Review of the novelties from the 32nd ECTRIMS Congress, 2016, presented at the 9th Post-ECTRIMS Meeting (II)

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Summary. For the ninth year in a row the Post-ECTRIMS Meeting has been held in Madrid (Spain) with the aim of presenting and discussing the hottest issues debated at the ECTRIMS Congress by renowned specialists in multiple sclerosis in our country. One outcome of this scientific activity, endorsed by the Spanish Neurology Society, is this review article, which is published in two parts. This second part reflects the current controversy over the management of multiple sclerosis, especially as regards the progressive forms and their differential diagnosis. The work presents the latest advances in remyelination, where the use of the micropillar technique in laboratory stands out, and in neuroprotection, which is reviewed through a study of the optic nerve. Anti-CD20 antibodies are a very promising development and we find ourselves before a new mechanism of action and therapeutic target in cells to which little attention has been paid to date. Another notable fact is the high correlation between the levels of neurofilaments in cerebrospinal fluid and in serum, which could make it possible to avoid the use of cerebrospinal fluid as a biological sample in future studies of biomarkers. The review also provides a preview of the advances in clinical research, which will converge in clinical practice in the future, thereby conditioning the steps that should be taken in the therapeutic management of multiple sclerosis.

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

Introduction and objectives of the conference

ECTRIMS has celebrated its twenty-first edition, and it continues to be the conference of reference for clinical and basic research on multiple sclerosis (MS), facilitating communication and promoting teaching among health professionals for the benefit of the patient. Attendance continues to rise, and Spain saw the third-highest attendance in the most recent edition in 2016.

The Post-ECTRIMS Meeting, organised by Teva Neuroscience, is very relevant to the area of MS in Spain and traditionally brings together the community of neurologists who specialise in MS in our country. The 2016 edition was the ninth conference held with the clear objective of analysing principle advances and reviewing the most-debated issues in ECTRIMS together with renowned national specialists.

Current controversy in MS management

Given the lack of consensus, the interest in establishing a guide for patterns of change from primary to secondary therapies is evident. An Italian study with newly diagnosed patients [1] showed that the rate of change after two years of treatment varied as a function of the drug used, and the principal predictor of change due to ineffectiveness was a first treatment with interferon or glatiramer acetate in younger, recently diagnosed patients with medullar lesions. Change due to safety problems was principally associated with treatment with fingolimod and natalizumab as a first treatment, a more recent diagnosis and baseline comorbidities.

Three years after beginning treatment, almost half of patients change treatment, overall due to lack of effectiveness. Given that initial therapies can fail to reach adequate disease control, it is recommended to make the change as soon as possible whenever there is suboptimal response or therapeutic failure to try to prevent the long-term disability shown in the natural development of the disease [2]. This decision would be the basis of the therapeutic scale, whose success is founded in defining, together with the patient, the limit of suboptimal response when the next therapeutic option should be introduced, assuming potential risks.

Induction treatment was reserved for cases of very active and aggressive MS, achieving stabilisation or

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Competing interests:
The Post-ECTRIMS working group

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receives aid that is not conditioned upon continuing medical education from TEVA Neuroscience Spain. O.F. has received honoraria as a reviewer in committees and as a moderator or speaker at conferences and scientific meetings and has participated in clinical trials and in other research projects promoted by Biogen, Bayer-Schering, Merck-Serono, Teva, Novartis, Genzyme, Almirall, Allergan, Actelion and Roche. A.O. has received economic compensation as a conference speaker from Teva, Biogen, Sanofi-Genzyme, Novartis, Allergan, Almirall, Glaxo, Merck and Metz and as an advisor from Biogen, Roche, Novartis, Sanofi, Genzyme and Allergan. In addition, he has participated in clinical trials sponsored by Allergan, Novartis, Lilly, Sanofi-Genzyme, Roche and Alder. C.O.G. has received honoraria as a conference speaker from Teva, Novartis, Merck, Genzyme, Roche and Biogen. J.M.P. is a consultant with Bayer HealthCare, Biogen Idec, Genzyme, Novartis, Sanofi-Aventis, Teva, Roche Pharma and Almirall Prodesfarma. He has participated as a speaker at meetings or symposia organised by Almirall Prodesfarma, Bayer HealthCare, Biogen Idec, Genzyme, Merck-Serono, Novartis, Sanofi-Aventis and Teva. He has received funding from Almirall Prodesfarma, Biogen Idec, Novartis and Sanofi-Genzyme to conduct research projects. J.A.G.M. has received compensation for travel costs and honoraria for presentations and consultancy from Bayer, Merck, Teva, Biogen Idec, Novartis, Roche, Almirall, Sanofi-Aventis and Genzyme. Ll.R.T. has received honoraria for meetings, training, conferences and consulting from Teva, Novartis, Biogen, Merck-Serono, Bayer and Sanofi. R.G. has received economic compensation for participating as a researcher in clinical trials, being part of consulting groups and giving scientific lectures from Bayer, Merck, Novartis, Teva, Biogen Idec, Genzyme, Roche and Almirall. J.E.M.L. has received honoraria as a consultant and speaker from Almirall, Biogen, Genzyme, Merck-Serono, Novartis, Roche and Teva. L.R.P. has received honorary compensation for participation in advisory councils and for acting as a consultant and speaker for Biogen Idec, Teva, Sanofi-Aventis, Merck-Serono, Novartis and Bayer-Schering. D.M. has collaborated with speeches at conferences and meetings of Teva, Biogen, Novartis, Merck, Sanofi and Almirall. P.O.N. has received honoraria for giving scientific talks for Almirall, Biogen Idec, Sanofi-Genzyme, Merck-Serono and Teva. He has participated in research projects financed by Biogen Idec, Merck-Serono, Sanofi-Genzyme and Teva. M.C.C.H. has participated

no evidence of disease as soon as possible. A candidate patient would be one who has the relapsing–remitting form, who is young, with high clinical activity, severe attacks that leave considerable disability and radiological activity [3]. The induction plan should be proposed in the initial phases of the disease because, after a first inflammatory phase, patients progress similarly [4]. In the BENEFIT study [5], patients treated in the beginning presented a lower rate of attacks during disease evolution, whereas those treated with lower disability maintained lower disability over the course of 11 years.

For now, there is no treatment that achieves complete remission of the disease, nor are there good measures to manage and identify induction therapies. Alemtuzumab, mitoxantrone and natalizumab, the latter with less consensus, are the current treatments considered when choosing an induction therapy [6]. Alemtuzumab significantly reduces disability and the rate of attacks in the initial phases of the disease, whereas in more advanced phases, it has less success [7]; that is, the same treatment in different phases of the disease can provoke different results. Another recent study with alemtuzumab in 87 patients after seven years of follow-up showed early improvement in the EDSS in 20% of cases, a late improvement in 23% and a stabilisation of disability in 57% [8]. Its safety profile is well defined, with the appearance of adverse events in the second and third year, and up to 50% of autoimmune reactions [8]. Mitoxantrona is mainly known for its elevated efficacy [9], although it needs close monitoring [10]. Natalizumab, however, is not considered by some experts as an induction therapy due to its elevated risk of reactivation of the disease after its withdrawal, and it is more suited for use as an escalated therapeutic treatment.

These treatments achieve relatively low levels of NEDA, on the order of 34% with natalizumab in the second year, 40% with alemtuzumab in the fifth year and 60% with a bone marrow transplant at five years. However, it is likely that patients who achieve NEDA would benefit less from an induction treatment because their own natural disease development presents a less aggressive form of the disease.

Among the weak points of an induction treatment is the fact that 20% of patients have 'benign' forms, that MS decreases life expectancy by 6-7 years, that 70% of patients treated with interferon β from presentation of clinically isolated syndrome maintain a low EDSS for 11 years, that there is no direct correlation between clinical and radiological factors and that immunological markers of onset and progression are lacking for the disease. Finally, the lack of scientific evidence does not make it possible to propose an induction treatment for the majority of patients with MS.

Other controversial questions that inevitably come forth in the management of these patients, such as progressive forms, differential diagnosis and pregnancy, which generates so much concern among patients and clinicians, were approached using the format of clinical case discussion (Table).

Pathology and pathogenesis of MS

Remyelination and neuroprotection mechanisms

While approaching clinical aspects of the disease, the latest advancements in remyelination and neuroprotection come to light. Although the findings are preliminary, it is a very active field with regards to the search for methodologies that, in some cases, begin to extrapolate to clinical practice.

Among the most relevant aspects is the use of micropile arrays as a new highly effective screening platform for regenerative therapies in MS [11]. These micropiles of poly-L-lactic acid simulate axons; they are designed with conic dimensions and allow the resolution of the length and area of the membrane cover to be increased from a two-dimensional image. Through cultivating progenitors of oligodendrocytes, myelin 'hoops' are created that can be detected via confocal imaging, which thereby allow the study of composites that promote remyelination. This technology has allowed for the selection of surprising myelination candidates, such as the T3 hormone, but also drugs used in neurology, such as quetiapine, oxybutynin, trospium and clemastine. Curiously, the latter, an antihistamine with a very low market price, has been effective in promoting axonal myelination. In transferring it to patients with MS and chronic optical neuropathy, clemastine improves the delay in latency of visual evoked potentials (VEPs) in the first clinical trial with a remyelinating candidate in MS [12].

In in vivo models, endogenous stem cell modulation through drugs promotes remyelination. A library search of small bioactive molecules in oligodendrocyte precursors of pluripotent epiblast mouse stem cells identified miconazol and clobetasol as drugs that have the capacity to promote early myelination in organotypic cerebellar cultures and in mouse litters [13]. Induced pluripotent stem cells derived from fibroblasts can be modified and reprogrammed and can also be grafted, all of which indicates that repairing myelin is an emerging area

in therapeutic MS trials, in terms of both drugs and electrical stimulation.

Repeatedly, researchers insist on the need for not only magnetic resonance biomarkers but also analytical ones, to optimise research in this field. Currently, research is centred around the Chi-3l3 family and its possible role in regeneration. Oligodendrogenesis is clearly induced in both in vitro and in vivo models. Therefore, we have a molecule that, through the EGFR-Pyk2 axis, will play a central role in oligodendrogenesis, with implications in autoimmune demyelination and even therapeutic advances [14].

Neuroprotection in MS through the study of the optic nerve

Neuroprotection in MS is reviewed through the study of the optic nerve by means of the instruments that measure neuroaxonal loss in the visual pathway. Multifocal VEPs in the acute phase predict the visual result in the long term through optical neuritis or the risk of developing MS. This approach is more comprehensive and is considered a useful exploration to understand the therapeutic window and to evaluate possible candidates for neuroprotection studies. In patients with a first attack of less than one month of evolution that may or may not be optical neuritis, the amplitude of multifocal VEPs, but not their latency, correlates with visual acuity and retinal atrophy at three months [15].

The drugs simvastatin, erythropoietin and memantine have been tested in the recovery after optical neuritis with marginal benefits for visual acuity, VEP, magnetic resonance measures and optical coherence tomography. The most important and most recent study is the use of phenytoin in optical neuritis of less than 14 days' evolution, with positive results in some measures of atrophy based on optical coherence tomography and neurofilament levels [16].

Segmentation of the retina provides well-known data on atrophy of the different layers, which is very useful for relating atrophy to measures of disability in the short and long term [17]. Over time, the thickness of the layer of ganglion fibres correlates with measures of cerebral atrophy in magnetic resonance in the eye unaffected by optical neuritis, correlating particularly with grey matter atrophy and, especially, in primary progressive forms [18], thus reflecting the neurodegenerative process. There are also changes in the depth of the retina, particularly microcystic macular oedema [19], and in specific subtypes of patients with MS, a hemimacular thinning pattern of the cells that reflect the posterior lesional topography is observed. In addition, there are correlation data between retinal atrophy and atrophy of the spinal cord that complement cerebral atrophy and that explain their contribution to the disability [20].

The predictive role of retinal atrophy in disability at 10 years was studied in a retrospective series of 158 patients, the majority with relapsing–remitting forms, with or without optical neuritis [21]. As a baseline form, the secondary progressive form has a thinner retinal nerve fibre layer (RNFL) and a lower total macular volume; this retinal atrophy increases with time and is associated with disability.

The association of retinal atrophy with NEDA was evaluated through the effect of VEPs on RNFL in optical neuritis and through the association between RNFL and NEDA [22]. In patients with MS and without optical neuritis during two follow-up years, the decrease in thickness of RNFL was not affected by having had a previous optical neuritis nor having altered VEP baseline levels. That is, six months after an optical neuritis, the evolution in the atrophy of the affected eye was the same as in the healthy eye. In addition, variations in the thickness of the RNFL correlated with changes in the EDSS and in clinical (attacks) and radiological activity, although the most important finding was that the atrophy of the RNFL was able to correctly classify 78% of patients with NEDA, a very relevant piece of information with a very small population that deserves validation in future studies. It is worth emphasising that a subgroup of patients with significant retinal atrophy conserved NEDA; these patients would be more likely to present neurodegeneration in the future.

However, McKee's work does not demonstrate the neuroprotective benefit of amiloride [23]. In patients with optical neuritis with less than 28 days of evolution, treated or not, amiloride did not affect the thickness of the RNFL, as evaluated by polarimetry and optical coherence tomography. Even the treated group presented greater deterioration in multifocal VEPs at six months than the control. The conclusion was that amiloride's effect on oligodendrocytes was not clear, and it should be noted that just as cerebral atrophy is not sought at six months, in optical coherence tomography, an interval of at least one year would be necessary.

Disease-modifying treatment

Immunomodulation and immunosuppression

Anti B-cell therapies are highly effective in inflammatory parameters and, therefore, play a role in the

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Table. Controversies in the current management of MS.

	Case 1 (woman, 26 years old)	Case 2 (man, 45 years old)	Case 3 (woman, 42 years old)
Medical history	Right ON with one month of evolution not responding to methylprednisolone Paraesthesia's in lower extremities eight weeks prior	Weakness in the lower left extremity with six months of evolution	Horizontal diplopia and sensitive syndrome on the left side of the body
Exploration	Normal, except decreased vision in the right eye Multiple cerebral lesions in MRI and OCB IgG in CSF	Exploration with bilateral hypaesthesia without a sensitive level, and bilateral pyramidal signs Cervical lesions in the MRI and OCB in the CSF	Exploration with tactile hypaesthesia on the side of the body Normal MRI and CSF Normal EP
Diagnosis		Given the progressive evolution, primary progressive MS is diagnosed *Key points:* – 15% of patients can present a cerebellar or medullar syndrome – 20% of lesions with gadolinium enhancement (McDonald, 2010)	Considered are MS onset, paraneoplastic syndrome, acute disseminated encephalitis, ONM spectrum, sarcoidosis After six days, the patient presents instability, hypo, MRI with a lesion in the postremal region. The diagnosis seems clearer Consensus Criteria for the Diagnosis of ONM Spectrum (2015) are reviewed: it is a clinical diagnosis, there are no pathognomonic findings and there are nuclear symptoms, such as the presence of optical neuritis or transverse myelitis or area postrema syndrome, a very characteristic datum of ONM *Key points in the diagnosis:* – ONM can present without ON and without transverse myelitis – Area postrema syndrome is very important – AQP-4 tests must be performed and stratified by positive or negative serology and, if the result is negative, an anti-MOG must be performed, given that 25% of patients will be positive and will present very defined characteristics of monophasic disease, with better evolution, and with a preference for the lumbar medulla, the optic nerve and deep grey matter
Treatment	It is decided to treat with NTZ with good clinical evolution and radiology	There are no specific treatments for primary progressive MS	It is decided to treat with methylprednisolone, and she improves after six weeks Therapeutic possibilities: methylprednisolone and plasmapheresis Preventative possibilities: azathioprine, mycophenolate, rituximab, among others If failure: possible combinations with rituximab, change to drugs with different action mechanisms
Controversy	Desire to become pregnant	*Rituximab?:* – ORATORIO: 25% ↓ risk of progression at two years – OLYMPUS: not demonstrative, except in a subgroup of men < 50 years, with primary progressive MS and gadolinium enhancement *Fingolimod?:* fails in primary progressive forms *Elimination of tobacco and salt?:* possible beneficial effect	The clinical forms of the ONM spectrum can worsen with interferon, natalizumab, fingolimod and alemtuzumab; it is a very important aspect because in the case of differential diagnosis with MS, it is advised to always treat patients as though it were an ONM spectrum Decision-making based on neuroimaging is very limited, and based on antibodies, very debatable; therefore, monitoring treatment should be based on clinical presentation, in the absence of relapses If there is good evolution, suspending treatment is not an option If there is a desire to become pregnant in a patient with azathioprine, a reasonable option is to use two doses of rituximab and then attempt becoming pregnant
Clinical judgement	Her doctor decides to suspend natalizumab and change to GA, maintaining it throughout the pregnancy. This is a high-risk patient, and it is necessary to maintain an immunomodulating drug	Multidisciplinary treatment with physical therapy, fampridine and oral baclofen. Smoking cannabis is discarded based on available studies of short-term cognitive effects	
Controversy	Breast feeding		
Evolution	2.5 months after birth, patient presents new lesions in T_2		
Clinical judgement	Breast feeding is suspended, GA is suspended and natalizumab is restarted		

GA: glatiramer acetate; OCB: oligoclonal bands; LE: lower extremities; MS: multiple sclerosis; CSF: cerebrospinal fluid; ONM: optical neuromyelitis; ON: optical neuritis; EP: evoked potentials; MRI: magnetic resonance imaging.

disease activity. The depletion of B cells translates into a decrease in the response of proinflammatory myeloid cells [24] and in a smaller activation of proinflammatory T cells [25]; that is, there is a bidirectional relationship between B cells, T cells and myeloid cells, which justifies selective action on different populations of B cells in MS [24].

The role of memory B lymphocytes is reviewed through the bidirectional relationship at the peripheral and central levels [26], but the question is to determine whether the B lymphocytes associated with MS acquire antigen experience in the peripheral lymphoid tissues or in the central nervous system and to be able to identify them by studying somatic hypermutations in well-identified type B lymphocyte populations [27]. Two aspects are proposed: on the one hand, immunity tied to the expression of MHC-II molecules in oligodendrocytes and involved in the activation of the immunological cascade dependent on the T-lymphocyte, and an immunity tied to MHC-I molecules expressed in neurons, which would act as presenter cells for antigens, more along the lines of the B lymphocyte, an already known idea [28-30].

Th17 cells, a subtype of CD4+ T cells, become part of the immunological repertoire due to their involvement in the disease activity, and a new phenotype of Th1 cells, producers of granulocyte-colony stimulating factor and interferon-γ, could be related to the development of the progressive phase [31].

The benefit of B-cell depletion (with anti-CD20 therapies) in relapsing–remitting forms was confirmed in the OPERA I and OPERA II studies [32]. Ocrelizumab significantly reduced the annual attack rate, gadolinium-enhancing lesions and the progression of disability in T_2. Although less notable, it also showed positive effects on the reduction of cerebral atrophy, and almost half of patients met criteria for NEDA at two years. Inhibition of the release of CD52+ T lymphocyte from lymphatic ganglia (with anti-CD52 therapies) inhibited rebound inflammatory activity. The anti-CD52 antibody alemtuzumab offers a unique approach to the treatment of patients with relapsing–remitting forms and offers a lasting efficacy in the absence of continuous treatment. In the extension phase of the CARE-MS I study at three and six years with *naïve* patients [33], disability remained stable or improved during the six years without treatment; similarly, 77% did not present confirmed worsening of disability in the period of six months to the sixth year, 34% improved in confirmed disability in the period from six months to the sixth year and 57% reached NEDA in the sixth year.

Recent data suggest that glatiramer acetate can play a role in inhibiting B-cell activation or maturation by blocking essential ion channels for cellular proliferation. Using B cells from patients with relapsing-remitting MS, the authors found that glatiramer acetate presents an action mechanism similar to that of CDK2 inhibitors and topoisomerase II, molecules capable of acting in the synthesis and topology of DNA [34]. Glatiramer acetate appears to immunomodulate the pathogenic function of B cells and to maintain the clinical benefit after anti-CD20 induction therapy [34,35], a therapeutic approximation in MS that could avoid continuous anti-CD20 treatment and an unknown immunological profile in the long term. Preliminary evidence showed that treatment with glatiramer acetate after one month of rituximab increased the median time until therapeutic failure and decreased the number of patients with relapses compared to monotherapy with glatiramer acetate [36].

The possible effect of laquinimod on the innate peripheral immune system is still being researched, with the research currently centring around the activation of the aryl hydrocarbon receptor (AhR), a path with an important role in neuroinflammation. An experimental design of experimental autoimmune encephalomyelitis (glucoprotein of the myelin of the oligodendrocyte) in control mice and KO-AhR showed that laquinimod reverted the profile of gene expression associated with experimental autoimmune encephalomyelitis in controls and induced the gene expression of AhR, while in KO-AhR, it did not produce any type of clinical variation, nor in other variables of demyelination, axonal harm or microglial activation [37]. Along the same lines, the role of AhR on the direct effect of laquinimod on the central nervous system in two experimental models was studied; in the autoimmune model, the controls treated with laquinimod improved clinically, as did the histological and cellular variables compared with KO-AhR and mice, while in the toxic cuprizone model, both the controls and the KO-AhR improved in clinical, anatomopathological and immunological parameters; that is, in addition to acting on AhR, laquinimod appeared to act on other protective mechanisms against demyelination [38].

Treatment of progressive MS

The fact that drugs that are effective on forms with attacks are not effective in progressive forms (SPECTRIMS, PROMISE and INFORMS studies) suggests the hypothesis that a therapeutic delay in

inflammatory therapies may occur in patients without the capacity for reserve and partial or complete neuronal recovery by compensatory mechanisms. This hypothesis has always been formulated but has never been directly studied. A post hoc analysis with data from the SPECTRIMS and PROMISE studies in secondary progressive and primary progressive forms, with interferon and glatiramer acetate, respectively [39], showed that the effect of both drugs became evident after 2-2.5 years from the start of treatment and that this delay in time depended on the baseline EDSS. These results support the hypothesis that in progressive MS, disease modifying treatments can take several years to manifest their effect on the progression of the disease, and they demand greater confirmation in independent clinical data in the long term.

In the primary progressive forms, the OLYMPUS study [40] did not show positive data for rituximab versus placebo, although the analysis of subgroups with more inflammatory forms, younger patients and with contrast-enhancing lesions did show a possible benefit with regards to accumulation of disability. Later, the ORATORIO study with ocrelizumab in younger patients and with oligoclonal bands demonstrated a 24% reduction of risk in confirmed progression at 12 weeks, a more modest benefit than in forms with attacks [41]. In secondary progressive forms, the RIVITALISE study [42] analysed a combination of intrathecal and intravenous rituximab on parameters of cerebrospinal fluid (CSF). The effectiveness data with these CSF biomarkers were insufficient to measure effectiveness in clinical results, and the criteria were not sufficient to continue the study. It appears that anti-CD20 therapies are highly effective for patients with attacks, but their efficacy is limited in progressive forms. As possible explanations, a hypothesis has been put forth that in these progressive forms of the disease, there are neurodegenerative mechanisms that do not depend on inflammation and that the action of B cells in the central nervous system is likely not accessible to anti-CD20 therapies, or that there is a smaller role of the peripheral immunological response in patients with progressive forms.

The results of the EXPAND study [43] with siponimod in patients with secondary progressive forms show a significant reduction of 21% in the risk of progression of disability at three months versus placebo. These results are moderate, but positive. Except for an improvement in the 25-step test in favour of siponimod that was not statistically significant, all of the secondary disability objectives were fulfilled at six months, such as change in lesion volume in T_2, annual rate of relapse and cerebral volume.

Another anticipated presentation was that of the results of the SYNERGY study, with the anti-LINGO 1 opicinumab, previously studied in RENEW phase II in patients with a first episode of optical neuritis and positive results in VEP. The efficacy of an increase in dosage of opicinumab versus placebo in patients with forms that have attacks or secondary progressive forms treated with interferon β-1a was evaluated with very ambitious variables, such as the reduction of one point on the EDSS or 15% of three components of the functional composition of MS (25-step test, Nine Hole Peg Test and 3-s Paced Auditory Serial Addition Test) over the course of 72 weeks. The results were disappointing because no improvement was shown in any of the individual components of the principal variable. In short, with the design of the SYNERGY study, opicinumab was not able to show efficacy in remyelination, and the U-shaped dosage-response curve leads one to think that the doses were not adequate. In the experts' opinion, the evaluation measures were inadequate, and one cannot expect such positive results with only anti-inflammatories. For example, one must take into account that the anti-LINGO-1 does improve the conduction capacity of the optic nerve, yet for this study, VEPs were not used as variables.

The FLUOX-PMS study [44] with fluoxetine did not show significant results in the percentage of patients without sustained progression of disability versus placebo, likely due to an insufficient progression of patients for the trial or a study of only two years.

A new model of experimental autoimmune encephalomyelitis with characteristics of progressive MS in mice deficient in oligodendrocyte peroxysomes and without mature B and T cells was presented, which showed improvement with laquinimod. These mice began with symptomatology at 3-4 months and progressed unnoticed, experiencing an apparent microglial activation before demyelination and axonal loss. Laquinimod significantly improved the clinical activity and reduced the number of active microglial cells and damaged axons in the corpus callosum [45], results more in line with what has been shown to date in humans.

Advances in the imaging of the physiopathology of MS

The neuronal compartment plays a more important role than previously thought in MS pathogenesis. Modern histopathology and imaging techniques

show that significant damage to neuronal structures already begins to occur in the first stages of the disease. As the disease progresses, the extension of the neuronal pathology accumulates, and neural homeostasis disappears. With the loss of immunological homeostasis, disruptions in the innate system occur and the neurodegenerative phenomena that are so hard to treat begin to appear [46,47]. The figure presents a general vision of how MS is currently treated as a function of the different immunopathogenic aspects of the disease.

Modern techniques of *in vivo* microscopy are improving our understanding of the mediating mechanisms of the neuroinflammatory tissue damage. Double photon microscopy, for example, is able to visualise, in a progressive MS model, the generalised deficits in organelle transport that precede structural alterations in axons and that could contribute to axonal dystrophy in advanced stages of the disease [48].

We can already objectively measure the activated microglia [49] if a cyclotron to produce the PK1119 isotope is available. Positron emission tomography (PET) also offers promising tools to define the physiopathological image of MS and to evaluate inflammation, demyelination, remyelination and neurodegeneration. The PET tracer [11C] PIB can quantify the evolution of a focal lesion in the long term [50] and can classify patients according to their remyelination potential. Marking with [11C] flumazenil decreases over the course of the disease, is not related to grey matter atrophy and, overall, shows alterations in cortical lesions.

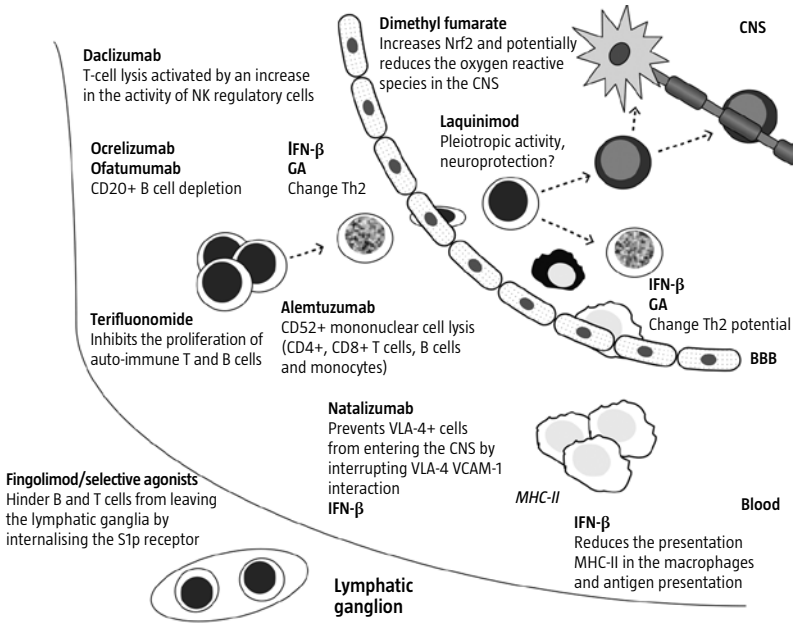
Next steps in blood and CSF tests in clinical practice

Recent data show that the anti-KIR4.1 antibodies expressed in astrocytes and oligodendrocytes do not play a pathogenic role [51,52], although anti-anoctamina 2 (ANO2) antibodies have been identified in 5-10% of patients with MS [53]. The ANO-2 protein is part of the calcium-activated chloride channels expressed in neurons and glial cells; increased reactivity has been observed for various peptides of the protein and an important interaction between the presence of these autoantibodies and the principal genetic risk factor HLA DRB1*15.

For the first time, a study of the complete genome association implies a very significant polymorphism of a single nucleotide with MS activity of patients treated with interferon β [54]. This polymorphism involves an intronic variant of the *SLC9A9* gene, which codifies an ionic transporter expressed in lysosomes. These findings were replicated in various independent cohorts, although in two Danish populations with large sample sizes, there has been no finding of association with either the risk of relapse or disease progression [55].

Thanks to the use of new technologies with greater sensitivity, the quantification of biomarkers in future studies is possible. The Quanterix Simoa is a high-sensitivity immunoassay very similar to the ELISA; the findings from one study in which the levels of neurofilaments in the CSF and in the serum of 33 patients with MS using three techniques (conventional ELISA, immunoassay based on electrochemiluminescence and Quanterix Simoa) showed better correlation in CSF and serum using Quanterix Simoa. With this technique, we can now detect levels of neurofilaments in serum, which are increased in patients with clinically isolated syndrome compared to controls; however, serum levels do not discriminate between patients with clinically isolated syndrome who evolve to MS and those who do not [56]. A good correlation has also been observed between levels of neurofilaments in CSF and in serum in patients with attacks [57]; in fact, work with patients from the FREEDOMS

Figure. Overview of current treatment by means of disease immunology. GA: glatiramer acetate; BBB: blood-brain barrier; IFN: interferon; CNS: central nervous system.



study shows serum levels of neurofilaments in patients with MS that are significantly higher than healthy controls (28 pg compared to 12.5 pg; $p < 0.0001$). Also observed is an almost linear relationship between neurofilaments in serum and gadolinium-enhancing lesions and, although not in such a marked form, relationships with EDSS and lesions in T_2 [58]. These findings propose levels of neurofilaments as a peripheral biomarker of neuronal damage and support serum as a much more accessible biological sample to detect neurofilaments in future biomarker studies.

The SOMAScan is a new-generation proteomic technique based on the technology of single-chain modified aptamers or nucleic acids, which present an elevated affinity and specificity for proteins. This highly sensitive technology allows us to detect a broad range of proteins in serum or CSF. In comparison to proteomic technologies based on mass spectrometry with nanomolar (10^{-9}) ranges or immunoassays with picomolar (10^{-12}) ranges, this technique can reach a sensitivity on the femtomolar (10^{-15}) order. Currently, there is an on-going study to identify predictive biomarkers of disease progression in patients with primary progressive MS, with initial attacks classified into slow and fast progression.

Final observations

In the first part of this review [59], we mentioned that ECTRIMS 2016 was characterised more by the still-unanswered questions that have emerged than by great advances. The two-way voting of those in attendance with regards to induction strategies and therapeutic scaling reflects, for example, the need to advance to define them correctly and to better understand their utility. The review of MS immunology shows the gaps in knowledge that still exist today regarding the innately acquired immunity connection.

The study of the optic nerve offers a window into neuroprotection in MS, but at the same time, it manifests the lack of biomarkers to be able to evaluate regeneration, despite the fact that techniques with synthetic micropiles already allow remyelination to be studied in the lab. In fact, currently, there are approximately 15-20 drugs that are being studied with regards to remyelination, some of them in phase II clinical trials.

Another interesting datum is the possibility of measuring the activation of the microglia objectively, if one has a cyclotron to produce the PK11195 isotope. The University of Málaga has an open project in which all of the neurodegeneration factors will be measured using a PET with PK11195.

The elevated correlation between the levels of neurofilaments in the CSF and in serum could avoid the use of CSF as a biological sample in future biomarker studies. However, the fact that quantifying in serum is only observed with new technologies highlights the low sensitivity of current techniques, which to some extent explains the existing gap in terms of biomarkers of the disease.

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Revisión de las novedades del XXXII Congreso ECTRIMS 2016, presentadas en la IX Reunión Post-ECTRIMS (II)

Resumen. Por noveno año consecutivo se ha celebrado en Madrid (España) la Reunión Post-ECTRIMS con el objetivo de presentar y discutir los temas más debatidos en el congreso ECTRIMS de la mano de reconocidos especialistas en esclerosis múltiple de nuestro país. Fruto de esta reunión científica, avalada por la Sociedad Española de Neurología, se genera este artículo de revisión que sale publicado en dos partes. En esta segunda parte se pone de manifiesto la controversia actual en el manejo de la esclerosis múltiple, especialmente en cuanto a formas progresivas y diagnóstico diferencial se refiere. Se presentan los últimos avances en remielinización, donde destaca el uso de la técnica con micropilares en el laboratorio, y en neuroprotección, la cual se revisa a través del estudio del nervio óptico. Los anticuerpos anti-CD20 ofrecen grandes expectativas, y estamos ante un nuevo mecanismo de acción y diana terapéutica en unas células a las que les habíamos prestado poca atención hasta la fecha. Otro hecho destacable es la elevada correlación entre los niveles de neurofilamentos en el líquido cefalorraquídeo y el suero, que podría evitar el uso del líquido cefalorraquídeo como muestra biológica en futuros estudios de biomarcadores. También se anticipan los avances en investigación clínica que en el futuro acabarán convergiendo en la práctica clínica, condicionando los pasos que se deberán seguir en el abordaje terapéutico de la esclerosis múltiple.

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