12th Post-ECTRIMS Meeting: review of the novelties from the 2019 ECTRIMS Congress (II)

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Introduction. Like every year, after the ECTRIMS Congress, renowned Spanish neurologists who are experts in multiple sclerosis presented the main novelties in research in this field at the Post-ECTRIMS Meeting.

Aim. To summarise the content presented at the 12th edition of the Post-ECTRIMS Meeting, which took place in September 2019 in Sevilla and is presented in two parts.

Development. In this second part, the most recent evidence on the use of disease-modifying treatments during pregnancy is presented. Details are provided concerning the results of phase 3 clinical trials conducted to evaluate the efficacy and safety of two potential disease-modifying treatments for relapsing-remitting multiple sclerosis: ponesimod and ofatumumab. For the progressive forms, both available disease modifying treatments and others still in the research phase are reviewed. In the field of stem cell therapies, the article includes the results of the only clinical trial carried out to date comparing patients with relapsing-remitting multiple sclerosis treated with autologous haematopoietic stem cell transplantation and those treated with disease-modifying therapies. There are no important developments as regards symptomatic treatments, although the European Academy of Neurology has published a guide on palliative care. The various sources of information that collect pharmacovigilance data in the post-marketing setting are reviewed.

Conclusions. Patients diagnosed in recent years tend to have less severe multiple sclerosis, probably due to the fact that it is diagnosed in its milder stages together with the steady increase in the number of treatments available.

Key words. Disease-modifying therapy. ECTRIMS. Multiple sclerosis. Post-ECTRIMS. Stem cell therapies. Symptomatic treatment.

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Introduction

The 35th Congress organised by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) was held in Stockholm from 11 to 13 September 2019. Two weeks later, and following what is now a tradition, the 12th Post-ECTRIMS Meeting was held on 27 and 28 September in Sevilla. It was attended by an important number of the neurologists with the most experience in multiple sclerosis (MS) in our country. Its main objective was to gather the latest developments from the ECTRIMS congress and disseminate them through an article, published in two parts. This article is the second part and basically covers the aspects dealt with in relation to the different disease-modifying or symptomatic treatments currently available or being researched.

Pregnancy in the treatment era

Family planning

MS is frequently diagnosed in women of childbearing age. In a recent study [1], up to 10% had had an unplanned pregnancy, while being treated with a disease-modifying therapy. In this scenario, it is essential to ask patients about their plans as regards reproduction and to inform them about all aspects of family planning, including the effects of MS on fertility, pregnancy and the postpartum period (Fig. 1).

Evidence of the protective effect of pregnancy on the occurrence of relapses had been found in historical cohort studies [2]. However, this decrease in the rate of relapses has not been shown to have any effect on disability in the long term. It has recently been seen that pregnancy does not modify

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Funding:
Teva has provided the funding and logistics for the preparation of this article, but has not participated in its conception, writing or any of the decisions made during the process.

Conflict of interests:
O.F. has received payment for consultancy work on advisory boards and as chairman or speaker at meetings, and has also participated or is currently participating in clinical trials and other research projects promoted by Actelion Pharmaceuticals, Allergan, Almirall, Biogen, Bayer, Merck-Serono, Novartis and Teva Neuroscience. R.G. has received payment for medical advice and for writing scientific papers, as well as receiving financial support from Teva, Roche and Novartis to attend scientific meetings. M.L.M.G. has been paid professional fees and for consultancy services by Merck-Serono, Biogen, Novartis, Sanofi-Genzyme, Almirall, Roche and Teva. L.R.T. has been paid professional fees and for consultancy services by Biogen, Novartis, Bayer, Merck-Serono, Sanofi, Teva, Almirall and Mylan. The other authors declare they have no conflict of interests.

Acknowledgements:
Our gratitude goes to Laura Prieto del Val, at Dynamic Science, for technical assistance in the writing of this article.

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

Accepted:
24.03.20.

How to cite this paper:
Fernández O, Aladro Y, Arroyo R, Brieva Ll, Calles-Hernández MC, Carrascal P, et al. 12th Post-ECTRIMS Meeting: review of the novelties from the 2019 ECTRIMS Congress (II). Rev Neurol 2020; 70: 417-29. doi: 10.33588/rn.7011.2020122.

Versión española disponible en www.neurologia.com

the risk of developing MS in patients with clinically isolated syndrome [3]. It could be that, although hormones play an important role in the risk of the disease, their involvement decreases once the disease has started. Other factors, such as the clinical and radiological activity of the disease, and early initiation of disease-modifying therapy, appear to be better predictors of disease progression than pregnancy *per se* [3,4].

Maternal perspective: when to stop and resume treatment and the risk of progression

Data available on 99 pregnancies have shown that the risk of relapses during pregnancy and after childbirth is 17% and 14%, respectively [5], which are figures that are higher than those reported in previous studies. The increased risk of relapses has been observed in patients treated with highly effective disease-modifying therapies (natalizumab and fingolimod) with prolonged washout periods prior to pregnancy [5]. In the case of treatment with natalizumab, the risk of postpartum relapses was significantly reduced with a proactive approach (last infusion after the last menstruation and resuming one month after childbirth), compared to a more conservative approach (last infusion before the last menstruation and resuming one month after childbirth) during six years' follow-up [4]. The risk of relapses during pregnancy and after childbirth was further decreased when treatment with natalizumab was continued after the first trimester of pregnancy compared to discontinuation during the first trimester or before the last menstrual period [6].

Based on the evidence available regarding this reduction in relapses, the UK consensus on pregnancy in MS (Fig. 1) recommends giving the last dose of natalizumab around 34 weeks of pregnancy and restarting it after childbirth (8-12 weeks after the last dose) in order to avoid rebound disease activity [7]. However, it must be borne in mind that we still have little data on the possible effects of this practice on the foetus, and the possibility of it leading to an increased risk of abortion or even teratogenicity cannot be ruled out [6,8].

Neonatal perspective: risks associated with exposure to the drug

The potential risks to the neonate from exposure to the various disease-modifying therapies during pregnancy that were presented during the ECTRIMS 2019 meeting are summarised in Table I.

It should be noted that in July 2019, the European Medicines Agency updated its recommendation on treatment with fingolimod during pregnancy, indicating that it should not be used in women who do not use effective contraception [9]. This recommendation is based on the observation that the risk of congenital defects in infants exposed to fingolimod during pregnancy was twice that of the general population. However, a study comparing the rate of congenital defects in neonates exposed to fingolimod collected in three different databases has shown the importance of methodological differences in this type of registries. The rate of congenital malformations was 2% in the Pregnancy Outcomes Intensive Monitoring programme, 3.7% in the Novartis safety database, and 5.3% in the Multinational Gilenya ® Pregnancy Exposure Registry [10]. In all the registries the absence of prenatal testing or unknown pregnancy outcomes were considered prospective cases; only the Pregnancy Outcomes Intensive Monitoring programme and the Novartis safety database included the cases in which, had prenatal testing been performed, the outcomes would have been normal or unknown.

Disease-modifying therapies in relapsing-remitting multiple sclerosis

Glatiramer acetate: long-term effectiveness and safety

Glatiramer acetate is the only disease-modifying therapy for relapsing-remitting MS that has been studied prospectively for more than a quarter of a century. The extension phase of the pivotal US study aims to assess the long-term efficacy of glatiramer acetate and compare the efficacy of early and late initiation (35-month delay) in patients with relapsing-remitting MS after 27 years' follow-up [11]. The results showed that the annualised relapse rate (ARR), the proportion of patients without relapses and the proportion of patients meeting the criteria for no evidence of disease activity (NEDA)-2 remained relatively stable from year 10 to year 25. The ARR in the first five years and patients meeting NEDA-2 criteria after 10 years' study were significantly lower in early-initiation compared to late-initiation patients.

The greater efficacy of early versus late initiation has also been observed in the extension phase of the GALA study, in which patients received glatiramer acetate 40 mg/mL three times a week [12]. During the seven years of follow-up, there were sig-

nificant differences in the ARR between early-initiation and late-initiation patients (early initiation: 0.26; late initiation: 0.31) and mean time from randomisation to first relapse (early initiation: 4.91 years; late initiation: 4.32 years). Although the proportion of patients who met the NEDA-2 criteria was higher for those with early initiation (49%) than for patients with late initiation (46%), this difference was not statistically significant (p = 0.27). In terms of the safety profile, no new or unexpected adverse effects occurred.

The intermediate analyses of visits 1, 2, 3 and 4 of the 1,334 patients included in the Spanish registry of patients treated with glatiramer acetate 40 mg/mL were presented [13]. In the second year of follow-up, the ARR was 0.1, with most patients having no relapses since the previous visit (95.1%). The mean number of gadolinium-enhancing lesions in T_1 was 0.2 and that of new lesions in T_2 was 0.4. Altogether, 18.8% of patients dropped out of the study due to non-response (46.2%) or adverse effects (32.4%). For the time being, these data support the safety and effectiveness of Copaxone® 40 mg/mL, but a deeper picture will not be possible until the full cohort is available.

Despite the fact that in recent years treatments have emerged with a similar mechanism of action to that of glatiramer acetate (follow-on glatiramer acetate product – FOGA), studies conducted with murine models of MS have observed that levels of glatiramer acetate antibodies are higher in animals treated with FOGA than in those treated with glatiramer acetate, which suggests the existence of differences in peptide composition that may trigger these higher levels of immunogenicity [14]. These differences should be taken into account especially when the automatic substitution of products occurs.

One mechanism of action by which glatiramer acetate may exert its effect is its ability to regulate the expression of the macrophage and the granulocyte colony-stimulating factors. In a study conducted on the animal model of MS, it was found that this is a key proinflammatory factor in the pathogenesis of the disease, and that treatment with glatiramer acetate regulated its expression at both the protein and the mRNA levels [15].

Results from clinical trials and real-life data

Some of the presentations that aroused the most expectation at the ECTRIMS congress were those related to the outcomes of the phase 3 clinical trials OPTIMUM [16] and ASCLEPIOS I and II [17], which were conducted to evaluate the efficacy and safety of ponesimod and ofatumumab, two treatments that have not yet been approved for use in MS. As shown in Table II, both treatments yielded favourable results and so they could be considered for approval soon.

In addition, information was presented on the analyses performed in a subgroup of patients with relapsing-remitting MS from the OPERA I and II phase 3 clinical trials [18], in which the rate of retinal thinning was assessed by optical coherence tomography. The results showed that patients treated with ocrelizumab remained free of changes in the papillary retinal nerve fibre layer (protective effect), whereas in patients treated with interferon β-1a changes did take place and a thinning of this layer of fibres was observed. There was also a low correlation between measures of atrophy and optical coherence tomography, in line with current scientific evidence [19]. These findings are consistent with a possible protective effect of ocrelizumab on optic nerve axonal integrity.

The design of randomised phase 3 clinical trials on MS is becoming increasingly complicated, because it is impossible to include a placebo arm as a control and due to the competitive recruitment of other studies. To overcome these difficulties, a Bayesian approach has been proposed which, al-

Figure 1. Relevant aspects during family planning.

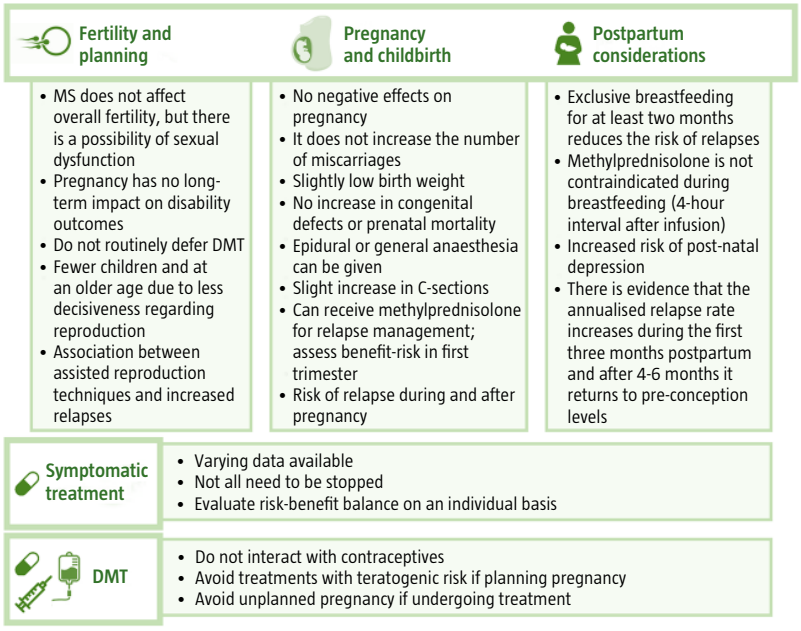


Table I. Effects of exposure to disease-modifying treatment (DMT) during pregnancy and proposed recommendations.

	Exposure in the first trimester	Exposure during pregnancy	Proposed recommendations [a]
Interferon-β	Not associated with negative pregnancy outcomes	Not associated with negative pregnancy outcomes	It is safe to continue until pregnancy May be continued during pregnancy and breastfeeding if the benefits outweigh the risks
Glatiramer acetate	Not associated with negative pregnancy outcomes	Not associated with negative pregnancy outcomes	It is safe to continue until pregnancy May be continued during pregnancy and breastfeeding if the benefits outweigh the risks
Teriflunomide	Possible slight increase in the risk of a miscarriage	Isolated cases after the first trimester	If pregnancy is desired, stop treatment, use contraception during the accelerated elimination process until a concentration level of < 0.02 mg/L is reached in two measurements made with a 14-day interval between them
Dimethyl fumarate	Not associated with negative pregnancy outcomes	Isolated cases after the first trimester	Contraception during treatment If pregnancy is desired, discontinue treatment and the contraceptive at the same time Discuss whether to switch to an alternative treatment if planning to become pregnant Interrupt during breastfeeding, as the effect is unknown
Fingolimod	Possible slight increase in the teratogenic risk	Limited information. Potential risks cannot be ruled out	If a pregnancy is planned, discontinue two months in advance and discuss alternative treatments In the event of an unplanned pregnancy, discontinue immediately Discontinue during breastfeeding
Natalizumab	Slightly increased risk of miscarriage and teratogenicity cannot be ruled out	Haematological abnormalities	Continue after conception and during pregnancy only after a risk-benefit assessment Complete blood count in the newborn if there has been exposure
Alemtuzumab	Slightly increased risk of miscarriage cannot be ruled out	Not available	Use contraceptives until four months after the last cycle. Perform pregnancy tests before each cycle. In the event of pregnancy, discontinue Monitoring of possible secondary autoimmune diseases and monthly follow-up of complete blood count and kidney function in the mother Monitor lymphocytes and possible secondary autoimmune diseases in the exposed newborn Discontinue during breastfeeding
Ocrelizumab	Not associated with negative pregnancy outcomes	Preterm birth Low weight Potential depletion of B lymphocytes	Contraception for at least six months after last infusion according to FDA and after 12 months according to the EMA Monitor B lymphocyte depletion in neonates. If levels are low, defer vaccination Discontinue during breastfeeding
Rituximab	Not associated with negative pregnancy outcomes	Preterm birth Low weight Transient depletion of B lymphocytes and lymphopenia	Contraception for at least 12 months after the last infusion Monitor the depletion of B lymphocytes in newborns. If levels are low, defer vaccination Discontinue during breastfeeding
Cladribine	Potential risk of teratogenicity cannot be ruled out	Not available	Use for up to six months after the last cycle Perform pregnancy tests before each cycle Discontinue six months before conception Consider seeking embryotoxicological advice in case of exposure Discontinue during breastfeeding

EMA: European Medicines Agency; FDA: Food and Drug Administration. [a] The recommendations proposed in this table are a synthesis of the recommendations published in the UK consensus on pregnancy in MS [7] and the recommendations included in Hellwig's oral presentation at ECTRIMS 2019 [68].

though well known, is not commonly used. This method would incorporate the information previously obtained in phase 2 into the design of phase 3, which would reduce the required sample size by up to 65% [20].

Although randomised clinical trials are considered the best tool to determine the efficacy of treatments in relapsing-remitting MS, the usual duration of clinical trials represents only a proportion of the disease and the treatment the patient receives. Differences between the efficacy of a treatment in a clinical trial and the effectiveness it demonstrates in actual clinical practice mean that it is difficult to make objective decisions on the risk-benefit bal-

Table II. Results of the OPTIMUM and ASCLEPIOS I and II clinical trials.

	Treatments	Patients (*n*)	Primary endpoint	Secondary endpoint	Outcomes
OPTIMUM [16]	Ponesimod 20 mg versus teriflunomide 14 mg	Ponesimod: 567 Teriflunomide: 566	ARR at 108 weeks	Changes in fatigue measured by the FSIQ-RMS from the baseline visit to week 108 Number of active gadolinium-enhancing lesions in T_1 at week 108 Time to confirmed disability progression measured at 12 and 24 weeks	Ponesimod reduced the ARR by 30.5% more than teriflunomide [a] Ponesimod was better than teriflunomide in fatigue (mean difference: −3.57) [a] Ponesimod reduced the number of new inflammatory lesions by 56% more than teriflunomide [a] Confirmed disability progression at 12 and 24 weeks was 17% and 16% respectively with ponesimod (less than with teriflunomide) Adverse effects with ponesimod were not serious. Hepatobiliary disorders/liver test abnormalities (22.7%), hypertension (10.1%) and pulmonary events (8%) were recorded
ASCLEPIOS I and ASCLEPIOS II [17]	Ofatumumab 20 mg versus teriflunomide 14 mg	ASCLEPIOS I: Ofatumumab: 465 Teriflunomide: 462 ASCLEPIOS II: Ofatumumab: 481 Teriflunomide: 474	ARR up to 2.5 years	Worsening of the confirmed disability at three and six months measured with the EDSS every three months until 2.5 years Improvement of confirmed disability at six months measured with the EDSS every three months until 2.5 years Gadolinium-enhancing lesions in T_1 and in T_2 (new or augmented) measured annually until 2.5 years Levels of neurofilaments light chain every three months up to 2.5 years Brain volume loss measured annually up to 2.5 years	Ofatumumab reduced the ARR by 50.5% (ASCLEPIOS I) and 58.5% (ASCLEPIOS II) more than teriflunomide [a] Ofatumumab reduced the risk of confirmed disability by 34.4% and 32.5% at three and six months, respectively, compared to teriflunomide [a] Ofatumumab increased the probability of an improvement in confirmed disability at six months by 35.2% more than teriflunomide Ofatumumab reduced the number of gadolinium-enhancing lesions in T_1 by 97.5% (ASCLEPIOS I) and 93.8% (ASCLEPIOS II) more than teriflunomide [a] Ofatumumab reduced the number of lesions in T_2 (new or increased) by 82% (ASCLEPIOS I) and 84.5% (ASCLEPIOS II) more than teriflunomide [a] There was no difference between treatments in terms of brain volume

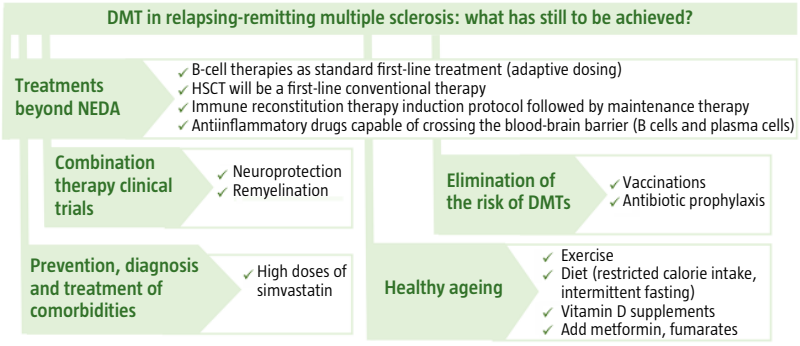
ARR: annualised relapse rate; EDSS: Expanded Disability Status Scale; FSIQ-RMS: Fatigue Symptoms and Impacts Questionnaire–Relapsing Multiple Sclerosis. [a] Statistically significant difference.

ance. Real-life studies help assess the variability of treatment response [21] and complement the information obtained from clinical trials [22] with a larger number of patients. One example of this is a study that included a cohort of more than 15,000 patients with relapsing-remitting MS and more than 10 years' follow-up from the Big MS Data network, which represents a total of 312,040 scores on the Expanded Disability Status Scale (EDSS). The study confirmed that exposure to disease-modifying therapies decreases the risk of confirmed disability progression at 12 and 24 months (though not at three months), as well as the likelihood of achieving scores of 4 and 6 on the EDSS in the long term [23].

It should be noted, however, that real-life data studies are not without their limitations, which include biases, incomplete data, inconsistent definitions, differences in the quality of different databases and systematic inconsistencies between health settings [24]. Knowing these limitations is essential to be able to improve the study design, select the most appropriate statistical method and encourage the inclusion of analyses with data mining, machine learning and simulation. These measures would make it easier to obtain quality information that reflects more reliably the actual effect of the various disease-modifying therapies on patients.

While it is true that in the last year significant progress has been made in the treatment of MS, several goals remain to be achieved [25], as shown in Figure 2. Giovannoni proposed a series of clinical trials to evaluate the following comparisons: ofatumumab versus ocrelizumab (OVO study), double dose ocrelizumab (1200 mg) versus standard dose (600 mg) (DODO study), standard dose interval versus adaptive dose interval (ADIOS study) and maintenance with teriflunomide (iTeri study) or with BTK inhibitor (iBrut study) after induction therapy [25].

Figure 2. Milestones still to be accomplished in the use of disease-modifying therapy in relapsing-remitting multiple sclerosis.



Disease-modifying therapies in progressive multiple sclerosis

Available treatments: identification of candidate patients

The concept of progressive MS has evolved in recent years from being categorised as primary progressive MS and secondary progressive MS to being classified according to the presence, or not, of activity and whether or not progression occurs, thus conceptualising it in a more unitary manner. This classification has been made possible by the advances in the understanding of the pathophysiology underlying MS in its different courses. There are different pathogenic mechanisms at different stages of the disease [26], but they also overlap to a large extent [27]. Although there is still a long way to go, the discoveries made in recent years [28] have led to the approval in some countries of effective treatments for the progressive course, such as siponimod, ocrelizumab and cladribine. Siponimod is expected to become available in Spain in the near future.

The availability of these and other possible treatments for primary progressive MS and secondary progressive MS, still undergoing research (Fig. 3), highlights the need to reach a consensus on the definition of secondary progressive MS and to achieve earlier identification of patients who are starting to find themselves on a progressive course. Some patients who apparently have clinically isolated syndrome without recovery could in fact be on a progressive course, and so, in addition to performing the corresponding scans and using the data collected in electronic devices, the patient's medical history is crucial [29]. Once the progressive course has been identified, it is important to specify which patient population could benefit most from the treatments, since some indices, such as age, comorbidities, duration of progression, and previous and current inflammatory activity, could modulate this effect [30]. For example, the phase 3 clinical trial EXPAND showed that patients with secondary progressive MS who benefited most from siponimod were those with previous relapses, a rapid course of progression, and baseline MRI activity [31], suggesting that the drug works best when there is an inflammatory component. It should also be noted at this point that siponimod delayed the progression of physical disability and the need for a wheelchair even in patients starting out from an EDSS score above 6.5.

In the case of ocrelizumab, the phase 3 extension of the ORATORY trial has shown that the confirmed progression of disability after six and a half years was lower when treatment was started earlier. Patients with primary progressive MS who were treated with ocrelizumab from the outset showed a 42% reduction in the risk of being confined to a wheelchair compared to the placebo group who switched to ocrelizumab 3-5 years later [32].

Designing clinical trials: endpoints

In order to advance in the development of treatments for the progressive phases, several aspects have been highlighted that need to be harmonised when designing clinical trials. There are differences among the studies in terms of the eligibility criteria, the years since diagnosis and the time at which the confirmed disability progression is evaluated.

Some of the variables proposed for measurement in phase 2 clinical trials are brain atrophy (for which a minimum follow-up period of 18 months is recommended), spinal atrophy, neurofilaments light chain, clinical variables such as Timed 25-Foot Walk and cognition. As for the design of phase 3, the EDSS has been considered to be the variable that best evaluates the effectiveness of the treatments. However, we know that it is not free of limitations, so it is increasingly common to use composite variables that, in addition to the EDSS, include other tests, such as the Timed 25-Foot Walk, the Nine Hole Peg Test or the Symbol Digit Modalities Test [33].

Stem cell therapies: efficacy and safety

Haematopoietic stem cells

Autologous haematopoietic stem cell transplanta-

tion (AHSCT) is a multi-step procedure that allows the near destruction of the immune system and its subsequent reconstruction from haematopoietic stem cells. Most of the results regarding the efficacy of AHSCT, although promising, have come from clinical trials which included a placebo group, but not a disease-modifying therapy group [34,35].

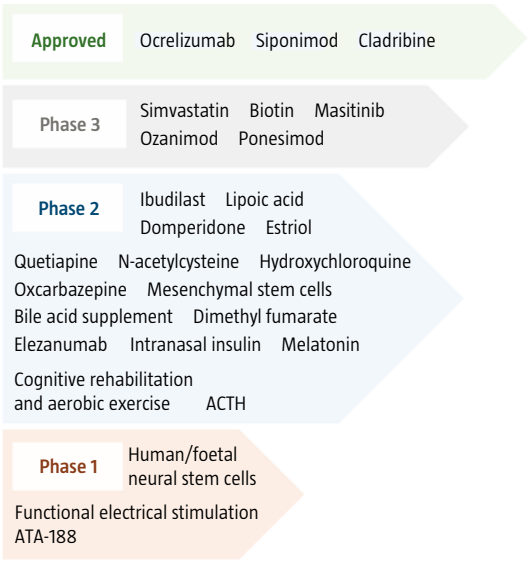
To date, only one crossover clinical trial has been published in which patients are randomised to receive non-myeloablative AHSCT together with cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (6 mg/kg) or disease-modifying therapy (except alemtuzumab and ocrelizumab, for safety reasons) [36]. The patients included in the trial had relapsing-remitting MS, EDSS between 2 and 6 points, at least two relapses in the last year under treatment with disease-modifying therapies, and treatment with disease-modifying therapies for a minimum of 6 months. The results of this study were excellent. Of the 110 patients included, disease progression was detected in 3 and 24 patients in the group with AHSCT and disease-modifying therapies, respectively. During the first year, the mean EDSS score improved in the group with AHSCT and worsened in the group with disease-modifying therapies (p < 0.001), and the ARR decreased by 97.5% more in the group with AHSCT (0.02) than in the group with disease-modifying therapies (0.78). There were no deaths or grade 4 toxicities in the AHSCT group.

Mesenchymal stem cells

Mesenchymal stem cells act through different mechanisms of action, such as decreasing the proliferation of microglia, neural protection against degeneration, promoting remyelination, inhibiting the astrocytes involved in glial scars, suppressing inflammation and inhibiting the proliferation of T and B cells.

The MESEMS phase 2 trial is a multicentre, randomised, double-blind, crossover study comparing patients receiving an autologous bone marrow mesenchymal stem cell transplantation against a placebo group, in which Spain participated [37]. Results in 144 patients (relapsing-remitting MS: 92; primary progressive MS: 17; and SPMS: 31) have shown that the reduction in the number of gadolinium-enhancing lesions was similar in both groups (primary endpoint), but the ARR was reduced by up to 36% more in the mesenchymal stem cell group than in the placebo group (p = 0.13) (secondary endpoint). Mesenchymal stem cell therapy has a good safety profile, as there was no difference in the number of adverse effects between treated and untreated patients in the first 24 weeks [37].

Figure 3. Treatments that have been approved or are under development for progressive forms of multiple sclerosis.



This good safety profile has also been observed in a phase 2b trial in 48 patients with secondary progressive MS, where intravenous and intrathecal administration was safe and no serious adverse effects were observed [38]. Additionally, 58.6% of patients treated with intrathecal mesenchymal stem cells and 40.6% of those treated with intravenous mesenchymal stem cells exhibited NEDA for six months, compared to 9.7% in the placebo group. Particularly significant benefits were also observed in the group treated with intrathecal mesenchymal stem cells in relation to the T_2 lesion load, the retinal nerve fibre layer in the optical coherence tomography scan, the Timed 25-Foot Walk, the Nine Hole Peg Test and the cognitive tests. A phase 3 trial is needed to confirm these results.

Pharmacovigilance in the post-marketing setting: opportunities and lessons learned

Clinical trials are insufficient to establish the full safety profile of a drug and to detect rare adverse effects and so other sources are needed to identify them. Health-related administrative data can be a powerful source of information in research, and are increasingly used for pharmacovigilance in MS. These data encompass the information generated

in routine clinical practice, including hospital, physician and pharmacy data. An exemplary safety data collection system is the one implemented in the state of British Columbia in Canada, where data of various kinds (prescription, hospital, medical claims, vital statistics, civil, demographic and clinical records) are collected from a cohort of individuals with MS exposed or not to disease-modifying therapies [39]. In Spain, the facilities exist to allow collection of this information, but it is not put into practice. Currently, the different Autonomous Communities or hospitals do not share these data. This lack of coordination and of information management is both a challenge and an opportunity to change the situation and invest the resources needed to be able to analyse the data for research purposes.

Another way to collect information on drug safety is through registries [40]. There are currently 19 registries of patients with MS in Europe (together with MSBase) [41]. The European Medicines Agency has launched an initiative to pool efforts and enhance the usefulness of the registries, which four European registries and MSBase have joined [42]. There are also cohort studies dedicated to collecting the long-term safety profile of a particular disease-modifying therapy, such as oral cladribine [43], and teriflunomide in pregnancy [44,45].

The safety profile of biological drugs can be altered over time, due to their high sensitivity to changes in production. These changes are more common than expected and, although relatively small and carried out with the intention of improving the properties of the drug, they are not all harmless [46]. Attention should therefore be paid to this 'biological evolution' in which sequential changes in production may cause the properties of the current biological to differ from the original and the impact on safety is unknown.

Optimising the long-term benefit of treatments

Real-life data studies [47,48] and nine-year extension periods of clinical trials with alemtuzumab (CARE-MS I and CARE-MS II) [49,50] have shown that long-term outcomes are more favourable in patients treated with early, highly effective disease-modifying therapies than in those who followed a escalating therapy strategy, suggesting that induction therapy should take precedence over the escalating type [51]. However, there are divergent views that point in the opposite direction and suggest that therapeutic escalation should be favoured if carried out at an early stage. This is based on the fact that treatments such as glatiramer acetate, fingolimod, dimethyl fumarate and natalizumab are effective, as well as safe and more economical [52].

A relevant aspect when choosing a disease-modifying therapy in clinical practice and designing clinical trials is age. Patients over the age of 40 when starting disease-modifying therapy are at increased risk of disability progression, regardless of other disease characteristics [53]. In addition, the more years of the disease course there is exposure to treatment, the lower the risk of progression will be [54].

Symptomatic treatment

In recent years, a great deal of progress has been made in the development of disease-modifying therapies in MS, resulting in a decrease in the ARR and the disability progression. Symptomatic treatment remains an open challenge, due to the wide variety of symptoms, their possible interactions, associated comorbidities and the poor understanding of the underlying pathophysiology. In addition, it is difficult to assess and quantify the severity of these symptoms or they are not defined with precision [55]. Applications on mobile devices are an appropriate tool for assessing symptoms and an alternative to the low reliability of self-reported data on, for example, mobility measures [56]. The MSCopilot MS self-assessment application, which combines four tests (gait, manual dexterity, cognition and low-contrast vision), has proved not to be inferior to the Multiple Sclerosis Functional Composite [55].

Non-invasive brain stimulation techniques

Neuromodulation through non-invasive brain stimulation techniques was presented as a potential approach for the treatment of the symptoms of MS, although there were no major developments in this area. Repetitive transcranial magnetic stimulation has already been approved by the American Food and Drug Administration for the treatment of drug-resistant major depression, migraine and obsessive-compulsive disorder. Research is being conducted on transcranial direct current stimulation to improve the sensory or motor symptoms associated with MS, such as chronic pain, fatigue, cognitive impairment and gait deterioration [57]. More studies are needed to define the most appropriate stimulation technique and doses, and to confirm whether the improvement persists in the long term.

Figure 4. Recommendations from the European Academy of Neurology guidelines on palliative care. + very low; ++ low; +++ moderate; ++++ high.

Clinical questions	Recommendations	Quality of the evidence
1 Symptomatic treatment	• To be defined. Possibility of including the use of cannabinoids	++
2 Multidisciplinary rehabilitation	• Should be offered to patients with severe MS • Rehabilitation can be offered at outpatients, at home or both	++
3 Planning	• Early discussion, with care planning, should be offered to patients, especially with impaired communication and cognition • There should be regular communication about the future progression of MS with patients and families	+
4 General (4) and specific (5) palliative care	• Patients with severe MS should be offered PC at home, by a healthcare professional with basic knowledge and skills in PC (general PC) or by a multidisciplinary team of PC specialists (specific PC)	+
5	• Patients with severe MS should be offered PC at outpatients. The patient's preferences, the conditions and the availability of PC services should be taken into consideration	++
6 Intervention with caregivers: educational (6) and emotional support (7)	• Caregivers of people with severe MS should be offered care education and training programmes • Caregivers of patients with severe MS should be offered emotional and practical support • The programme mode (hospital, home or online) should be offered according to the caregiver's preferences in both cases	+
7		
8 Intervention with healthcare professionals	• The principles of PC should be included in the training and continuing education of neurologists and other professionals involved in the care of these patients • The principles of MS patient management should be included in the training and continuing education of PC specialists	+
9		
10 Discussion about the desire to die	• Encourage patients to discuss their wishes about future care, including restriction of treatment/interventions and the desire to hasten death • Healthcare professionals should be aware of the possibility that the patient may wish to die, and encourage discussion of this issue and the most appropriate way of managing it	+

Palliative care

A proposal has been made for a comprehensive integration of neurology, rehabilitation and palliative services through an interdisciplinary and multiprofessional team [58]. The European Academy of Neurology has published a guide on palliative care in severe MS. To develop the guide, 10 questions were posed based on information gathered through literature searches and meetings with patients and caregivers. A survey of patients and caregivers in eight European countries, including Spain, was also conducted [59]. Figure 4 shows a summary of the recommendations included in this guide.

Although patients with advanced MS and high disability have few therapeutic options open to them, they see the neurologist as having three main roles: a source of hope and information on therapeutic advances, an educator about the disease and its treatment, and a source of support [60].

Has MS become a milder disease?

Various patient registries have shown that patients diagnosed in recent years tend to have less severe MS, regardless of the duration of the disease, compared to patients diagnosed further back in time [61]. This could be partly due to the change in diagnostic criteria and the fact that MS is now recognised from the mildest stages [62]. The availability of treatments has also undoubtedly played an important role. Patients treated with disease-modifying therapies take longer than those without treatment to reach an EDSS disability of 6 and to progress to secondary progressive MS [47,63,64]. The risk of mortality is also lower in treated patients and it decreases by up to 32% when they have been exposed to interferon β for a long time [65].

The incidence of MS has stabilised, but the prevalence increased by 10% in several regions from 1990 to 2016 [66]. This increased prevalence may be reflecting the ageing of the population and the overall improvement in survival [67].

Conclusions

The availability of more and more disease-modifying therapies poses new challenges when it comes

to defining the treatment regimen for patients. In the case of pregnant women or patients planning to become pregnant, emphasis was placed on the fact that they should be asked about their reproductive plans and that informed decisions should be made. Delaying or discontinuing disease-modifying therapy due to pregnancy could deprive patients of the benefit of treatment and expose them to a potential risk of relapses and disease progression, especially after childbirth. The Association of British Neurologists has published a consensus guide which offers recommendations based on current evidence on treatment and pregnancy.

Regarding disease-modifying therapies for relapsing-remitting MS, the results of the studies reinforce the long-term effectiveness of glatiramer acetate. The phase 3 clinical trials OPTIMUM and ASCLEPIOS I and II, which evaluate the efficacy and safety of ponesimod and ofatumumab, respectively, yielded favourable results. Although there is no agreement on which therapeutic strategy (induction or escalation) leads to better outcomes, there is consensus that treatment needs to start as early as possible.

Therapeutic options for progressive MS remain very limited. Siponimod, ocrelizumab and cladribine have been approved in different parts of the world, and several studies are under way with other drugs. Since the number of disease-modifying therapies available for progressive forms could increase in the coming years, it is important to work on the early identification of these patients, on the definition of the most likely profiles that could benefit from such therapies and on more precise measurement of the effectiveness of the treatments.

Available evidence on stem cell therapies shows that mesenchymal stem cell treatment has a good safety profile. Studies with a larger sample size and an active comparator are needed to provide more evidence of efficacy. On the other hand, low intensity AHSCT has shown that, if patients are selected well, we can obtain very high efficacy accompanied by a good safety profile. Although more studies are needed to confirm these results and to evaluate their effectiveness against other disease-modifying therapies, such as alemtuzumab and ocrelizumab, the possibility of treating patients with AHSCT seems to be getting closer.

Real-life studies help assess the variability of treatment response and complement the information obtained from clinical trials with a larger number of patients. In terms of pharmacovigilance in the post-authorisation setting, health-related administrative data and patient registries have great potential. Several successful initiatives are already under way, such as the one carried out in British Columbia. Willingness and coordination between centres are needed to maximise and exploit this potential.

Advances in symptomatic treatments are limited. The use of digital and remote communication technologies is presented as a tool to identify symptoms earlier and more accurately, and as a way to personalise symptomatic therapy. A truly multidisciplinary and multi-professional approach is required, including rehabilitation and palliative care for symptomatic management. The European Academy of Neurology has published a guide on palliative care in severe MS that was developed in collaboration with patients and their caregivers.

In general, the prognosis of MS has improved, as the disability progression time has been delayed. Part of this improvement is attributed to treatments and early identification of the disease and so MS can be expected to become a milder disease as new therapies and diagnostic biomarkers become available.

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XII Reunión Post-ECTRIMS: revisión de las novedades presentadas en el Congreso ECTRIMS 2019 (II)

Introducción. Como cada año, tras la celebración del Congreso del ECTRIMS, reconocidos neurólogos españoles expertos en esclerosis múltiple expusieron en la Reunión Post-ECTRIMS las principales novedades en investigación en este ámbito.

Objetivo. Sintetizar el contenido presentado en la XII edición de la Reunión Post-ECTRIMS, que tuvo lugar en septiembre de 2019 en Sevilla y que se presenta en dos partes.

Desarrollo. En esta segunda parte, se exponen las evidencias más recientes sobre el uso de tratamientos modificadores de la enfermedad durante el embarazo. Se detallan los resultados de ensayos clínicos en fase 3 en los que se ha evaluado la eficacia y la seguridad de dos potenciales tratamientos modificadores de la enfermedad para la esclerosis múltiple remitente recurrente: ponesimod y ofatumumab. Para las formas progresivas, se revisan los tratamientos modificadores de la enfermedad disponibles y en investigación. En el ámbito de las terapias con células madre, se incluyen los resultados del único ensayo clínico hasta la fecha que compara a pacientes con esclerosis múltiple remitente recurrente tratados con trasplante autólogo de células madre hematopoyéticas y a los tratados con tratamientos modificadores de la enfermedad. No hay grandes novedades sobre tratamientos sintomáticos, aunque la Academia Europea de Neurología ha publicado una guía sobre cuidados paliativos. Se revisan las distintas fuentes de información que recogen datos de farmacovigilancia en el entorno poscomercialización.

Conclusiones. Los pacientes diagnosticados en los últimos años tienden a tener una menor gravedad de la esclerosis múltiple, probablemente debido al diagnóstico desde sus estadios más leves y al continuo aumento de tratamientos disponibles.

Palabras clave. ECTRIMS. Esclerosis múltiple. Post-ECTRIMS. Terapias de células madre. Tratamiento modificador de la enfermedad. Tratamiento sintomático.