Review of the novelties from the 2014 ECTRIMS-ACTRIMS Joint Congress, presented at the 7th Post-ECTRIMS Meeting (II)

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Summary. For the seventh year in a row the Post-ECTRIMS Meeting has been held in Madrid (Spain). Renowned specialists in multiple sclerosis and national leaders in this area have gathered once again to discuss the novelties presented at the 2014 ECTRIM-ACTRIMS World Congress. That meeting gave rise to this review, which is published in two parts. This second part shows that immunological phenomena are increasingly more present in the pathogenesis of the disease, and that the interaction between inflammation and neurodegeneration is becoming more apparent. Metabolic, mitochondrial dysfunction and oxidative stress phenomena are also involved in axonal degeneration and the experimental models open up the way to promising new therapeutic approaches for regenerative strategies. Although ambitious, inducible neural progenitor cells have become a promising alternative to the conventional treatments with stem cells, and the identification of new genetic variants of susceptibility to multiple sclerosis opens up the way to the discovery of new drugs. Reconsidering the value of old drugs and procedures would be another alternative therapeutic development.

Key words. ECTRIMS. Multiple sclerosis. Post-ECTRIMS.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international congress regarding this disease. Its last meeting was held with its American counterpart, ACTRIMS, and this meeting became the largest meeting of Multiple Sclerosis (MS) professionals, with approximately 9,000 attendees from 90 countries.

The 7th Post-ECTRIMS meeting, a meeting that was institutionalized through its clear scientific focus and practical interest for the MS collective and that depends on scientific endorsement from the Spanish Society of Neurology, was held in Madrid (Spain). As in previous years, this meeting involved the participation of national opinion leaders in the presentation and discussion of the topics presented at the 2014 ECTRIMS-ACTRIMS World Congress, which represents the forefront of MS research and treatment. The objectives of this review, which also contains a first part [1], are to summarize the most important aspects of the aforementioned congress under the criteria and experience of our country's specialists and to thus present a basis for updating the knowledge of medical professionals.

Pathophysiology of multiple sclerosis

Immunological phenomena

T cell regulators

A new subpopulation of regulatory T cells capable of suppressing the immune response *in vivo* has emerged as a future therapeutic candidate with immunomodulatory and immunosuppressive effects on autoreactive cells. This refers to the CD4+ HLA-G+ cells that express the HLA-G antigen and exert an immunosuppressive physiological effect described in pregnancy or pathologically in the development of neoplasms. The molecular characterization developed by Ruck et al. [2] shows a clearly different phenotype from that of classical T cells without constitutive expression of CD25 and FoxP3 as well as a different pattern of cytokine secretion. CD4+ HLA-G+ cells constitute 0.1%-8.3% of the total CD4+ population and present a different cytokine secretion pattern, showing an exclusive release of interleukin IL-35 and soluble HLA-G and a greater release of IL-10 than CD25+ and FoxP3 cells.

In animal models, CD4+ HLA-G+ cells increase the risk of survival against the host. The repertoire

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of T lymphocyte markers in the peripheral blood is more diverse in patients with MS than in patients with other non-inflammatory neurological diseases. In MS, the number of clones is higher in the cerebrospinal fluid than in the peripheral blood, and the clones with greater expansion in the cerebrospinal fluid do not proceed to the peripheral blood [3]. These discoveries confirm the expected results because MS is a disease of the immune system.

Inadequate activation of T cells

T cells are directly responsible for tissue damage of the central nervous system, and recent genetic studies and experimental models implicate the T cell subpopulations CD4 and CD8 [4]. It has been demonstrated that Th1, Th17 and Th9 induce experimental autoimmune disease after adoptive transfer [5], although each subset of T cell effectors produce different pathological phenotypes [6], which could explain the pathological heterogeneity of the disease [6]. The altered function of the regulatory CD4+ CD24hi T cells in MS, along with inhibition of the proliferation of uncontrolled T lymphocytes [7], can produce proinflammatory cytokines, such as interferon γ [8].

Interaction of B and T cells

The independent immunological potential of B lymphocyte antibodies has gained interest in the last decade because the innate and adaptive immune systems can be regulated through the release of cytokines [9]. An exhaustive review of the immunological and immunopathological potential of B cell subpopulations describes their positive and negative role in the regulation of immunity, and their inhibitory function was recently associated with IL-35 [10]. In addition to the continued stimulation and maturation of B cells that occur in the central nervous system, B cells that have previously participated in intrathecal immune stimulation and in the production of oligoclonal bands are also identified in the peripheral blood [11]. These cells appear to contribute to antigen restimulation in the periphery and perpetuate the immunological response in MS. Some data support the concept that the molecular sequencing of B cell receptors could be used as a diagnostic tool and for monitoring the activity of the disease. Other work has demonstrated that patients with MS suffer a defect in peripheral B cell tolerance, which is potentially attributable to an altered function of regulatory T cells and may drive the accumulation of autoreactive B cell clones in the peripheral blood that react against specific antigens of the myelin [12]. In contrast, the depletion of B cells impacts the activation of proinflammatory T cells [13].

As an additional discovery regarding the role of B cells, B10 cells act as powerful negative regulators of the T cell immune response. In experimental models, the maturation of B cells in effector cells that release IL-10 require interactions with IL-21 and CD40+ T cells to inhibit the experimental autoimmune disease [14]. The *ex vivo* clonal expansion of these B cells through IL-21 and CD40 is being considered a therapeutic possibility.

In contrast, it has been demonstrated that the regulation of the calcium sensors STIM1 and STIM2 in the endoplasmic reticulum is critical for the regulatory function of B cells. In experimental models, the specific deletion of STIM1 and STIM2 in B cells suppresses the release of IL-10, with a resulting exacerbation of the experimental autoimmune disease [15].

Parasitic infestation in multiple sclerosis

The changes in hygiene that occurred in the last decades in industrialized countries have resulted in different patterns of contact with established infectious agents. As such, epidemiological studies have evidenced a decrease in the incidence of infectious disease that correlates with an increase in autoimmune diseases [16,17]. In light of these discoveries, the hygiene hypothesis has been postulated. The various works conducted by Correale followed this line of evidence with a great deal of consistent results [18]. Uninfected patients with MS experience more exacerbations, a progressive increase of the disability, and greater activity in the MRI compared with infected patients. Furthermore, these patients have lower levels of IL-10 and transforming growth factor β, and higher levels of IL-12 and interferon γ [19]. An even more interesting finding is that the anthelmintic treatment is associated with the clinical and radiological activity of the disease and with an increase in the IL-12 and interferon γ levels [20]. The theory suggests that retinoic acid serves as an intermediate in the modulation of the immune response by the parasitic infestation [21] and that the suppression of autoreactive T cells Th1/Th17 may be a possible mechanism underlying this immune regulation [22].

Cellular traffic in the central nervous system

The rapid beneficial effect of the treatment with anti-CD20 antibodies suggests another function of B cells in the MS pathogeny that is distinct from the production of antibodies and that could include the blocking of antigen presentation and other effects

on T cells. The BAFF and APRIL trophic factors promote the activation and survival of B cells [23], and surprisingly, limiting BAFF/APRIL activation with atacicept exacerbates MS [24].

Relationship between inflammation and neurodegeneration

Fibrin and microglia

Fibrinogen is a powerful proinflammatory mediator through the activation of the CD11b/CD18 integrin receptor in microglial cells. In experimental models of experimental autoimmune disease, Akassoglou [25] has demonstrated that genetic or pharmacological depletion of the fibrin-CD11b interaction decreases microglial activation and leukocyte chemotaxis and protects against axonal damage. These discoveries suggest that selective inhibition through the action of an anti-fibrin γ377-395 antibody may be a useful therapeutic strategy to inhibit inflammation in relapsing-remitting forms and to protect from axonal damage in progressive forms.

Metabolomics, mitochondria, and energetic disequilibrium

In MS, the processes of inflammation, demyelination/remyelination, and axonal lesion increase the demand for energy. In response, a brief mitochondrial proliferation is produced, which ends in failure when faced with an excessive energetic demand, as occurs in the demyelination process. This mitochondrial dysfunction causes ionic and oxidative stress that drives a progressive axonal loss [26,27]. The oligodendrocytes are particularly vulnerable to oxidative and mitochondrial damage and to energetic deficit. Oligodendrocytes play a critical role in the metabolic support of axons, and their alteration drives axonal dysfunction and neurodegeneration [28].

Through an experimental model of medullary demyelination by lipopolysaccharides, it has been demonstrated that an early lesion emerges from the activation of innate immunity, which provokes a metabolic affectation due to hypoxia and reactive oxygen and nitrogen species. The most affected areas are those of the perivenular oligodendrocytes that are found in regions of limited vascularization. This finding explains why the histological exam will show that the lesion occurs toward the center of the medulla and not at the exact site of the lipopolysaccharide injection.

Innate immunity and axon-specific antibodies

T-γδ cells are involved in the pathogeny of MS, and anti-neurofascin antibodies are found to be elevated in the serum and the cerebrospinal fluid of patients with MS. The co-culture of cells transfected to express neurofascin with T-γδ cells in the presence of anti-neurofascin antibodies increases the lysis of cells that express neurofascin via antibody-dependent cell-mediated cytotoxicity [30]. These results propose a new mechanism of axonal damage mediated by cells of the immune system.

Acquired immunity and oligodendrocyte-specific toxicity

B cells secrete cytotoxic factors for oligodendrocytes and can contribute to lesions from progressive subpial cortical demyelination, which induce the infiltration of lymphoid follicles in the meninges [31].

Pathology of gray matter and mechanisms of progression

The pathology of gray matter is heterogeneous and largely affects the thalamus, cerebellum, and medulla. Furthermore, it increases with progression of the disease and presents phenotypic variability. Autopsy studies show a large effect on the cortex and deep structures of the gray matter in patients with progressive forms, contrary to what occurs in patients with acute exacerbations or lesions [32]. Individual variability is also characteristic of gray matter pathology. Autopsy cases have demonstrated that cortical lesions that border activated microglia are observed in younger patients with a more aggressive course of the disease [33]. A recent discovery has associated this phenomenon with the HLA-DRB1*15 allele [34]. Studies of biopsies of patients with relapsing-remitting MS have demonstrated that the cortical lesions are frequent, exhibit an inflammatory profile and are associated with meningeal inflammation [35]. This heterogeneity may be indicative of the disappearance of the disease's first events throughout time.

The clinical correlations of gray matter demyelination are more complicated to evaluate. The new DIR and PSIR techniques have improved the detection of cortical lesions, but anatomopathological correlation studies show that 80% of the lesions are not visualized by MRI, which explains why the results of studies that attempt to correlate cortical lesions and disability show doubtful results. The relevance of cortical lesions in diagnostic and prognostic precision, as well as their role as a risk factor in early conversion, is known, but the atrophy of gray matter is a better candidate to explain the progression of physical and cognitive disability [36]. Thalamic atrophy is probably another good target

based on its predictive value for cognitive deficit and conversion to MS [37].

The possible role of cortical atrophy measured *in vivo* by MRI as an indicator of neuronal loss has been supported by the work conducted by Carassiti et al. [38]. In addition to showing an increase in neuronal loss between 28 and 35%, which is higher than that described in previous studies, the number of cortical neurons correlated positively with the cortical volume. The vascular contribution may be the link between neuronal degeneration and myelinating pathology in white matter. In this respect, Haider demonstrated that cortical demyelination is associated with meningeal inflammation, white matter demyelination is related to perivenous inflammation, and neurodegeneration is associated with retrograde degeneration [39].

The primarily progressive form of MS presents itself as an ideal model for studying the underlying mechanisms of progression. Controversy exists over considering it a different disease with distinct epidemiological and clinical aspects [40]. However, some cases develop toward a progressive relapsing course [41], and the time passed until reaching a score in the Expanded Disability Status Scale (EDSS) of 6 or 7 [42], the age of initiation and the age of the progressive stage are similar, independent of the initial form. This includes the observation that the morphology of the gray matter and white matter lesions is identical in the primarily progressive and relapsing-remitting forms [43]. In the end, we are likely dealing with the same disease.

Evaluation of neuroprotection

Unconventional methods of quantitative MRI have contributed to improving the image of neurogeneration in MS. The diffusion tensor image overcomes the limitations of conventional MRI through specific pathological markers and a greater sensibility of the magnitude of damage [44]. Diffusional kurtosis imaging detects microstructural changes in white and gray matter [45]. Sodium MRI detects the accumulation of sodium related to disability [46] and that present in progressive forms of the disease [47].

Evidence of the importance of optical coherence tomography in MS continues to increase. A longitudinal study conducted over a period of two years demonstrated a progressive slimming of the superficial retinal layers. This degradation is more accentuated in patients with a history of optical neuritis than those without such a history; in addition, it is also significantly associated with the duration of the disease and is more pronounced in the initial stages [48].

New objective variables in clinical trials

The volume of the thalamus and basal ganglia has been proposed as a measure in clinical trials of motor rehabilitation due to its association with ambulation. It has been demonstrated that 24% and 17% of the variation in gait observed in the six-meter test are due to atrophy of the putamen and the globus pallidus, respectively [49].

New measurement tools

[^{11}C] PBR28 is a new-generation marker specific for the translocation of mitochondrial proteins that are found to be overexpressed in activated microglia and macrophages [50]. Through the combination of 7T MRI and [^{11}C] PBR28-PET, Gianni et al. has continued to detect the presence of apparently normal, activated microglia and macrophages *in vivo* in white matter and in cortical sulci [51]. In addition, diffusion spectrum imaging is being validated for the quantification of myelin and axon integrity in the presence of inflammation. The work conducted by Wang has examined the correlation between diffusion spectrum markers and histological autopsy images as well as the clinical viability of diffusion spectrum imaging in comparison with the diffusion tensor image to distinguish lesion types [52]. The results of a good correlation with the lesion histopathology makes diffusion spectrum imaging an element that should be considered in clinical trials of reparative treatments.

New potential biomarkers

This section focuses on the new biomarkers that have recently shown promising results and to update those that are known to date. Although these biomarkers have not been validated, the efforts to identify future candidates continue (Table I).

In summary, because cholesterol is an important constituent of the myelin sheath and axonal membranes, its utility as a biomarker does not escape attention, and furthermore, evidence demonstrates its relation with a reduction in nerve layers of the retina through optical coherence tomography. Recent results show lanosterol and 24S-hydroxycholesterol as potential biomarkers of safety and progression of the disease [53]. In addition, the new immunological biomarkers will contribute to the

Table I. Future biomarkers of multiple sclerosis (MS).

	Subtype	Fluid	Results
Cholesterol and related molecules [53]	Lanosterol	CSF	Correlation of total lesion volume in T_2 (R = 0.24; p < 0.3)
	24S-hydroxycholesterol	Plasma	Correlation of cerebral volume (R = –0.326; p = 0.004)
B and T lymphocyte immunological markers [54]	↑ CD8+ perforin+ T cells	Blood	Absence of disease activity (p = 0.006)
	% CD5+ B lymphocytes ≤ 3 before initiation of interferon β	Blood	Better predictor of absence of disease activity (odds ratio = 15.8; CI 95% = 4.6-60.8; p = 0.0002)
Non-histone proteins [55]	HMGB1	Blood	↑ HMGB1 expression in PBMCs from the start of MS exacerbations compared with PPMS (p = 0.0003 for RRMS; p = 0.003 for SPMS) and compared to controls (p = 0.002 for RRMS; p = 0.03 for SPMS) ↑ HMGB1 serum levels from start of MS exacerbations compared with PPMS (p = 0.001 for RRMS; p = 0.03 for SPMS)
Chloride channel [82]	ANO2	Plasma	↑ IgG in MS compared with controls (p < 0.05)

ANO2: anoctamin 2; CI 95%: confidence interval at 95%; CSF: cerebrospinal fluid; HMGB1: high-mobility group box 1 protein; PBMCs: peripheral blood mononuclear cells; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

age of personalized medicine for the identification of optimal responders to treatment [54], and transcriptional regulators, such as HMGB1, reinforce the value of RNA messenger expression in the discrimination between the more-inflammatory relapsing-remitting and the less-inflammatory primary progressive phenotypes [55].

Furthermore, the utility of micro-RNAs as biomarkers in MS has been reflected in the work conducted by Weiner [56]. The results of a study of the differential expression profiles between the relapsing-remitting and secondary progressive forms of MS and between patients with gadolinium-enhanced lesions compared with those with non-enhanced lesions suggest a potential role of micro-RNA as a diagnostic and inflammatory activity marker. The differences in the micro-RNA profile between 'benign' MS and MS with the same EDSS and a distinct disease duration reflect the prognostic role of micro-RNA. A population of specific micro-RNAs is associated with the response to treatment with glatiramer acetate.

Hope for regenerative strategies

The epigenome, which encompasses changes in chromatin components, micro-RNA, and DNA modifications without changes in the DNA sequence, is induced by the environment and is implicated in remyelination processes. The current studies are adding momentum to the hypothesis that epigenetic regulation is a source of potential regenerative strategies that are being investigated [57]. Other mechanisms and perspectives implicate immune system genes and proteins implicated in axonal guidance and support the physiological role of the cerebral extracellular matrix as a new therapeutic target for remyelination [58]. Table II offers a complete summary of the effect of these strategies on experimental models.

Present and future in the treatment of multiple sclerosis

This section presents a general overview of the current situation in the treatment of MS. Table III provides a complete summary of the results of studies with glatiramer acetate and laquinimod that are currently in progress.

It should also be noted that the 20-year American study with glatiramer acetate has demonstrated that the cerebral volume and gray matter volume are predictive factors of disability after an average of 20 years of treatment. This study is a clear example of the short-term benefits that are maintained throughout a prolonged period. According to the National Institute of Health and Care Excellence, UK, glatiramer acetate may be considered a profitable treatment, and recent data from a cost-effective analysis support this claim as well as the effica-

Table II. Potential regenerative strategies.

Therapeutic target	Mechanism of action	Effect in experimental models
Epigenomic changes	Histone acetylation through histone acetyltransferase	Inhibits differentiation in oligodendrocyte progenitors
	Histone deacetylation by HDAC 1/2 (histone deacetylase)	Results in the inhibition of differentiation in oligodendrocyte progenitors
	Inhibition of brimonidine BET by the olinone molecule	Accelerates the differentiation of oligodendrocyte precursors [83]
	Hypermethylation of the *BCL2L2* and *NDRG1* genes	Affects oligodendrocyte survival [84]
	Hypomethylation of the *LGMN* and *CTSZ* genes	Favors the proteolytic process [84]
Proteins implicated in the migration of the progenitors	IL-1β and CCL2	Activates and recruits adult oligodendrocyte progenitors, increasing the movement toward the demyelinating lesion [85]
	Class 3 semaphorins	Attracts oligodendrocytes toward the demyelinating plaque [86]
	Netrin-1	Blocks the recruitment of oligodendritic precursors [87]
Growth factors	TGF-β	Induces the activation of Smad3 present in oligodendrocyte progenitors, promoting their proliferation [88]
	Activin B	Promotes the differentiation of oligodendrocyte precursors [88]
	TGF-β + activin B	Promotes complete remyelination with the formation of mature and compact myelin [88]
Chondroitin-sulfate proteoglycan	Reduction of the synthesis of chondroitin-sulfate proteoglycan by fluorosamine	Increases oligodendrocytes and myelinated axons [89]

cy of interferon β [59]. The new glatiramer acetate dosage regimen of 40 mg/mL three times per week is a favorable treatment option for patients who prefer a lower number of injections. Comparative studies of 20 mg of glatiramer acetate through predictive models and meta-analyses show a similar efficacy between the two dosages, as measured by the annual rate of exacerbations and new T_2 lesions [61,62]. The complete cohort genotype of the GALA and FORTE studies identify the 11-SNP footprint as a predictor of patients who respond well to glatiramer acetate. In contrast, laquinimod reduces gray and white matter atrophy after two years of treatment [63] and can delay the start of irreversible disability in relapsing-remitting MS. Furthermore, this drug exhibits potential as a new treatment for progressive MS. In another investigation, the phase II study RADIANCE [63] analyzed the efficacy and safety of the oral administration of the RPC1063 molecule, a new modulator of the sphingosine 1-1-phosphate (S1P1) receptor. Doses of RPC1063 of 0.5 and 1 mg show an 86% reduction in the number of accumulated enhancing lesions between 12 and 24 weeks compared with the placebo. Reductions of up to 91% and 94% have been found for doses of 0.5 and 1 mg, respectively, through comparisons between the baseline and week 24 values. The number of accumulated or new T_2 lesions is also reduced to 91% with doses of 1 mg, and the annual exacerbation rate is reduced to 53%. These results, together with the favorable discoveries regarding safety, have promoted a phase III study with RPC1063 rather than interferon in relapsing-remitting MS (SUNBEAM).

Cellular therapy

Induced neural progenitor-like cells (iNPCs) have been shown to exhibit immune reparation and modulation capacity in animal models. Beginning with reprogrammed fibroblasts (among other somatic cells), these inducible NPCs have the potential to be derived from specific cell lines, and the extracellular vesicle membranes are implicated in the cellular signaling process through the production of exosomes [65]. Therefore, iNPCs have be-

Table III. Primary results of the last studies with glatiramer acetate (GA) and laquinimod.

	Study	Primary results
Glatiramer acetate	GLACIER study [60,90] Observational, open, randomized and multicentric study of the safety and tolerability of 40 mg/ttw GA compared with 20 mg/FT GA	*Analyzed rate of IRAE:* ↓ 50% with 40 mg/ttw GA (RR = 0.5; CI 95%: 0.34-0.74; p = 0.0006) *Analyzed rate of moderate/severe IRAE:* ↓ 60% with 40 mg/ttw GA (RR = 0.4; CI 95%: 0.23-0.72; p = 0.0021) *Reaction rates at the site of injection:* ↓ with 40 mg/ttw GA compared with 20 mg/FT GA *Convenience of the treatment (TSQM-9):* 40 mg/ttw GA resulted in more convenience than 20 mg/FT GA from the start and was maintained throughout the study
	Predictive model of indirect comparison of GA 20 (BEYOND, REGARD, and CONFIRM) compared with GA 40 (GALA) [62]	*ARE:* The estimated ARE for patients of the REGARD, BEYOND and CONFIRM studies receiving GA 40 coincides with those that were described in the three studies with GA 20 The estimated ARE for patients of the GALA study receiving GA 20 coincides with those described in the typical study
	Meta-analysis of individual patients and cumulative data [61]	*ARE:* similar effect of GA 20 (↓ 30%) compared with GA 40 (↓ 34%) with overlapping confidence intervals *New T_2 lesions:* similar effect of GA 20 (↓ 43%) compared with GA 40 (↓ 35%) with overlapping confidence intervals
Laquinimod	Phase III BRAVO study Radiological subanalysis of atrophy levels of gray and white matter [63]	*Gray matter atrophy:* Significant effect of laquinimod compared with placebo (51% in the first year and 28% in the second year; p < 0.001) Decline with interferon β-1a (31% after the first year and 12% in the second year; p = 0.075) *White matter atrophy:* Significant effect of laquinimod on white matter atrophy of 39% in the first year (p = 0.001 compared with placebo) and 15% in the second year (p = 0.015 compared with placebo)
	Phase III BRAVO study Analysis of the extension phase resulting from the change from interferon β-1a to laquinimod [91]	*ARE:* stable during the entire extension phase in 78% of the patients who changed to laquinimod *Treatment interruption:* 8% interrupted the treatment voluntarily and 2.6% interrupted it for safety reasons *Safety:* Rate of adverse effects similar to what is described in the double blind phase Improvement of the adverse effects associated with the use of interferon ↑ of the adverse effects associated with laquinimod (for example, gastrointestinal and musculoskeletal changes)
	ALLEGRO and BRAVO combined analysis [92-94]	*Confirmed progression of the disability:* 19 and 11% of the effect of laquinimod in the confirmed progression of the disability at 3 and 6 months were measured by its effect on exacerbations, and 0% was determined by its effect on T_2 lesions *Effect of laquinimod in patients with poor prognosis and EDSS > 3:* ↓ 25% of exacerbations ↓ 40% and 53% of the confirmed progression of the disability at 3 and 6 months, respectively ↓ Multiple Sclerosis Functional Composite ↓ atrophy *Motion benefit in MS patients with EDSS > 3:* Laquinimod improved motion by 59% (Time 25-Foot-Walk)

ARE: analyzed rate of exacerbations; CI 95%: confidence interval at 95%; EDSS: Expanded Disability Status Scale; FT: four times a day; IRAE: injection-related adverse effects; RR: relative risk; TSQM-9: Treatment Satisfaction Questionnaire for Medication, version 9; ttw: three times per week.

come a promising alternative to conventional treatments with stem cells, and their therapeutic potential is reflected by the findings reported by Peruzzotti-Jametti et al. [66]. In experimental models, the intracerebroventricular injection of iNPCs improves the chronic experimental autoimmune disease in rats, decreases inflammatory infiltrates, reduces demyelination and axonal damage as well as *in vitro* macrophagic activation, and remains undifferentiated with the inflammatory infiltrates up to 30 days after transplant.

In addition, Mozafari et al. researched the scarcely addressed topic of the remyelination potential and safety of these cells [67]. The primary objectives of Mozafari's work were to characterize iNPCs compared with their embryonic progenitors in rats *in vivo* and *in vitro* after their transplant into a demyelinized adult brain and to compare the iNPCs of MS patients with those of control subjects. In immunodeficient rats, or rats demyelinized with lysolecithin, these researchers observed an iNPC behavior that is similar, in terms of differentiation and migration, to that of natural NPCs, without evidence of tumor formation.

To addresses the previous case, which, according to the authors, evaluated the regenerative capacity

of neural progenitors in multiple sclerosis, Harris et al. evaluated the intrathecal administration of mesenchymal medullary stem cells with neural differentiation induced by epidemic growth factors and fibroblasts [68]. In preclinical models, the intrathecal administration of these cells is associated with a migration toward the lesion area, trophic support to damaged cells, and suppression of the local immune response [69]. A pilot study demonstrated that the intrathecal administration of three to five injections of escalating doses improved the EDSS, vesicle function, speech, and finger movement in six patients with MS (four secondary progressive and two primary progressive). The phase I study is already in progress, with a predicted participation of 20 patients (16 with secondary progressive MS and four with primary progressive MS) treated with three doses of more than a million cells every three months during a nine-month period and a two year follow-up period.

In line with other works that are currently in progress, Cohen et al. addressed the autologous transplantation of medullary mesenchymal stem cells in MS [70]. Using a design and methodology that are standard to this type of studies, the results did not show any serious adverse effects, significant modification in EDSS, or any evidence of measured activity by gadolinium in the first, second, third, or sixth months. No clinical measures of MRI, optical coherence tomography, or evoked potentials showed evidence of improvement or deterioration.

New paths of therapeutic development

Reconsideration of disease-modifying drugs

Although the reconsideration of drugs has already commenced through the reconstruction (interferon β-1[a] administered every two weeks), reformulation (subcutaneous glatiramer acetate three times per week), etc., the path followed by the pharmaceutical industry in the development of new drugs for MS involves the reuse and modification of molecules employed in other pathologies (teriflunomide, fingolimod, dimethyl fumarate, oral cladribrine, laquinimod, ocrelizumab, daclizumab, etc.). It is a clearly different approach than that used by clinicians who reconsider the value of pharmaceuticals with little or no industrial interest. These clinicians propose the use of simvastatine to slow down disease progression based on a recent phase II clinical trial showing a reduction in cerebral atrophy of up to 45% [71]. Another example is cladribine, whose clinical trials were interrupted due to a supposed increase of tumors that was not observed in a current study of clinically isolated syndrome (ORACLE) [72] or in a recent meta-analysis. Undoubtedly, phase III clinical trials for alternative drugs are needed.

The expiration of patents opens the door for the development of generic medications. Adding to the controversy surrounding generic drugs is their similar efficacy and safety to those of the original drugs. Although it is true that the regulatory approval of a generic medication requires the demonstration of a pharmaceutical equivalence and bioequivalence, this can be much more complicated in biosimilars given their biological complexity. Changes in the composition, tertiary structure, aggregation, and posttranslational modifications can affect the efficacy, safety, or biosimilar antigenicity. As with all drug development, the equivalence trials are unavoidable, and it is essential to optimize the results to appropriate establish the primary evaluation variable. An example of such a variable is observed in clinical trials with generic glatiramer acetate. The clinical trial with a generic version of glatiramer acetate shows equivalence for the primary variable of gadolinium-enhancing lesions [73].

First steps in genetics

The identification of new genetic variants of susceptibility to MS [74] opens a new path for the discovery of pharmaceutical treatments. Furthermore, there are currently treatments available, or in the research phase, for MS that act upon the metabolic pathways of genes related or not related to MS. The ability to draw a framework of the relationship of the metabolic pathways of proteins encoded by genes associated to MS is considered an approach for drug discovery and repurposing [75].

Management of risk with current treatment

The incidence of progressive multifocal leukoencephalopathy is increasing, and given the cases of severe seizures, early treatment with antiepileptic agents after diagnosis is starting to be considered [76]. The new available therapies, such as fingolimod and dimethyl fumarate, have been proposed as possible predisposing agents because there has been a case of multifocal progressive leukoencephalopathy in a patient treated with fingolimod and another patient treated with dimethyl fumarate in the context of severe and prolonged lymphopenia. Neither patient had received previous immunosuppressive treatment nor natalizumab. The risk of disease activity relapse after natalizumab withdrawal

and the fact that, according to the RESTORE study [77], no pharmaceutical treatment helps avoid relapse as of three months of withdrawal indicate the necessity to avoid stopping treatment and suggest a second treatment option. Because it was not evaluated in the RESTORE study due to unavailability, fingolimod may be this second option.

For the detection of progressive multifocal leukoencephalopathy in patients treated with natalizumab and in patients at a high risk of developing this infection, conducting an MRI every three months is recommended in cases of high risk. Gradient-echo imaging of T_2^* gray/white matter junctions detects hypointense bands that are characteristic of progressive multifocal leukoencephalopathy and related with the iron accumulation found in anatomopathological studies. These weighted T_2 bands may be useful for distinguishing between progressive multifocal leukoencephalopathy lesions and new lesions in MS and to monitor the progress of the patient because they grow over time [78].

Variations of the JC virus (JCV) can infect neurons, resulting in two different clinical entities, encephalopathy and granule cell neuronopathy (JCV-GCN) [79]. Although scarcely described, one must also consider these possible outcomes in patients treated with natalizumab. The second case described in the bibliography of JCV-GCN in MS corresponds to a seropositive JCV patient treated with natalizumab during a five-year course of monotherapy that experienced a decline of changes in the cerebellum and showed cerebellar atrophy in the MRI [80].

In the absence of clinico-radiological discoveries, the isolated presence of JCV in the cerebrospinal fluid of patients treated with natalizumab is not indicative of progressive multifocal leukoencephalopathy. Virus reactivation also occurs in peripheral blood mononuclear cells, and viral aggregation is detected in distinct subpopulations of lymphocytes, particularly CD34+ cells and monocytes. Furthermore, these CD34+ cells and monocytes are not correlated with the presence of the virus in urine or cerebrospinal fluid. Some results indicate that the presence of JCV in peripheral blood mononuclear cells could be a future substitute marker of viral reactivation. Risk markers of progressive multifocal leukoencephalopathy recognize the role of the JCV index and the low levels or absence of L-selectin in the lymphocyte surface. The possible biological interaction between both parameters has been studied, revealing a significant correlation with the prediction of progressive multifocal leukoencephalopathy risk, which was found to only occur in patients without a history of immunosuppression [81].

Conclusions

For 25 years, the ECTRIMS congress has served as Europe's and the world's largest professional organization dedicated to the understanding and treatment of MS, and its vision and mission have been strengthened by the participation of its American counterpart, ACTRIMS.

Some of the highly emphasized topics in the meetings, conferences, and multidisciplinary sessions that were developed in the last meeting were exposed in the Post-ECTRIMS Meeting that has been held in our country for seven years. In some way, the Post-ECTRIMS Meeting acts as a representative of the MS research community in our country, facilitates communication, and promotes and improves the research between health professionals to benefit MS patients.

Although the mechanisms implicated in the pathogeny and progression of the disease have not been entirely established, there are clear immunological phenomena involved. The evident role of B and T cells in MS continues to increase with the discovery of new regulatory subpopulations. Furthermore, it is likely that retinoic acid acts as an intermediate in the modulation of the immune response to parasitic infection through the suppression of Th1 and Th17 autoantigen-specific responses.

In addition to inflammation, there are sufficient tests to indicate that mitochondrial dysfunction and oxidative stress play an important role in axonal degeneration. T-γδ cells participate in a highly selective mechanism of axonal damage mediated by immune system cells. Some experimental results make way for new therapeutic focuses, but these are mostly too preclinical to predict their impact on the progression of the disease. Moreover, the primary progressive form of the disease is presented as an ideal model to study the underlying mechanisms of progression. The expression of messenger RNA and micro-RNA in the discrimination between phenotypes of MS has been reinforced in the search for new biomarkers, some of which are contributing to the advancement of personalized medicine regarding the identification of optimal responders to treatment.

The modifications in the chromatin, micro-RNA, and DNA components induced by the environment appear to be implicated in remyelination processes. Several studies in experimental models show that these components stimulate epigenetic regulation and may, at the very least, be a source of potential regenerative strategies. Future clinical trials of reparative treatments and motor rehabilitation will be

able to depend on new tools for measuring neuroprotection and new evaluative variables.

The present of MS treatment relies on drugs such as glatiramer acetate, which, after 20 years, continues to yield positive results. These results are clearly demonstrated not only in terms of efficacy and safety but also in the cost-effectiveness and patient preference for the new dose of 40 mg/mL. In contrast, laquinimod stands out as a future treatment for progressive MS if previous data are confirmed by studies that are currently in progress. Although it may be ambitious, we can state that iNPCs have become a promising alternative to the conventional stem cell treatments and that the identification of new genetic variants of MS susceptibility makes way for the discovery of new medications. Reestablishing the value of older medications and procedures may be a therapeutic development alternative if these medications are not of marginal interest to the industry.

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Revisión de las novedades del congreso conjunto ECTRIMS-ACTRIMS 2014, presentadas en la VII Reunión Post-ECTRIMS (II)

Resumen. Por séptimo año consecutivo se ha celebrado en Madrid (España) la Reunión Post-ECTRIMS. Reconocidos especialistas en esclerosis múltiple y líderes de opinión nacionales se han reunido un año más para exponer las novedades presentadas en el Congreso Mundial ECTRIMS-ACTRIMS 2014, y fruto de esa reunión se genera esta revisión que se publica en dos partes. En esta segunda parte se pone de manifiesto que los fenómenos inmunológicos cada vez están más presentes en la patogenia de la enfermedad, y que la interacción entre inflamación y neurodegeneración es más evidente. Fenómenos metabólicos, de disfunción mitocondrial y de estrés oxidativo también se implican en la degeneración axonal, y los modelos experimentales abren paso a nuevos enfoques terapéuticos con esperanza para las estrategias regenerativas. Aunque resulte ambicioso, los progenitores neurales inducibles se convierten en una prometedora alternativa a los tratamientos convencionales con células madre, y la identificación de nuevas variantes genéticas de susceptibilidad a la esclerosis múltiple abre camino al descubrimiento de nuevos fármacos. Replantear el valor de antiguos fármacos y procedimientos sería otra alternativa de desarrollo terapéutico.

Palabras clave. ECTRIMS. Esclerosis múltiple. Post-ECTRIMS.