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

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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 first part addresses family planning, pregnancy management and the role of breastfeeding in women with multiple sclerosis. Attention is drawn to the paediatric population, to magnetic resonance imaging features and to the genetic-environmental risk factors for developing the disease in children, without neglecting the risk factors for development in adults. The review updates the epidemiology of cognitive deterioration in patients with multiple sclerosis, the advantages and disadvantages of available assessment tools, and current management approaches, while also insisting on the importance of cognitive involvement during the course of the disease. Furthermore, the concept of individualised, precision medicine is introduced, from the diagnosis of the disease until its treatment, with the controversies that inevitably arise in patient management, above all with regard to the change of treatment and the handling of associated risks.

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.

Family planning, pregnancy and lactation

MS is a disease that mainly affects women of reproductive age. Currently, there are no conclusive data showing that the disease decreases fertility, although it does appear that women with MS tend to have fewer children, likely not only through reproductive choice. The use of assisted reproduction techniques is more frequent in this population and, although the evidence is scarce and in very small populations, the results point in the same direction: if the technique is not successful, in the three months following treatment with assisted reproduction techniques, there can be an increase in attacks [1], especially when gonadotropin-releasing hormone agonists are used. The disease does not appear to negatively affect pregnancy, nor has pregnancy been shown to affect the mother's disability in the long term.

An important issue in clinical practice is the use of MS drugs in patients who hope to become pregnant. The US Food and Drug Administration (FDA) recently replaced the teratogen classification of risk during pregnancy (A, B, C, D and X) [2] for new drugs with a new system based on potential risks, and it plans to rewrite the classification of existing drugs in the coming years. To date, the available data for MS drugs during pregnancy have been limited. Therefore, lacking clinical practice guides and con-

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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

Table I. Results of pregnancies in patients with multiple sclerosis (MS) exposed to drugs and recommendations for management in clinical practice.

	Pregnancies exposed	Results	What to do in clinical practice
Teriflunomide	70 pregnancies exposed (studies in phase III TEMSO, TOWER, TENERE, TOPIC)	Without more complications in comparison to the general (unhealthy) population (Kieseier et al, Neurol Ther 2014. 3; 133-8)	Discontinue the drug before pregnancy and perform a quick elimination or wait two years
Fingolimod	240 pregnancies exposed as of February 2015 (Gilenya ® registry and security database of Novartis)	There was no association between exposure to the drug and an increase in congenital malformations compared to other MS populations (Mult Scler 2015; 23 (Suppl 11): S293 (abstract P611).	It is recommended to cease treatment two months before pregnancy and, in cases of accidental exposure, to perform serialised sonograms
Natalizumab	363 results from pregnancies in 355 patients (TPER registry, of exposure to Tysabri ®)	No specific pattern of malformations was observed that suggested an effect of the drug, and the spontaneous abortion rate was consistent with the general population (Friend et al, BMC Neurol 2016)	With natalizumab, there is the problem of possible rebound effect after discontinuing use. The most conservative choice is to discontinue the drug 2-3 months beforehand. If it is continued during the pregnancy, it should only be taken until the 26th week because haematological abnormalities appear in the third trimester
Alemtuzumab	193 pregnancies exposed as of July 2015, 185 of which occurred four months after the final dose	The results from the pregnancies were comparable to the general population. A thyrotoxic crisis was observed in one mother with Graves' disease (Achiron et al, ECTRIMS London, 2016)	It is recommended to interrupt treatment before gestation and to use contraception until four months after discontinuing use
Daclizumab	Few data; to date, 38 exposures	The data did not suggest a greater risk of adverse foetal or maternal results, although the numbers were too small for definitive conclusions	–

forming to the technical indications, discontinuing treatment has been recommended before pregnancy. Since 2014, obstetric results and those from pregnancies exposed to medication have been increasing exponentially, especially with classic drugs, such as interferons and glatiramer acetate. With glatiramer acetate, for example, we only had evidence of 300 pregnancies exposed to this medication [3], whereas data are available for more than 7,000 pregnancies. The data are much more limited for new drugs (Table I). With regards to optical neuromyelitis, its physiopathology is different, and it also functions differently in pregnancy; data with rituximab are limited, and the advice is to wait to conceive until 12 months after discontinuing its use [4].

The impact of exclusive breastfeeding in some studies is associated with a decrease in the risk of relapse during the first six months after birth [5].

However, these results are controversial because there can be a bias in their selection. Nevertheless, patients with elevated activity are advised not to breastfeed and to restart treatment as soon as possible.

Regarding the use of oral contraceptives, the data are scarce and contradictory with regard to the risk of suffering from MS. More than 25,000 cases of exposure to oral contraceptives would be needed to obtain one additional case of MS. Dr Hellwig herself casts doubt on her latest findings [6] because the risk of suffering from MS increasing with exposure time to oral contraceptives cannot be demonstrated. Most interestingly, her work is pioneering in evaluating results according to the content of progestogens. It is worth noting that drospirenone, an anti-androgen frequently used today, does not increase the risk of MS, in contrast to levonorgestrel. There have been attempts to reproduce the 'hormonal environment' during pregnancy [7], with moderate results with regards to reducing activity using magnetic resonance imaging (MRI) with high doses of oestrogens. The POPART'MUS study [8], designed to determine whether ingesting sexual hormones at the level of pregnancy protects from postpartum attacks, did not offer good results. In short, the immunobiology of pregnancy is more complex than a solely hormonal issue.

Paediatric population

Some 5% of patients diagnosed with MS present their first symptoms before the age of 18 years. In 2013, the definitions of different demyelinating diseases occurring in childhood were updated. The prognosis of paediatric MS is not as favourable as was historically believed. Patients remain in relapsing–remitting evolution longer, but they can convert to the secondary progressive form at an earlier age than adult patients. We currently have drugs that have demonstrated efficacy and safety with relapsing–remitting forms of MS, so it is advised to consider treating the disease from its onset because early treatment reduces the number of attacks and delays the accumulation of disability [9]. Treatment with interferon β and off-label use of glatiramer acetate is recommended [10], with particular precaution with minors under 11 years of age, particularly with interferon β, due to cases of hepatotoxicity. Paediatric patients present elevated inflammatory activity, for which natalizumab (used off-label) can be an effective option, especially in patients with negative serology of the JC virus. Currently, there are on-going clinical trials with new immunosuppressant drugs, such as fingolimod and teriflunomide, although, given the difficulty in recruiting paediatric patients, the data are currently scarce. The principal problem presenting with treatment with immunosuppressants is premature immunosenescence in the long term, given the thymus' relevant role at the paediatric age.

Oligodendroglial damage and remyelination are also being studied in the paediatric population, in which better and faster recovery from attacks could be attributed to a more efficient recovery process. The immunohistochemical analysis of biopsies has shown that, effectively, there is less myelin loss and a greater number of oligodendrocytes in the paediatric population [11]. These findings align with the results obtained from clinical studies with children that show a decrease in remyelination capacity at an adult age [12] and from experimental models that show that remyelination after a toxic demyelination is observed at an accelerated rate in young mice compared with adult mice, a product of a premature and increased proliferation of oligodendrocyte precursor cells [13].

Cognitive decline affects more than 30% of children with MS [14]. Patients who begin at a younger age present lower scores on the Symbol Digit Modalities Test and the Trail Making Test over time; in fact, age at onset is the most important predictive factor of cognitive deterioration in the long term [15], which somewhat distances the general idea that, at a younger age, cerebral plasticity could counteract the aggressiveness of MS. Given the great repercussions the cognitive disruptions have on the intellectual level, in daily life activities and in family and social relationships [16], it is recommended to include children and adolescents in a follow-up programme for MS, but especially because practically all children with cognitive disruptions present psychiatric disturbances in the form of depression or anxiety [17].

Cognitive decline in adults

The MINIMUS study [18], including more than 1,000 patients, showed that there was a greater prevalence of cognitive disturbance in the progressive forms of the disease, although the most relevant finding is that 35% of patients with clinically isolated syndrome (CIS) also show cognitive dysfunction, especially in the first five years, a rate that practically doubles, regardless of whether they develop MS, and do not show no any changes on the Expanded Disability Status Scale (EDSS) [19].

The fact that secondary progressive forms are most affected is related to the evolution time. A post hoc analysis in patients with cognitive impairment at the time of diagnosis and an evolution to MS ≤ 1 year showed that the cognitive disorder had begun previously and, in cases of having performed an MRI, those patients would have shown a radiologically isolated syndrome. In fact, some studies of radiologically isolated syndrome have shown that 27% of patients have cognitive deterioration [16], suggesting that these are patients with CIS or MS with cognitive deterioration, but that, as they are not cognitively evaluated, they are not correctly diagnosed.

The presence of cognitive deterioration in 45% of patients with 'benign' MS [20] suggests that to define 'benign' MS, the absence of cognitive impairment must be included as a requirement [21]. MRIs would help because cognitive deterioration is related to a greater number of lesions in the white matter and in T_2, lower cortical volume and lower global and regional magnetisation transfer [22].

As a result, cognitive deterioration is extremely important to perform cognitive evaluations in clinical practice annually since, in addition, it is a prognostic factor in MS conversion in patients with CIS [23], of higher EDSS scores at five and seven years in patients with premature relapsing-remitting MS [24] and of reaching an EDSS score of four more

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quickly and evolving to secondary progressive at 10 years if it is present at the time of diagnosis [25]. It would be very useful for clinicians to have a tool to identify cognitive impairment in their daily practice; the BICAMS battery is recommended because it does not require special equipment and because it requires a mere 15 minutes to be applied.

With regards to treatment, cognitive stimulation shows class I evidence of utility and efficacy, significantly improving the learning curve and maintaining it for six months [26]. Despite the modifying treatments of the disease reducing the lesional load in T_1 and T_2, the progression of cerebral atrophy and the number of inflammatory lesions in subcortical association areas, there is currently no evidence to recommend a determined modifying treatment for the disease or a symptomatic treatment, based on cognitive state, due to the design problems that clinical trials have. To date, there is no clinical trial that presents cognitive decline as a principal variable.

Progression risk factors

Genetic factors

Nine years after the first findings of familial factors associated with susceptibility and the clinical course of MS [27], there is still no known genetic determinant implicated in the progression of disability, despite numerous genetic studies conducted in the last decade.

In a very critical way, the value of genetic data in MS derived from studies of single-nucleotide polymorphisms (SNPs), of genome-wide association studies (GWAS) and of risks associated with the greater complex of histocompatibility was reviewed. It was concluded that individual genetic variants have a very small impact on risk of MS, that aggregated data explain 30% of susceptibility and that the predictive value is poor, principally due to the absence of a unique variant or groups of variants.

The prevalence of hereditary MS is estimated to be approximately 3-5%, indicating a polygenic inheritance. Ligament and GWAS studies reveal that the human leukocyte antigen (HLA) is the strongest genetic determinant, but other genetic variants that contribute more modestly are also necessary. The functional significance of the association with HLA has been reviewed, and the idea has been proposed that genetic alterations at this level would have an effect on central and peripheral tolerance, that is, on the first phases of development of immunological disturbance in the cascade of immunopathogenic events of MS. However, the non-HLA associations, which could be double the 100 identified so far, mainly occur in genes that are not related to the neurological disturbance, but rather with the functioning of the immunological system; that is, the genetic alterations would be more related to the immunopathogeny underlying the disease than with the disturbance in the central nervous system.

Environmental factors

Observational studies identify the Epstein-Barr virus, tobacco, vitamin D and sodium intake as contributing factors; however, there are many limitations to the observational studies, which emphasises the importance of studying these factors in controlled cohorts. In addition, to discover their possible prognostic role, they should be analysed from the first episode of the disease, which is what was evaluated in the BENEFIT study. In this study, neither the elevated levels of Epstein-Barr antivirus antibodies nor the elevated levels of cotinine, indicative of tobacco consumption, were associated with an increase in the risk of MS conversion or with clinical or radiological evolution at five years [28].

The negative result does not contradict the results previously observed that tobacco is a factor that favours the evolution to a secondary progressive form because the BENEFIT study analysed patients in the first phases of the disease and, in addition, the evolution at five years is a very short period to respond to the question of its contribution in the long term.

Regarding vitamin D, evidence continues to mount, but currently, the data as a possible treatment for MS are still inconclusive [29]. The BENEFIT study analysed the state of vitamin D at one year, to eliminate possible seasonal differences, and evaluated the results obtained at five years [30]. The patients with lower levels of vitamin D converted to clinically defined MS sooner. Also observed was a greater number of active lesions in the five subsequent years in patients with lower levels of vitamin D, along with a greater lesion load, loss of cerebral volume and progression of disability. These data should be taken with caution because they refer to a specific population of patients with a specific treatment, aspects that should be taken into account when extrapolating them to other groups. In the CIS group of Barcelona [31], 72% presented low levels of 25-OH-vitamin D (< 20 ng/mL), a deficiency that was not associated with the risk of converting to MS according to the McDonald criteria,

but it was associated with the risk of disability (EDSS, 3). Low levels of cotinine (< 14 ng/mL), present in 57% of patients, were associated with a lower risk of reaching an EDSS score of 3, but the impact on conversion to MS was less consistent.

Salt intake continues to be a controversial issue. Although *in vitro* and *in vivo* studies show an association with the progression of the disability [32], the data from the BENEFIT study, through analysis of sodium in the urine and creatinine every six months as an approximate measurement of salt intake, did not show any association with conversion to MS, nor with clinical activity or by MRI [33].

Personalised medicine in MS

Individualised and precision medicine is beginning to be feasible in approaching MS. In the combined cohorts of the FORTE and GALA studies, SNPs were identified associated with the response to glatiramer acetate, whose discriminating capacity and specificity were later confirmed in an independent analysis of five additional cohorts [34]. These SNPs are involved in the immunomodulating response to treatment and in the pathogenesis of the disease. The results are of particular interest because the allele involved is the HLA-DQB2, strongly associated with DRB*15, which, in animal models, confers susceptibility to the disease. The clinical utility of these SNPs lies in their potential to distinguish patients who are going to suffer attacks or present lesions in the MRI or who are going to progress to or even achieve NEDA (no evidence of disease activity).

That said, it is necessary to continue advancing in the identification of factors of greater precision that can determine exactly the prognosis and response to treatment; until then, personalised medicine in MS will continue to be based on concepts such as improving diagnosis, prognosis, monitoring the therapeutic response and monitoring treatment (Figure).

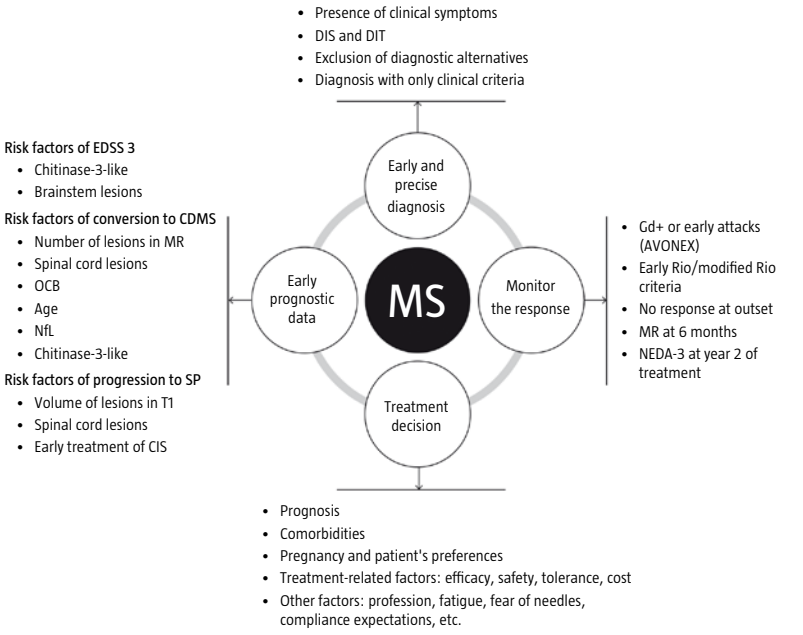
Early and precise diagnosis

To date, multiple diagnostic criteria have been defined with the intention of minimising errors, unifying criteria to be used in clinical trials and managing a common language, although not always based on clinical evidence.

All forms of MS evolution are based on at least one clinical episode [35]. In radiologically isolated syndrome, approximately two-thirds of people present radiological progression, and one-third develop neurological symptoms during a follow-up period of five years. Cervical medullary lesions are an important predictor of clinical conversion. Given that one-third of patients with radiologically isolated syndrome will have a demyelinating episode within five years [36], it is important to define the need for treatment if they present a spread in time and space, if new lesions appear and if cognitive decline, atrophy or black holes occur. The MRI criteria to diagnose MS were updated recently [37]: lesions in the optical nerve were included for the spatial spread, cortical and juxtacortical lesions were grouped together, the number of periventricular lesions was increased to three and symptomatic lesions were included in the recount. The exclusion of diagnostic alternatives is especially relevant in the early phases of the disease, in which there is more difficulty in the differential diagnosis between optical neuromyelitis and CIS [38], especially because some MS treatments can worsen the progression of optical neuromyelitis [39].

The diagnosis can be made only with clinical elements; in fact, there are patients without lesions on

Figure. Personalised medicine in multiple sclerosis (MS). OCB: oligoclonal bands; CIS: clinically isolated syndrome; DIS: dissemination in space; DIT: dissemination in time; MS: multiple sclerosis; CDMS: clinically defined multiple sclerosis; NEDA: *no evidence of disease activity*; NfL: neurofilaments light chain; MR: magnetic resonance; SP: secondary progressive.



MRI when they have CIS who develop clinically defined MS [40,41]. In the latest MAGNIMS diagnostic criteria [37], black holes do not have diagnostic value when they fulfil the spatial spread, and a recent study showed that in patients who do not fulfil the criteria for spatial and temporal spread, the presence of oligoclonal bands plus ≥ 3 lesions in T_2 or oligoclonal bands plus ≥ 1 lesions in T_2 with typical localisation could help predict a second attack [42].

Early and prognostic data

In the cohort with CIS from Barcelona, factors were defined for high, medium and low risk of conversion to clinically defined MS and for reaching an EDSS score of 3. Oligoclonal IgG bands in cerebrospinal fluid, in addition to doubling the risk of a second attack [43], are associated with a greater risk of developing disability (evaluated by the time it takes to reach an EDSS score of 3) [44]. Oligoclonal IgM bands could also play a relevant role in prognosis [45], as they are associated with greater cerebral atrophy [46], although there is currently some resistance to including them as a biomarker [44]. Lesions in the brainstem, but not cerebellar lesions, increase the risk of reaching an EDSS score of 3 [47], and medullar lesions decrease the probability of remaining in the CIS form [48]. The volume of lesions in T_1 and medullar lesions are predictive factors of progression from CIS, with a sensitivity of 75% [49].

Neurofilament light chains in cerebrospinal fluid continue to be confirmed as a prognostic biomarker, as they increase the risk of conversion to clinically defined MS and correlate with cerebral atrophy at one and five years [50]. Chitinase-3-like-1 protein (CHI3L1) (> 170 ng/mL) also increases the risk of conversion and of reaching an EDSS score of 3 [51] and is similarly validated as a prognostic biomarker of MS conversion in a recent international study with more than 800 samples of cerebrospinal fluid and 15 participating European countries [52]. Recent publications from independent groups reinforce the role of CHI3L1 in the development of neurological disability [53-55].

The influence of treatment on the prognosis of CIS was analysed in the series of CIS from Barcelona [44] in a total of 401 patients, with an average age of 29 years and a follow-up of more than 10 years. The majority of patients (79%) converted to MS (according to McDonald 2010), 24% reached an EDSS score of 3 and 4% reached a score of 6. It is worth noting that 47% had not received treatment. The comparative analysis between treated and untreated patients showed that CIS is usually treated in its more aggressive phenotypes and that, in general, the waiting period to introduce a treatment is very long – approximately four years in patients with more benign forms and two years in patients with the more aggressive forms. Consequently, when treating patients with more severe forms of the disease, their evolution is worse. Compared with series with natural development, the Barcelona series showed a lower proportion of patients who reach elevated disability at 15 years (EDSS of 3, 71% versus 51%; EDSS of 6, 53% versus 12%). However, when compared with the current series of patients with CIS treated in the BENEFIT study [56], the data were similar, with 30% and 6% reaching EDSS scores of 3 and 6, respectively, versus 27% and 7% in the Barcelona series. Ultimately, early treatment appears to prevent the accumulation of disability and progression to the secondary progressive form. Other studies of databases and long-term prognosis offer a measure of the degree to which classic medications have changed the natural development of the disease [57].

Response to treatment

Correctly identifying which patients respond is fundamental in personalising treatments, although it is not easy in practice. Studies should be linked to measuring response, in favour of a faster response, but especially aimed at a more adequate and optimal therapeutic decision. A review of Sormani and De Stefano [58] concludes with using the EDSS, attacks and MRI, but there is no agreement, due in part to the fact that the definition of the simplest non-response would be the progression of one point in the EDSS (confirmed at six weeks), whereas substantial MRI activity, particularly in combination with attacks, would be the most exact criterion for therapeutic failure, all as a function of the definition we choose for non-response.

Starting with the follow-up to the pivotal study of interferon β-1a, we know that patients with gadolinium-enhancing lesions or early attacks have a greater increase in EDSS score at 15 years [59]; these patients can be defined as non-responding, partially responding, with insufficient response or active despite treatment. Other definitions of non-response are based on the Rio or modified Rio scores [60], which, separately or combined, predict a suboptimal response with interferon in the long-term. Patients who are initially nonresponsive behave like those treated with placebo. There are very recent MRI criteria [61], but the most important is

to define the moment of performing the baseline MRI to compare with treatment response, which will depend on the speed of the medication's action, with six months being considered a good period [62,63]. A systematic review of 31 clinical trials showed that the effect of treatment with regard to MRI in the first six months predicted the effect of the same treatment after two years in respect to attacks. More important when making therapeutic decisions are the combined clinical (attacks) and MRI results [64], and especially new lesions in T_2 or increased lesions in T_2 during the first year because these findings predict disability in the second year. The infratentorial or spinal localisation of the new lesion in T_2 is a better predictor of future risk of worsening disability than the lesion count [65].

We know that patients with NEDA 3 in the second year of treatment will have a null or minimal increase in EDSS score at seven years, although less than 20% will reach a NEDA 3 starting in the third year. It is also known that disability and atrophy are related, especially if one adds the load of lesions in T_2 [66], and that patients with a greater loss of cerebral volume over time will be clinically worse and with greater disability in the fourth year [67].

In addition, the question of whether we should consider new treatment objectives is posed. Cerebral atrophy, as a measurement related to progression, could be incorporated with the concept of NEDA and allow a more global and balanced evaluation of diffuse and focal disease activity. The concept of NEDA is an important therapeutic objective, but it is difficult to use and to achieve in clinical practice, and perhaps we should not be so strict in our expectations of no activity to be able to discuss treatment response. Therefore, a new concept is introduced: minimal evidence of disease activity (MEDA), which proposes the minimal clinical or radiological activity that does not show therapeutic failure as an objective. This concept is reflected in the recent study of the MAGNIMS group [68], with more than 1,000 patients treated with interferon β for more than three years, which established three risk scores based on the number of attacks and T_2 lesions during the first year. According to experts, this concept would not add anything new to the Rio or modified Rio scores [69]; however, it does again expose the lack of agreement when defining a minimal quantity of clinical or radiological activity permissible to not count as therapeutic failure.

Monitoring and modifying treatment

The head-to-head comparisons available in the MSBase database [70], with more than 40,000 patients from more than 200 centres, showed that, after a relapse with interferon or glatiramer acetate, a change to natalizumab led to better results in all aspects evaluated [71]. Similarly, the results indicated that changing from an injectable immunomodulator to fingolimod was associated with lower relapse rates, with a more favourable result in terms of disability, and with greater persistence of treatment compared with changing to another injectable [72].

The decision to choose or change the drug will depend on various factors, always in consultation with the patient. ECTRIMS and the European Academy of Neurology have joined forces to formulate the first European guidelines for the treatment of MS following the GRADE system (a methodology to form recommendations in clinical practice), many of which we already know (Table II) [73].

Table II. Updated recommendations based on evidence for pharmacological management in multiple sclerosis.

Patients should be treated in centres with infrastructure that allows for adequate follow-up, detailed evaluation, detection of secondary effects and the capacity to address them immediately
Consider interferon or glatiramer acetate for patients with clinically isolated syndrome and magnetic resonance for those who do not fulfil the criteria for multiple sclerosis
Early treatment should be offered to patients with active relapsing–remitting multiple sclerosis, defined by the presence of attacks and/or activity in magnetic resonance imaging (lesions that are enhanced with contrast and/or new and/or unequivocally increased in T_2, evaluated at least annually)
The decision to choose or change the drug will depend on the following factors and always in consultation with the patient: – Patient's characteristics and comorbidities – Severity of the disease/activity – Safety profile of the drug – Access to treatment
It is recommended to use radiological and clinical measures to monitor the evolution of the disease
In monitoring the response, it is recommended to perform a cerebral magnetic resonance image as a reference, usually within the first six months of treatment, and to compare it with a new resonance image performed usually 12 months after start of treatment
The timings of both magnetic resonance images should be adjusted, taking into account: – The action mechanism of the drug (especially the speed of action) – The disease activity
Consider a more effective drug for patients treated with interferon or glatiramer acetate who show evidence of disease activity
If a high-effectiveness treatment is interrupted due to ineffectiveness or safety concerns, an attempt should be made not to change to a lower level treatment
When changing between highly effective drugs, the following factors must be taken into account: – Disease activity (the greater the activity, the greater the urgency to begin a new treatment) – Half-life and biological activity of the previous treatment – Potential of disease reactivation or rebound (particularly with natalizumab)

Final observations

In this iteration of ECTRIMS 2016, what emerged, more than the great advances or high-impact news, were the still-unanswered questions; however, the quantity of information and the numerous tools that are currently available for managing the disease also stood out. These facts reflect that MS is no longer an orphan disease, and it requires a very elevated level of specialisation to offer the best treatments to our patients.

The natural history of the disease has changed, and the classic medications offer a better future to patients when they are diagnosed. A new concept is approached that is more feasible in clinical practice: MEDA, along with how the attacks and lesions of only T_2, now without gadolinium enhancement, could be useful to evaluate response to treatment. Family planning in women, pregnancy and breast feeding are discussed because they are current issues and because they are considered controversial and generate unease. Paediatric MS is a more complex issue, especially in its therapeutic approach, given that it is difficult to perform clinical trials in this age group. The concepts of personalised medicine and precise medicine are introduced in all aspects, from diagnosis until treatment, and a warning emerges regarding our scarce evaluation of cognitive decline in the clinic, despite its importance in the disease.

The second part of this article discusses the current controversy in MS management, presents the latest advancements in remyelination and neuroprotection and anticipates advancements in research which, in the future, will converge in clinical practice [74].

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

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 actividad científica, avalada por la Sociedad Española de Neurología, se genera este artículo de revisión que sale publicado en dos partes. Esta primera parte aborda la planificación familiar en las mujeres con esclerosis múltiple, el manejo del embarazo y el papel de la lactancia. Se dirige la atención a la población pediátrica, a las características de la resonancia magnética y a los factores de riesgo geneticoambientales para el desarrollo de la enfermedad en niños, sin olvidar los factores de riesgo de progresión en los adultos. Se actualiza la epidemiología del deterioro cognitivo en los pacientes con esclerosis múltiple, las ventajas e inconvenientes de las herramientas de evaluación disponibles, y los enfoques actuales de manejo, y se insiste en la importancia de la afectación cognitiva en el curso de la enfermedad. Además, se introduce el concepto de medicina individualizada y de precisión, desde el diagnóstico de la enfermedad hasta el tratamiento, con las polémicas que inevitablemente surgen en el manejo de los pacientes, principalmente en lo relacionado con el cambio de tratamiento y el manejo de riesgos asociados.

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