Review of the novelties presented at the XXVI Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (II)

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Summary. The new insights presented at European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in the city of Gothenburg, Sweden, in October 2010, have been summarized at the third edition of Post-ECTRIMS meeting held in Madrid in November 2010. Encouraging findings from the 5-years follow up extension from PreCISe study confirm the benefit of early treatment with glatiramer acetate in patients with clinically isolated syndromes (CIS) against the conversion to clinically definitive multiple sclerosis and cerebral atrophy with an adequate safety and tolerability. Regarding treatment decision with escalation or induction therapy, different strategies have been proposed depending on to the characteristics of the individual patient with CIS. Findings from several of the reported studies have revealed the favorable role of combined therapy on relapse rate but not on magnetic resonance parameters in patients with recurrent-remittent multiple sclerosis. Novel therapies such as alemtuzumab, daclizumab ofatutumab or ocrelizumab have shown promising findings regarding efficacy. Nevertheless, safety findings for these emerging therapies have detected some severe adverse events, the main ones being potentially fatal opportunistic infections such as progressive multifocal leukoencephalopathy (PML) caused by JC virus, mainly linked to natalizumab treatment. In this regard, clinicians will face the assessment of he benefit-risk ratio when deciding on the adequate treatment for each patient in the clinical setting. In this regard, determination of antibodies to JC virus by a novel two-step enzyme-linked immunosorbent assay (ELISA) could provide clinicians with a useful tool to stratify PML risk in patients. Regarding non pharmacologic therapies, behavioral intervention has emerged as an effective therapy in the treatment of depression in multiple sclerosis, showing additional benefits on fatigue, disability and adherence to treatment.

Key words. Monoclonal antibodies. Multiple sclerosis. Safety. Treatment.

Treatment Strategies for multiple sclerosis

Early treatment strategies for multiple sclerosis

In recent years, a debate has existed regarding the timing of the onset of multiple sclerosis (MS). Probably the greatest advancement in MS made in the last ten years has been related to the early treatment of this disease. Thanks to new techniques, it is possible to diagnose MS faster, which greatly impacts the timeframe for starting treatment.

Various arguments have been made in favour of treating clinically isolated syndromes (CIS), due in great part to the presence of irreversible axonal damage in the early stage of the disease. In this sene, all the studies performed up to now are in favour of an early therapy. In this context, the PreCISe study [1] represents an important example of the significance of early treatment.

Dr. Comi presented the results of five years of the extension of the PreCISe study, whose main goal was to evaluate the long-term effects of early versus late treatment with glatiramer acetate (Copaxone ®) in CIS patients.

The PreCISe trial [1] was a three-year, multicentre, randomised, placebo-controlled, double-blind trial in which 481 randomised patients were divided into two parallel groups, with 243 patients treated with 20 mg glatiramer acetate and 238 patients treated with placebo. The patients received clinical and radiological follow-up. All of the patients who suffered a second exacerbation were

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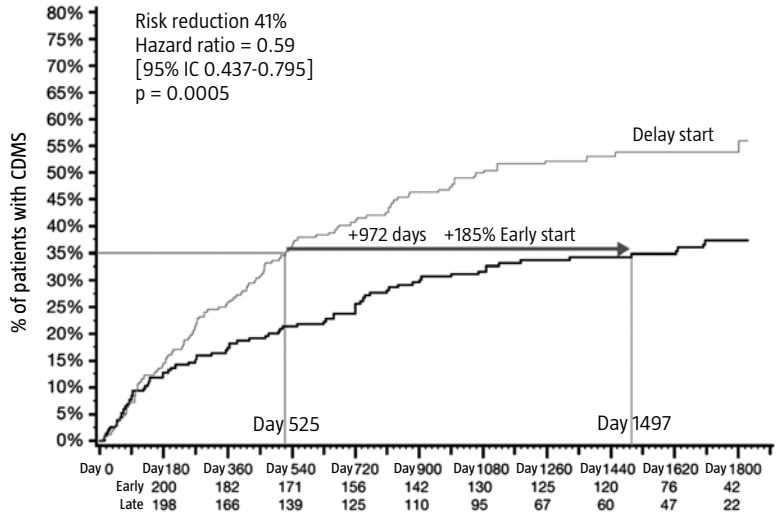
Figure 1. Percentage of patients who become clinically defined multiple sclerosis in the five-year period covered by the PreCISe study (presented by Dr. G. Comi at ECTRIMS 2010).



given the choice of being treated with glatiramer acetate and continuing on the trial, as open label in this case. Those patients who do not had another exacerbation, but who had completed three years of treatment, were given the option to continue treatment with glatiramer acetate for two more years. Therefore, after conversion to clinically definite MS (CDMS) or after three years, whichever occurred first, both treatment groups were assigned to active treatment with 20 mg glatiramer acetate for a total observation period of five years.

Thus, 198 patients with early treatment and 211 patients with late treatment were included in the extension study; the basal characteristics of the two groups were well-balanced. For patients with a late start of treatment, including those patients randomly assigned to the placebo group who began treatment with glatiramer acetate when they suffered a second episode or completed three years of treatment, approximately 50% underwent conversion. However, in the early treatment group, approximately 33% of the patients converted. It should be noted that, once patients were treated with glatiramer acetate, the difference in the conversion rate between the two groups was insignificant, with 6.85% in the late treatment group versus 9.09% in the early treatment group. The key outcomes of the five-year study were a highly significant reduction in the risk of conversion to CDMS after five years of follow-up, with a delay of 972 days with early treatment versus late treatment and a risk reduction of 41% (hazard ratio = 0.5; 95% confidence interval = 0.437-0.795; p = 0.0005). In addition, it is important to mention that there was smaller brain volume loss in the early treatment group (p = 0.0209). With respect to the Expanded Disability Status Scale (EDSS), only 21% of patients showed confirmed progression in the five-year follow-up, and there were no significant differences between the groups, with 20.5% of patients with early treatment compared to 21.4% with late treatment experiencing progression in their EDSS scores (Fig. 1).

With respect to safety, differences have not been found between the incidence of adverse events for early and late onset of treatment. The most frequent adverse events related to glatiramer acetate were local reactions at the injection site. Serious adverse events were reported in 28 and 32 individuals in the early and late treatment groups, respectively. There were no significant differences between the groups in terms of laboratory parameters, vital signs or electrocardiograms.

Finally, the results of the PreCISe study have shown a persistent benefit of glatiramer acetate in preventing conversion to CDMS at five years of follow-up and a favourable effect of early treatment on brain atrophy. These findings were achieved with adequate safety and tolerance to the drug.

The PreCISe and BENEFIT (Betaferon ®) studies are similar in several aspects.The population of the BENEFIT study was both unifocal and multifocal; however, the PreCISe study was exclusively unifocal. The percentages of patients admitted to the extension phase were similar and extremely high in both studies (88% in PreCISe and 89% in BENEFIT). The percentages of patients who completed the study after five years were 60 and 76% in PreCISe and BENEFIT, respectively. The reduction in the risk of CDMS was 41 and 37% in PreCISe and BENEFIT, respectively. No significant differences in disability were found between early treatment and late treatment in either study. Only in the PreCISe study was a beneficial effect of early treatment on the degree of brain atrophy observed [1-4] (Table).

All CIS trials (ETOMS, CHAMPS, BENEFIT and PreCISe) are in agreement that more than nine lesions in T_2 imaging, more than one lesion that captures gadolinium, multifocal or multiregional presentation, serious exacerbation, more severe clinical and magnetic resonance (MR) imaging from the beginning and persistence of inflammatory activity detected in MR imaging are prognostic factors for CIS conversion to relapsing-remitting MS (RRMS).

Note:
O. Fernández-Fernández and X. Montalban contributed equally as principal authors in the drafting of this manuscript. All of the authors from the Post-ECTRIMS group contributed equally to the writing of this manuscript.

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Table. Comparison of the percentage of conversion to clinically definite multiple sclerosis (CDMS) and the time of delay for the conversion.

	PreCISe [1] Copaxone (n = 481)		CHAMPS [2] Avonex (n = 383)		ETOMS [3] Rebif (n = 308)		BENEFIT [4] Betaferón (n = 468)	
% of patients with CDMS	Placebo 43%	GA 25%	Placebo 50%	IFN 35%	Placebo 45%	IFN 34%	Placebo 45%	IFN 28%
Delay to conversion to CDMS (days)	722 versus 336 days + 386 days Five-year results		Not applicable		569 versus 252 days + 317 days		618 versus 255 days + 363 days	

GA: glatiramer acetate; IFN: interferon.

The importance of reviewing MR imaging after a year of treatment and evaluating whether there is activity or even new lesions has been highlighted, whereas some authors have established a limit of more than two lesions as a predictor of bad response to immunomodulatory treatment. Furthermore, it has been reported that, independent of MR imaging, showing a CIS with more than three altered evoked potentials predicts a worse prognosis.

Current first-line treatments are moderately effective and safe, whereas second-line treatments are more effective but have infrequent, though serious, adverse effects. Thus, it is necessary to obtain efficient prognostic markers to begin an appropriate individualised treatment or to be able to predict efficiency, failure or toxicity of a treatment early.

Discussions surrounding induction therapy (for patients with a bad prognosis) versus escalation therapy have the ultimate goal of a complete remission of the disease, or a "disease-free patient".

Dr. G. Comi has suggested a strategy for escalation therapy that entails first-line treatment with interferon (IFN)-β, glatiramer acetate, laquinimod, BG-12 and teriflunomide; second-line treatment with natalizumab and fingolimod/cladribine; third-line treatment with mitoxantrone/cyclophosphamide; fourth-line treatment with alemtuzumab/rituximab; and as the final step in this escalation schema, bone marrow transplantation (Fig. 2).

For induction therapy, the proposed strategy has been first-line treatment with mitoxantrone, cyclophosphamide, natalizumab and rituximab, among other drugs; second-line treatment with IFN-β, glatiramer acetate or laquinimod; third-line treatment with combination therapy; and lastly, bone marrow transplantation (Fig. 2).

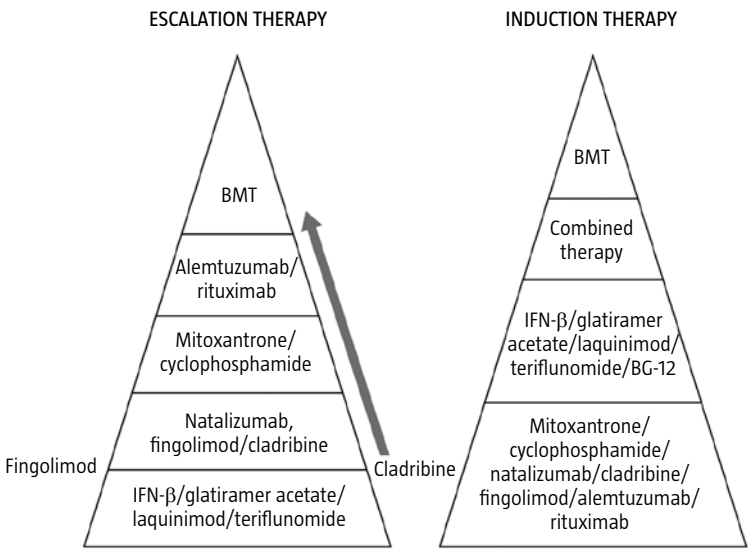
Regarding the decision of when to treat, several strategies have been proposed that depend on the characteristics of the CIS. Thus, in patients with CIS suggestive of MS and one or more factors indicative of bad prognosis, defined as more than nine T_2 lesions, more than one lesion that enhances with contrast, multifocal presentation or serious initial exacerbation, it has been proposed that treatment should begin early and that induction therapy should perhaps be established. In patients with CIS suggestive of MS without factors of bad prognosis, escalation therapy has been proposed as the initial treatment strategy. For patients with normal or inconclusive MR imaging, it is recommended that they repeat the imaging in three months, and if there is evidence of temporal dissemination, begin with escalation therapy.

Combination therapy in the treatment of patients with relapsing-remitting multiple sclerosis

The rationale for administration of combination therapy is that MS is a heterogeneous disease, in the sense that the pathological substrates of the exacerbations and the progression of disability can be different. Thus, a single therapy cannot control all the clinical manifestations of the disease. First-line drugs, such as IFN and glatiramer acetate, are safe but only partially effective, and second-line drugs are more effective, but with potential serious side effects. It is likely that a combination of a first-line therapy and another treatment with a similar safety profile could add effectiveness, acting sinergically, without risking safety.

In the NORdic trial (NORMIMS study), published by the group headed by Dr. P.S. Sorensen [5], the addition of oral corticosteroids to ongoing therapy was evaluated in RRMS patients who had experienced more than one exacerbationand whose disease was not controlled. Oral doses of 200 mg of 6-methylprednisolone were added for five consecutive days every four weeks, for a follow-up of 96

Figure 2. Escalation therapy and induction therapy strategy (presented by Dr. G. Comi at ECTRIMS 2010).



weeks. In spite of the inclusion of 130 patients in the study, with 66 patients randomised to each group (IFN-β-1a (Rebif ®) and methylprednisolone or IFN-β-1a and placebo), only 49 and 53 patients of each respective group completed the 96 weeks of follow-up. Nevertheless, extremely favourable results were found, emphasising a 62% reduction in the average number of exacerbations ($p < 0.0001$). Furthermore, a tendency towards improved disability and decreased volume of lesions in T_2 imaging was observed.

The multicentre, double-blind, randomised, placebo-controlled MECOMBIN study, recently published in the journal Lancet Neurology by Dr. M. Ravnborg's group, evaluated the addition of 500 mg of 6-methylprednisolone to therapy with IFN-β-1a (Avonex ®) during three consecutive days each month in a follow-up period of 3 to 4 years [6].

The exacerbation results were positive, and a significant reduction in the average annual relapse rate was observed in the group that received additional therapy with oral methylprednisolone instead of placebo. However, clearly significant differences in disability were not observed between the groups. In this study, it should be noted that the administration of significant doses of oral corticosteroids was not associated with the appearance of noticeable adverse effects in the bone mass.

The ACT study [7] evaluated the safety, tolerability and efficacy of IFN-β-1a combined with methotrexate, 4-methylprednisolone or both in patients with RRMS and the continued activity of the disease in patients undergoing IFN-β-1a monotherapy. This study, which included 300 patients, did not reach a clear conclusion regarding the effectiveness of additional therapy with methotrexate or with methotrexate and corticosteroids as a control treatment.

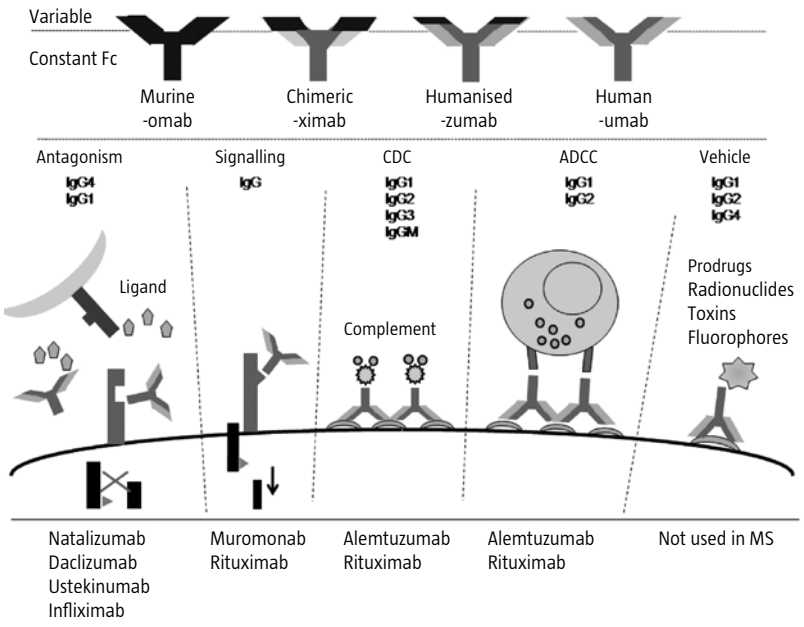
Based on the results of trials with added therapy with corticosteroids (NORMIMS, MECOMBIN and ACT), Dr. Sorensen concluded that the addition of oral corticosteroids to therapy could be a second-line treatment because it could reduce the exacerbation rate between 38% and 63%, compared with placebo, despite producing a moderate effect on MR measures. Treatment with corticosteroids is also effective in naive patients or patients with prior treatment failure. With respect to safety, this treatment strategy is associated with reasonable tolerability, although the dropout rate is more than 20%. Neither an increase in infection or changes in bone mass have been observed, nor have effects on diabetes been observed. Due to these factors, combination therapy with oral methylprednisolone as a second-line treatment could represent a favourable alternative in therapeutic options for RRMS patients.

At ECTRIMS, Dr. P.S. Sorensen [8] presented recent results obtained in a broad phase II, multicentre, double-blind, placebo-controlled trial that evaluated the effect of IFN-β-1a therapy combined with simvastatin in RRMS patients with EDSS scores between 0 and 5.5. The main goal of the study was to evaluate the average annual exacerbation rate and secondarily MR parameters of patients treated with IFN-β-1a and an addition of 80 mg simvastatin dose, compared with a group of well-matched patients treated with IFN-β-1a without it . They do not found significant differences in the annual exacerbation rate or in the presence of new T_2 lesions. Significant differences between the groups were not observed in terms of the "disease-free patient" goal. In this study, the addition of 80 mg simvastatin to IFN-β-1a therapy was not beneficial to the treatment of RRMS patients. These findings even raise the question of whether incorporation of simvastatin can increase the activity of the disease in this type of patient, due to the greater annual exacerbation rate and number of new T_2 lesions observed with additional therapy with this statin, although these differences were not statistically significant.

Monoclonal antibody therapy in multiple sclerosis

New monoclonal antibodies incorporated into the current therapeutic arsenal for MS treatment are the following: alemtuzumab, daclizumab, rituximab, ocrelizumab and ofatumumab. The tendency is to use humanised antibodies in therapy to have fewer side effects and a higher efficiency. The importance of monoclonal antibodies relative to other treatments is that they present a specific mechanism of action (Fig. 3), which indicates the importance of monoclonal antibodies in searching for specific targets that can lead to personalised medicine with more efficient specific treatments. There are three types of monoclonal antibodies distinguished by their mechanisms of action: antibodies that inhibit adhesion molecules in a selective way (natalizumab), those that are cytotoxic or specific for one type of cell (including alemtuzumab and rituximab) and those that act against a specific immune target (daclizumab).

Figure 3. Mechanism of action of the new monoclonal antibodies.



Natalizumab

Regarding the effects of natalizumab on MS, data from the AFFIRM study [9] show a mechanism of action of specifically blocking VLA-4, which prevents access of lymphocytes to the central nervous system through the blood-brain barrier. In an analysis of all AFFIRM patients, it was observed that natalizumab has many biological actions and diverse effects. This antibody is not as specific as was earlier thought, but it has multiple actions.

The AFFIRM study results showed that, after two years, 37% of patients treated with natalizumab had no disease activity, compared with 7% of the placebo group. A 68% reduction in the exacerbation rate was found with natalizumab, with an aboslute risk reduction of 0,55 after two years of treatment. The risk reduction of progression of maintained disability was 42% to 54%, being observed even improvement in some of the patients treated with natalizumab.

The AFFIRM post-analysis performed by Dr. E. Havrdova included the concept of "disease-free patients". This analysis found that after two years, 62% of the patients were free of disease activity, 78% were free of clinical activity and 71% were free of MR activity.

The most serious side effect found in treatment with natalizumab is progressive multifocal leukoencephalopathy (PML). There are 75,500 patients treated with natalizumab in the world, and the total risk of PML is 1/1,000. In relation to the risk-benefit ratio of natalizumab treatment, Dr. L. Kappos [10] has concluded that the benefits of this therapy outweigh the risks.

Alemtuzumab

Alemtuzumab is a monoclonal humanised anti-CD52 antibody. It exhibits a cytotoxic effect, reducing the levels of T lymphocytes (CD4-CD8), B lymphocytes, NK cells and monocytes in the long term.

The efficacy of alemtuzumab has been evaluated in the CAMMS223 phase II trial with a follow-up of five years, with two arms receiving two different doses of alemtuzumab (12 or 24 mg/day) and one arm receiving IFN-β-1a [11]. This study showed a high efficacy of alemtuzumab compared with IFN-β-1a. The main side effects described were autoimmune-type thyroid disease in 25% to 30% of patients and idiopathic thrombocytopaenic purpura, which was the cause of death of one patient during the study. The results showed that the patients who began with elevated basal levels of IL-21 had a greater risk of developing an autoimmune secondary disease. Therefore, it would be recommended

that these patients not be treated with alemtuzumab. There are important risks associated with this treatment, which will be assessed in more detail in the phase III trial, which is in progress (CARE-MMS 1 and 2).

Rituximab

Rituximab is a chimeric anti-CD20 antibody that exhibits cytotoxic action, inducing a marked depletion of B cells, but has no influence on mature plasma cells.

In a phase III trial published in the New England Journal of Medicine in 2008 [12], rituximab showed a clear effect on MR parameters and in the reduction of exacerbations. However, rituximab did not show a significant effect in a study of primary progressive MS.

Ocrelizumab

Ocrelizumab is a cytolytic, humanised, anti-CD20 antibody. In a phase II trial, its efficacy was assessed for MR parameters. This monoclonal antibody is associated with a high efficacy and fewer side effects than is rituximab.

Daclizumab

Daclizumab is an anti-CD25 antibody that interacts with the high-affinity IL-2R receptor (IL-2R alpha subunit). This treatment is given subcutaneously once a month. Daclizumab reduces T cell activation, and unlike the rest of the monoclonal antibodies, it increases CD56 (bright) cells. In the phase II CHOICE trial [13], daclizumab was observed to reduce the exacerbation rate by one third, and this effect was correlated with an increase in CD56 (bright) NK cells, which could be a potential biomarker.

A phase III study, DECIDE, in which treatment with INF-β-1a will be compared to daclizumab, has been initiated. In addition to analysing the effects of these drugs on exacerbations, regulatory and NK cells will be evaluated.

Ofatumumab

A paper presented by Dr. P. S. Sorensen [14] in the most recent edition of ECTRIMS analysed the results of a 24-week follow-up phase II trial of patients with RRMS (with EDSS scores of 0 to 5.5) treated with the new monoclonal chimeric anti-CD20 antibody ofatumumab. The main goal of this study was safety, including adverse effects, laboratory parameters and antibody development. The secondary objective was the evaluation of MR activity parameters. Thirty-eight patients were included, 12 of whom were assigned to the placebo group. There were three arms of ofatumumab treatment, including doses of 100, 300 and 700 mg, with 8, 11 and 7 patients in each group, respectively. The data obtained pointed to a remarkable effect of ofatumumab on the activity in MR. It was observed that MR activity was permanent in most patients of the placebo group and in only two of the patients treated with ofatumumab (one in the 100 mg group and one in the 300 mg group). In terms of safety, ofatumumab was generally well tolerated, with the exception of three serious reactions related to perfusion in the group treated with ofatumumab, corresponding to more than 10% of the total of 26 patients treated with this monoclonal antibody.

Long-term follow-up of the effectiveness and safety of treatments for multiple sclerosis

The group from Nova Scotia led by Dr. M.G. Brown [15] presented conclusions derived from a long-term study (from 1979 to 1998) of 803 patients with MS who had never been treated with immunomodulators. Therefore, the natural progression of the disease was available, including data on the EDSS, 9-HPT, ambulatory index, quality of life measures (HUI Mark III, SF-6D and EQ-5D) and quality-adjusted life years (QALYs). As has been widely observed, the speed of progression is faster in patients with high initial EDSS scores and in the secondary progressive form of MS. In this study, patients treated with immunomodulators (1998 to 2004) progressed more slowly than did patients from the pre-treatment period (1979 to 1998). In addition, quality of life was higher in patients treated with immunomodulators, with HUI Mark III being the best quality of life measure.

The systematic recording of patient data is necessary due to two fundamental goals: the long-term efficacy and safety of the chronic administration of a drug. The following European databases were highlighted: the Danish MS Treatment Registry, IMSE (Immunomodulation and MS Epidemiology) and TYSEDMUS.

TYSEDMUS was an observational prospective study of MS patients treated with natalizumab, which used the EDMUS database [16] and included a follow-up of 1,528 patients from September 2008 to September 2010. Among the most relevant data is that neutralising antibodies were found in 9% of

the patients. Important side effects have been described, among them PML in four patients (one after 19 doses), one case of leucoencephalitis, one case of colorectal cancer, one case of haemolytic anaemia and anaphylactic reactions in twelve patients.

In terms of efficacy, a decrease in the annual exacerbation rate from 2.07 to 0.36 was noted. The results of this study are similar to the AFFIRM study, except for some of the aspects of EDSS evolution or the rate of "disease-free patients", which could be explained by the one- to two-year duration the French study follow-up. A notable aspect of this study is that ten patients became pregnant; five had therapeutic abortions, and the other five completed the pregnancies.

Risks and benefits of new therapies in multiple sclerosis

With respect to the risks and benefits of cytotoxic therapeutic agents, those of mitoxantrone have been assessed. The available data suggest that mitoxantrone therapy is more useful in relapsing-remitting forms of MS than in patients with secondary progressive MS, and this treatment is more recommended for patients with an EDSS < 4 [17]. Findings shown in a paper published by Vollmer et al. [18] and study not yet published from the group of Dr. G. Edan [19] concluded that mitoxantrone seems to have a role as an inductive therapy.

Relative to the adverse effects of mitoxantrone, recently published data [20] show that up to 5% of patients present with a reduction of more than 50% in the ejection of the left ventricle, and up to 2% of patients present with heart failure. Additionally, a 0.8% incidence of leukaemia with a 30% mortality have been observed. Ultimately, it will be necessary to rethink and individualise the risk-benefit ratio of mitoxantrone.

Fingolimod is a specific agonist of the S1P1 receptor, which is found mainly in the lymph nodes, the central nervous system and organs such as the heart and lungs. Regarding safety data, two cases of patients who died during the TRASFORMS trial due to herpetic infection are highlighted. One was a woman who completed nearly a year of treatment with fingolimod, developed varicella virus infection affecting the viscera, and died after a few days. Because of this case, it was proposed to confirm the presence of anti-varicella-zoster antibodies before the initiation of treatment with fingolimod, and it would be recommended to extend this practice to the clinic. It would probably be prudent to vaccinate any negative patients before initiating therapy.

The location of the S1P1 receptor in the heart means that fingolimod also presents cardiac implications. Another side effect described for fingolimod is macular oedema; however, it appears that this complication is less frequent than initially expected. This is a dose-dependent complication; hence, the use of low doses can decrease its incidence. Furthermore, many cases are resolved when the drug is stopped.

Regarding the emergence of cancer in patients treated with fingolimod, the data obtained from phase II and III trials suggest that there is no increase in the incidence of cancer in these patients compared to the placebo group. Nevertheless, these data were obtained on a short-term basis, and therefore, long-term follow-up should be performed to obtain conclusive results.

The second generation of S1P1 agonist drugs (BAF312), which are currently in phase II trials, aim to be more selective for S1P1 and D1P5. Because of this selectivity, they may have fewer side effects.

Monoclonal antibodies have more specific mechanisms of action; thus, it could be possible to use them for personalised medicine. However, the risk-benefit ratio must be assessed when using them, given that treatment with monoclonal antibodies increases the risk of opportunistic infections. In this sense, PML is a rare but fatal opportunistic infection that has afflicted some patients treated with monoclonal antibodies.

The risk of PML with natalizumab treatment increases with the number of perfusions, especially after two years of treatment or prior treatment with immunosuppressants [21].

Dr. Vermersch [11] presented in the ECTRIMS the first 35 PML cases associated with natalizumab treatment, whose survival pattern has been scrutinized for factors that are associated with a longer survival. The analysis of these patients found that of the 35 cases, 71% survived. The patients who survived were younger, had less disability at the beginning of PML and presented a more localised disease and less time between the onset of the symptoms and diagnosis (based on MR), which indicated the importance of an early diagnosis in this type of patient. Of the patients who survived PML, approximately one third presented a minor disability, one third moderate disability and the other third serious disabilities because of this event.

Dr. T. Subramanyam [22] presented in the last ECTRIMS edition a paper about the prevalence of JC virus antibodies detected using ELISA in a wide cohort of patients treated with natalizumab. This study was based on the current lack of means to

define the risk profile of patients when starting PML treatment because all attempts to confirm JC virus in these patients have failed so far. In this sense, detection of DNA of the JC virus has not been useful in determining the risk of PML. However, a large percentage of patients with no JC viral DNA in their urine have JC antivirus antibodies detected with ELISA.

Thus, in more than 5,000 patients from the AFFIRM, TIGRYS and STRATIFY-1 studies and the Swedish record of MS, the prevalence of antibodies against the JC virus tested using ELISA has been analysed. The prevalence has been found to vary between 48 and 61%. In terms of demographic factors, the JC virus is observed less often in women and shows a linear increase with the age of the individual. Nonetheless, it is not influenced by factors considered to increase risk, such as previous exposure to immunosuppressants and the length of time of natalizumab exposure. JC virus antibodies were detected in 100% (n = 20) of patients prior to PML diagnosis. The incidence of PML is low in patients without JC virus antibodies, with no cases of PML detected in any of the 5,655 'negative' patients treated with natalizumab.

Overall, detection of antibodies against JC virus through ELISA may be useful for determining the risk profiles of patients, along with other factors, such as exposure to immunosuppressants or treatment time with natalizumab.

At present, PML is treated with plasmapheresis, mirtazapine, mefloquine and methylprednisolone 1 g for three days in case of immune reconstitution syndrome.

To date, 57 cases of PML have been described in patients taking rituximab, most of them with lymphoma. All the patients with lymphoma who presented with PML died. The risk of PML in patients treated with rituximab is 1 out of 15,000 to 20,000 patients treated. Decreased IgG levels related to an increased risk of infections and PML have been observed prior to the commencement of treatment. In addition, some cases of rheumatoid arthritis and PML have been described in patients treated with rituximab.

Infliximab has been associated with favourable results in the treatment of refractory neurosarcoidosis. However, it increases the risk of tuberculosis in those patients (6 to 10 patients out of 100,000) and increases the risk of reactivation of latent tuberculosis in patients with rheumatoid arthritis.

The results of a phase II, multicentre, randomised, double-blind trial [23] with firategrast were presented at ECTRIMS, in which three doses of firategrast (150 mg twice a day, 600 mg twice a day and 900 to 1,200 mg twice a day) or placebo over six months were compared. The results indicated that only the two highest doses were efficacious, decreasing the number of gadolinium-enhancing lesions during the six-month treatment by up to 50%. Serious adverse events have not yet been detected, including opportunistic infections and PML, and the rate of adverse effects is not significantly higher among patients treated with firategrast,or placebo. Ultimately, firategrast is a promising therapy with adequate safety and tolerability. It should be evaluated in a phase III trial soon to confirm the favourable results observed so far.

Dr. L. Kappos [24] presented the results of a phase II, multicentre, randomised, placebo-controlled trial in which the efficacy and safety of ocrelizumab in RRMS patients was assessed compared to placebo and an arm of active treatment with intramuscular IFN-β-1a. It has been observed that ocrelizumab in 200 and 600 mg doses is significantly effective in terms of reduction in the number of gadolinium-enhancing lesions and decreases of up to 80% in the number of exacerbations. This trial has revealed an adequate safety profile for ocrelizumab, with no opportunistic infections or PML and with an infection rate similar to that found in the placebo group. Only one patient died during the trial, and this death was attributed to a systemic inflammatory response, which was later confirmed in the autopsy.

Non-pharmacological therapies in multiple sclerosis

Behavioural interventions in multiple sclerosis

MS disrupts patients' lives at the time of highest development and productivity. This disruption can lead to the emergence of significant psychosocial effects: fear, anxiety, social isolation, cognitive changes and fatigue.

Symptoms of anxiety are present in 43% of patients during the diagnosis period (especially in women with related depression symptoms), whereas depression symptoms are present in 11% of patients (more often in older patients and in those with anxiety symptoms).

Pain, fatigue and depression are factors related to low sexual satisfaction and are present in some MS patients. Improvement in these symptoms can contribute to an increase in sexual satisfaction.

The available treatments for MS have produced

little improvement in health-related quality of life, so it is necessary to develop complementary therapies to improve patient wellbeing.

Behavioural therapy is effective in treating depression related to MS and surpasses other types of therapies in cases of executive dysfunction. Moreover, the improvement due to behavioural therapy is sustained over time. Behavioural therapy has additional benefits for fatigue, disability and adherence to treatment. Obstacles to the application of therapy can be overcome through the use of the new technologies (currently being developed).

Intervention based on mindfulness is effective in improving different aspects of the quality of life of patients with MS (such as depression, anxiety and fatigue).

Currently, there is an increasing desire to help patients make evidence-based decisions about MS treatment; in this way, favourable results from shared decisions can be obtained. For this reason, many decision assistance programs for patients with CIS and relapsing-remitting forms of MS are being developed regarding immunotherapy. These evidence-based information programs improve patients' knowledge and autonomy without adverse emotional effects. In this way, patients communicate their values more successfully, and the critical approach reduces the use of ineffective or dangerous therapies. It has been proposed that there are measurable biological correlates (hormonal and anatomical) of depression, which might be modifiable by pharmacological therapies or psychotherapy.

Rehabilitation in multiple sclerosis

Programs of individual and group physiotherapy have significant effects on balance in patients with MS who need bilateral assistance with ambulation. Furthermore, it has been demonstrated that rehabilitation treatment with the Wii balance board is a useful tool to improve balance skills in patients with MS.

Conclusions

Research on the natural course of MS has shown that it can be less aggressive than initially thought. Furthermore, the generalised use and improvement of certain aspects of MR imaging have allowed an earlier diagnosis of the disease. Although a diagnostic marker that is 100% effective is not yet available, oligoclonal bands stand out among the diagnostic biomarkers. It has been demonstrated that gender influences the progress and severity of disease symptoms, with an observed increase of MS prevalence among women and a more pronounced female to male ratio in northern countries.

Findings about the genes involved in MS are promising, although the most recent associations have not yet been published. After defining the genetic components of MS, a new phase of research could begin in which the biological and clinical values of genes that contribute to the genetic risk of the disease are defined. Regarding environmental factors implicated in MS, vitamin D deficit stands out as a risk factor. Other factors, such as infection with the Epstein-Barr virus, appear to also increase the risk of developing MS.

Currently, controversies surround the pathogenesis of MS and the relationship between degeneration and inflammation. In this context, innate immunity is becoming more important, particularly the role of the microglia. In terms of remyelination in MS, there is not yet a regenerative treatment, and we are still in the field of basic research. Nonetheless, the potential therapeutic effects of mesenchymal stem cells have been recently revealed, given their implication in the repair of the central nervous system.

Possibly the greatest advancement in MS in the last 10 years is related to the early treatment of this disease. All studies conducted so far have suggested the advisability of an early onset of treatment, highlighting promising results obtained in the PreCISe study regarding CDMS conversion and brain atrophy. On the other hand, combination therapy has shown efficacy in the rate of exacerbations, but not in MR parameters, in RRMS patients. Based on the available treatments for the management of MS, several strategies of induction therapy and escalation therapy have been proposed.

The arrival of the new therapies has shown promising results regarding efficacy; however, the risk-benefit ratio ultimately must be assessed by closely monitoring opportunistic infections, such as PML, and other adverse effects, such as neoplastic diseases.

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Revisión de las novedades presentadas en el XXVI Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS) (II)

Resumen. Las novedades presentadas en el XXVI Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2010 en la ciudad sueca de Gotemburgo, han sido resumidas en la tercera edición de la reunión Post-ECTRIMS celebrada en Madrid en noviembre de 2010. Se han presentado los prometedores resultados de la extensión a cinco años del estudio PreCISe, que confirman la importancia del tratamiento temprano con acetato de glatiramero en pacientes con síndrome clínicamente aislado (SCA) frente a la conversión a esclerosis múltiple (EM) clínicamente definida y la atrofia cerebral, con una seguridad y tolerabilidad adecuadas. Respecto a la decisión de tratamiento con terapia de escalado o inducción, se proponen diferentes estrategias, dependiendo de las características del SCA. Por otro lado, varios estudios han demostrado el papel favorable de la terapia combinada en pacientes con EM remitente-recurrente sobre la tasa de brotes, pero no sobre parámetros de resonancia magnética. Las nuevas te-

rapias, como alemtuzumab, daclizumab ofatumumab u ocrelizumab, han mostrado resultados esperanzadores de eficacia. No obstante, los resultados de seguridad han detectado varios efectos adversos graves, entre los que destacan las infecciones oportunistas, como la leucoencefalopatía multifocal progresiva causada por el virus JC, asociada principalmente al tratamiento con natalizumab. En este sentido, los clínicos deberán valorar el beneficio-riesgo de estas nuevas terapias al decidir el tratamiento adecuado para cada paciente en el ámbito de la práctica clínica. En este contexto, la detección de anticuerpos antivirus JC mediante un nuevo ELISA podría proporcionar a los clínicos una herramienta útil para estratificar el riesgo de desarrollar leucoencefalopatía multifocal progresiva en los pacientes. En relación con las terapias no farmacológicas, la terapia conductual ha resultado eficaz en el tratamiento de la depresión en la EM, demostrando beneficios adicionales sobre la fatiga, la discapacidad y la adhesión a los tratamientos.

Palabras clave. Anticuerpos monoclonales. Esclerosis múltiple. Seguridad. Tratamiento.