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

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 relevant data presented at the 28th edition of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) held in October 2012 in France have been summarised in the fifth edition of the Post-ECTRIMS Expert Meeting held in Madrid in October 2012. This review is the result of the meeting, which is being published in three parts. This second part of the Post-ECTRIMS review discusses the biology of recovery and remyelination in multiple sclerosis (MS) as well as the different repair and endogenous and exogenous remyelination strategies currently being evaluated based on the fact that resident microglia and oligodendroglial progenitor cells have been implicated in the remyelination process. This review also discusses the current state and future use of biomarkers in MS and proposes as markers of neurodegeneration the following: T_2 lesion volume and brain atrophy using MRI and the loss of the ganglion cell layer as assessed by optical coherence tomography. A greater future utility for double inversion recovery (DIR) sequences is proposed to correlate cognitive impairment with MS impairment, given its higher diagnostic yield in locating and defining cortical lesions. The availability of novel biomarkers in the future requires strict validation. In this context, this paper proposes possible areas of action to improve the current situation and also presents the latest research results in identifying potential candidates with useful diagnostic characteristics, prognostic characteristics, treatment responses, and safety procedures.

Key words. Biomarkers. Cognitive impairment. Demyelination. Multiple sclerosis. Neuroimaging. Remyelination.

Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international conference on this disease. The last edition, held in October 2012, brought together a total of 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 is an annual meeting that brings together renowned national opinion leaders to present the most relevant data discussed at the Congress of the ECTRIMS and has the scientific backing of the Spanish Society of Neurology.

This paper incorporates a full review, which is being published in three parts, and includes the latest developments in basic and clinical research presented at the largest international conference devoted to the understanding and treatment of MS.

Biology of recovery and remyelination

The remyelination process is variable and may be influenced by the location and size of the lesion as well as by individual genetic factors. For patients in the end-stage of the disease, only 20% of the lesions exhibit remyelination, compared with 70% of those in earlier stages; however, in chronic lesions, there is a relative preservation of mature oligodendrocytes and oligodendroglial progenitor cells (OPCs). The involvement of OPCs in the remyelination process is also evident in the study of Strijbis et al. [1], confirming a greater remyelination in cortical lesions than in white matter, without evidence of OPC recruitment failure in grey matter.

Strategies to promote endogenous remyelination

As OPCs are the main source of remyelinating cells in the central nervous system, strategies to promote

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.

Fax:
+34 951 291 157.

→

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

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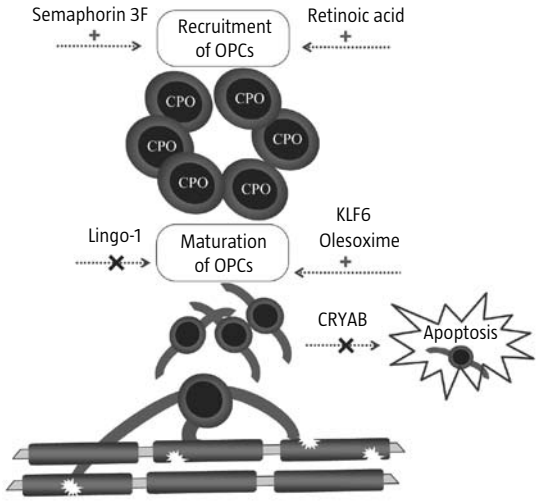
Figure. Endogenous remyelination strategies.



endogenous remyelination would include identifying signals that would act on the change from quiescent OPCs to activated OPCs, guidance cues that would facilitate recruitment and migration, and signals that would facilitate cell maturation (Figure).

Differentiation of OPCs

With the objective of identifying inducers of the development of OPCs, the Eleuteri group [2] screened a library of 2000 pharmacologically active compounds. The first screening phase was conducted in a purified population of murine OPCs by assessing the effect on cell metabolism, proliferation, and differentiation; in a second phase, the ability of compounds to stimulate differentiation of OPCs was evaluated in mixed glial cell cultures. In screening phases 4 and 5, remyelination activity was evaluated in demyelinated cerebellar sections. Finally, three compounds that stimulate the differentiation of oligodendrocytes, myelin development, and remyelination were selected as candidates to be evaluated in clinical trials (unpublished data).

Recruitment, migration, and maturation of OPCs

In summary, Lubetzki [3] presented the results of different studies that are evaluating strategies of recruitment, migration, and maturation (Table I). The overexpression of semaphorin-3F increases the recruitment of OPCs, which is associated with an increase in remyelination [4]; retinoic acid binds to its Retinoid-X receptor gamma (RXRG), expressed during remyelination, and accelerates this process [5]. Similarly, olesoxime (a small cholesterol type compound) accelerates the maturation of OPCs and promotes remyelination [6]. Furthermore, the hypothesis of a block in the maturation of OPCs mediated by the lingo-1 protein, which has been implicated in the inhibition of axonal growth and remyelination, has been put forward. In studies *in vitro* and in animal models of experimental autoimmune encephalomyelitis, the overexpression of lingo-1 inhibits remyelination.

Meanwhile, Asp et al. [7] established that Krüppel-like factor 6 (KLF6) is required for oligodendrocyte maturation and myelination. A *knockout* mouse model for KLF6 resulted in widespread brain demyelination and in an absence of myelin protein expression in the spinal cord. The animals exhibited tremors and ataxia and died within three weeks of birth. The study of microarrays revealed a loss of oligodendrocytes and myelin markers without associated inflammation or neurodegeneration. In short, if KLF6 is muted in cultures of OPCs, there is a loss of mature oligodendrocytes due to maturation-dependent apoptosis, a finding that suggests that KLF6 coordinates the transition of OPCs to maturation and thus constitutes an interesting target in repair and remyelination strategies (Table I).

Anti-apoptotic role

In line with the mechanisms involved in remyelination processes, Kuipers et al. [8] discussed the role of the small heat-shock protein alpha B-crystallin (CRYAB), starting with its anti-apoptotic and inflammatory functions, which have been demonstrated in the experimental autoimmune encephalomyelitis model. Applying the cuprizone (CPZ)-induced demyelination model for cat CRYAB –/–, the authors found a smaller number of demyelination lesions compared to controls, which were less severe and less inflammatory and expressed less reactive astrocytosis but also fewer OPCs. In the cat CRYAB –/–, CPZ-induced lesions exhibited severe demyelination but also less efficient remyelination. The authors conclude that CRYAB may have a protective role for both cell types mediated by its anti-apoptotic potential.

Exogenous remyelination procedures

To promote exogenous myelin repair, different cell types are being evaluated in experimental models for their ability to direct remyelination once transplanted, some in the clinical phase, such as haematopoietic and mesenchymal stem cells, and others

in the preclinical phase, such as neural stem cells (Table I). Although of different origin, olfactory bulb cells have also exhibited preclinical activity in repairing injured bone marrow. By contrast, clinical assessment of the autologous transplant of these cells into patients with paraplegia did not reveal magnetic resonance imaging (MRI) or functional changes compared with the pre-transplant period, although there was no evidence of adverse events after three years [9].

Table I. Possible future therapies for the treatment of multiple sclerosis.

Therapies directed at the trimolecular complex (T-cell receptors, HLA-class II antigens and receptors)	Treatments aimed at the elimination of autoreactive clones: Autologous transplant of haematopoietic stem cells
	Treatments aimed at inhibiting T cell proliferation: Transplantation of mesenchymal stem cells
	Treatments aimed at selectively blocking the deleterious action of autoreactive cell function: Myelin MBP 82-98 peptide Altered peptide ligand (APL) DNA vaccine
	Treatments aimed at inducing changes in the functionality of encephalitogenic cells: Immunisation with altered peptides (AQP4-NMO)
Therapies aimed at modifying the infiltrate and/or cell accumulation in the brain parenchyma	Th17 cells
	Haematogenous macrophages
Therapies aimed at promoting remyelination	Treatments aimed at increasing the recruitment and maturation of oligodendrocytes Semaphorin 3F Retinoic acid-RXRG Olesoxime Lingo-1 Krüppel-like factor 6
	Treatments with anti-apoptotic potential in oligodendrocytes Heat-shock protein alpha B-crystallin (CRYAB) Fingolimod
	Transplantation of haematopoietic stem cells, mesenchymal cells, neural cells, and olfactory bulb cells

Biomarkers in MS: the current state and their future use in clinical daily practice

A biomarker is a molecule that can be measured objectively and indicates a normal or pathological biological process or the response to a therapeutic intervention [10]. The identification of biomarkers requires three phases: discovery, validation in an independent cohort, and, most importantly, validation in multicentre studies, which requires collaboration between researchers to establish large biobanks of well-defined samples. The BioMS-eu network for biomarker research in MS has developed a consensus document with standardised protocols to preserve the statistical power achieved with a larger number of samples that might otherwise be compromised by pre-analytical factors [11].

Defining control groups is also critical to avoid the disparity in the values of biomarkers in blood and cerebrospinal fluid, which is observed in healthy subjects or those who have non-inflammatory or inflammatory neurological diseases. The BioMS-eu network [11] provides several group categories for the study of biomarkers: healthy controls, patients undergoing epidural anaesthesia, neurological patients categorised as non-symptomatic who have inflammatory and non-inflammatory diseases, and, finally, non-includable patients with infectious diseases or without a definite diagnosis. By applying these categories, it is expected to largely homogenise studies of biomarkers in cerebrospinal fluid, improving their quality and optimising the use of available resources.

Biomarkers related to the pathogenesis of MS

There are numerous observational and epidemiological studies relating vitamin D concentrations with the risk of MS. The utility of the Epstein-Barr virus is questioned, given that 95% of the overall population is seropositive for the virus, so it could only be applied in everyday practice to diagnose borderline cases, whereas strict validation is required for routine application.

Diagnostic biomarkers

IgG oligoclonal bands (OCBs) are present in over 95% of MS patients. The analysis of IgG OCBs, as a qualitative measure of intrathecal IgG synthesis, has a diagnostic sensitivity for MS of 93%, with a specificity of 94%. Petzold [12], on the results of a study by Freedman et al. [13], noted that this

analysis is a substitute for dissemination in space by MRI for clinically definite MS, according to McDonald [14] and Polman criteria [15], and remains so in Polman's review in 2011 for the diagnosis of the primary progressive form [16]. It should be noted that to date, no relevant antigens associated with OCBs have been identified, with the most robust being myelin-associated lipids, such as phosphatidylcholine, sulfatides, and oxysterols.

As for autoantibodies in MS, anti-aquaporin-4 (anti-AQP4) antibodies are currently validated for the differential diagnosis of neuromyelitis optica. However, the diagnostic role of antibodies against oligodendrocyte-myelin glycoprotein (OMgp) has not been demonstrated. Recently, in a study by Srivastava et al. [17], it has been shown in two independent cohorts that serum levels of anti-Kir4.1 antibodies, an ATP-sensitive potassium channel, are significantly increased in MS patients compared with other neurological diseases or healthy subjects.

The importance of anti-Kir4.1 antibodies could be due to the physiological role of these molecules, whose expression is restricted to oligodendrocytes and astrocytes near synapses and blood vessels. It has been proposed that expression of Kir4.1 plays a role in maintaining the electrochemical gradient across the cell membrane of presynaptic astrocytes, which is critical for potassium transport and glutamate uptake. Anti-Kir4.1 antibodies are able to eliminate Kir4.1 from glial cells and interfere with their function in potassium transport. The antibodies can also induce antibody-mediated cytotoxicity, producing astroglial cell damage that can lead to tissue damage and the absence of remyelination, although these results could indicate that this new biomarker may be useful for identifying a new pathophysiological mechanism present in a group of MS patients; these data have yet to be validated by other authors.

Prognostic biomarkers

Some studies have shown that intrathecal IgM synthesis is associated with worse prognosis [18,19] and with early conversion to clinically definite MS and is associated short-term with greater disability. Another study showed that the IgM index was associated with periventricular and cortical lesion load and with atrophy assessed by the bicaudate index [20].

In the detection of potential prognostic biomarkers for neurodegeneration, Petzold [12] proposed a hypothesis consisting of measuring proteins that are released after the destruction of the neuron or oligodendrocyte. The levels of these proteins would be directly related to the actual damage of axons. In this regard, the authors suggested the study of neurofilaments and presented their research results in an experimental autoimmune encephalomyelitis model, demonstrating a negative correlation between the number of axons/mm^2 and the concentration of heavy neurofilaments (R = –0.805; p < 0.001). In this sense, the study of Yablonskiy et al. [21] concluded that neurofilaments are a marker of axonal destruction in MS; additionally, other studies have reported their correlation with disability [22-25].

Biomarkers for monitoring and treatment response evaluation

The analysis of the presence of anti-interferon-β and anti-natalizumab antibodies is well established in routine monitoring of a disease-modifying treatment [26].

Other studies have investigated the effect of treatment with interferon-β in gene expression using DNA arrays, resulting in a strong but transient induction of changes in a wide variety of genes in circulating blood cells [27]. Such changes could be used to assess if treatment-induced gene expression is associated with treatment response. It has also been suggested, although only in one study, that increased endogenous expression of interferon-1 is associated with a worse response to treatment with interferon-β [28], which can also vary depending on Th1 immunity against Th17 [29]. The prognostic value of elevated serum levels of IL-7 requires confirmation. In predicting an individual response to treatment, contributing factors could be as follows: IL-10 levels in cerebrospinal fluid [30], gene expression patterns [31], and the level of induction of ISG [32].

According to Sellebjerg [33], the challenges in the use of biomarkers include a better understanding of the aetiology and pathogenesis of the disease, the heterogeneous clinical and pathological manifestations, and the diverse response to treatment. In the future, efforts will be focused on the use of currently useful biomarkers and the development of novel biomarkers for diagnosis, prognosis, treatment response, and safety (Table II). It is expected that genomic research, transcriptomics, proteomics, and microRNA research will allow the identification of innovative markers to improve the current situation.

Safety biomarkers

Natalizumab-treated patients may develop progressive multifocal leukoencephalopathy, especially if

there is a combination of certain risk factors, namely, the presence of antibodies against the JC virus, the duration of treatment, and prior immunosuppression. Approximately 50-60% of patients treated with natalizumab and the same percentage of the normal population have anti-JC antibodies. 98.8% of patients who develop progressive multifocal leukoencephalopathy have beeen exposed priorly to JC virus and show positive anti-JC antibodies.

Table II. Current and future biomarkers in multiple sclerosis.

	Current biomarkers	Future development
Diagnosis	IgG oligoclonal bands, anti-aquaporine-4 antibodies	Anti-Kir4.1, other biomarkers in the blood or cerebrospinal fluid
Prognosis	IgM oligoclonal bands, CXCL13 in the cerebrospinal fluid	Vitamin D, Epstein-Barr virus, genetic markers, other markers in the blood or cerebrospinal fluid (neurofilament)
Response to treatment	Anti-interferon-β antibodies, anti-natalizumab antibodies	Genetic markers –*SLC9A9* (interferon) and *ERAP2* (glatiramer acetate)– as well as markers in the blood or cerebrospinal fluid before or after starting early treatment
Risk of therapy	JC virus antibodies	Interleukin 21 (alemtuzumab), genetic markers, markers in the blood or cerebrospinal fluid before or after starting early treatment

Genetic susceptibility to MS and to treatment response

In studies of genetic susceptibility to MS, there is the possibility that findings could represent only artefacts, that the associations found might be real but minor, and that the effects would be too small to be considered significant [34].

Susceptibility genes identified in the latest genome-wide association study may be associated with alterations of the proteins they encode. As an example, a genetic association study with a functional correlate is prominent, which could have a role in the pathogenesis of the disease [35]. Thus, the *rs1800693* gene, belonging to the family of the tumour necrosis factor receptor type 1A (TNFRSF1A), strongly associated with the disease, encodes an isoform without exon 6 in G allele carrier patients, both in monocytes and in T cells [36].

'Omics' expectations in MS are presented as promising approaches to a better understanding of the complex pathogenesis of MS, although more studies are needed. In this regard, Brassat [37] noted that the design of this type of studies requires a cohort of patients with well-characterised MS, exhaustive extraction and storage of biological samples, equipped facilities with experience in this type of approach and, above all, important quality control; it is a complex analysis that also requires specialists in bioinformatics and statistics. Outside the field of MS, there are some omics studies, as the one published by Chen et al. [38], a panomics study that includes genomic, proteomic, and transcriptomic analyses, among others, with follow-up of healthy subject samples for 14 months. The first results predicted a high risk of developing type II diabetes, which the subject indeed developed during the study on day 369. Other genome-wide association studies identified the *IL28B* gene as associated with the response to treatment with interferon-α in patients with hepatitis C [39,40]. Examples of omics studies in MS include those published by Sawcer et al. [35] Comabella et al. [41], and Baranzini et al. [42] with monozygotic twins discordant for MS.

The presence of OCBs in CSF is a specific finding in MS patients. In line with previous studies that have involved the HLA-DRB1 alleles, Harbo [43] has studied the genetic differences related to the presence or absence of OCBs. This is a subanalysis of the genetic study published in 2011 with the group of patients for whom data were available for cerebrospinal fluid with positive or negative OCBs. In the first analysis, nine genes were selected for further replication in an independent cohort of patients. Out of the nine single nucleotide polymorphisms (SNPs), three were located within the HLA-class II region, and the rest were located on another chromosome. The only genes replicated were *BTLN2* and *HLA-DRA*, which had a significant association, and a smaller but significant association was found with the calsyntenin-2 gene (*CLSTN2*), which increased the risk of being negative for OCBs. The analysis of HLA class II genes regarding susceptibility to the presence of OCBs identified several *HLA-DRB1* gene alleles; in particular, HLA-DRB1*15:01 proved a stronger risk factor for OCBs (+) than for OCBs (–) in MS. The presence of the HLA-DRB1*4:04 allele increases the risk of MS in patients with OCBs (–).

De Jager, based on a previous genetic analysis [35], has performed eQTL (expression quantitative trait *locus*) mapping [44]. For each SNP of the previous study, they analysed the influence of neighbouring genes in a 2-Mb window (cis effect) and the influence of each polymorphism in more distant genes within the same chromosome or on dif-

ferent chromosomes (trans effect). The results identified six polymorphisms that increased *ICAM3* expression. This gene could play a role as a key regulator that integrates the effect of several susceptibility genes to trigger an inflammatory response in MS patients.

Response to treatment with interferon-β

Esposito et al. reported the results of a pharmacogenetic study designed to identify genes associated with response to treatment with interferon-β in patients with relapsing-remitting MS for at least six months of treatment and follow-up of two years [45]. Patients were classified based on clinical and MRI criteria. The authors conducted an initial screening in 116 patients, both responders and non-responders, later replicated in three cohorts, studying a total of 996 patients. The rs9828519G allele, located in the *SLC9A9* gene, which encodes a soluble cation transporter, was significantly associated with an increased risk of non-response to interferon-β; in addition, the proportion of non-responders was higher among patients with additional copies of the G allele, suggesting an additive effect. This gene was validated only in the American cohort, and although more studies are required for validation, the *SLC9A9* gene may be a biomarker of response to treatment with interferon-β in MS patients.

Response to treatment with glatiramer acetate

Comabella et al. reported the results of their study aimed at identifying the differential gene expression profile between patients with relapsing-remitting MS, responders, and non-responders to glatiramer acetate [46]. Response criteria were defined by the behaviour of the following variables: attacks (presence/absence), neurological disability (progression/no progression), and MRI radiological activity (presence/absence) during the first 12 months of treatment. A total of 15 patients were included (6 responders, 15 non-responders), as well as 15 control subjects. Blood samples were collected before treatment and then after 3, 6, 12, and 24 months for processing and analysis using exon microarrays. The pattern of gene expression prior to treatment with glatiramer acetate revealed a number of genes differentially expressed between responders and non-responders, and the *ERAP2* gene, which codes for an aminopeptidase of the endoplasmic reticulum, exhibited greater differential expression at baseline and during the course of the disease, primarily at 3 and 12 months. The evolution of expression over 24 months was lower for patients who had a good response.

ERAP2 is not a gene that is induced by treatment with glatiramer acetate as its expression is not modified after its administration at any point in time. Furthermore, the expression levels of *ERAP2* are similar in healthy controls and bad responders and clearly decreased in the good responders. These differences were validated by polymerase chain reaction in real time, but were not observed with the *ERAP1* gene as a specificity control.

ERAP2 has proven to be one of the most promising predictor genes in a study of genome-wide association [47]. Its involvement in the response to glatiramer acetate could be due to its role encoding an aminopeptidase that processes peptides for their antigenic presentation in the context of HLA class I, in agreement with the mechanism of action attributed to the drug.

Neuroimaging of demyelination and remyelination

According to Barkhof [48], a more effective assessment of demyelination would be to show early demyelination changes that can be detected with MRI, such as pre-lesional changes in normal-appearing white matter. Thus, the quantification of the magnetisation transfer ratio (MTR) of normal-appearing white matter or conducting serial and weekly diffusion MRI for several months will allow the observation of changes before the onset of a new lesion as changes are evident with both diffusion and transfer techniques in the area in which the injury will later appear.

A study of 72 patients with relapsing-remitting MS who underwent serial MRI for four months demonstrate that, prior to the occurrence of a lesion, the diffusion coefficient decreases in that area, which is indicative of a T_2 lesion. Another measure of early demyelination change is perivenular growth and perivenular and juxtacortical lesions, although these are difficult to identify. According to the study of Abdel-Fahim et al. [49], which involved patients with relapsing-remitting MS and control subjects, the use of 7-T MRI, especially with the magnetisation transfer technique, improves the identification of cortical lesions compared with 3-T MRI. On the other hand, volumetric changes in grey matter that occur in primary progressive forms after five years are sensitive to tensor-based morphometry. In their study, Eshaghi et al. [50] were able to see in these patients early

limbic atrophy and posterior cingulate atrophy associated with a worsening of functionality.

Remyelination lacks a specific marker on MRI. A study of shadow plaques in post mortem brain MRI revealed the remyelinated area as hyperintense on T_2. Based on these findings, the Barkhof group [48] has shown an increase in the MTR in the possible remyelinated areas. MTR is a feasible technique for use in longitudinal clinical trials. Although a sufficient sample size is required to observe a slight drug effect, fewer subjects are required than those who are currently included in clinical trials. The assessment of the presence of black holes also appears as a measure of remyelination in longitudinal studies, especially those that, by magnetisation transfer, appear hypointense at first but follow an isointense course and that, according to the authors, would be a pattern indicative of remyelination.

Using positron emission tomography (PET) in MS, according to Stankoff et al. [51], may allow the evaluation of different pathogenic mechanisms of the disease, in contrast with current MRI techniques, as it shows a cellular/molecular image of the central nervous system. Myelin activation imaging techniques using specific markers are currently under development. Promising results were obtained with the Congo red derivative BMB marker with affinity for myelin in murine models of experimental autoimmune encephalomyelitis, revealing patterns of demyelination or remyelination according to the lower or higher marker uptake, respectively [52]. The disadvantages of the marker include the lack of differentiation between grey and white matter and the fact that it is a carbon marker, with the intrinsic problem of the need for a cyclotron in the hospital. Another promising marker in research is ^{11}C PIB, whose uptake pattern in experimental murine models reflects demyelination and remyelination processes and marks grey matter and white matter, results that were replicated in monkeys and in two MS patients in the study of Stankoff et al. [53]. These findings led the authors to conduct a longitudinal pilot study with six patients. The authors observed that in 60% of the lesions, the variation in PIB uptake between first and second PET was less than 10%, marking them as inactive lesions; 19% of the lesions were active, with a decrease in PIB uptake greater than 10%; and 21% of the lesions were remyelinating, with an increase in PIB uptake. The problem with this marker is its quantification, which can be difficult with the limited transport time. Therefore, the identification of novel fluorinated compounds with more benefits is needed.

With respect to microglia marking, research continues with the peripheral or mitochondrial receptor of benzodiazepines (^{11}C PK11195). One of the most recent studies [54] demonstrates differences between demyelinated and remyelinated areas and areas with and without microglia between MS patients and controls. On the other hand, many efforts are being devoted to developing new compounds targeting the TSPO receptor, expressed by activated microglia, and the radioligand PRB28 has been identified with a variable affinity depending on the subjects [55].

Neuroimaging of disability and neurodegeneration progression

MRI markers of neurodegeneration

A review of the value of T_2 lesion volume with regard to survival and evolution after 20 years [56-58] identified a relationship between T_2 lesion load with mortality and disability in patients with clinically isolated syndrome. The results of the 3-year study with interferon-β-1b in secondary progressive forms demonstrated a therapeutic benefit for T_2 lesions but not for disability.

Brain atrophy as a marker of neurodegeneration was reflected in the study of Fisher et al. [59], who demonstrated its disability-predicting value after eight years of progression; in studies of atrophy, baseline MRI should be performed six months after starting treatment to avoid the phenomenon of pseudoatrophy. The clinical trial of Barkhof et al. [60] with ibudilast in 200 patients has demonstrated that this phosphodiesterase inhibitor with a role in inflammation and neurodegeneration in MS decreases brain atrophy by 30% and decreases the progression of disability. For its part, the Phase II study of Chataway [61] in patients with secondary progressive MS treated with simvastatin versus placebo reflects a significant change in white matter brain volume, without differences in the Expanded Disability Status Scale (EDSS), albeit with a minor loss in patients treated with simvastatin.

Based on the study of Kapoor et al. [62] with lamotrigine, whose results were negative, Miller [63] highlighted the importance of analysing volume changes in different compartments of the central nervous system, such as white matter, grey matter, and spinal cord, for future neurodegeneration clinical trials. The sample size to obtain a therapeutic effect with measures of atrophy differs depending on whether grey matter or the cervical spinal cord

are involved; therefore, to obtain a therapeutic effect with atrophy measures of the grey matter of 30%, there is a need to analyse at one year a patient population three times greater than what is necessary to evaluate the effect in the cervical cord.

Diffusion MRI studies allow estimations of axonal parameters, such as diameter and density, and optimise the previous protocols requiring high field experimental systems and acquisition times that are too long and therefore impractical for use in clinical studies [64].

There are clinically relevant microstructural changes in the spinal cord that are not detected by conventional MRI and that contribute substantially to disability in MS. These changes could explain the disagreement between clinical and radiological findings, which is common in MS. This hypothesis was confirmed in the study of Oh et al.[65], in which the authors proposed alternative methods, such as diffusion tensor imaging (DTI) and serial MTR images. Patients were categorised into four subgroups according to the number of spinal cord injuries (≤ 2 and > 2) and the EDSS score (≤ 6 and > 6). The results demonstrated that in patients with a higher EDSS, regardless of the number of lesions, all parameters that measured fine cord involvement were severely altered, indicating that there were clear differences in quantitative MRI indices between patients with different levels of disability but with similar numbers of cervical cord lesions.

Markers of neurodegeneration for optical coherence tomography

High-resolution optical coherence tomography allows the visualisation of the retinal nerve fibre layer (RNFL) and also of the atrophy that occurs in patients if we focus on the ganglion fibre layer. In fact, with this technique, we can quantify each of the retinal layers and see exactly what happens. The study by Gabilondo et al. [66] deserves special mention. The study aimed to evaluate a possible contribution of the atrophy of the visual cortex and optic radiation in patients with retinal atrophy as proof of trans-synaptic retinal degeneration. The authors used the latest optical coherence tomography, plus all of the real techniques currently available, to assess axonal and white matter damage. The authors analysed the visual cortex with spectroscopy, volumetry, white matter mapping, and measurement of the optic radiations. Among the many results, the authors noted that the visual cortex atrophy and RNFL thickness were correlated throughout the series (r = 0.63). More importantly, in patients who have not had optic neuritis, this correlation remains (r = 0.75), contrary to what happened in those with a history of optic neuritis (r = 0.25). One interpretation of these data could be the added damage to the optic nerve by inflammation, which does not clearly reflect what happens in the brain. Furthermore, the levels of N-acetyl aspartate (NAA) in the visual cortex and lesion volume in the optic radiations were associated with retinal atrophy. The authors suggest that the involvement of the posterior visual pathway is specifically associated with retinal atrophy, which supports trans-synaptic neuronal degeneration as a mechanism of axonal lesions in MS patients without a history of optic neuritis. Calculating a decrease of 1 cm^3 in the visual cortex volume predicts a reduction of 0.7 µm on the retina. The authors also propose a model that includes the mean thickness of the RNFL and the volume or NAA levels in the visual cortex that could be a biomarker of trans-synaptic degeneration, with prior validation and longitudinal studies directed at defining the causality of diffuse trans-synaptic degeneration as a mechanism of injury in MS.

Neuroimaging of the mechanisms of progression

The value of optical coherence tomography in the mechanisms involved in inflammation is evidenced by the findings of microcysts in the retinal nuclear layer in patients with a very aggressive form of MS [67]. With respect to energy failure mechanisms, prominent findings include Na^+ levels in MRI, associated with disability [68,69]; NAA concentrates in MRS as a measure of mitochondrial dysfunction; and cerebral hemodynamics by infusion and arterial transit time.

Morphological and functional imaging of cognitive disorders

Approximately 43-70% of MS patients suffer cognitive disorders, largely related to the speed of information processing and working memory [70]. Cognitive disorders occur in both relapsing-remitting forms as well as in secondary progressive forms, but they are most common in the latter, especially with regard to processing speed. De Stefano [71] summarised the previously published data. In general, morphological findings observed by conventional techniques correlate well with the different cognitive tests, except in volume lesion for T_1 and T_2, which, if measured globally, provides inconclusive results. Conversely, frontal and parietal lesion

volume has exhibited good correlation with the results derived by applying the tests exploring executive functions, working memory, and processing speed using the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT).

In the posterior fossa, there is good correlation between cerebellar lesion volume and the Sternberg task that studies processing speed; the dilation of the third ventricle is correlated with the PASAT and SDMT tests; hippocampal atrophy is correlated with altered working memory and cortical volume loss in all tests. It should be noted that relapsing-remitting forms and secondary progressive forms share a similar cortical atrophy pattern, different from primary progressive forms. Due to the higher diagnostic yield of double inversion recovery (DIR) sequences in locating and defining cortical lesions, in the future, this technique will likely be more useful in correlating cognitive impairment with MS disturbances.

According to Enzinger [72], when examining patients performing certain tasks or tests, functional MRI reveals compensatory adaptive changes, specifically brain reorganisation, which could partly explain the clinical paradox of patients with high lesion load and little functional or cognitive impairment. These compensatory mechanisms are related to the patient's age, clinical state, time course of the disease, and the disease lesion load. According to this hypothesis, more areas of activation should be initiated in MS patients than in control subjects; however, in very advanced cases of MS, a great number of active areas exist, but active zone volume is much less than in control subjects [73]. In patients with cognitive fatigue, there is a greater activation of the superior and inferior frontal gyrus, the cingulate gyrus, superior temporal gyrus, and the insula; thus, cognitive fatigue can also interfere with MRI findings and may be useful only at the individual level [73]. However, the level of difficulty of the task type that the patient is given could also interfere with the results of functional MRI. In this sense, an easy task activates temporal and parietal areas in both relapsing-remitting forms and secondary progressive forms, although there is a lower reuptake in brain areas with the execution of the most difficult tasks [74]. In short, age, time since onset, type of task performed and the presence of cognitive fatigue may interfere with the results of functional MRI.

Diffusion tensor MRI (DTI) enables the analysis of white matter and normal-appearing white matter areas by conventional MRI. There are data demonstrating a relationship between normal-appearing grey matter alterations and cortical lesion volume, especially with the degree of disability [75]. Cognitive testing results differ significantly depending on the studies and according to Enzinger [72], possibly due to the findings that demonstrate an increase in the anisotropy fraction and increased diffusion in white matter lesions, unlike what happens in grey matter and which indicates a good therapeutic evolution.

Of increasing interest, and in line with previous studies identifying the thalamus as the region where there is a stronger correlation between thalamic atrophy and cognition, Benedict et al. [76] have evaluated the contribution to cognitive impairment of the thalamus based on DTI evaluations of the thalamus. It should be remembered that the thalamus is part of the limbic system and the Papez circuit and has functional nuclei related to multiple emotional aspects and memory. Alterations of the thalamus could explain fatigue and some cognitive impairment, mainly those related to working memory and processing speed, common in MS. The results demonstrated that 78% of the lesions affected thalamocortical fibres, so the results in visuospatial memory and language processing tests should be altered; however, there was no better correlation with thalamic atrophy than with other neuroimaging parameters.

In cognitive networks of children with MS, abnormalities in functional connectivity at rest are visualised. Information from the study by Filippi et al. [77] to explore, using functional MRI and structural MRI, such alterations and functional interactions between cognitive networks demonstrates that in children, there is an alteration in the following cognitive networks: DMN (default mode network), ECN (executive control network), attention, and LWMN (left working memory network). Additionally, abnormal connectivity is observed between the DMN and parietal attention network. This result suggests the preservation of connectivity between networks in these patients, which may have an impact on the favourable course of the disease.

Conclusions

In the pathogenesis of MS, inflammatory and neurodegenerative phenomena occur and likely exhibit a cause-and-effect or shared relationship. The early disruption of astrocytic processes may precede demyelination and contribute to the pathogenesis of demyelinating disorders, and resident microglia are related to myelin debris cleaning, an essential role in remyelination [78].

OPCs are the main source of remyelinating cells in the central nervous system, and the strategies to promote endogenous remyelination include identifying signals that would facilitate the change from quiescent OPCs to activated OPCs, guidance signals that would facilitate recruitment and migration, and signals that would facilitate cell maturation.

The challenges in the use of biomarkers include a better understanding of the aetiology and pathogenesis of the disease, in addition to the heterogeneous clinical and pathological manifestations and diverse response to treatment. Genomic studies, transcriptomics, proteomics, and microRNA studies will allow the identification of new markers to improve the current situation. In fact, there are studies that have identified genes associated strongly with the disease, susceptibility genes that trigger an inflammatory response, and genes involved in the response to treatment with interferon-β and glatiramer acetate.

Regarding neuroimaging markers of demyelination and remyelination, conducting serial MRI enables the observation of early changes in diffusion, and the quantification of the MTR offers results of a higher proportion of MTR in the possible remyelination areas. Assessing the presence of black holes also arises as a measure of remyelination in longitudinal studies, and PET imaging of myelin activation with specific markers is in progress, with BMB and ^{11}C PIB as promising candidates. T_2 lesion volume and brain atrophy are proposed markers for neurodegeneration, and attention is focused on emerging MRI measures, such as diffusion MRI, the evaluation of the spinal cord by DTI or MTR, and the loss of the ganglion cell layer by optical coherence tomography.

Due to the higher diagnostic yield of DIR sequences in locating and defining cortical lesions, in the future, these sequences will likely be more useful in correlating cognitive impairment with MS disturbances. An increase in the anisotropy fraction and increased diffusion in white matter lesions indicates good therapeutic development. There is no better correlation between thalamic atrophy and cognition than with any other neuroimaging parameters.

The landscape of MS treatment is rapidly changing with the current clinical development of new agents that can replace the currently available treatments [79].

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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) (II)

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. En esta segunda parte de la revisión Post-ECTRIMS se analiza la biología de la recuperación y remielinización en la esclerosis múltiple (EM), y se discuten las diferentes estrategias de reparación y remielinización endógena y exógena que actualmente están siendo evaluadas, sobre la base de que la microglía residente y las células precursoras de oligodendrocitos se han visto implicadas en el proceso de remielinización. Asimismo, se expone el estado actual y uso futuro de los biomarcadores en EM, y se proponen como marcadores de neurodegeneración el volumen lesional en T_2 y la atrofia cerebral mediante resonancia magnética, así como la pérdida de capa de células ganglionares mediante tomografía de coherencia óptica. Se plantea una mayor utilidad futura de las secuencias DIR para correlacionar las alteraciones cognitivas con las alteraciones de la EM, dado su mayor rendimiento diagnóstico en localizar y

definir lesiones corticales. La disponibilidad de nuevos biomarcadores en un futuro requiere una validación estricta. En este sentido, se plantean posibles áreas de actuación dirigidas a mejorar la situación actual, y además se presentan los resultados de las investigaciones más recientes en la identificación de posibles candidatos con utilidad diagnóstica, pronóstica, de respuesta al tratamiento y de seguridad.

Palabras clave. Alteración cognitiva. Biomarcadores. Desmielinización. Esclerosis múltiple. Neuroimagen. Remielinización.