Review of the novelties from the 31st ECTRIMS Congress, 2015, presented at the 8th Post-ECTRIMS meeting

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Summary. Renowned national specialists in multiple sclerosis (MS) met, for the eighth year in a row, to give details of the latest novelties presented at the last ECTRIMS Congress 2015, which are included in this review. One of the highlights at this Congress was the new classification of the phenotypes of MS. Both the diagnostic criteria of the neuromyelitis optica spectrum and the problems involved in the differential diagnosis derived from the lack of definition of the radiological spectrum were reviewed. The microbiota comes to the fore as a possible factor determining the disease, together with extrinsic factors such as tobacco, salt ingestion or vitamin D deficiency. Advances made in immunomodulation are driving the progress being made in the treatment of MS. Ocrelizumab is the first treatment with positive results in the primarily progressive forms and tocilizumab, a drug product for rheumatoid arthritis, stands out as a potential candidate for the treatment of neuromyelitis optica. Certain antibiotics and vitamins could also play a role in the treatment of MS. In this edition of the Congress special attention was paid to personalised therapy. To date, 11 drugs have been approved for use in Europe. There is a need for therapeutic algorithms that help us to choose the best treatment for each patient. Likewise, we need to be able to identify, in the early stages of the disease, the risk of developing disability, so as to be able to design therapeutic strategies. To do so, molecular biomarkers and other predictive tools are required. The problems that still exist in software technology in magnetic resonance hinder its application in daily clinical practice.

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

Introduction

The ECTRIMS Conference continues to be the meeting that leads the way in cutting-edge multiple sclerosis (MS) research and its dissemination. In addition to facilitating communication, it leads to the creation of synergies and promotes research and learning amongst professionals, to the ultimate benefit of patients. The most recent edition included more than 9000 participants, showing growth of over 5% versus 2014 and 2013, and Spain was the country that provided the third-highest number of attendees. Additionally, the Post-ECTRIMS Meeting, which has now convened for eight sessions and received the scientific endorsement of the Spanish Society of Neurology, has been institutionalized due to its clear scientific focus and practical interest for the MS community, serving as a base for updating the knowledge of medical professionals in our country. The eighth Post-ECTRIMS Meeting was convened in Madrid. For another year, recognized leaders in national opinion were given time to present and discuss the highlights of ECTRIMS 2015.

Clinical aspects of MS

Diagnosis and differential diagnosis

The detection of cortical lesions in the diagnosis of MS can aid in identifying patients with clinically isolated syndrome (CIS)a t risk of converting to MS and in differential diagnosis, although the best method has yet to be defined and standardized. Symptomatic lesions are an important factor in the prognosis of CIS, as they increase the sensitivity of MS diagnosis; for this reason, it is suggested that current diagnostic criteria should be reconsidered for dissemination to include these lesions. The significance of these lesions has been confirmed in patients with infratentorial lesions in the cerebellum and brain stem or the spinal cord [1]. Moreover, symptomatic and asymptomatic lesions at the infratentorial level increase the risk of a second attack, at the risk of short-term disability [2].

The IgG-AQP4 (or NMO-IgG) antibodies allow clear identification of patients presenting neuromyelitis optica (NMO) and those within the NMO

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spectrum (NMOSD). The new diagnostic criteria for NMOSD [3] (Table I) are currently in the validation phase in different cohorts because the radiologic spectrum is still not completely defined, as localizations and characteristics as specific as those associated with MS do not yet exist. This lack of definition likely results in an increase in the number of anti-MOG (+) patients who meet these criteria. When patients with probable NMOSD are studied, up to 10% are anti-MOG (+), and the most frequently associated phenotype is that of recurrent isolated optic neuritis [4]; due to the new criteria, these patients currently do not qualify as NMOSD. A higher prevalence and earlier age at onset in non-Caucasian populations, along with a higher frequency of neuropathic pain, are data that should be highlighted in patients with NMO or NMOSD [5]. There is also a small percentage of anti-AQP4 (+) patients with small spinal lesions who exhibit radiological characteristics that may suggest MS [6]. Another recent study [7] showed that patients with NMO who are anti-AQP4 (+) present with higher levels of glial fibrillary acidic protein(GFAP) than patients with NMO who are anti-MOG (+) or patients with MS. In these cases, the levels of myelin basic protein (MBP) do not allow differentiation between the two serotypes of NMO.

Additionally, some percentage of patients who are anti-MOG (+) (4% in adults and 27% in children) are young (children or young adults), exhibiting lesions of the following types: acute disseminated encephalomyelitis, bilateral optic neuritis, and/or transverse or longitudinal myelitis with characteristic conus medullaris impairment [8].

Clinical phenotypes of MS

The clinical course of MS was redefined in one of the most important articles published in 2014 [9]. One of the main disadvantages of this classification is that radiologically isolated syndrome (RIS) is not considered a phenotype of MS due to a lack of clinical evidence and the non-specificity of magnetic resonance (MR), compounded with the lack of orientation and definition by experts. Additionally, the new definition of the 'activity' of the disease is not easily assessed because atrophy is not considered, nor is the pathology of the grey matter, which is known to correlate with disability [10] as well as cognitive impairment and fatigue [11].

One advantage is that recommending an annual clinical and radiological evaluation could be considered in relapsing-remitting (RR) cases, which would encourage better follow-up and treatment optimization, contributing to a more favourable prognosis over the long-term; this would reveal the maximal interval between the first and second flare up and aid in early prevention of flare ups. Clinical and radiological activity are currently given the same weight in defining the 'activity' of the disease, which is important if we consider that the accumulation of lesions in T_2 in CIS presupposes a risk of transformation to the secondary progressive (SP) form in 10 and 20 years [12]. Additionally, flare ups are no longer defined as 'mild', 'moderate', 'severe', or 'incapacitating', which will allow treatment independent of the severity of the flare up and of the necessity to use or not use corticosteroids [9].

Paediatric MS

The efforts of international collaborative study groups on paediatric MS have contributed to a revision of the new clinical diagnostic criteriafor identifying clinical characteristics that differ according to age of onset and to the establishment of recommendations regarding treatment, which advocate for an early start to treatment [13].

Advances in magnetic resonance (MR) have allowed identification of the effects of MS in the CNS and differentiation from acute disseminated encephalomyelitis (ADEM). In addition, the findings of genetic, epigenetic, and epidemiological analyses, showing that early menarche, obesity during puberty, and low vitamin D levels are potential risk factors, all support the existence of common biological characteristics in all age groups. Recent immunological studies have identified paediatric patients with anti-MOG antibodies who may ultimately develop non-MS acquired demyelinating disease [14,15].

Epidemiology

The 2015 update to the European MS Platform [16] shows the necessity of the employment, care, support, treatment, and living environments of the more than 700,000 patients throughout Europe, which vary according to the country of origin. Based on the notable north-south and east-west differences, this update proposes that the representation of patients in consultative bodies of European agencies should be encouraged, as should boosting their participation in employment programmes and research projects and promoting self-help courses. For the next 5 years, it prioritizes strategies for improving accessibility to treatment, rehabilitation, and services; encouragement of employ-

Table I. New diagnostic criteria for the neuromyelitis optica spectrum [3].

IgG-AQP4 positive	IgG-AQP4 negative or not evaluated
1. At least one nuclear clinical characteristic: – Optic neuritis – Acute myelitis – Area postrema syndrome (hiccup, nausea, and vomiting) – Acute trunk syndrome – Symptomatic narcolepsy or diencephalic syndrome with characteristic MR – Symptomatic cerebral syndrome with a characteristic lesion in MS 2. Positive IgG-AQP4 test 3. Exclusion of diagnostic alternatives	1. At least two nuclear clinical characteristics as a result of one or more clinical episodes and meeting the following requirements: – One nuclear episode should be optic neuritis, or acute longitudinal myelitis (≥ 3 vertebral bodies: LETM or area postrema syndrome) – Dissemination in space (recurring optic neuritis or recurring LETM does not qualify) – Meeting the following additional characteristics of MR (when applicable): • Optic neuritis with normal cerebral MR, or non specific or optic nerve with a T_2 lesion, or Gd+ that extends more than 1/2 the length of the nerve or affects the chiasm • Acute myelitis with extension ≥ 3 contiguous vertebral bodies, oratrophy of this length in patients with prior history • Area postrema syndrome, requires lesions of the area postrema/bulbar dorsal • Cerebral syndrome, requires cerebral lesions in periependymal areas 2. Negative or unavailable IgG-AQP4 test 3. Exclusion of diagnostic alternatives

AQP4: aquaporin-4; LETM: longitudinally extensive transverse myelitis; MR: magnetic resonance.

ment and education; and research on MS and paediatric MS as well as the role of caregivers in MS.

As a determining factor in the disease, the microbiota is now considered to play a major role, given its contribution to organ-specific immunity through the regulation of pro-inflammatory responses or bacterial types [17]. In patients with MS, the microbiota has been found to be altered and to show dysbiosis, with a striking absence of species in the genus *Clostridium* [18]. Moreover, faecal inoculation from patients with MS favours the spontaneous development of EAE in comparison with faeces from healthy individuals [Berer et al, unpublished data]. The most recent data on tobacco usage show that smoking decreases the time before a second flare up in CIS and the time until progression [19]. In addition, it increases the response to Th17 and Th22 and the expression of particular pro-inflammatory cytokines, while decreasing regulatory T lymphocytes [20]. Melatonin [21] and salt consumption [22] are other examples of extrinsic factors that can affect T-cell differentiation as well as the clinical and radiological activity of the disease. Intrinsic factors such as having a parent with MS (most importantly the mother) increases the risk of suffering emotional disorders [23]. The risk of completed suicide, which is greater in men between 18 and 40 years of age and independent of education level, does not appear to have changed in the last 48 years [24].

MS, pregnancy, and lactation

MS does not affect fertility or the development of a pregnancy, and there currently exists sufficient evidence to support and advise patients who wish to become pregnant, although there is a lack of management guides in clinical practice. The risk of flare ups returns to previous levels from birth to 4-6 months after birth [25], but pregnancy has not been observed to affect disability over the long term. Pregnancy outcomes also do not indicate a risk of spontaneous abortion or birth defects greater than that in the general population or an altered course of pregnancy, apart from a higher frequency of assisted births, caesareans, and reduced birth weights [26].

The lack of adequate and well-controlled studies on pregnant women in FDA risk categories B and C, which include the majority of current treatments, limits the available safety data [26]. Nevertheless, the risks and benefits support discontinuation of medication before pregnancy and resumption thereafter [26]. At some health centres, to avoid recurrences, Natalizumab is given up to the confirmation of pregnancy and, in exceptional cases, is only discontinued in the last trimester of gestation to avoid haematologic alterations in the foetus [27], but safety data related to this issue are scarce. The teratogenic effect of teriflunomide in animals and its mechanism of prolonged action require its rapid removal, using colestyramine or acti-

vated carbon in case of prior exposure or during the first stages of pregnancy [28].

Exclusive breastfeeding can be beneficial [29] and should not be discouraged in favour of resuming treatment, except in cases of very active disease [26].

Pathologic anatomy and pathogenesis

Pathologic anatomy

The iron bands around MS plaques are observed in active chronic lesions in particular and in all forms of the disease [30]. Anatomopathological analysis and radiologic follow-up of these lesions show that plaques with iron bands exhibit a higher initial volume and greater growth over time [31]. The presence of these rings likely allows the identification of a patient subgroup with more rapid progression towards disability.

Normal-appearing white matter (NAWM) in cases of MS and NMO presents growth similar to parenchymal T-cells in comparison with control subjects. However, a higher frequency of microglial nodules and significant active axonal loss at the medullar NAWM level can only be observed in MS [32] and likely contribute to the progression suffered by MS patients in comparison with patients with NMO. In both conditions, the expression of glucose-specific transporters (GLUT) and monocarboxylate transporters (MCT) in active lesions is altered; specifically, decreased expression of the lactate transporter MCT4 in astrocytes can result in inadequate transportation of energy through the glia and trigger demyelination [33].

Genetics

The role of genetics and its interaction with the environment in MS is evident. The most recent data focus on the identification of 4 modules of enriched co-expressed genes in susceptibility variants 8, 9, 12, and 14 found in mononuclear cells in the peripheral blood of MS patients but not in cerebral tissue or in the CD4+ cells of healthy individuals. One of these modules includes elements associated with T-cell differentiation and cellular activation, and another is related to cerebral atrophy [34]. In a previous study [35], through deep sequencing of the CD4+ and CD8+ lymphocyte transcriptome in patients and control subjects and using a combination of published data on RNA-seq in other immune cell types, the locus of a candidate gene was identified in more than 50% of the variants associated with MS, along with RNA potentiators located at some distance in non-gene regions. Some of these potentiators proved to be active only in the disease.

Imaging

MR in the monitoring and management of MS

Cerebral MR is the method of choice for monitoring MS, given its value for obtaining predictive early findings during the course of the disease. Furthermore, it provides complementary information regarding disease activity, atypical or unanticipated clinical events, safety, and inadequate therapeutic response (Fig. 1), as shown by a meta-analysis performed by Dobson et al [36] on interferon-beta, or the work of Uher et al [37], who demonstrated a direct relationship between the appearance of new lesions during treatment with interferon and atrophy and long-term disability. In fact, the annual findings related to MR aid in determining the level of concern at the time of considering a change in the course of treatment [38].

Visual counting of lesions is useful in the diagnosis and prognosis of disability up to 10 years in RR [39] and in the prediction of treatment response [40]. The main problems that continue to complicate the methods of application are the lack of a definition of a suboptimal response, the difference in the criteria for predictive MR, and the variability in specificity and sensitivity. The lack of studies on oral and second-line medications further complicates this situation. Technical limitations and volumetric errors in methods of automatic segmentation point to semiautomatic measurement as the ideal method for quantifying the lesional load. In this regard, a study by the MAGNIMS group [unpublished] reflects a great disparity in the results obtained according to the centre and the segmentation method. The most promising of these methods appears to be 3D image subtraction to show differences over time [41].

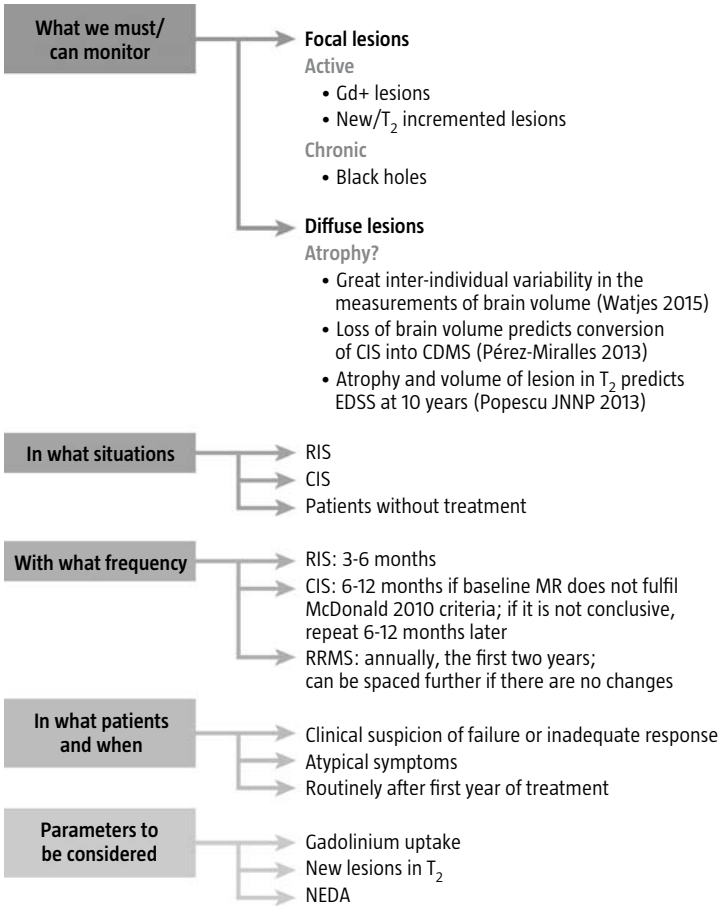
The importance of measuring cerebral atrophy is highlighted because this method is sensitive, shows axonal damage, and correlates very well with disability. Currently, there is available software that can be installed in MR machines to provide figures on atrophy or cerebral volume, and this software has begun to be used in some centres in an individualized manner.

A very interesting element is the study of functional reorganization of the CNS, as such research shows that cognitive alterations lie more in the number of connections and less in structural problems [42].

MR in clinical trials

The utilization of MR instead of flare ups could be employed as a principal variable of efficacy in phase III trials evaluating anti-inflammatory medications, to demonstrate the relationship that exists between the effects of an anti-inflammatory treatment on MR and flare ups [43]. This method would allow precise calculation of the desired effects on flare ups based on the effect on MR. In phase II trials of natalizumab, a 91% reduction in the MR findings allowed the estimation of a 72% theoretical reduction in flare ups, which became 68% in phase III. This method could be applied in a paediatric population or in the evaluation of biosimilars or generics, although the validation would be specific to a particular treatment [44]. What is clear is that MR cannot be used as a principal variable in clinical trials whose objective is disability, even though atrophy measurements are promising [44]. The issue is whether measurements beyond T_2/Gd+ inflammatory lesions are necessary, such as measurements of cortical lesions, demyelination, atrophy, and cortical reorganization [45]. Many doubts exist regarding the possibility of using MR as a primary objective, doubts that are not strictly limited to technical aspects. Conventional techniques do not encompass focal and diffuse pathology and fail to evaluate critical regions such as the cortex or spinal cord. In addition to the limited correlation between flare ups and disability, the relevance of conventional measurements to long-term prognosis is uncertain, and some clinical trials show variable effects in MR, despite similar clinical effects. Measures of atrophy generate confusion about the effect of factors such as comorbidities and hydration [45].

Figure 1. Magnetic resonance to monitor activity, progression, and therapeutic response [12,42,90-92]. CDMS: clinically definite multiple sclerosis; CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; Gd+: lesions captured with gadolinium; NEDA: no evidence of disease activity; RIS: radiologically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis.



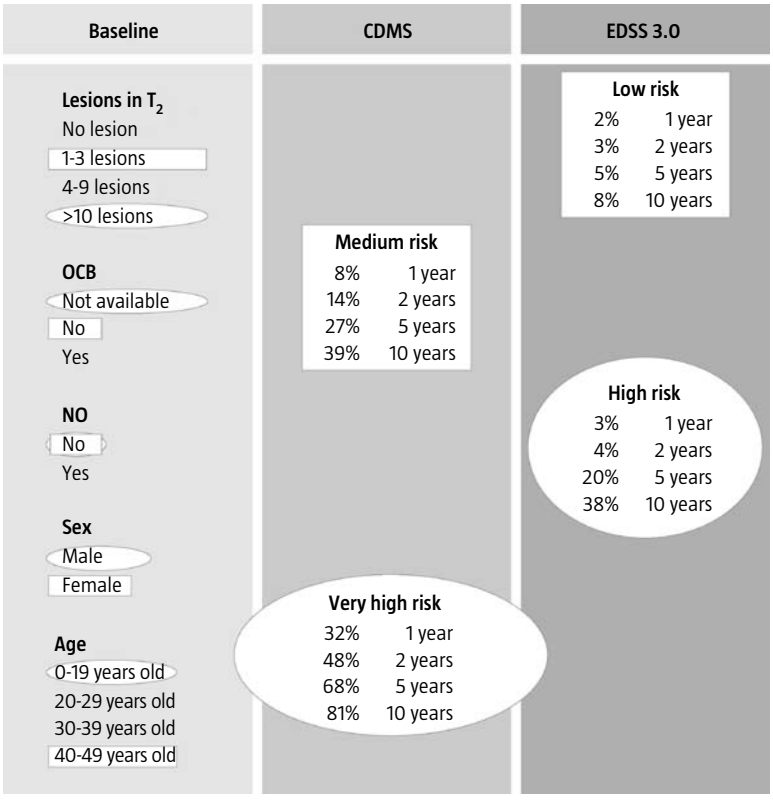
Neuropsychology

The lack of a tool for identifying cognitive affectation in clinical practice continues to be an issue, despite its impact on MS patients and their work situation, as shown by the degree of short-term memory affectation. A new computerized test detects the reduction in information processing speed in 30 seconds, as opposed to the usual 90 seconds required. These data come from an original study, but the planned international validation of the BICAMS battery [46] is without a doubt the most imminent step towards a cognitive valuation that is brief, practical, and universal. This is important because cognitive deterioration in young patients can be an early indicator of the disease [47]. It has been demonstrated that RR-type patients perform poorly in cognitive tests 2 years prior to disease onset, which is significantly present 10 years earlier in PP cases. Also of interest is the positive effect of vitamin D supplements on cognitive performance and anxiety in patients with a deficit [48]. The phenomenon of cognitive-motor interference, which prioritizes cognitive tasks over postural tasks [49], is a suggested cause of accidental falls in MS patients.

Molecular biomarkers and predictive tools

The most recent data regarding predictive molecular biomarkers in CIS show that light-chain neuro-

Figure 2. Baseline personalized risk categories for patients with CIS. CDMS: clinically definite multiple sclerosis; EDSS: Expanded Disability Status Scale; OCB: oligoclonal bands; ON: optic neuritis.



filaments (NfLs) predict long-term disability, as evaluated using the MSSS severity index [50], and are associated with cerebral volume loss over the medium-term [51]. In MS, NfLs are correlated with inflammatory parameters in MR [52], and the levels in LCR are modified with fingolimod administration, reflecting the neuroprotective effects of this medication [53]. In some cases, elevated levels of CHI3L1at the time of first flare up are associated with a shorter conversion time and more rapid development of disability [54], and the predictive role of this parameter in the development of disability was confirmed by recent studies [50,55,56]. The next steps are directed at the study of biomarker combinations.

The global nature of large databases contributes to the elucidation and validation of new associations of predictive risk factors in patients with CIS and early MS, which is of great utility in creating predictive tools. Such is the case with the Barcelona CIS cohort in which more than 1000 patients have been followed over 20 years, allowing the development of a model for personalizing the baseline risk of conversion to clinically definite multiple sclerosis (CDMS) and the build-up of disability (Fig. 2) [57]. This model is a dynamic tool that allows incorporation of new information during the first year and actualization of the base-level risk; its validation would represent an important step towards personalized medicine.

The predictive value of achieving no evidence of disease activity (NEDA) in RRMS patients treated with fingolimod supports the use of NEDA-4 versus NEDA-3 as a better predictor of outcomes related to the development of disability and cerebral volume loss [58].

Treatment: modifying the disease

Personalized therapy

Personalized therapy continues to be a necessity in MS, though there is currently a lack of response markers for each treatment. We provide 10 medications for treating RRMS, but we still need to determine how to use them and, most importantly, if they will work, indicating a requirement for new therapeutic algorithms that may aid in choosing the best treatment for each patient.

One outstanding predictor of interferon-beta failure is the topography of new lesions, particularly infratentorial and spinal cord lesions [59]. Under fingolimod treatment, the presence of flare ups, radiologic activity, or a combination thereof during the first year predicts clinical activity at 2 to 4 years [60]. In these patients, activity in MR (≥ 1 Gd+ or ≥ 2 new T_2) is now considered the best predictor of a failure to achieve NEDA-3. The prediction rating based on data from the MAGNIMS group is combined with the rising tendency to combine clinical and radiological data during the first year of treatment to predict response [Sormani et al, unpublished].

Large databases also aid in understanding the therapeutic focus in patients with poor responses to a first-line medication. Switching to fingolimod or natalizumab in place of an injectable immunomodulator is more favourable in terms of the efficacy and permanence of the medication [61,62]. In patients who require an interruption in natalizumab treatment, a change to fingolimod is more effective than a change to first-line disease-modifying treatments (DMTs) to control reactivation of the

disease during the first year [63]. The concept of NEDA, which is often mentioned in this edition, is ideal as an efficacy variable, especially in second-line treatments [64], but is a difficult objective to maintain over the long-term in clinical practice [65,66].

In choosing from new treatments, the hope is that stratification and risk-mitigation will continue, which guide us in current therapies [67]. The values of the anti-JVC antibody index [68], L-selectina CD62-L levels [69], and BOC-IgM-LE [70] determine the risk of PML. Risk tolerance is another aspect to consider, given the higher variability demonstrated by patients and its relationship with sex, age, disability, and improved patient information [71].

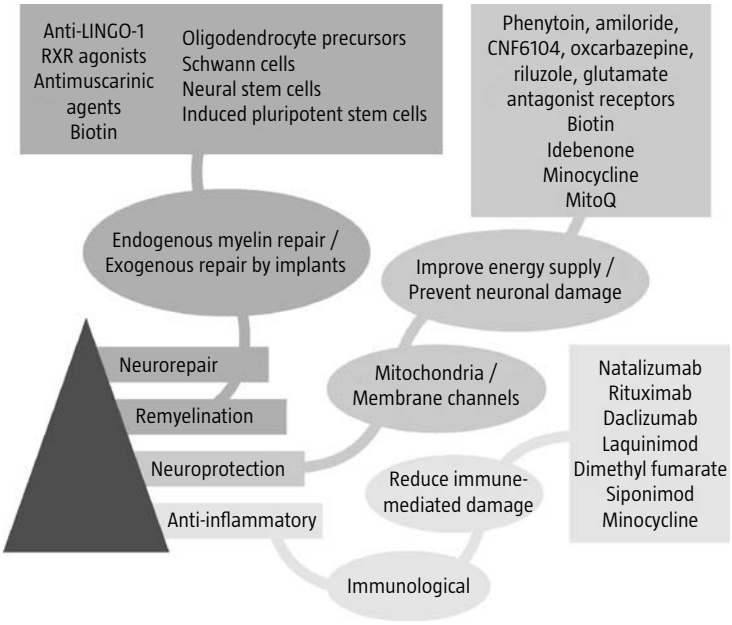
Ground breaking strategies and advances in the treatment of MS

Anti-inflammatory treatments constitute the base of the therapeutic pyramid in MS and represent the basis of the majority of novel treatments (Fig. 3). Studies using experimental models and analyses of MS lesions are directed at reducing axonal degeneration and promoting remyelination via repair strategies that are either endogenous or exogenous via implants (Fig. 3). The new focus on the anti-Lingo 1 antibody allows the prediction that myelin repair will become a treatment option.

Independent T-cells of the major histocompatibility complex II (MHC-II)type protect against axonal damage via the IL-4 receptor [72], which interferes with the addition of the anti-IL-4 neutralizing antibody in experimental models. In fact, mice deficient in IL-4 show poorer functional outcomes, although transfection with CD4+ T-cells from animals with wild-typeIL-4+ increases neuronal survival. The role of TNF-α continues to be controversial, given that it may temporally coincide with remyelination while causing neurodegeneration over the long-term due to its continued action on AMPA receptors.

Other repair strategies focus on remodelling the microenvironment of the lesion [73] (which can prove hostile to remyelination) through either intrinsic targets, such as the retinoid X receptor, which encourages the differentiation of oligodendrocytes, orextrinsic targets, such as semaphorin 3 and its function in inducing the release of proteoglycans [74]. Likewise, an experimental model of demyelination due to lysolecithin has demonstrated that physical exercise promotes the expansion of oligodendrocytes and remyelination [75]. In fact, children with MS who exercise exhibit reduced disease activity [76]. However, reliable measures of repair and optimal designs to evaluate remyelination therapies are still required.

Figure 3. Pyramid of therapeutic innovation in MS.



Tocilizumab (TCZ), a monoclonal antibody against the interleukin 6 receptor (IL-6R) used for treating rheumatoid arthritis, is in a position to be a strong candidate for the treatment of NMO through decreasing the rate of flare ups and, above all, markedly improving neuropathic pain and fatigue [75]. In refractory cases, we also see surprising results related to flare ups, disability, and MR measurements [77]. The signal-blocking of IL-6R may decrease the level of the anti-aquaporin 4 antibody (anti-AQP4), which accompanies NMO. The efficacy of TCZ may also be explained by an inflammatory effect dependent on IL-6, which is related to Tregand NKCD56 cells [78,79].

One of the most frequently mentioned medications is ocrelizumab, due to its use as a primary treatment with positive results in PP-type disease (Table II). Furthermore, MT-1303 (amiselimod), in contrast to fingolimod, selectively modulates the S1P1 receptor. This novel oral treatment, evaluated in different doses in the MOMENTUM study, reduces the number of Gd+ lesions in T_1 without causing cardiac anomalies [80]. Agents as varied as antibiotics and vitamins may also play a role in MS. Minocycline reduces the relative risk of MS in pa-

Table II. Clinical trials involving an ocrelizumab course.

	Design	*n*	MS type and patients	Main results
OPERA I [84]	Phase III randomized, multicentre, DB, DD of 96 weeks	821 (1:1) Ocrelizumab 600 µg IV infusion every 24 weeks: IFN-β-1a 44 µg sc 3/w	RRMS (McDonald 2010) 18-55 years ≥ 2 flare ups in 2 years ≥ 1 flare up in 1 year and EDSS 0-5.5	Flare ups: ↓ 46% vs IFN-β-1a Lesions in T_2: ↓ 77% vs IFN-β-1a Lesions Gd+: ↓ 94% vs IFN-β-1a NEDA: 47.9% (vs 29.2% IFN-β-1a)
OPERA II [84]	Phase III randomized, multicentre, DB, DD of 96 weeks	835 (1:1) Ocrelizumab 600 µg IV infusion every 24 weeks: IFN-β-1a 44 µg sc 3/w	RRMS (McDonald 2010) 18-55 years ≥ 2 flare ups in 2 years ≥ 1 flare up in 1 year and EDSS 0-5.5	Flare ups: ↓ 47% vs IFN-β-1a Lesions in T_2: ↓ 83% vs IFN-β-1a Lesions Gd+: ↓ 95% vs IFN-β-1a NEDA: 47.5% (vs 25.1% IFN-β-1a)
ORATORIO [85]	Phase III randomized, multicentre, DB, of 120 weeks	732 (2:1) Ocrelizumab 600 µg IV infusion every 24 weeks: PCBO	PPMS (McDonald 2005) 18-55 years EDSS 3-6.5 Increase of IgG or OCB in cerebrospinal fluid	Progression at 12 weeks: ↓ 24% (p = 0.032 vs PCBO) Progression at 24 weeks: ↓ 25% (p = 0.036 vs PCBO) Time in 7.62 min: ↓ 29% (p = 0.04 vs PCBO) T_2 volume: –3.40% (p < 0.0001 vs PCBO) Cerebral volume: 17.5% (p < 0.0001 vs PCBO)

3/w: 3 times per week; DB: double blind; DD: double dummy; MS: multiple sclerosis; OCB: oligoclonal bands; PCBO: placebo; PG: parallel groups; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Table III. Recent studies involving glatiramer acetate.

Study	Main results
Extension phase open reference study GALA [86]: data at 36 months on patients who began GA 40 mg 3/w from initiation (ES) and patients who switched to GA mg 3/w from placebo after one year of treatment (DS) [87]	Annualized rate of flare ups: similar between ES and DS groups (0.209 vs 0.201; p = 0.7756) Time until first recurrence: ↑ ES vs DS (HR = 0.746; 95% CI = 0.628-0.887; p = 0.0009) New/worsened lesions in T_2: no differences between ES (1.62) vs DS (1.78) (p = 0.5112) Gd+ lesions in T_1: no differences between ES (0.46) vs DS (0.39) (p = 0.4886)
Study by Zivadinov et al [88]: binomial negative regression model with MR data at 6 and 12 months from patients in the reference study GALA	Conversion to black holes at month 12: ↑ con GA mg 3/w (0.31) vs placebo (0.45); p = 0.026.
Study by Zivadinov et al [89]	Loss of cortical grey matter: ES (–1.16) vs DS (–1.53); p = 0.015 (month 12 → month 36) Cerebral volume % change: ES (–1.13) vs DS (–1.27); p = 0.080 (month 12 → month 36)

3/w: 3 times per week; 95% CI: 95% confidence interval; DS: delayed start; ES: early start; GA: glatiramer acetate; Gd+: lesions captured with gadolinium; HR: hazard ratio; MR: magnetic resonance.

tients with CIS [81], and high-dose biotin (MD1003) decreases the deterioration of disability in the SP form of the disease [82]. In another vein, intake of sodium propionate, a short-chain fatty acid, increases the percentage of Treg cells [83].

The broad experience with GA 20 mg over the course of more than 20 years is again being mentioned, as are the advantages offered by the new formulation of 40 mg/three times per week, not only in terms of efficacy (Table III) and safety but also in terms of patient comfort.

As an advance in ON, the effect of anti-Lingo1 stands out due to preventing loss of amplitude in the multifocal visual evoked potential in the contralateral eye of patients with a first episode of acute unilateral ON [78].

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Revisión de las novedades del XXXI Congreso ECTRIMS 2015, presentadas en la VIII Reunión Post-ECTRIMS

Resumen. Reconocidos especialistas nacionales en esclerosis múltiple (EM) se han reunido, por octavo año consecutivo, para exponer lo más novedoso que se presentó en la última edición del congreso ECTRIMS 2015 y que recoge esta revisión. En esta edición ha destacado la nueva clasificación de los fenotipos de la EM. También se revisaron los criterios diagnósticos del espectro de la neuromielitis óptica y los problemas en el diagnóstico diferencial derivados de la falta de definición del espectro radiológico. La microbiota adquiere protagonismo como posible factor determinante de la enfermedad, junto con factores extrínsecos como el tabaco, la ingesta de sal o el déficit de vitamina D. Los avances en inmunomodulación impulsan el progreso en el tratamiento de la EM. El ocrelizumab es el primer tratamiento con resultados positivos en las formas primariamente progresivas, y el tocilizumab, un fármaco para la artritis reumatoide, destaca como candidato potencial para el tratamiento de la neuromielitis óptica. Ciertos antibióticos y vitaminas también podrían tener un papel en el tratamiento de la EM. En esta edición se prestó especial atención a la terapia personalizada. Actualmente disponemos de 11 fármacos aprobados en Europa. Se necesitan algoritmos terapéuticos que nos ayuden a elegir el mejor tratamiento para cada paciente. Asimismo, necesitamos poder identificar en los estadios precoces de la enfermedad el riesgo de desarrollar discapacidad, para diseñar estrategias terapéuticas, para lo que se precisan biomarcadores moleculares y otras herramientas pronósticas. Los problemas aún existentes en la tecnología del *software* en resonancia magnética dificultan su traslación a la práctica clínica diaria.

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