammation of the central nervous system experienced substantial improvement in their disability, with better progression-free survival in patients < 40 years of age.

The mechanism of action and the therapeutic efficacy of haematopoietic stem cell transplantation are not fully established, although Burman et al. [40] hypothesised that elimination of autoreactive clones or restitution of tolerance to autoantigens may be involved. This was investigated in a study of transplant patients, patients treated with natalizumab, and control subjects, in whom memory T cells, regulatory T cells, Th1, Th17, and responses to myelin oligodendrocyte glycoprotein (MOG) were assessed. The transplant patients showed levels of natural regulatory T cells (CD3+, CD4+, Foxp3+, Helios+) similar to those of controls, while the levels of such cells were lower in patients treated with natalizumab, with no differences in the numbers of peripheral regulatory T cells. Th1 and Th17 levels were similar in transplant patients and controls and higher in the patients treated with natalizumab. There were no differences in T-cell proliferation in response to MOG or in the number of central memory T cells upon activation by CD4+ in the three groups of patients. However, some differences were seen in patients treated with natalizumab; after polyclonal stimulation, there was a Th1 response, and after MOG administration, these patients produced less interferon-γ, no IL-17 and increased levels of TGF-b1. Ultimately, these data are compatible with the elimination of autoreactive clones after transplantation.

As a surprising finding, it is worth mentioning the failure of haematopoietic stem cell therapy to interrupt demyelination and neurodegenerative processes [41] and the lack of an effect of such therapy on brain atrophy. Such atrophy seems to continue after the first year after transplantation as a result of oedema resolution, although it progresses more slowly in the second year [42].

Symptomatic treatment in MS

The use of cannabinoids in MS raises the question of whether the improvement observed after their use in the progressive forms of the disease is merely symptomatic or is actually caused by a disease-modifying effect. Among studies that have evaluated the effect of cannabinoids, the CAMS study is prominent. Although it showed no significant differences in the Ashworth scale in groups of patients treated with placebo, cannabinoid extract or THC after 15 weeks, there were significant differences in subjective variables, such as pain, spasms and stiffness. At 12 months, the mean score on the Ashworth scale was lower and the ambulation index improved; these findings led some authors to propose a disease-modifying effect of cannabinoids.

A phase III study conducted by Novotna et al. [43] showed significant differences in reduction of spasticity after 12 weeks in patients who were randomised to receive Sativex ® or placebo once they had improved spasticity by at least 20% on the spasticity numerical scale after four weeks of treatment with Sativex. In a similar study, the MUSEC study, 279 patients were randomised to receive an oral extract of THC or placebo, and significant differences were found after 12 weeks in the spasticity variable as well as in secondary variables, such as pain, spasms and perceived spasticity evaluated using a subjective scale. Among studies involving experimental models, that of Panikashvili et al. [44] is notable because its results led to the hypothesis of a neuroprotective effect of cannabinoids. The authors

observed an increase in 2-AG endocannabinoid levels secondary to a closed head injury. The administration of exogenously synthesised 2-AG in another murine model of closed head injury produced a marked reduction in cerebral oedema, cerebral infarct area and the loss of hippocampal cells and further improved clinical recovery. These findings led to the design of the CUPID study, in which patients with secondary and primary progressive forms of MS were treated with oral THC extract and time to progression of disability was assessed. In the overall study population, there was no difference in this parameter after three years of follow-up; however, in the subgroup of patients with EDSS between 4.5 and 5, which constituted 22% of the sample, there was a significant reduction. Selection bias could be responsible for the negative results because in patients with higher baseline EDSS, progression is faster; in this study, the proportion of patients with less disability (EDSS between 4 and 5.5) was very low. Studies with populations of patients with EDSS between 4.5-5 are therefore needed to assess the effectiveness of cannabinoid treatment in the progression of disability and its potential as a drug modifier of the disease course.

In another line, the use of transcranial magnetic stimulation to improve walking ability is being investigated [45]. This therapeutic modality consists of the transcranial administration of repeated discharges of magnetic stimulation. It is non-invasive, safe and well tolerated. Its long-term effects are attributed to the stimulation of synaptic terminals and a resulting enhancement of neuronal plasticity. There is evidence of its effectiveness in neurological diseases such as stroke and in psychiatric disorders such as depression, and it has recently received FDA approval for use in depressed patients who do not respond to first-line drug treatment. In MS, transcranial magnetic stimulation could act on spasticity via motor cortex activation, inhibiting efferent signals on medullary interneurons and decreasing spinal cord excitability. Effects on plasticity could occur through modification of motor neuron excitability by activation of sensorimotor circuits and by modulation of the excitability of ipsilateral and contralateral motor areas. Currently, there are two model devices for transcranial magnetic stimulation. One, the *Focal Coil*, has been approved by the FDA, while another model, the *H Coil*, which is still in the experimental stage, achieves greater depth and can stimulate motor brain areas related to mobility of the lower extremities. A phase II study conducted by an Italian group is currently underway to determine whether transcranial magnetic stimulation with the *H Coil* increases the effect of intensive neurorehabilitation on the ability to walk in patients with progressive MS and spasticity. After three weeks, patients who received transcranial magnetic stimulation showed significant improvement over placebo in all evaluated gait scales.

Pharmacoepidemiology

Current pharmacovigilance programs are ineffective and inefficient. Added to the difficulty in reporting adverse events are low funding and methodological difficulties arising from the operating policies of different countries.

According to Tognoni [46], drug development should ideally proceed stepwise, beginning with studies focusing on the drug and the quantification and description of adverse effects, proceeding to studies focusing on the overall risk-benefit profile for different population groups, measures of the acceptability of the therapeutic strategy to patients and their environment and of potential risks due to inaccessibility to appropriate drugs, and, finally, progressing to epidemiological studies oriented toward public health goals. The latter include studies already mentioned, such as EDMUS and MSBase.

The emergence of new drugs with unknown toxicity profiles reinforces the importance of developing risk management plans (RMPs). New designs would be focused on developing a drug-specific RMP, a single record of multiple drug side effects or a single disease registry for different drugs. The expected increase in RMPs suggests the need for new organisations that could facilitate the provision of a single shared RMP for MS to respond to the needs of each RMP with respect to safety, effectiveness, appropriate use, and risk-benefit balance in collaboration with health authorities, academia and industry. Within the OFSEP (French observatory for MS) project, a study is under development to determine the safety profile of short-and long-term treatments in MS; this study involves the participation of patients who, over the course of the disease, have been treated with some of these drugs.

Epidemiology of progressive multifocal leukoencephalopathy and IRIS associated with natalizumab

The concept of progressive multifocal leukoencephalopathy (PML), as can be discerned from the history of this disease, has changed radically based on

the different contexts in which it is currently presented (e.g., whether it originates from infection with a human immunodeficiency virus, cancer, immunosuppression for transplantation or an autoimmune disease). Cases of PML are often very different in terms of prognosis and clinical presentation according to the underlying disease. In patients treated with natalizumab who develop PML, treatment suppression leads to stabilisation of the infection and arrest of its progression, something that does not happen in other conditions. Hence, early diagnosis of the condition is very important. The clinical and radiological presentation of PML in MS patients is also different, with more crises, greater contrast uptake, a higher frequency of immune reconstitution syndrome (IRIS) and a much more favourable prognosis.

As of September 2012, 285 cases of PML had been reported in patients treated with natalizumab, with a mortality rate of 22%; this can be compared with patients with AIDS and transplant patients, for whom the mortality rate exceeds 50% per year. Life prognosis for PML in MS patients is determined by the precocity of its diagnosis and by normalisation of immunity by treatment suppression. Frontal lesions usually have little clinical expression; hence, it is essential to closely monitor those patients at risk of developing PML by MRI. Once the patient has survived the critical phase of IRIS and has had an early diagnosis, the prognosis of disability is significantly better than in other diseases, with a high percentage of patients who have a good functional status.

Currently, we can modify the prognosis of PML in MS patients by estimating their risk of contracting this infection and adapting the strategy of clinical and radiological follow-up for early diagnosis. Risk stratification is based on measurement of JC virus antibodies and on other clinical variables, primarily the patient's history of treatment with other immunosuppressive agents and the duration of treatment with natalizumab. Some patients have very high levels of JC virus antibodies, while others have antibody titres near the cut-off point, resulting in variation in the annual seroconversion rate from 2-3% to 5-10%. An epidemiological record of 7,000 patients shows an overall prevalence of positive JC virus serology of 57.1%, although the prevalence varies in different countries. A study by Vermersch [47] of a French cohort of 350 patients shows that the probability of being positive for the JC virus is directly and indirectly related to age (odds ratio = 2.03) and race, according to previous studies, and to treatment duration (odds ratio = 2.25).

As risk factors for developing PML, Vermersch [47] emphasised the increase of JC virus antibody titres, contrary to previous reports in which patients who survive had very high levels of antibodies and evidence of viremia, especially persistent viremia associated with repeat sequences in the regulatory region of the viral genome. Other possible risk factors include molecular factors related to the host and ineffective response of CD4 and CD8 T cells.

To facilitate early diagnosis, Richert et al. [48] evaluated the radiological characteristics of PML patients treated with natalizumab. At the time of diagnosis, unilobar extension, primarily located in the frontal areas (48%) with very little clinical expression, was the most frequent finding; this represents a more localised disease that is associated with better survival. Fluid-attenuated inversion-recovery (FLAIR) is more sensitive than T_2, and diffusion sequences allow viewing of lesions in the locations of previous MS injuries. In addition to the classical concept of lesions in cortical U fibres that fill the gyrus and extend into the cortex, FLAIR shows a hyperintense cortical rim as an early sign. The characteristics of the lesions in terms of contrast uptake very frequently demonstrate the presence of perivascular inflammation early in the disease (35%) that is unrelated to prognosis. Throughout the course of PML, 74% of patients develop lesions that capture gadolinium and that differ from those observed in MS plaques, with more nodular involvement. Based on these results, the authors remarked that early detection of localised disease may improve clinical outcome.

Conclusions

In recent decades, there has been an increase in the prevalence and incidence of MS, with doubts about the existence of a latitudinal gradient. Among those affected, the female/male sex ratio is increasing, but the reason for the increased incidence of MS in women is still unknown. Exposure to current treatments during pregnancy does not lead to serious adverse effects on the newborn, although it is recommended that treatment be discontinued during one menstrual cycle prior to the administration of classical immunomodulators and for two months in the case of natalizumab and fingolimod [49].

The treatment landscape of MS is rapidly changing as a result of the current clinical development of new agents that can replace currently available treatments. At the time of establishing and continu-

ing treatment, each patient should be considered individually within the context of the complications and complexity of new therapies and the characteristics of the patient, his or her family and social environment, and the disease. In addition to follow-up and management of current and emerging disease-modifying treatments, there should be an optimisation of symptom management and rehabilitation techniques because these techniques offer enormous benefits to patients in reducing symptom burden and improving the quality of life. Current hypotheses suggest that there may even be a possible modifier effect of cannabinoids on the course of the disease.

In summary, there are opportunities for future research in the management of MS patients who are receiving disease-modifying treatments, although clinical trials that use the currently available designs involve increasing difficulty, both for technical reasons associated with the measurement of variables and the recruitment of active patients and for ethical reasons related to the use of placebo. New design strategies are directed to the use, following validation, of surrogate markers, new statistical applications, interaction tests, clinical trials of superiority, inferiority and equivalence, customisable designs and compound objectives of clinical and radiological parameters.

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

Resumen. Los datos más relevantes presentados en la XXVIII edición del Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2012 en Francia, han sido resumidos en la quinta edición de la Reunión de Expertos Post-ECTRIMS celebrada en Madrid en octubre de 2012, fruto de la cual nace esta revisión que se publica en tres partes. Esta tercera parte de la revisión Post-ECTRIMS expone los resultados de los últimos estudios realizados con los tratamientos modificadores de la enfermedad, concretamente con acetato de glatirámero, laquinimod, ponesimod, BG-12, teriflunomida, daclizumab, natalizumab y secukinumab (AIN457). Asimismo, se abordan las razones que justifican la búsqueda de tratamientos innovadores para la esclerosis múltiple, destacando la terapia antigenoespecífica, la terapia celular y la terapia dirigida a promover la remielinización entre las futuras estrategias terapéuticas. La disponibilidad de nuevos fármacos y la complejidad de la futura terapia de la esclerosis múltiple necesitan nuevas direcciones y estrategias de diseño en los ensayos clínicos, entre ellas el uso de marcadores subrogados, nuevas aplicaciones estadísticas, ensayos clínicos de superioridad, inferioridad o equivalencia, y diseños adaptables.

Palabras clave. Acetato de glatiramero. Cannabinoides. Esclerosis múltiple. Laquinimod. Terapia celular.