Review of the novelties presented at the 2018 ECTRIMS Congress: 11th Post-ECTRIMS Meeting (II)

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Declaration of interests:
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Summary. The Post-ECTRIMS Meeting was held for the eleventh consecutive year in October 2018 in Madrid, with the aim of analysing the advances made in multiple sclerosis that were highlighted at the latest ECTRIMS annual congress. Based on the issues discussed at this meeting, attended by the nation's foremost opinion leaders on multiple sclerosis, two review articles are presented. This second part includes the growing body of evidence confirming the safety of exposure to disease-modifying treatments in women planning a pregnancy, and the beneficial effect of breastfeeding, provided that the disease is not very active. It addresses data showing how the application of the 2017 McDonald criteria in the paediatric population has significantly improved diagnosis compared to the previous criteria. With regard to progressive multiple sclerosis, the results of neuroprotective drugs are inconclusive, but biomarkers are proposed to improve the evaluation of the therapeutic response. Studies on myelin repair treatments suggest that remyelination in multiple sclerosis is possible. Likewise, there are favourable indications for haematopoietic stem cell transplantation, provided that patients are selected appropriately. On the other hand, we also conduct a review of the similarities and differences of the recommendations in the new clinical practice guidelines. Finally, the positive results of cognitive and motor rehabilitation with the use of new technologies point to the systematic incorporation of these tools in the treatment of the disease in the near future.

Key words. Disease-modifying therapies. ECTRIMS. Multiple sclerosis. Paediatric population. Post-ECTRIMS. Pregnancy. Rehabilitation. Treatment with stem cells.

Introduction

After the 34th edition of the Congress organised by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Berlin, the Post-ECTRIMS Meeting took place in Madrid. The aim of this meeting was to discuss and disseminate the latest developments in the field of multiple sclerosis (MS), with the participation of the most prominent national experts in this field.

Family planning, pregnancy and breastfeeding

The risk of flare-ups during pregnancy and after childbirth has decreased in recent years. The most recent data from cohort studies show that the rate of flare-ups during pregnancy is 8.4%, which is considerably lower than the 27% reported in studies 20 years ago [1]. Similarly, although the number of flare-ups increases in the first trimester after childbirth, it does so to a lesser extent and more gradually. One of the factors protecting against the appearance of flare-ups in the postpartum period is the fact that we are now seeing more benign forms of the disease, due to changes in the diagnostic criteria and the use of disease-modifying treatments (DMTs). In addition, this reduction in the number of flare-ups may also be favoured by breastfeeding, especially if it is exclusive [1]. Interestingly, the beneficial effect of breastfeeding appears to go further still, with women who breastfeed for at least 15 months being reported to have a lower risk of developing MS or presenting a clinically isolated syndrome [2]. In patients with high disease activity, however, breastfeeding is best avoided and treatment should be restarted as soon as possible.

Data from the Spanish population indicate that the pregnancy-related results in MS (n = 76) are similar to those in the general population [3]. Nevertheless, a North American cohort study with a much higher number of pregnancies (n = 3,875) showed that while many pregnancy-related aspects

were similar between MS and the general population, the risk of infection and preterm birth was higher in MS [4].

The use of DMTs three months before or during pregnancy does not appear to affect fertility or pregnancy outcomes, according to observations made by a retrospective study in patients who gave birth between 2002 and 2017 [5]. Table I summarises the latest updates presented at the ECTRIMS Congress on pharmacovigilance data related to pregnancy and childbirth for specific DMTs.

With regard to symptomatic treatment for MS patients during pregnancy, this edition of the Congress concluded that it is preferable not to administer any pharmacological treatment and that starting with new drugs should be avoided, especially in the first trimester. If necessary, they should be used in monotherapy and with the lowest effective dose, always taking into account the benefit/risk. Corticosteroids cross the placental barrier and increase the risk of cleft palate and low birth weight when used in the first trimester. Prednisone, prednisolone and methylprednisolone may be given during pregnancy with low foetal exposure (but not dexamethasone or betamethasone), although it is always better to avoid them altogether in the first trimester [6].

Paediatric population

About 5% of MS patients present their first clinical manifestation before the age of 18. Paediatric patients reach higher disability – Expanded Disability Status Scale (EDSS) score of 4 – at an earlier age, present acute axonal degeneration earlier and in more severe forms, and have a higher rate of flare-ups than adults, although they recover more quickly. As in adults, the differential diagnosis is based on evidence of dissemination of lesions in time and in space. Diagnosis in the paediatric population may be more complex, however, due to the significant clinical and radiological overlap of MS and other frequent demyelinating syndromes in childhood.

A considerable amount of progress has been made in this population in the last year. A prospective study of a Spanish cohort, in which 67% of patients were under the age of 12, showed that application of the 2017 McDonald criteria in this group is feasible and allows an early diagnosis. The presence of oligoclonal bands and the absence of anti-MOG antibodies (myelin oligodendrocyte glycoprotein) were useful markers for the diagnosis of MS in the paediatric population [7]. In line with these findings, the presence of anti-MOG antibodies has been associated with acquired demyelinating syndromes other than MS [8].

Another promising biomarker in the paediatric population is neurofilaments light chain, elevated levels of which have also been observed in children with clinically isolated syndrome, and they have been associated with a shorter time to the diagnosis of clinically defined MS. In fact, levels of neurofilaments light chain in children with clinically isolated syndrome and a future diagnosis of MS were significantly higher ($p = 0.007$) than in adults with this syndrome [9].

With regard to DMTs, the results of the Phase 3 clinical trial that has allowed fingolimod to be approved by the Food and Drug Administration (FDA) as the first DMT in the paediatric population were presented at the Congress. The results of this and another prospective study, as well as the measurements of outcomes that are evaluating other ongoing studies, are shown in table II.

Disease-modifying therapies

Efficacy and safety of glatiramer acetate: randomised studies and real-life data

In 1991, a pivotal glatiramer acetate study was started in the United States, which to date represents the longest prospective monotherapy study with a DMT [10]. The aim was to assess the safety of glatiramer acetate (20 and 40 mg/mL) in patients with long-term relapsing-remitting MS (RRMS). The results showed that 50% of the patients continued with glatiramer acetate after 10 years, and 22% after 25 years. The highest percentage of dropouts occurred in the first five years due to adverse effects. Severe adverse effects were experienced by 37.5% of patients and 23.7% suffered reactions immediately after the injection. This study shows that the safety profile of glatiramer acetate is maintained in the long term without any new safety concerns.

Due to the good safety profile demonstrated by glatiramer acetate, other treatments with a similar mechanism of action – follow-on glatiramer acetate product (FoGA) – have emerged in recent years, including the one developed by Synthon. The functional characteristics of the active substances in batches of Synthon's FoGA have been compared directly to batches of glatiramer acetate [11]. These comparisons have shown differences in the genomic profile that support the notion that this is a different biological profile. Synthon's FoGA was also associated with a higher frequency of reactions at

receives financial support that is not conditioned to continuing medical education from TEVA Neuroscience España.

Note:
All the authors in the Post-ECTRIMS group have made a similar contribution to this review.

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Table I. Safety data obtained during and after pregnancy, published in 2018, according to treatment.

	Ref.	Pregnancies (*n*)	Observations	Conclusions
Interferon β	[68]	948 (ER), 875 (NR)	Rate of spontaneous abortions similar to an untreated cohort (10.7% ER and 7.9% NR versus 11.1%) and similar rates of congenital anomalies (1.8% ER and 1.8% NR versus 3.3%) and ectopic pregnancy (0.4% ER and 1.5% NR versus 2.9%)	There was no evidence that exposure to interferon β prior to conception or during pregnancy had any adverse effect on the pregnancy or the neonate
	[69]	1,351 pregnancies with documented results	Congenital malformations (1.6%) and miscarriages (11.8%) were comparable to the estimated rates for the general population	The risk of congenital anomalies and miscarriages didn't increase with interferon β
Teriflunomide	[70]	Of 2,639 pregnancies, 47 were exposed to teriflunomide	After an average exposure to teriflunomide of 45 days during the pregnancy, there were 23 live births (47.9%), 22 voluntary or medical abortions (46.8% versus 10.3% with interferon β/glatiramer acetate and 15.3% without treatment) and two spontaneous abortions (4.2% versus 4.6% with interferon β/glatiramer acetate and 5.1% without treatment)	Despite the recommendations, a high number of pregnancies have been reported in women treated with teriflunomide. The high rate of abortions is consistent with probably unwanted pregnancies
Dimethyl fumarate	[71]	187 patients being treated with dimethyl fumarate, 132 pregnancies	126 (95%) live births, of which eight were preterm, and six (5%) miscarriages (< 22 weeks). There were four (3%) children with congenital malformations	Exposure to disease-modifying therapy during pregnancy appears to be safe, although evidence is limited
Fingolimod	[72]	7 patients, 3 pregnancies	After discontinuing treatment due to a desire to become pregnant, the average number of flare-ups was 5.3 in three women who became pregnant. The EDSS score rose by three points and there was an average increase of 27 new gadolinium-enhancing lesions and 38 new T_2 lesions in the three weeks after delivery. A strong correlation was detected between the lymphocyte count at the start of treatment and the annual rate of flare-ups in the period with no treatment	The rebound effect with fingolimod affected 40% of the women who stopped treatment because they wanted to get pregnant
Natalizumab	[73]	83 women on natalizumab, 92 pregnancies	The rate of flare-ups during and after pregnancy was higher in women treated with natalizumab (36%) than in a historical control group of women who were not treated or were treated with injectable immunomodulators (10%). A longer washout period was the only predictor of flare-ups during pregnancy. Disability increased in 16% of the women after discontinuation of natalizumab and decreased with early reintroduction of the drug	Avoiding the washout period with natalizumab and resuming disease-modifying treatment soon after childbirth may be the best option for reducing the risks associated with motherhood
Alemtuzumab	[74]	58 women, 59 pregnancies	18 pregnancies were exposed to alemtuzumab (< 4 months before the last menstrual period) and the remaining 41 were not exposed (pregnancy > 4 months since the last infusion of alemtuzumab). There were three (7.7%) miscarriages and one voluntary abortion. Of the 36 births to date, four (8.3%) children were born with malformations (three exposed to alemtuzumab and one not exposed). 12 women (21%) developed autoimmune diseases and none of those with a full-term pregnancy had any flare-ups during pregnancy	Alemtuzumab is an interesting option in women with multiple sclerosis and high disease activity who are planning a pregnancy, as it is quickly eliminated after exposure, although its biological effect continues
Ocrelizumab	[75]	108 pregnancies in 106 women with multiple sclerosis (*n* = 68), rheumatoid arthritis and SLE (n = 31); seven patients with no reported indication of ocrelizumab	Of the 68 pregnancies in multiple sclerosis patients, 38 were exposed to ocrelizumab (< 3 months before conception or during pregnancy), 17 were not exposed and 13 could not be evaluated. Preliminary outcomes of 68 pregnancies showed that 20 were ongoing and 14 were spontaneous or voluntary abortions or foetal deaths	The number of pregnancies is too small to be able to draw conclusions. Use of contraceptives is recommended during treatment with ocrelizumab and up to 12 months after the last infusion

EDSS: Expanded Disability Status Scale; ER: European registry; NR: Nordic registry; SLE: systemic lupus erythematosus.

the injection site, an increase in spleen size and elevated levels of anti-glatiramer acetate antibodies. It is important for this information to be taken into account, especially in the context of automatic drug substitutions.

It has also been seen that among patients treated with FoGA, in this case Glatopa ®, 58% discontinued treatment after an average period of 112 days and 43% switched to glatiramer acetate [12]. These figures highlight the importance of understanding a patient's adherence to treatment and changing behaviours when starting a new treatment for MS.

In order to determine the effectiveness and safety of the different formulations of glatiramer acetate in routine clinical practice, studies with real-life data are being carried out. One of them is the Spanish

Table II. Studies of disease-modifying treatments in the paediatric population.

	Treatment arms	Patients (*n*)	Status	Main outcomes / Main efficacy variable
PARADIGMS (phase 3, randomised) [76]	Fingolimod versus interferon β-1a	215 included	Finished	Fingolimod was associated with lower flare-up rates and less accumulation of MRI lesions after two years, but also with a higher rate of severe adverse effects
FOCUS (phase 2) [77]	Dimethyl fumarate	22 included (RRMS)	Finished	Significant reduction in the incidence of hypertensive lesions at T_2 from baseline to the last eight weeks of treatment. Adverse effects and pharmacokinetic parameters were comparable to those observed in adults. No serious adverse effects were related to the treatment
TERIKIDS (phase 3, randomised) [78]	Teriflunomide versus placebo	165 planned (RRMS)	Ongoing	Time to first clinical relapse
CONNECT (phase 3, randomised) [79]	Dimethyl fumarate versus interferon β-1a	142 planned (RRMS)	Ongoing	Percentage of patients without new or increased hypertensive lesions in T_2
LEMKIDS (phase 3, not randomised) [80]	Alemtuzumab	50 planned	Ongoing	Number of new or increased lesions in T_2

RRMS: relapsing-remitting multiple sclerosis.

registry, with 1,331 patients treated with 40 mg/mL of glatiramer acetate. Data at 6 and 12 months since the baseline visit showed that these patients had low disease activity, evidenced by a low rate of flare-ups, low MRI activity and relatively low disability scores (1.9 and 2 at 6 and 12 months, respectively) [13]. The intermediate analyses of another real-life multicentre study (*n* = 1,010) have shown that treatment with 40 mg/mL glatiramer acetate, three times a week, is more effective than treatment with 20 mg/mL in reducing the rate of flare-ups and improving cognitive performance [14].

Along with evidence of the effectiveness of glatiramer acetate in decreasing disease activity in clinical practice, it has been shown that, after an average of seven years of follow-up, this treatment reduced progression on the EDSS by 16.5% [15]. These long-term clinical benefits were also cost-effective, as their cost (£17,841) is well below the cost per quality-adjusted life-year considered effective by the British National Health Service (£30,000) [15].

Discontinuation of immunomodulator treatments

Histological studies of the pathology of MS have shown that active plaques are present during the early years of the disease, while in more advanced stages they rapidly decrease and latent, inactive and shaded plaques predominate instead. From the age of 47, a balance is observed between active and inactive plaques, and latent plaques reach their maximum peak [16].

Consistent with the impact of age on the pathology of MS, the efficacy of DMTs on disability is also influenced by the passage of time. A meta-analysis of 38 randomised clinical trials (*n* = 28,000) showed that the efficacy of DMTs on disability decreased considerably with age [17]. High efficacy treatments (ocrelizumab, mitoxantrone, alemtuzumab, daclizumab and natalizumab) performed better than low efficacy treatments (fingolimod, dimethyl fumarate, interferon β, teriflunomide and glatiramer acetate) in patients under the age of 40.5 years. In addition, the regression model estimated that DMTs would have no benefit in the 'average' patient over 53 years of age. To confirm to what extent it is safe to discontinue DMTs in MS patients over 55 years of age, a randomised clinical trial with 300 patients (DISCOMS) is under way, the results of which are expected to be known by 2021 [18].

There is currently no definitive evidence as to the age or the stage of the disease at which it would be appropriate to discontinue DMTs. The available guidelines [19,20] recommend not dropping out of treatment in the presence of flare-ups and evaluating the age, degree of disability and the activity and progression of the disease in progressive forms. What does seem clearer is that in older patients (> 70 years) who have reached the progressive phase of MS, DMTs can be safely discontinued only if there is no evidence of acute illness in the previous two years [21] or of gadolinium-enhancing lesions in the last three years [22].

Table III. Results of randomised clinical trials with neuroprotective treatments in progressive forms of multiple sclerosis.

	Treatment arms	Patients (*n*)	Outcomes
RENEW (phase 2) [81]	Opicinumab versus placebo	82 (with a first unilateral episode of optic neuritis)	There was no difference between groups in terms of remyelination, defined as the recovery of the latency in optic nerve conduction (assessed with full-field visual evoked potentials)
SYNERGY (phase 2b) [82]	Opicinumab versus placebo	418 (RRMS or SPMS)	Satisfactory tolerability of opicinumab, although the potential therapeutic benefit is unclear
Randomised placebo-controlled pilot study [83]	Lipoic acid versus placebo	51 (SPMS)	68% reduction in the annualised percentage change in brain volume
Double-blind, randomised, placebo-controlled study [84]	MD1003 (high doses of biotin) versus placebo	154 (PPMS or SPMS)	12.6% of patients in the MD1003 group achieved a reversal of disability – defined as a decrease in EDSS > 1 point (> 0.5 for EDSS 6-7) or a 20% decrease in the timed 25-foot walk – versus 0% in the placebo group
MS-SMART (phase 2b) [85]	Amiloride, fluoxetine, riluzole or placebo	445 (SPMS)	No neuroprotective benefits were evidenced with any of the three treatments with different possible therapeutic targets

EDSS: Expanded Disability Status Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

General safety aspects

Progressive multifocal leukoencephalopathy, caused by the JC virus and whose risk increases with the use of certain drugs for MS, continues to be a concern in the therapeutic approach to the disease. It is for this reason that the stratification of the different DMTs according to their risk of progressive multifocal leukoencephalopathy is essential in making decisions about a possible treatment [23]. There are consolidated and validated risk factors that can determine the likelihood of developing progressive multifocal leukoencephalopathy in the patient, such as previous immunosuppression, duration of treatment, serological status for JC virus, CD62L and IgM bands [24]. Although it is not a treatable disease, it has recently been reported that of three patients treated with T cells sensitised against the BK virus (a virus similar to JC), two of them had a favourable prognosis and the other died [23], which is, *a priori*, encouraging.

Regarding immunotherapy, analysis of cerebrospinal fluid samples from MS patients collected immediately before and 12 months after the first use of alemtuzumab showed a decrease in CD4+ T cells after those months, while CD8+ T cells and CD19+ B cells remained stable. CD4+ T cell reduction was accompanied by a high number of monocytes and NK (natural killer) cells and the B lymphocytes/monocytes ratio correlated with disease progression [25].

Moreover, recent cohort studies have offered positive results regarding the safety of DMTs. First, the KPSC and COMBAT-MS cohorts of patients treated with rituximab have shown that mortality rates in clinical practice are lower than previously reported, and that no deaths associated with infusion or suspicion of Kounis syndrome occur [26]. Second, a Swedish cohort of patients treated with rituximab has shown that the incidence of cancer with this treatment is not greater than with fingolimod or natalizumab, and is comparable to the incidence in the general population [27].

Myelin repair

The typical neural damage of MS is caused both by the direct impact of the inflammatory cascade, which is targeted by immunomodulator drugs, and by axonal demyelination. The capacity for remyelination depends on oligodendrocyte precursor cells, which originate in the subventricular area, and varies greatly from one patient to another [28]. One of the most revolutionary techniques for detecting the mechanisms responsible for the differentiation of oligodendrocyte precursor cells and remyelination is the micropillar assay (BIMA). The high resolution of this test makes it possible to observe the length of the membrane envelope from a single two-dimensional image. Through this technique, eight antimuscarinic compounds, approved by the FDA, capable of stimulating the differentiation of oligodendrocyte precursor cells and remyelination have been identified, one of the most important of which is clemastine [29,30].

The remyelinating role of clemastine has also been demonstrated in the ReBUILD clinical trial. In this study, patients with RRMS and chronic demyelinating optic neuropathy treated with clemastine had a reduction in the latency of the P100 evoked visual potential, and this improvement persisted even after treatment was discontinued [31].

Another possible strategy to promote remyelination is through the transplantation of progenitor glial cells obtained from foetal brain tissue, embryonic stem cells or induced pluripotent stem cells. In order to assess the extent to which embryonic stem cell transplantation, using intracranial injections, is effective in myelin repair, a highly complex phase I clinical trial is being designed with 36 patients and is scheduled to begin in 2021 [32].

Progressive forms of multiple sclerosis

Recent studies on the benefit of neuroprotective drugs in progressive forms have yielded inconclusive results in terms of their ability to reduce the level of atrophy and their effect on remyelination (Table III).

One possible explanation for the lack of consistency in the results lies in the methodological limitations inherent in studies conducted with progressive forms. The criteria used to assess treatment effect, such as global atrophy, may not have been the most appropriate. In fact, it has been observed that even when the difference in global atrophy between treated and untreated patients is significant, this difference is minimal, has a large dispersion and its impact on clinical improvement is unknown [33]. Therefore, other biomarkers have been proposed to observe a possible treatment effect more clearly than with global atrophy: magnetisation transfer ratio (myelin integrity marker), cortical thickness, neurofilaments light chain and assessment of slowly evolving lesions [33-36].

In line with previous studies, the most recent work indicates that not all patients with progressive MS benefit from treatments in the same way. The patients with primary progressive MS (PPMS) who respond best have a younger age profile with greater active inflammation [37] and in the case of secondary progressive MS (SPMS) are those with a history of previous flare-ups, rapid evolution, active baseline magnetic resonance imaging, are younger and with a short duration of the disease [38]. However, not all studies find a greater benefit of treatment in SPMS patients with these characteristics [39].

As regards DMTs, favourable results were presented for the efficacy and safety of ocrelizumab [40,41], the first treatment approved for PPMS. The data derived from the open-label extension phase of the ORATORIO study have shown that ocrelizumab reduces disability progression, especially if started early [40].

Stem cell treatment: where we stand and where we are heading

Despite the spectacular advance in the development of new drugs for MS, these treatments are only partially effective in preventing inflammation and tissue damage in the central nervous system, although unable to promote repair processes. Cellular therapies, such as haematopoietic or mesenchymal stem cell transplantation, have been presented as possible candidates in the immunomodulation and repair of the damage to the central nervous system that occurs in MS [42].

Mesenchymal cells

Mesenchymal stem cells are present in most tissues, including bone marrow and adipose tissue, and can be obtained from adults and injected without the need for immunosuppression. They have properties with great therapeutic potential, including immunomodulation and inhibition of T-cell proliferation, neuronal protection, reduction of oxidative stress, remyelination, and restoration of the blood-brain barrier.

The studies published to date on the efficacy and safety of mesenchymal stem cell transplantation in MS are limited and involve few patients, due to the ethical aspects and methodological difficulties that this type of study entails. One of the most promising studies being carried out is the MESEMS study (Mesenchymal Stem Cells for Multiple Sclerosis) [43], consisting in a set of independent clinical trials in nine different countries, including Spain, that follow the same protocol and inclusion and exclusion criteria. The main safety and efficacy variables are the number, time and intensity of adverse effects, and the number of gadolinium-enhancing lesions, respectively. As of October 2018, 120 patients had completed the treatment, four were ongoing and five had not yet received the second infusion. So far, 16 serious adverse effects have been reported, but none related to the treatment [43].

The preliminary analyses of a Phase IIb trial [44] in 48 patients with progressive MS who did not respond to other treatments, in which the efficacy and safety of mesenchymal stem cell transplantation

was evaluated, found that nearly half of the patients (22 out of 48) showed increased disability (EDSS) during the two months prior to initiating treatment, thus indicating high disease activity. After treatment, the mesenchymal stem cell group showed improvements in EDSS compared to the placebo group (at months 1, 3 and 6; $p = 0.0003$) and a lower rate of flare-ups (13.3% versus 36.3% in the placebo group).

Autologous infusion of mesenchymal stem cells derived from adipose tissue was evaluated in a phase I/II safety and feasibility study, in which 34 patients with SPMS were randomised to receive a single low-dose (1×10^6 cells/kg), high-dose (4×10^6 cells/kg) or placebo infusion [45]. After 12 months of follow-up, a single severe, non-transplantation-related adverse effect (urinary tract infection) was recorded in the treatment groups. In terms of the results regarding efficacy, although the analyses did not show any significant differences in EDSS and MRI measures, an inconclusive trend in efficacy was detected. Therefore, although the autologous transplantation of mesenchymal stem cells from adipose tissue has been shown to be safe and viable in SPMS, broader studies conducted in earlier stages are needed to determine its potential therapeutic benefits.

Infusion with mesenchymal stem cells in MS and in other neurodegenerative diseases faces several issues that need to be resolved, such as dosage, number of infusions, cell preparation (e.g. purified homogeneous cell populations, mixed preparations) and the most optimal route of administration.

Haematopoietic cells

The procedure used in the autologous transplantation of haematopoietic stem cells (HSC) allows almost complete destruction of the immune system and its subsequent reconstitution based on HSC, thus inducing long-term suppression of inflammatory activity [46,47]. Depletion of proinflammatory T cells and regeneration of new T cells has been identified as an underlying mechanism for the effect of this type of treatment [48], thereby shifting the balance of the immune system from a proinflammatory state to an anti-inflammatory phenotype [46].

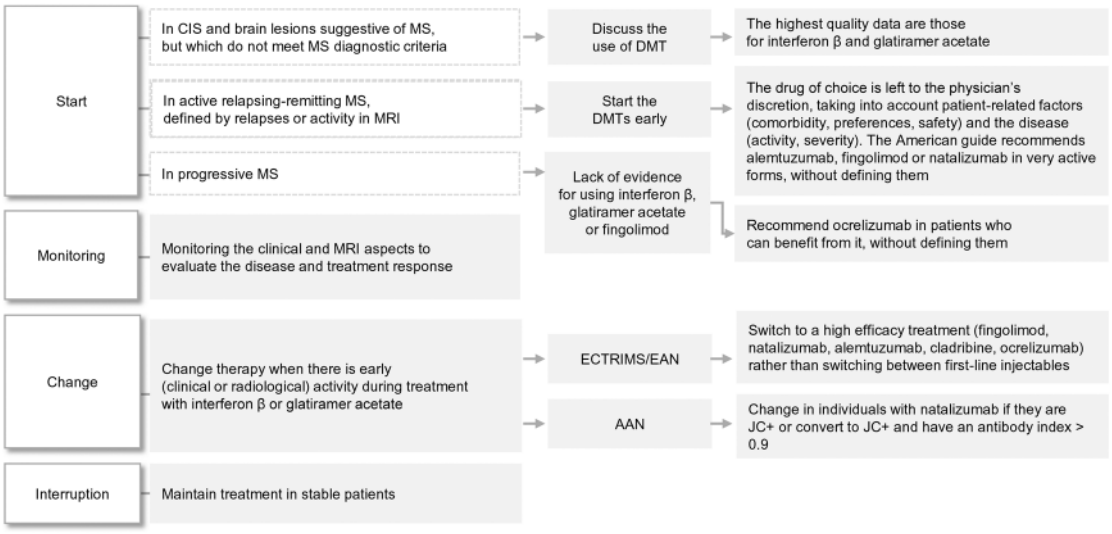
The latest evidence suggests that autologous MHC transplantation reduces the rate of flare-ups and the number of gadolinium-enhancing lesions, improves disability and suppresses the inflammatory activity of MS for 4-5 years in 70-80% of patients with RRMS [49-51]. The percentage of patients who achieve no evidence of disease activity (NEDA) two years after transplantation is considerably higher (70-92%) than with other therapies for MS (13-48%) [47]. However, most studies that have evaluated the efficacy of autologous MHC transplantation are not randomised; indeed, to date, only two studies have compared the efficacy of autologous MHC transplantation against another DMT. The first of them, the ASTIM study, evaluated the effect of transplantation compared to mitoxantrone in patients with aggressive RRMS or SPMS with disease activity assessed by magnetic resonance imaging. Despite the small number of patients ($n = 21$), it was observed that autologous MHC transplantation reduced the number of new lesions in T_2 by 79% after four years, as well as the number of gadolinium-enhancing lesions and the annualised relapse rate. However, there was no difference in the disability progression [52]. The second randomised clinical trial, which involved a greater number of patients ($n = 110$), evaluated whether autologous transplantation of non-myeloablative MHC was superior to DMTs in patients with highly active RRMS [53]. Preliminary results showed that, after an average of three years, treatment failure was significantly higher in the DMT group compared to the group receiving an autologous MHC transplant (60% versus 6%; $p < 0.001$). During the first year, the mean score on the EDSS improved from 3.5 to 2.4 in the autologous MHC transplant group, while it worsened from 3.3 to 3.9 in the DMT group ($p < 0.001$). There were no deaths or grade 4 toxicities in the group of transplant patients.

One of the main problems with autologous MHC transplantation has been the high rate of treatment-related mortality reported in the early studies. Fortunately, optimisation of protocols and patient selection have reduced mortality rates from 3.6% in patients transplanted before 2005 to 0.3% in those transplanted after 2005 [54]. The patient profile that would benefit most from autologous MHC transplantation is a young patient (< 45 years) with inflammatory activity, short duration MS (< 10 years), low to moderate disability (EDSS < 6) and who has failed in no more than two DMTs [47,54].

New guidelines on recommendations for clinical practice

In 2018, the ECTRIMS, in cooperation with the European Academy of Neurology, on the one hand, and the American Academy of Neurology, on the other, simultaneously published a set of guidelines on the use of DMTs in MS [19,20]. In general, these guidelines propose similar recommendations for certain scenarios (Fig. 1) and divergent ones in others, especially in aspects related to pregnancy (Fig. 2)

Figure 1. Similarities between the ECTRIMS/EAN and the AAN guidelines. AAN: American Academy of Neurology; CIS: clinically isolated syndrome; EAN: European Academy of Neurology; MS: multiple sclerosis; JC+: positive for John Cunningham virus; DMT: disease-modifying treatment.



[55]. It should be noted that the content of both guides has been met by some critical voices [56]. One of the aspects to be improved in the guidelines is the lack of any definition of key concepts when making decisions, such as 'very active forms of the disease', 'tolerable clinical or magnetic resonance activity' or 'patients who may benefit'.

In addition, these guidelines do not cover important aspects for disease management such as the relative efficacy of the different therapies, the efficacy of horizontal changes versus escalating therapy, the effectiveness of the different escalating strategies, the long-term progression after beginning therapy with high efficacy drugs, the response to treatments in advanced phases and the efficacy of DMTs in the long term, among others [57].

Rehabilitation of gait dysfunction, fatigue and cognition

In order to update the evidence available on rehabilitation that can be used to guide the decisions made by medical professionals, the Appeco platform (www.appeco.net) has been created. This tool helps to implement effective rehabilitation protocols in clinical practice based on quality evidence.

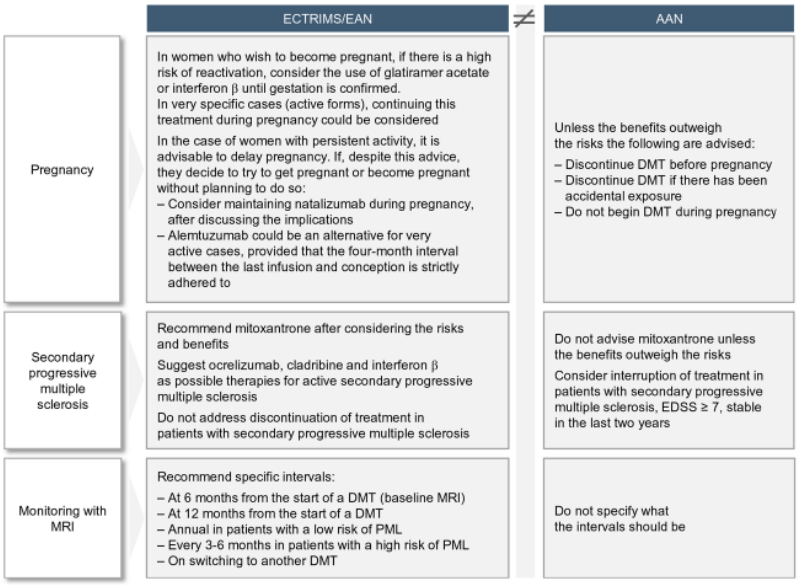
The results derived from the latest studies on the efficacy of rehabilitation in MS show positive results in the impact of cognitive-behavioural therapy on fatigue [58], physical exercise on gait dysfunction [59] and cognitive training and physical exercise in different cognitive domains, such as memory and processing speed, at least in the short term [60-63].

The current technological revolution offers the ideal scenario for the implementation of new rehabilitation techniques. Digital therapeutic tools that facilitate the installation of rehabilitation exercises in electronic devices such as tablets or computers and the possibility of carrying out rehabilitation in a telematic manner have been shown to be effective in improving cognitive functions, without demonstrating any kind of problem regarding therapy adherence [60,62]. Furthermore, robot-assisted training has a positive impact on gait rehabilitation, especially in more disabled patients, although its effectiveness compared to conventional therapy remains to be determined [64].

Unmet social and health needs

As a novelty in this Post-ECTRIMS Meeting, the president of *Esclerosis Múltiple España* gave voice to patients by addressing their unmet social and health needs. First, he highlighted the high rate of access of patients to information without any scientific evidence disseminated on social networks [65]

Figure 2. Differences between the ECTRIMS/EAN and the AAN guidelines. AAN: American Academy of Neurology; EAN: European Academy of Neurology; EDSS: Expanded Disability Status Scale; PML: progressive multifocal leukoencephalopathy; MRI: magnetic resonance imaging; DMT: disease-modifying treatment.



and the need, therefore, to help them discriminate interesting and reliable information. Second, he showed that, although rehabilitation is perceived as beneficial or very beneficial by 39% and 27% of patients, respectively, 57% of all MS patients do not receive rehabilitation, half of them (52%) because their neurologist has never told them about it or because he or she does not advise it [66]. Finally, she explained the difficulty patients have in maintaining employment after being diagnosed with MS, mainly due to the symptoms of fatigue [67].

Final observations

The 34th edition of the ECTRIMS Congress brought with it important contributions in the field of the therapeutic management of MS. In particular, it was noted that the risk of flare-ups during pregnancy and after childbirth has decreased dramatically in recent years. Equally encouraging is the fact that the 2017 McDonald diagnostic criteria and the use of biomarkers in paediatric patients allow progress to be made in early diagnosis, the role of neurofilaments light chain also standing out in this population. The latest studies indicate that, once MS has been confirmed in the paediatric population, it is necessary to be proactive in the therapeutic strategy from the beginning.

Regarding treatments aimed at myelin repair, current results are not conclusive and the role of progenitor glial cell transplantation as a treatment option in remyelination remains to be seen in future studies. Another therapeutic area in which interesting findings were presented was that of autologous MHC transplantation, with the preliminary results concerning efficacy being considerably superior to those of conventional treatments and with fewer safety issues than those traditionally associated with these treatments.

The new clinical practice guidelines in MS were reviewed, the recommendations of which have been limited by the difficulty in translating results from randomised clinical trials to the general population. In fact, it was agreed that these guidelines would need to be updated in the near future based on the findings from clinical trials and from real life, which would thus provide a more global overview of the efficacy of treatments.

All this, together with the development of long-term collaborative registries, technological advances in the field of rehabilitation and the consideration of the patient as a key element in therapeutic decision-making, is expected to ultimately result in better treatment of MS.

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Revisión de las novedades presentadas en el Congreso ECTRIMS 2018: XI Reunión Post-ECTRIMS (II)

Resumen. La reunión Post-ECTRIMS se celebró por undécimo año consecutivo el pasado octubre de 2018 en Madrid, con el objetivo de analizar los avances en esclerosis múltiple destacados en el último congreso anual ECTRIMS. Fruto de esta reunión, formada por los líderes de opinión en esclerosis múltiple de ámbito nacional, se presentan dos artículos de revisión. En esta segunda parte, se incluye el creciente número de evidencias que confirman la seguridad de la exposición a los tratamientos modificadores de la enfermedad en mujeres que planifican un embarazo, y el efecto beneficioso de la lactancia, siempre y cuando la enfermedad no esté muy activa. Se abordan los datos que muestran cómo la aplicación de los criterios de McDonald de 2017 en población pediátrica ha mejorado considerablemente el diagnóstico en comparación con los criterios anteriores. En cuanto a la esclerosis múltiple progresiva, los resultados de los fármacos neuroprotectores son poco concluyentes, pero se proponen biomarcadores para mejorar la evaluación de la respuesta terapéutica. Los estudios sobre tratamientos de reparación de la mielina sugieren que la remielinización en la esclerosis múltiple es posible. De igual manera, se exponen indicios favorables sobre el trasplante de células madre hematopoyéticas, siempre que se seleccione adecuadamente a los pacientes. Por otro lado, se revisan las similitudes y diferencias de las recomendaciones de las nuevas guías de práctica clínica publicadas. Por último, los resultados positivos de la rehabilitación cognitiva y motora con el uso de las nuevas tecnologías vaticinan la incorporación sistemática de estas herramientas en el tratamiento de la enfermedad en un futuro próximo.

Palabras clave. ECTRIMS. Embarazo. Esclerosis múltiple. Población pediátrica. Post-ECTRIMS. Rehabilitación. Tratamientos con células madre. Tratamientos modificadores de la enfermedad.