Review of the novelties from the 2017 ECTRIMS Congress, presented at the 10th Post-ECTRIMS Meeting (II)

Óscar Fernández, Mar Tintoré, Albert Saiz, M. Carmen Calles-Hernández, Manuel Comabella, Lluís Ramió-Torrentà, Agustín Oterino, Guillermo Izquierdo, Nieves Téllez, Juan A. García-Merino, Lluís Brieva, Carmen Arnal-García, Yolanda Aladro, María del Mar Mendibe-Bilbao, José E. Meca-Lallana, Lucía Romero-Pinel, Ricardo Ginestal, M. Luisa Martínez-Ginés, Rafael Arroyo, Alfredo Rodríguez-Antigüedad

Hospital Universitario Carlos Haya; Málaga (O. Fernández). Cemcat-Hospital Universitari Vall d'Hebron; Barcelona (M. Tintoré, M. Comabella). Hospital Clínic; Barcelona (A. Saiz). Hospital Universitari Son Espases; Palma de Mallorca (M.C. Calles-Hernández). Hospital Universitari Dr. Josep Trueta; Hospital Santa Caterina de Salt; Institut d'Investigació Biomèdica de Girona, IDIBGI; Salt, Girona (Ll. Ramió-Torrentà). Hospital Universitario Marqués de Valdecilla; Santander, Cantabria (A. Oterino). Hospital Universitario Virgen Macarena; Sevilla (G. Izquierdo). Hospital Clínico Universitario; Valladolid (N. Téllez). Hospital Universitario Puerta de Hierro; Madrid (J.A. García-Merino). Hospital Universitari Arnau de Vilanova; Lleida (Ll. Brieva). Hospital Universitario Virgen de las Nieves; Granada (C. Arnal-García). Hospital Universitario de Getafe; Madrid (Y. Aladro). Hospital Universitario de Cruces; Bilbao (M.M. Mendibe-Bilbao, A. Rodríguez-Antigüedad). Hospital Universitario Virgen de la Arrixaca; Murcia (J.E. Meca-Lallana). Hospital Universitari de Bellvitge; L'Hospitalet de Llobregat; Barcelona (L. Romero-Pinel). Hospital Universitario Fundación Jiménez Díaz; Madrid (R. Ginestal). Hospital General Universitario Gregorio Marañón; Madrid (M.L. Martínez-Ginés). Hospital Universitario Quirónsalud; Madrid (R. Arroyo). Complejo Hospitalario Ruber Juan Bravo; Madrid, Spain (R. Arroyo).

Corresponding author:
Dr. Óscar Fernández Fernández. Instituto de Investigación Biomédica de Málaga. Hospital Universitario Regional de Málaga. Universidad de Málaga. Avda. Carlos Haya, s/n. E-29010 Málaga (España).

E-mail:
oscar.fernandez.sspa@gmail.com

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Summary. The Post-ECTRIMS Meeting is an emblematic event in the field of multiple sclerosis in Spain. Its chief aim is bring together the country's leading specialised neurologists to analyse the main advances made in multiple sclerosis and to review the most important topics addressed at the ECTRIMS Congress. The tenth Post-ECTRIMS Meeting was held in November 2017. Over the years this event has firmly established itself as an important meeting point where experts from all over the country get together to foster communication, establish synergies and promote and enhance research ultimately aimed at improving the prognosis and quality of life of patients with multiple sclerosis. This second part addresses the different strategies for the management of patients in advanced stages of the disease and the safety of therapy in multiple sclerosis. Likewise, attention is also drawn to the areas that require further scientific and clinical evidence. In this edition, particular importance is given to multiple sclerosis in the paediatric population and ageing in the disease. At the same time emphasis is placed on the need to conduct collaborative studies and to foster greater awareness among specialists regarding the detection and management of the comorbidities in multiple sclerosis.

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

Cognition and cognitive repair in multiple sclerosis

Cerebral connectivity and cognitive impairment

Multiple sclerosis (MS) causes damage in the grey matter resulting in physical and cognitive deterioration. It also affects the white matter, with consequences affecting cognition; that is, there is not only a correlation with the volume of the lesion in T_2 and the Paced Auditory Serial Addition Test (PASAT), but also between the anisotropy measured by diffusion and cognitive tests such as the PASAT, Benton Visual Retention Test or California Verbal Learning Test in areas such as the corpus callosum, the thalamus, the right posterior cingulum or the fornix [1,2]. Social cognition, or the ability to guess a person's mood by seeing their eyes or watching them walk, has recently been analysed, results showing that, compared to healthy controls, patients with MS have a poor perception of the mood of the people they are shown in both the eyes test and the video test [3]. These results are again related to a deficit of connectivity by anisotropy in the corpus callosum, the fornix, the uncinate fasciculus and even the cerebellar peduncle. It has been proved that a greater predictive capacity of cognitive impairment is related to anisotropy in the cingulum for the PASAT and for nearly all the subtests of the Rao battery [4]. Supporting these data, it has recently been shown that the superior cerebellar peduncle and the cerebellar lobes are related to cognitive impairment in patients with MS. This is known as cognitive dysmetria, which consists in a reduced capacity of the cortico-cerebellar-cortical loop to maintain the cognitive capacity [5].

Anatomical connectivity is diminished in certain areas of the brain and the cerebellum, but what happens with the capacity for functional connectivity? In contrast to what occurs in Alzheimer's disease, in an attempt to compensate the cognitive impairment due to a lack of anatomical connectivity, patients with MS present greater functional connectivity with lower cognitive efficiency [6]. The connection network that is most affected is the default mode network, which is related to the connectivity of the thalamus. There appears to be a negative relationship, and the greater the connectivity of the thalamus with the cerebellum, the temporal lobe or the cortical areas is, the lower the cognitive capacity will be, and the poorer the results on the PASAT will be [7].

Cognitive impairment is also related to emotional problems, especially depression. A depressed patient has a diminished attentional capacity, poorer working memory and a lower executive capacity, although this relationship could also occur the other way around. In any case, it seems that depression aggravates cognitive impairment in patients with MS. Another hypothesis points to the possibility of a diminished processing speed, which would lead to a decrease in memory and executive function [8]. Depression is the determining factor of a decrease in the capacity for leisure in 17% of patients with MS. The intelligence quotient and premorbid leisure activity are predicting factors of lower processing speed, memory, learning and executive function [9]. Furthermore, patients with MS who present depression obtained poorer results on the Symbol Digit Modalities Test, especially if there are distractions [10].

Management of cognitive impairment in multiple sclerosis

The question is: what can we do to improve the cognitive capacity of patients with MS as regards connectivity? Cognitive rehabilitation over a period of five weeks improves the results on the California Verbal Learning Test for a period of more than six months [11], with additional benefits in terms of quality of life and symptoms of depression [12]. Practising the 'brain training' method for eight weeks improves the results on the PASAT and the Stroop test [13], which has been related to an increase in functional connectivity above all in cortical regions. The short-term positive effects of neuropsychological rehabilitation on the cognitive deficits perceived by the patient are maintained for at least a year after beginning the intervention, although they gradually diminish [14]. The problem lies in the need to reach all the patients, in the need for repeated sessions and in supervised telerehabilitation. One recent study has shown that rehabilitation at home, over 12 weeks, improves the results on a number of cognitive scales [15]. Another study on patients who received repeated transcranial stimulation sessions at home, monitored by a neurophysiologist or neurologist, yielded positive results for complex attention and fatigue, and also for cognitive capacity, functional connectivity and, surprisingly, anatomical connectivity. Thus, there could be a certain degree of plasticity with a structural correlate [16]. Transcranial magnetic stimulation in the right dorsolateral prefrontal cortex improves scores on the cognitive tests and patients' functional connectivity [17]. In conclusion, there is a need for better tools to detect patients who are at risk of cognitive impairment and its progression, better techniques for improving social well-being and cognitive functioning, appropriate management of comorbidities (such as mood and sleep) and fostering healthy habits in terms of diet, physical exercise, social interaction and control of stress.

Ageing and multiple sclerosis

In the update of the Queen Square CIS series at 30 years [18] it was observed that 40% of the patients who converted to MS had a score on the Expanded Disability Status Scale (EDSS) < 3.5 and the others had an EDSS score > 4 or had died from MS. Moreover, the majority of patients with an EDSS < 3.5 continued with a relapsing-remitting development and those who had an EDSS > 3.5 were secondary progressive forms or had died. It is interesting to note that after 30 years there are patients grouped around an EDSS score of 1.5-2, or 6-7 or dead, but none with an EDSS of 3-5.5, which could be due to a methodological bias or reinforce the theory of the existence of benign MS.

Age *per se* is a risk factor of disability. With the same time to progression, patients below the age of 30 will present a lower degree of disability than those over 55 years old; in the same way, the older the patient and the higher the EDSS score are, the greater cognitive impairment will be [19]. The influence of age on treatment efficacy and management has been analysed in the phase III studies of the main disease-modifying therapies for the disease. In the TEMSO study with teriflunomide, the risk of relapses and of progression was higher, close to placebo, in patients over the age of 38 compared to those below that age [20]; similarly, in the FREEDOMS study, with fingolimod [21], the hazard ratio of the annualised relapse rate was close to 1, that is, to that of the placebo group, in patients over the age of 40 years. The AFFIRM study with natalizumab yields similar data for the risk of disability progression, which is higher in patients over 40 years old [22]. Treatment with interferon β-1b in secondary progressive forms [23] and with rituximab in primary progressive forms [24] diminishes the risk of disability progression in younger patients, although with greater clinical and radiological activity. In the ORATORIO study with ocrelizumab in primary progressive forms, the risk of disability progression comes close to that of placebo in patients without radiological activity and in patients over the age of 45 [25].

Note:
All the authors in the Post-ECTRIMS group have contributed to an equal extent in the preparation of this review.

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The debate is focused on whether ageing justifies discontinuation of disease-modifying therapies. There are no evidence-based data for older patients, only data from clinical experience. This decision should take into account the greater risk and severity of progressive multifocal leukoencephalopathy, but also the comorbidities inherent in age. The DISCOMS study (ClinicalTrials.gov identifier: NCT03073603) aims to recruit 300 patients with relapsing-remitting and progressive forms to evaluate the effects of withdrawing medication as of the age of 55.

Comorbidity

Hypertension, diabetes, ischaemic heart disease, fibromyalgia, inflammatory bowel disease, pulmonary disease, epilepsy, depression and some psychiatric disorders are more prevalent in MS than in the general population [26]. Comorbidity in MS could have an influence on attacks, treatment, hospitalisation [27], mortality [28] and disability progression. In fact, the percentage of patients who do not need help is significantly higher if they do not present any kind of vascular comorbidity [29]; specifically, patients with a vascular comorbidity need unilateral help to walk around six years earlier those who do not have any vascular comorbidity, a risk that increases as the number of vascular comorbidities rises. The different comorbidities have distinct influences if they are diagnosed at the onset or during the course of the disease. Regardless of whether they are present in the diagnosis or at a later stage of the disease, diabetes, hypertension, hypercholesterolemia and peripheral vascular disease are associated with greater disability progression [29]. Cardiovascular risk also appears to be associated with the severity of MS [30]. The presence of comorbidities in MS indirectly affects the patient's quality of life due to their impact on anxiety, depression and fatigue [31].

Clearly there is a need to take action for the prevention and treatment of these comorbidities, although it is necessary to define the different specialists' responsibilities and competencies with the aim of preventing redundancy and inefficiency.

Paediatric population

Although MS is a disease that starts around the age of 20-30 years, 5% of patients begin with the disease before reaching the age of 18, a stage in which the central nervous system and the immunological system are still immature [32]. The innate response, in patients under 14 years of age, is far more important and the adaptive response is especially predominant. Paediatric patients present high levels of inflammation in the central nervous system and an important degree of acute axonal damage, with clinical consequences not only involving the accumulation of disability but also the structural deterioration of the brain [33]. The paediatric population is ideal for researching risk factors, since the interval between exposure to the factor that hypothetically causes MS and onset of the disease is very short. Yet, the prevalence of MS in this age group is very low, hence the importance of collaborative studies.

The diagnosis of MS is based on McDonald-2010 criteria, although in patients under 14 years of age these criteria have a lower level of sensitivity and specificity. The key to diagnosing MS in the paediatric population is the differential diagnosis of other demyelinating diseases that are far more frequent at these ages [34]. The younger the children are (< 11 years old), the more multifocal attacks they represent accompanied by a diminished level of consciousness and even epileptic seizures; as the children get older, the course of the disease tends to match that of adults, with greater involvement of the brainstem and cerebellum due to the development of primary myelination that follows a rostrocaudal direction. Practically all cases of childhood MS are relapsing-remitting forms. Cognitive impairment can be detected in very early stages and can occur in up to a third of patients. Magnetic resonance imaging (MRI) lesions are far less strictly defined, with greater inflammatory involvement and less atrophy in the early phases [35,36].

The prognosis in paediatric MS is very severe. One natural history study showed that children maintain a more stable situation for a longer time than what usually occurs, but they reach a secondary progressive form sooner than adults. Children take around 20 years to reach an EDSS of 4 and about 29 years to reach an EDSS of 6 [37]. The most important variables that influence the change to a secondary progressive course are age and the number of relapses.

Of all the children with childhood demyelinating diseases, 40% can present anti-myelin-associated oligodendrocyte glycoprotein antibodies; current data show that these antibodies are observed more frequently in non-MS demyelinating diseases, such as acute disseminated encephalitis, recurrent optic neuritis and the acute disseminated encephalitis-optic neuritis phenotype [38]. A special phenotype of neuromyelitis optica in children that is accompanied by negative anti-aquaporin-4 antibodies and

positive anti-myelin-associated oligodendrocyte glycoprotein antibodies is more frequent in males; these patients present less compromise of the area postrema, more lesions in the cerebellar peduncle, but a more favourable prognosis [35].

Treatment of paediatric multiple sclerosis

The treatment of paediatric MS has changed considerably in recent years, as current criteria recommend starting treatment as soon as a definitive diagnosis is available. In patients with more active forms, some cases have been treated with natalizumab, which offers a high degree of efficacy, and in which case it must be taken into account that, fortunately, the JC virus serological status in patients under the age of 18 is much lower than in adults.

In recent years a number of clinical trials have been conducted in the paediatric population. The first randomised controlled phase III study designed in a paediatric population was the PARADIGMS study with fingolimod versus interferon β-1a. The results of this study showed a reduction in the annualised relapse rate of close to 82%, but, surprisingly, 85% of these patients were over 15 years old (that is, with characteristics that more closely resembled those of MS in adults). In this same study, it should be noted that 92% of patients continued with it, which confirms the importance of treatment compliance in this population of patients [39]. Another study involving teriflunomide versus placebo (TERIKIDS) is underway with a recruitment that is more complicated than in the case of adults, and CONNECT is going to start with dimethyl fumarate versus interferon β-1a (ClinicalTrials.gov identifier: NCT02201108). LEMKIDS has been started with alemtuzumab in the 60 children included to date and a more exhaustive MRI follow-up, lasting around four months (ClinicalTrials.gov identifier: NCT03368664).

Update on the treatment of relapsing-remitting multiple sclerosis

One of the notable contributions of 2017 ECTRIMS was the announcement of the publication of the new European and American clinical guidelines on the use of disease-modifying therapies in MS. These new guidelines include recommendations aimed at optimising patient care, based always on a systematic review of the available evidence, and of the evaluation of the possible benefits or risks of the therapeutic options. The varied therapeutic arsenal available today, the development of clinical trials on forms of MS that present a single demyelinating event or in progressive forms and, therefore, the increase in complexity of decision-making are some of the reasons for posing new questions (Table I).

Table I. Questions that need to be answered about the new American [85] and European [86,87] guidelines on the use of modifying therapies in multiple sclerosis.

American guidelines (AAN):
In patients with relapsing-remitting or progressive forms, is the use of disease-modifying therapies superior to placebo or other treatments in terms of the reduction in the rate of attacks, the improvement in the magnetic resonance parameters or the disability progression?
Safety of disease-modifying therapies versus placebo
In patients with clinically isolated syndrome, is the use of disease-modifying therapies superior to placebo in reducing conversion to multiple sclerosis?
European guidelines ECTRIMS-EAN:
What is the benefit to be gained from using disease-modifying therapies versus no treatment in patients with clinically isolated syndrome, relapsing-remitting, secondary progressive or primary progressive forms?
In patients who drop out of a high-efficacy treatment, what is the risk of a rebound effect?
In stable patients with disease-modifying therapies, what is the benefit to be gained from continuing with treatment versus discontinuing it?
What is the therapeutic approach in pregnant patients?

AAN: American Academy of Neurology; EAN: European Academy of Neurology; ECTRIMS: European Committee for Treatment and Research in Multiple Sclerosis.

No evidence of disease activity (NEDA) appears to be the aim of the new paradigm, but achieving it in clinical practice is no simple matter. In fact, only 9% of the patients treated with first-line drugs fulfil NEDA after 10 years [40] and 8% maintain NEDA after seven years [41]. Nevertheless, it is a marker with a good prognosis, since 80% of patients with NEDA at two years remain without progression in the long term [41]. Adding the measurement of brain volume to the concept of NEDA-3, which includes not having relapses, new lesions or disability progression, gives rise to NEDA-4. Several authors suggest incorporating neurofilaments in the cerebrospinal fluid as a biomarker in the development of this disease-free status score.

The treatment of MS is complex, and even more so in patients with high activity and a desire for pregnancy, and it becomes necessary to make shared decisions. Certain drugs can take up to six months to display their therapeutic effect, which is the reason underlying the recent suggestions to perform a rebaseline MRI scan six months after starting treatment. In this way, if the patient presents new lesions in T2 at month 6, the MRI scan at

Table II. Update of treatment of active relapsing forms.

	Study	Main results
Glatiramer acetate	CONFIDENCE study [64] Phase IV multinational and multicentre study on satisfaction with 40 mg GA versus 20 mg GA	40 mg GA increases the score on the MSQ questionnaire on treatment satisfaction compared to 20 mg GA (p = 0.037) Patients treated with 40 mg GA consider this treatment as more appropriate than those treated with 20 mg GA, as measured by the TSQM-9 scale (p < 0.01) 40 mg GA improves the impact of fatigue in their daily lives according to MFIS (p = 0.043)
	COPTIVITY study [65] Preliminary analysis of a real open study lasting two years to evaluate the efficacy, safety and quality of life with 40 mg GA	Annualised relapse rate: ↓ from 0.96 to 0.25 Expanded Disability Status Scale: stable Symbol Digit Modalities Test: ↑ information processing score, from 49.7 to 53.2 Safety: low rate of side effects (10%), with predominance of radiologically isolated syndrome
	Pregnancy and GA [66] First global study to evaluate the results of exposure throughout the whole pregnancy versus reference data on the general population from EUROCAT Analysis of data on more than 8,000 patients from the Teva global pharmacovigilance database	No differences as regards gestational age, intrauterine deaths or births of children who died at later stages The 216 children from pregnancies exposed during the three trimesters had weight and gestational age distributions similar to the general population Seven cases of congenital anomalies, similar to the EUROCAT reference rate Rate of congenital anomalies of 1.29, with no significant differences compared to EUROCAT
	AMPS: active support programme for patients with multiple sclerosis treated with GA [67]	High levels of compliance among patients who participated in the programme, with dropout rates of 10%
Laquinimod	CONCERTO study [68] Randomised, double-blind study with daily doses of 0.6 and 1.2 mg of laquinimod versus placebo for 24 months, followed by an active treatment phase	The 1.6 mg laquinimod arm was discontinued due to cardiovascular effects The main disability objective at three months evaluated by the Expanded Disability Status Scale was not met (is it a suitable scale for rating disability?) Annualised relapse rate: ↓ 30% with 0.6 mg laquinimod Gadolinium-enhancing lesions: ↓ 30% with 0.6 mg laquinimod Percentage change in brain volume: ↓ 27.8% versus placebo Its safety profile is maintained
Ozanimod	RADIANCE study [69] Phase III, multicentre, double-blind, double simulation, of parallel groups with 0.5 or 1 mg of oral ozanimod daily versus intramuscular interferon β-1a weekly	Annualised relapse rate: ↓ 36% with 1 mg ozanimod versus interferon β-1a at two years Significant reduction in loss of brain volume measured in the grey matter or the thalamus No positive data on disability probably due to the scarce progression with interferon Good cardiac safety profile, without second-degree auriculoventricular block, and infrequent cardiotoxic effects
	SUNBEAM study [70] Phase III, multicentre, double-blind, randomised with 0.5 or 1 mg of ozanimod daily versus intramuscular interferon β-1a weekly	Annualised relapse rate: ↓ 48% with 1 mg ozanimod versus interferon β-1a Gadolinium-enhancing lesions: ↓ 63% with 1 mg ozanimod versus interferon β-1a Lesions in T_2: ↓ 48% with 1 mg ozanimod versus interferon β-1a Positive effects on brain volume and disability progression Similar rate of side effects: headache, nasopharyngitis, alteration of transaminases Cardiac safety: no symptomatic bradycardia or second-degree auriculoventricular blocks; no increase in the risk of infections or herpes infections

AMPS: Assessment of Motor and Process Skills; EUROCAT: European Surveillance of Congenital Anomalies; GA: glatiramer acetate; MFIS: Modified Fatigue Impact Scale; MSQ: Medication Satisfaction Questionnaire; TSQM-9: abbreviated Treatment Satisfaction Questionnaire for Medication.

12 months will make it possible to identify new lesions that have developed during treatment [42,43]. In the Rio Score, the appearance of new lesions, in addition to attacks, is an important factor predicting disability. It is not clear, however, that patients who present evidence of activity are going to have an unfavourable long-term prognosis; this is probably due to the fact that small changes in the MRI scan are not associated with a poor prognosis in the long-term, in contrast to what occurs with a substantial number of new lesions [44]. These data are in agreement with those of the MAGNIMS group in a much larger number of patients treated with interferon and glatiramer acetate [45], and which show that very small changes in the MRI are not associated with an unfavourable prognosis. Therefore, the more realistic concept of minimal evidence of disease activity (MEDA) is introduced, which means that a certain degree of new lesions during treatment can be tolerated, above all at the beginning.

The effect of early establishment of high-efficiency modifying treatments (alemtuzumab, natalizumab or fingolimod) in relapsing-remitting forms was proved in a study published with data from the MSBase registry on over 55,000 patients from 117 centres and 33 countries [46]. The results confirm the superiority of these drugs with respect to first-line drugs in younger patients, with a lower development of the disease, less disability and more inflammatory phenotypes. Prevention of the accumulation of disability was more pronounced in younger patients, and the earlier treatment was established, the more evident recovery from disability was, especially in the four years following diagnosis. The latest data with the classic glatiramer acetate, but also the potential of ozanimod as a new therapeutic alternative in this population of patients, can be seen in table II.

Induction therapy: why, how and when

Escalating therapy aims to calibrate the most effective response with the lowest risk; the fundamental advantage is that it is safer, with the possible disadvantage of a loss of treatment time needed to prevent the phase that follows the inflammatory one. Induction therapy aims to control the inflammatory phase as early as possible; the first phases of the disease can be modulated, but once an EDSS of 3 has been reached, immunomodulator and immunosuppressant drugs may not be so useful. Induction therapy would be more effective, but entails a greater risk.

Induction therapy could be considered in most patients with active forms very close to the onset. Another theory points to commencement in a selected group of patients with factors predicting an unfavourable prognosis [47], with a highly variable window of therapeutic opportunity. These patients would be the ones with relapsing-remitting forms, under the age of 40, very active, with at least two relapses in the last 12 months, with severe attacks that cause an important degree of disability (EDSS 4), a rapid exacerbation of disability due to attacks (an increase of at least two points in the last 12 months) and activity in the MRI (two or more new gadolinium-enhancing lesions in the last 12 months) [48]. That is, in young and clinically and radiologically active patients, an induction therapy would have to be considered.

In actual fact it is difficult to maintain a prolonged remission of the disease. Alemtuzumab has a clear impact by slowing the disability progression in patients with very active and aggressive relapsing-remitting forms and those who respond poorly to other disease-modifying therapies [49,50]. Furthermore, it offers consistent data in the annualised NEDA variable, with a high percentage of patients with no clinical or radiological activity. In other words, it maintains the long-term effect, although with the probable appearance of sustained side effects. Mitoxantrone will also be useful in very active forms, both in previously treated and naïve patients, although with cardiotoxic safety problems that limit the amount of time it can be used and the risk of leukaemia. The use of natalizumab as induction therapy is questionable; it could have its advantages in very active recurring forms, despite the risk of progressive multifocal leukoencephalopathy and reactivation of the disease following its withdrawal. Ocrelizumab and cladribine have also been proposed as induction therapies, but require further research. Perhaps the solution would be to have markers available that can really be evaluated and MRI is the only variable, for the time being, that could resemble a response marker, given the variability in MS.

Therefore, in the typical forms of MS conventional therapies would initially be used while in the very active forms these more effective drugs could be considered as an initial therapy. The time to change would depend on the level of activity and the same treatment could be maintained in cases of little activity or changed to another drug in the same line, but without forgetting the time that could be lost in the shift to high activity.

Safety in the treatment of multiple sclerosis

The risk-benefit balance favours treating patients, a statement that has been a long time coming, because it was thought that not treating was a clear option. Nevertheless, in contrast to the more severe risks such as neoplasias, haematological risks, infections and liver diseases, in general we have a better quality of life and a lower social cost of the disease. Table III sums up the main safety findings with the moderately effective drugs versus others that are more effective but more aggressive against the immune system and with which more risks are taken in both escalating and induction prescription. Most of them are very rare or infrequent adverse events, but must be taken into account.

Multiple sclerosis and reproduction

Discussing reproduction and family planning with female patients is essential, and the clinician must

Table III. Safety findings in the therapeutic management of multiple sclerosis.

		Incidence/risk	Preventive measures/treatment
Natalizumab	PML	In (–) anti-JCV patients: < 0.07/1,000 In (+) anti-JCV patients: Accumulated probability over six years of 2.7% if there is previous immunosuppression 1.7% with no previous immunosuppression, the estimated annual risk varying according to the value of the index [71] The weight of the previous use of immunosuppressants is minimised [72]	Diagnostic keys: progressive clinical deterioration of any area, including cognitive Clinical pictures of headache, fever or meningitis are rare Confirm the radiological diagnosis: presence of hypointense progressive subcortical lesions in T_1 Definitive diagnosis either in the brain or replication of the virus in CSF There is no viral treatment for PML (mefloquine and mirtazapine are used), apart from withdrawing natalizumab and performing plasmapheresis for immune reconstitution with the subsequent risk of IRIS Treat IRIS with corticosteroids that ↓ CD8 A balance between plasmapheresis/cortico-steroids is required Diagnose the patient by magnetic resonance even before giving another drug in view of the appearance of PML lesions five months before the clinical diagnosis reported in 71% of patients [73]
Dimethyl fumarate	PML Sustained lymphopenia Ketonuria Liver disorders Skin reactions	4 cases in MS/270,000 patients < 100 times the risk than with natalizumab Sustained lymphopenia associated with risk	
Teriflunomide	RI/UTI Arterial hypertension Elevated ALT Peripheral neuropathy Interstitial PD	 Very low risk < 1/1,000 < 1/1,000	Frequent laboratory determinations are recommended initially because liver enzymes increase in the first two months In situations in which the patient has a desire for pregnancy, pregnancy or change of treatment, accelerated elimination of teriflunomide with resin/activated carbon
Cladribine	Leukopenia Herpes Severe infections Hepatitis/tuberculosis	 < 1/100 < 1/1,000	
Rituximab	PML	400 cases / > 4 million patients 0 cases in MS Estimated risk: 1/30,000	
Fingolimod	PML	13 cases (exclusively due to fingolimod)/213,000 patients Risk: 0.061/1,000 Risk factors: age, prolonged exposure, prolonged prior immunosuppression, other as yet unknown individual factors	Risk factors: age, prolonged exposure, prolonged prior immunosuppression, other as yet unknown individual factors
Ocrelizumab	PML	0 cases/20,000 patients 1 case in MS following natalizumab	This incidence does not justify monitoring JCV
Alemtuzumab	PML *Listeria* Herpes Cytomegalovirus *Nocardia* Severe infections Dysimmune disorders	0 cases/16,000 patients Hypothetical risk of lymphopenia 32 cases/16,000 patients (0.26%) 16.5% 0.13% One isolated case 2.8% in clinical studies	*Listeria*: Establish a diet free of lightly cooked meat or non-pasteurised dairy products three months prior to treatment Implement diet in the second cycle if treatment needs to be started as early as possible Treatment for at least one month with Septrin ® three times a week or amoxicillin Management of other drugs, such as methylprednisolone or cetrizine, in order to prevent reactions to infusion Prevention plan according to daily practice Herpes: treatment for at least one month with 200 mg acyclovir twice a day Dysimmunity: keratinocyte growth factor

Table III. Safety findings in the therapeutic management of multiple sclerosis. *(cont.)*.

		Incidence/risk	Preventive measures/treatment
Daclizumab (EXTEND study, intermediate analysis at six years)	Severe side effects	20%	Recent withdrawal of the marketing authorisation in the European Union (2018-05-02)
	Severe infections	5%	
	Severe skin disorders	3%	
	Liver disorders:		
	ALT or AST > 10 × NLV	4%	
	ALT or AST > 5 × NLV	8%	
Interferons	Cerebral cardiovascular event	Odds ratio: 1.89	
	Neutropenia/thrombocytopenia		
	Production of neutralising antibodies		
	Dysthyroidism		
	Thrombotic microangiopathy	< 1/1,000	
Glatiramer acetate	Local atrophy		
	Abscesses/focal cellulitis		
	Hypersensitive reactions	< 1/1,000	
	Change of consideration according to risk in pregnancy		

ALT: alanine transaminase; AST: aspartate aminotransferase; CSF: cerebrospinal fluid; IRIS: immune reconstitution inflammatory syndrome; JCV: JC virus; MS: multiple sclerosis; NLV: normal laboratory value; PD: pulmonary disease; PML: progressive multifocal leukoencephalopathy; RI/UTI: respiratory infection/urinary tract infection.

be proactive and settle any doubts his or her patients may have. It is essential to ask about the contraceptive method being used, especially if they are being treated with certain drugs. A recent review on contraception and MS [51] advises against the use of combined contraceptives in patients with reduced mobility due to the high risk of vein thrombosis; other contraceptives would not be contraindicated, as there is no evidence of their interaction with the drugs being used.

To date MS has not been shown to reduce fertility. Nevertheless, Houtchens presented data on more than 90,000 patients that showed a higher rate of diagnoses of infertility in women with MS than in those without the disease, although these latter use fertility treatments to a greater extent [52]. Women with MS use gonadotropin agonists less frequently, as they increase the risk of relapses. Likewise, there is no evidence of a negative effect of MS on pregnancy or of a higher number of miscarriages, although some studies have shown a slight increase in the number of cases with low birth weight.

Medication, pregnancy and breastfeeding

The number of pregnancies exposed to a certain drug needed to double the risk of a particular side effect is very high. They are side effects that are very infrequent in the general population and therefore it is difficult to prove an increase in risk derived from MS. Table IV shows a summary of what has been addressed in 2017 ECTRIMS with regard to the safety of current drugs and some recommendations for management before and during pregnancy.

Evolution of evidence within the context of pregnancy and breastfeeding

The paradigm of pregnancy in MS has changed from the times when patients were advised against having children and breastfeeding, or in which possible treatments for use during pregnancy were not available, to the situation today in which many of these problems have been overcome. Attacks prior to and during pregnancy are associated with a greater risk of relapses in the postpartum period, although they predict them in only 12.7% of cases [53,54]. One of the largest studies analysing the indicators of occurrence of at least one attack in the postpartum period, conducted with data from the MSBase with 893 patients, showed that only 14% presented attacks following childbirth [55]. The tendency is towards a reduction in the number of

Table IV. Summary of safety and some pregnancy- or breastfeeding-related recommendations from summary of product characteristics of the main treatments for multiple sclerosis.

	Current data on exposure during pregnancy	Recommendations
Glatiramer acetate	Global pharmacovigilance database > 8,000 reported cases of pregnancy [66] No increase in the risk of malformations, of the gestational age or of birth weight (*n* = 216)	Discontinue with a positive pregnancy test In active disease, maintain throughout entire pregnancy
Teriflunomide	Global pharmacovigilance database (*n* = 83 pregnancies; *n* = 22 pregnancies in the partners of male patients) [74]: inconclusive data Clinical studies and post-authorisation data (*n* = 129 with known outcome of pregnancy) [75]: No anomalous results Rate of miscarriage lower than expected for the mean age of the exposed patients The few cases of malformation in full-term infants do not follow a defined pattern of malformation No malformations are observed in foetuses from voluntary interruption of pregnancy Current registry underway in 17 countries (objective, *n* = 196) [76]	Reduce the levels to < 0.02 mg/L with a quick washout or wait for eight months to two years
Dimethyl fumarate	No effects shown in the number of side effects during pregnancy (n = 400) Current registry Tecgistry [77] (objective, *n* = 300) followed up throughout the entire pregnancy, and the babies' health up to 12 months	
Fingolimod	Inconclusive data (*n* = 512 in the safety database) [78] The few malformations do not follow a specific pattern	Withdrawal of the drug two months before pregnancy and strict ultrasound monitoring are recommended
Natalizumab	No specific pattern of malformations and rate of miscarriages similar to the general population (*n* = 363) [79] Mild and transitory haematological abnormalities in 10 children (*n* = 13 in the third trimester) [80]	Following the change in the summary of product characteristics, it can be continued until conception or until week 28
Alemtuzumab	Few data during pregnancy and in the ensuing four months Most of the 248 pregnancies in the current registry occur as of four months after the last dose [81]	Waiting until four months after the second dose is recommended
Daclizumab	Few data (38 pregnancies in 36 women exposed to daclizumab, in treatment ≤ 6 months since the last dose) [82]	Discontinue the drug three months before withdrawing contraception
Ocrelizumab	Risk no higher than in the general population [83] Cases of lymphopenia and transitory B lymphocyte depletion in newborns (*n* = 25)	Contraception during at least the six months following the last infusion
Cladribine	Possible problems (*n* = 44) [84] Maximum period of risk of teratogenicity: six months following the last dose	Pregnancy is not advised during the six months following the last dose both in men and in women Double contraception in the first four weeks following the last dose

attacks, possibly due to the diagnosis of milder forms and a greater number of patients treated if compared with the results of the PRIMS study conducted in 1998 [53]. There are no important changes if we take into account the fact of starting treatment in the immediate postpartum period, which is logical, given the time the drugs usually take to achieve their effects. Meta-analyses show that breastfeeding does not increase the risk of attacks in the postpartum period, but instead protects against them; moreover, exclusive breastfeeding for at least two months reduces the risk of attacks in the first six months after childbirth [56]. As a novelty, one study concludes that mothers who breastfeed their child for a longer period have less risk of developing MS [57].

Contribution of cohort studies, clinical trials and registries

Clinical trials provide limited knowledge about long-term safety and efficacy. Certain very rare side effects require a large number of patients and the longitudinal evaluation of efficacy is limited by the lack of a non-treated reference group. Furthermore, the censoring of information regarding the main sources of bias, such as the dropout rate, can lead to inaccurate conclusions [58].

On the other hand, cohort studies have provided important information about the natural history of disability progression. The data from these cohort studies are an essential reference for the neurologist in the individual management of patients and

in the shared decision-making carried out with them. The problem is how to correlate the data from short-term clinical trials with these long-term real-life data, given the differences between the two types of studies and the limitations of observational studies [59].

The unquestionable value of population health registries for evaluating the long-term efficacy and safety of the treatments was made quite apparent in this edition of the ECTRIMS. A nested case-control study was presented with data from databases from British Columbia, Canada and France which, additionally, were compared with other registries. The results concluded that interferon β was associated with a lower risk of mortality due to all causes among patients with MS treated over an 18-year period; these findings were consistent in two geographically different regions [60].

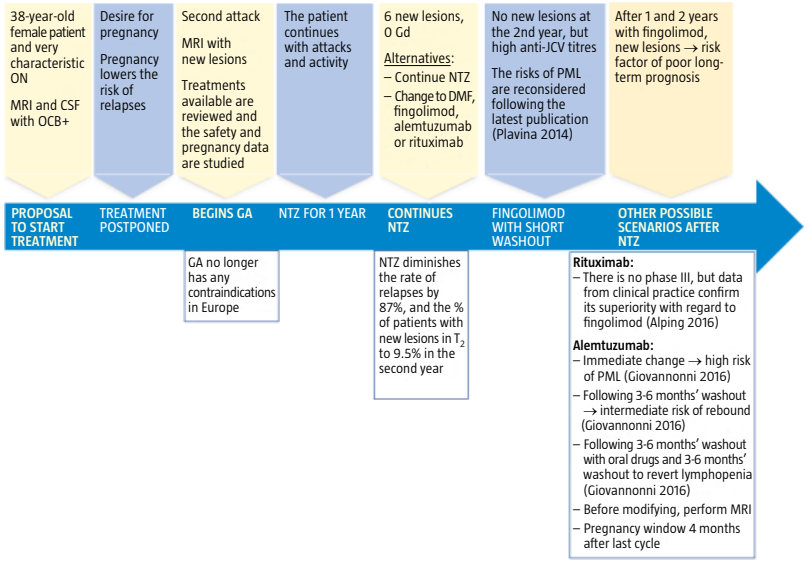
The retrospective cohort of patients with MS (n = 7,731) based on the Swedish registry SMSreg (n = 18,567), concludes that, today, recurrent onset MS is a slower disease and that the risk of disability landmarks has diminished significantly in the last decade [61].

Registries undoubtedly open up enormous possibilities for the study of any aspect. At present, in our country, plans are underway for a national registry by the Spanish Neurology Society (SEN).

Final observations

To conclude, we must ask ourselves whether, despite all these advances, the neurologist is fulfilling patients' expectations. A recent study showed that, as the disease advances, patients feel less satisfied [62] and that the neurologist and the patient differ in their perceptions of the challenges and aims of treatment. The neurologist is more optimistic with regard to the impact of the treatment on the patient's everyday life in terms of a reduction in the number and severity of attacks, as regards safety, etc. In 1997 one study already warned of the fact that the concerns of doctors might not coincide with those of their patients, and suggested taking the patient's opinion into account when it came to designing a study [63]. As 20 years ago, clinicians today seem to continue to be more concerned about the physical manifestations of the disease, unlike their patients, who are still more interested in the aspects related to their mood and quality of life. This view reinforces the fact that there is also a need to continue to work on the aspects that really matter to patients (Figure).

Figure. Case report of a patient with high activity and the desire for pregnancy [88-90]. CSF: cerebrospinal fluid; GA: glatiramer acetate; Gd: gadolinium; MRI: magnetic resonance imaging; NTZ: natalizumab; ON: optic neuritis; PML: progressive multifocal leukoencephalopathy.



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Revisión de las novedades del Congreso ECTRIMS 2017, presentadas en la X Reunión Post-ECTRIMS (II)

Resumen. La reunión Post-ECTRIMS es una reunión emblemática en el ámbito de la esclerosis múltiple en España, con el claro objetivo de analizar, de la mano de reconocidos neurólogos especialistas nacionales, los principales avances en esclerosis múltiple y revisar los temas más importantes del congreso ECTRIMS. En noviembre de 2017, la reunión Post-ECTRIMS celebró su décima edición, y se ha consolidado como un importante foro de encuentro de expertos en nuestro país para favorecer la comunicación, establecer sinergias, y promover y potenciar la investigación para mejorar, en última instancia, el pronóstico y la calidad de vida de los pacientes con esclerosis múltiple. En esta segunda parte se abordan las diferentes estrategias para el manejo de los pacientes con enfermedad avanzada y la seguridad de la terapia en esclerosis múltiple, y se resaltan las áreas que requieren una mayor evidencia científica y clínica. La esclerosis múltiple en la población pediátrica y el envejecimiento en la enfermedad cobran especial importancia en esta edición, remarcando la necesidad del desarrollo de estudios colaborativos y de una mayor concienciación de los especialistas en la detección y el manejo de las comorbilidades en la esclerosis múltiple.

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