Review of the novelties presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (III)

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Summary. The most relevant data presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held in October 2013 in Denmark, were summarised at the sixth edition of the Post-ECTRIMS Expert Meeting held in Madrid in October 2013, resulting in this review, which is being published in three parts. This third part of the Post-ECTRIMS review discusses the effects of immunomodulatory therapy on the natural history of multiple sclerosis, with special attention to the assessment of long-term effects and the use of historical controls as an alternative to randomised trials compared with placebo. This article contains possible future therapeutic strategies to be tested in experimental models and discusses clinical trials that are underway and future treatments. It also summarises the results of recent studies of disease-modifying treatments and developments in symptom management. Briefly, on the horizon are many drugs with different mechanisms of action, although new strategies and treatment algorithms are needed, as are new biomarkers and assessment measures of secondary progression and long-term records to assess safety. As for the symptomatic treatment of the disease, the proposal is a personalised treatment plan and a multidisciplinary approach to improve the quality of life of patients.

Key words. Disease-modifying treatment. Monoclonal antibodies. Multiple sclerosis. Oral drugs.

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Introduction

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is the most important international meeting on this disease. In its last edition, held in Denmark in October 2013, over 8,000 specialists in multiple sclerosis (MS) gathered from around the world.

For the sixth consecutive year, the Post-ECTRIMS Expert Meeting was held in Madrid, a meeting that is scientifically supported by the Spanish Society of Neurology and that invites recognised national authorities to assemble to present the most relevant data addressed at the ECTRIMS Congress.

This article incorporates a full review, to be published in three parts, including the latest developments in basic and clinical research presented at the largest international conference devoted to the understanding and treatment of MS.

Immunomodulatory therapy on the natural history of multiple sclerosis

Clinical experience of the long-term effect

Measuring the long-term effect of therapy on MS is a challenge. It is true that randomised clinical trials have demonstrated their validity for measuring the efficacy of many drugs, but only over a limited period of one or two years, hence the need for observational studies or extended studies that provide long-term data in real time, despite the biases by confounding factors that are found in non-randomised cohorts. In an effort to minimise these biases, the application of new statistical methods, such as propensity score-matching, should be noted.

These observational studies differ widely in methodology, and most are biased in terms of design. For example, in a study by Shirani et al. [1] to

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evaluate the effect of interferon-β in long-term progression, the comparison of the active arm with two control arms (one contemporary cohort and one historical cohort) led to misleading results despite a sound statistical methodology. Specifically, the hazard ratio for the time needed to get to an Expanded Disability Status Scale (EDSS) of 6 followed a similar trend across all variables except for exposure to interferon; thus, it was concluded that the administration of interferon-β in relapsing-remitting (RR) patients was not associated with a decrease in long-term disability. That is, the application of two different control groups makes the comparison more difficult and introduces the possibility of yielding contradictory results. Other examples are observational studies in a single cohort before and after treatment, which may be valid to measure the effect of long-term treatment but which may sometimes have unmeasurable confounding factors [2]. Similarly, observational studies in cohorts with early versus delayed treatment may permit meeting the objective of assessing the effect of long-term treatment, but only provided that the statistical methodology is flawless.

For its part, the interpretation of extension studies must be done critically, taking into account possible biases. For example, in three studies of interferon versus placebo followed at 16 [3], 15 [4] and 8 years [5], not all randomised patients were followed over the long term. Surprisingly, the study at 16 years [3] showed no significant differences between the placebo group and the active group relative to the time variable up to an EDSS of 6 after 16 years of starting treatment –results that were biased due to the exclusion from the study of 28 deceased patients, most of them in the placebo group. A prominent example of a well-designed and methodologically perfect extension study is the 21-year extension of the pivotal interferon-β-1b [6] randomised trial, which benefitted from a recruitment rate of 96.4% without informative censoring. Hence, its main remarkable finding was that a delay of just two years of starting treatment with interferon-β caused a significant difference in the risk of long-term mortality. That is, well-designed extended studies without confounding factors can measure the effect of long-term treatment.

Using historical controls

The use of historical controls could be an alternative to randomised trials and those compared with placebo for circumstances in which the use of a placebo is unethical, in cases of cost reduction, for long-term studies, or for evaluating the effect of treatment in routine clinical practice. Historically, changes in clinical activity of the disease have not been attributable to demographic or clinical activity changes of early disease but instead to non-visible or confounding factors that may lead to erroneous results, despite the implementation of propensity score matching. Some published studies, such as historical cohorts versus contemporary cohorts or placebo controls in phase III clinical trials published over the last 20 years, offer example scenarios. A study by Kister et al. [7] evaluated six cohorts from 1996 to 2007 and showed significant differences in disease progression by year of recruitment, with a tendency towards later progression in contemporary cohorts compared to older cohorts. In contrast, the study of Shirani et al. [8] on four cohorts from 1975 to 1990 found no significant differences by year of recruitment with regard to reaching an EDSS of 6. Hence, other causes unrelated to the year of recruitment are raised as factors involved in the progression found in historical cohorts. The tendency to a change of activity in historical cohorts throughout the years towards more 'benign' cohorts is reflected in the update of the Danish registry, which, in 1996, already showed a tendency to increased survival at 10 years in contemporary cohorts [9]; its 2013 update has revealed an increase in mortality and a decrease in the survival rate in older cohorts. In line with the above, the results of randomised clinical trials show a higher frequency of relapses in the placebo arms of the oldest studies versus contemporary studies [10,11] –i.e., the placebo arms of the most recent randomised clinical trials have recruited less active, more benign patients.

Future strategies in the treatment of multiple sclerosis

Experimental models of therapeutic studies

Cell depletion

In animal models, cell depletion can occur via inhibition of cell trafficking to the central nervous system, promoting depletion (Table I), modifying their function or inhibiting replication [12]. A theoretical explanation of the mechanism of action of certain drugs, such as, for example, alemtuzumab-mediated autoimmunity, which is observed in experimental autoimmune encephalomyelitis (EAE) models and in patient samples, is associated with excessive apoptosis. In fact, patients developing some

type of autoimmune disease against alemtuzumab show IL-21 levels twice those of control subjects.

Remyelination in animal models

The role of oestrogens in MS appears to be related to aspects of neuroprotection and remyelination. Yarger et al. [13] have chemically synthesised analogues of 17β-estradiol (E2) that could favour the remyelination of damaged axons by acting on oligodendrocyte precursor cells (OPCs) through oestrogen receptors, thereby inducing their maturation and activation. Specifically, the analogue of E2 cyclodextrin (NDC-1308) was the only one with a very selective effect on the maturation of OPCs by activating genes that induce their differentiation. In cuprizone-demyelination models, treatment with NDC-1308 induced myelination, and in EAE mice, it delayed the onset and severity of the disease for more than two weeks. In short, the NDC-1308 oestrogen derivative can induce OPC differentiation in vivo, causing remyelination of damaged axons due to a dual protective and anti-inflammatory effect.

The inhibition of OPC maturation is the underlying cause of remyelination failure. In the search for strategies to promote remyelination, Sherman et al. [14] propose PH20 hyaluronidase, based on the results of their own previously published studies showing a) an accumulation of glycosaminoglycan hyaluronan in demyelinating lesions, predominantly synthesised by reactive astrocytes [15], and b) inhibition of remyelination by digestion products of glycosaminoglycan hyaluronan generated by hyaluronidase PH20 [16]. In this respect, inhibition of PH20 promotes OPC maturation and remyelination.

Stabilisation of the blood brain barrier

The inhibition of protein kinase C-β by a small oral molecule known as enzastaurin (LY-317615) has been proposed as a therapeutic target involved in the stabilisation of the blood-brain barrier [17]. The integrity of the blood-brain barrier is tightly regulated by a cascade of signalling events mediated by the intercellular tight junction proteins claudin-3 and claudin-5 and the occludens area. In animal models, treatment with LY-317615 induces the expression of these proteins and inhibits the migration of activated T cells across the blood-brain barrier, leading to both suppression of the infiltration and demyelination as well as to an improvement of EAE symptoms.

Regulation of Th17 cells

Klotz et al. [18] proposed a new T cell regulatory pathway not mediated by the PD-1 co-stimulatory molecule on which B7-H1 acts; this pathway should be studied to control Th17 cell-mediated autoimmunity. In vitro, B7-H1 blocks Th17 differentiation and promotes the induction of regulatory T cells; in vivo, B7-H1 increases IL-17, decreases interferon-γ, and inhibits the formation of the trimolecular complex. Consequently, B7-H1 has also been linked to improvements of symptoms in two different EAE models.

Table I. Theoretical treatment strategies in experimental models.

Cell depletion	Treatments aimed at eliminating myeloid cells	
	Treatments aimed at depletion of B and T cells	
	Treatments aimed at selective T-cell depletion	Alemtuzumab
	Treatments aimed at selective B-cell depletion	CD20 receptor: rituximab, ocrelizumab and ofatumumab
		CD19 receptor: MEDI-551
		CD27 receptor: CDX11-27
		CD22 receptor: epratuzumab
Th17-mediated autoimmunity	Treatments aimed at a new T-cell regulatory pathway not mediated by PD-1	B7-H1
Remyelination	Treatments aimed at promoting differentiation and maturation of oligodendrocyte precursor cells	Analogue of 17β-estradiol cyclodextrin (NDC-1308)
		PH20 hyaluronidase
Integrity of the blood-brain barrier	Treatments with potential stabiliser effects on the blood-brain barrier	Enzastaurin (LY-317615)
		Protein kinase C-β inhibitor

Ongoing clinical trials and future treatments

Strategies to improve future treatments require greater efficiency, better tolerance and greater long-term safety. 'Old' drugs are being studied in new formulations, such as pegylated interferon and glatiramer acetate administered on alternate days, and 'new' drugs are being studied for other indications, such as natalizumab for progressive forms, fingolimod for primary progressive forms and teriflunomide for clinically isolated syndromes.

Regarding oral drugs, the new sphingosine-1-phosphate receptor (S1P1) antagonists, such as siponimod and ponesimod, have higher affinity for the receptor, which, together with a shorter half-life

Table II. Summary of recent studies with glatiramer acetate and laquinimod.

	Study	Treatment	Key efficacy results
Glatiramer acetate	20-year extension study (n = 74)	GA 20 mg/day	Annualised attack rate during the 20 years of study: 0.2 Percentage of patients free of relapses: 24.3% Percentage of patients free of progression of disability: 48.6% EDSS score: 63% EDSS < 4; 79% EDSS < 6
	COPTIMIZE study (n = 672)	GA 20 mg/day after another disease modifier treatments	Annualised attack rate: ↓ 73.3% • ↓ 0.54 at the end of follow-up after the change vs. baseline, p <0.0001 • ↓ 0.66 in patients who switched to GA due to lack of efficacy • ↓ 0.36 in patients who switched to GA due to AA, p <0.0001 vs. baseline Impact on fatigue, quality of life, depression, and cognition: • Patients switching due to lack of GA efficacy ↓ 6.01 points on the MFIS fatigue scale (p = 0.0006 vs. baseline) • Patients switching to GA due to adverse efects ↑ 10.81 points on the FAMS quality of life instrument (p = 0.012) • Patients switching to GA due to a lack of efficacy ↓ 4.48 points on the CES-D Depression Scale (p <0.0001)
Laquinimod	Open-label extension phase of the BRAVO trial (n = 929)	Early laquinimod administration: laquinimod 0.6 mg in DB phase and again in OE phase Late oral placebo administration: oral placebo in DB phase + laquinimod 0.6 mg in OE phase Late interferon-β-1a: interferon 30 μg/week in DB phase + laquinimod 0.6 mg in OE phase	Cumulative annualised attack rate: 0.29 at 4 years • 0.28 in the early-administration laquinimod group • 0.33 in the late-administration placebo group • 0.27 in the late-administration IFN-β-1a group Risk of disability: 87% progression-free • 12.7% with confirmed progression in the early-administration laquinimod group • 14.4% in the late-administration placebo group • 13.2% in the late-administration IFN-β-1a group
	Radiological subanalysis study from the ALLEGRO trial (n = 306)	Laquinimod 0.6 mg versus placebo	Cumulative number of new T_1 lesions: ↓ after 12 and 24 months (p = 0.004 vs. placebo) Thalamic volume loss: ↓ after 12 and 24 months vs. placebo (p = 0.005; p = 0.003) Number of permanent black holes: ↓ after 12 and 24 months vs. placebo (p = 0.004; p = 0.002) Mean values of MTR: • ↑ MTR in normal-appearing brain tissue after 12 and 24 months vs. placebo (p = 0.015) • ↑ MTR in white matter after 12 and 24 months vs. placebo (p = 0.011) • ↑ MTR in grey matter after 12 and 24 months vs. placebo (p = 0.034)

GA: glatiramer acetate; CES-D: Centre for Epidemiological Studies-depression; DB: double blind; OE: open extension; EDSS: Expanded Disability Status Scale; FAMS: Functional Assessment of Multiple Sclerosis Quality of Life Instrument; MFIS: Modified Fatigue Impact Scale; MTR: magnetisation transfer ratio.

and the possibility of titration, reduces toxicity. Siponimod is being evaluated in secondary progressive forms in the current EXPAND study. For its part, the modest anti-inflammatory effect of laquinimod, due to a possible dose-response effect, contrasts with its effectiveness on atrophy and disability, having yielded a 46% decreased risk of progression at six months. Its indication in progressive forms of the disease and its use in combined administration are still open questions.

Currently, monoclonal antibodies are available that act on cytokines and on B cells; among future approaches, anti-LINGO1 is prominent in promoting remyelination. Briefly, daclizumab is an antagonist antibody of the IL-2 receptor that was shown to reduce the attack rate at two years by 62% in the SELECT study [19], and it is currently being evaluated against interferon β-1a in the DECIDE study. Secukinumab is an anti-IL-17 antibody that has been shown to reduce Gd+ lesions and annualised attack rates in the relapsing forms; however, these results were not significant, most likely due to the sample size and short time allowed for disease progression. Ocrelizumab is a drug widely studied in both primary progressive forms and relapsing forms, for which it has shown to reduce Gd+ lesions at three years at doses of 600 mg and to sustain the depletion of B cells.

Modifying treatments for multiple sclerosis: results of recent studies

Glatiramer acetate

With regard to the novel developments involving glatiramer acetate, special mention should be given to a 20-year extension study whose results concluded that daily treatment with 20 mg glatiramer acetate for 20 years is associated with stable disease activity and low disability progression [20] (Table II).

The COPTIMIZE observational study [21], which evaluated the course of the disease in patients who switched to glatiramer acetate from other disease-modifying treatments, concluded that switching to glatiramer acetate in RRMS patients is associated with positive outcomes, and the study highlighted the importance of timely change in patients with suboptimal response to their current treatment regimen (Table II).

Laquinimod

Advances in laquinimod research continue in the direction of evaluating the relationship between its effect on relapses and the progression of disability. To this end, Sormani et al. [22] analysed the results of the combined analysis of the ALLEGRO [23] and BRAVO [24] laquinimod phase III trials. The observed reduction in the risk of disability, based on a reduction in the attack rate, was six times higher than expected. That is, the therapeutic effects of laquinimod on the progression of disability were attributable to its alleged neuroprotective activity and, in part, to its anti-inflammatory properties, findings that still support the idea of a dual mechanism of action for laquinimod.

This same line of inquiry was followed by the study of Comi et al. [25], which assumed that 88% of patients in the combined analysis of the ALLEGRO [23] and BRAVO trials [24] had no progression of disability, regardless of the state of their attacks. The results showed that most (68%) patients with confirmed progression of disability also experienced attacks during the study, although one-third of the patients in the placebo group who had progressed were free of attacks. In the laquinimod subgroup free of attacks, 95% of the patients had not progressed, and a treatment effect of 38.9% was observed for the reduction of the risk of progression compared with placebo. To complement the data that had already been published, a Bayesian analysis conducted by Cutter et al. [26], using the data from the combined analysis of ALLEGRO and BRAVO, showed a 21% average reduction in attacks for laquinimod and an average reduction of the risk of progression of 32.3% compared with placebo, results that are in line with those offered by classical statistics on the effect of treatment on clinical parameters.

The open extension phase of the BRAVO trial [27] showed data on attack rate, EDSS and confirmed disability progression at six months; these data supported the positive effects of laquinimod achieved during the double-blind phase (Table II).

The radiological subanalysis of the recently published ALLEGRO trial [28] evaluated the potential effects of laquinimod 0.6 mg on inflammation and neurodegeneration using magnetic resonance techniques sensitive to the most destructive aspects of the disease (Table II). Compared with placebo, laquinimod showed lower rates of white matter, grey matter and thalamic atrophy and fewer permanent black holes and lower lesion load in normal-appearing brain tissue. The neuroprotective effect of laquinimod was manifested by a lower irreversible loss of brain tissue, which may explain the drug's ability to slow the progression of disability in RRMS patients.

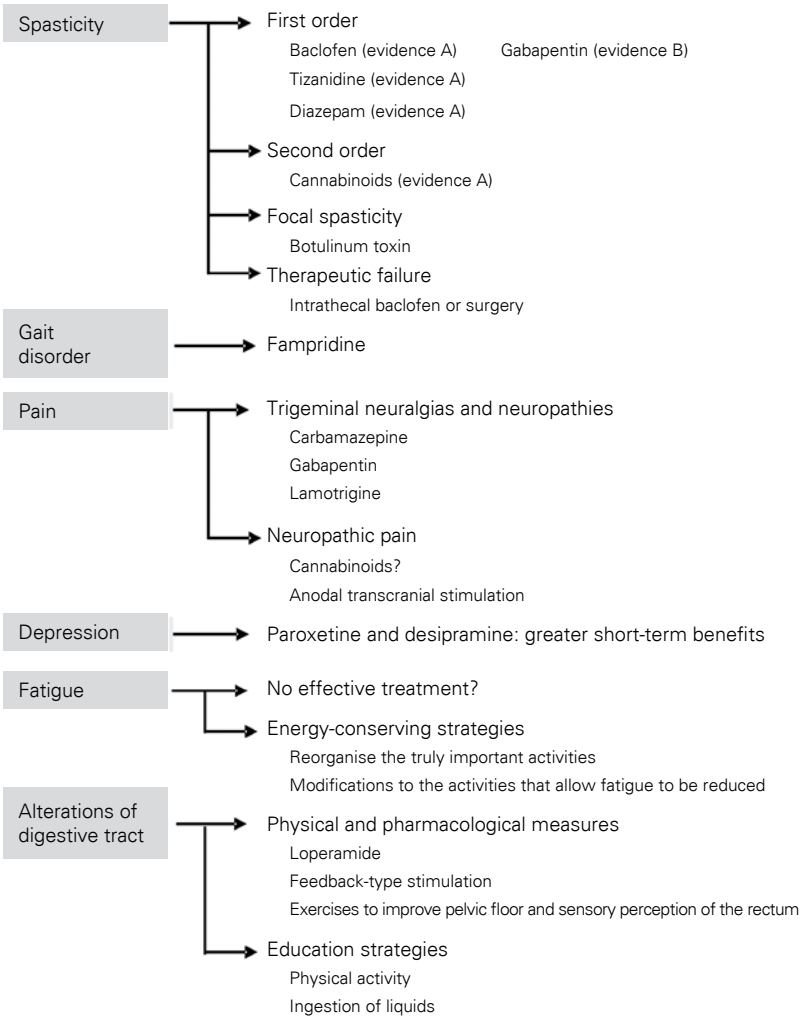
Meanwhile, Rocca et al. [29] have evaluated whether baseline magnetic resonance measures and changes in magnetic resonance parameters during the first year of the ALLEGRO trial are predictors of brain atrophy accumulation at two years. Baseline T_2 lesion volume, changes at one year in grey matter volume, and changes at one year in thalamic volume were predictors of brain atrophy at two years. The cumulative number of new T_1 hypointense lesions in the first year was a predictor of brain atrophy between the first and second year.

The CONCERTO [30] study is a phase II trial currently underway to evaluate the efficacy, safety and tolerability of two doses of laquinimod (0.6 mg/day or 1.2 mg/day) versus placebo in a total of 1,800 RRMS patients; it is intended to provide data on the dose-response effect of this drug with a therapeutic target in the central nervous system, an effect that would complement currently available drugs.

Teriflunomide

The TOPIC [31] study provided the first results pertaining to the efficacy and safety of teriflunomide in patients with clinically isolated syndrome. It is a phase III randomised, double-blind, placebo-controlled trial to evaluate two doses of teriflunomide (7 mg and 14 mg) versus placebo in a total of 618 patients with clinically isolated syndrome with

Figure. Symptomatic treatment of multiple sclerosis.



a two-year follow-up. The results show that teriflunomide 14 mg reduced the risk of conversion to clinically definite MS by 42.6% compared to placebo (37% with teriflunomide 7 mg); moreover, teriflunomide 14 mg reduced the risk of a relapse or MRI lesion by 35% compared to placebo (31% with teriflunomide 7 mg). Additionally, the results for total lesion load and reduced enhanced lesions were more favourable for the 14 mg dose. The safety profile was similar for both doses, with elevated alanine aminotransferase being the main adverse event, although at rates similar to those observed in the placebo group.

Intramuscular interferon β-1a: combination with riluzole study

The neuroprotective effect of riluzole has been the object of study in patients with early MS of less than one year of duration [32]. This randomised, double-blind, placebo-controlled study investigated the addition of riluzole to intramuscular interferon β-1a; the study's main objective was to assess brain volume (SIENA), and its secondary objectives were to analyse the atrophy of white matter and grey matter (SIENAX), measured with the Multiple Sclerosis Functional Composite Scale, to analyse the atrophy of the retinal nerve fibre layer, and to observe changes in performance on the Symbol Digit Modality Test. The results showed that brain volume in the placebo group decreased by 0.49% per year, compared with 0.89% in the active group (0.37% more per year, $p = 0.065$). No significant differences were found between the groups on the other parameters. Patients on riluzole developed more new T_2 lesions compared to placebo. Ultimately, riluzole did not reduce the progression of brain atrophy in RRMS patients in early stages.

Symptomatic management

Many of the symptoms of MS are often ignored in the evaluation of the patient and are sometimes not related to the disease, which neglects the fact that their diagnosis and treatment (Figure) can improve the quality of life of patients and their families. Among the most common are spasticity, fatigue, sexual problems and urinary dysfunctions [33]. Approximately 84% of patients experience spasticity during their lifetime [34], a symptom associated with other symptomatic burdens, including painful spasms, sleep disturbance, gait problems and urinary infections. Recently, a consensus document on spasticity has been published by a subgroup of the Spanish Society of Neurology specialising on demyelinating diseases; this document summarises all treatment recommendations in a practical algorithm [35].

Gait disorder is a rather complex symptom, and its treatment is difficult because it is influenced by various factors: spasticity, ataxia, fatigue, visual disturbances and sensory disturbances; 93% of patients have a gait disorder, and it is the most important symptom for 70% of them [36]. Fampridine is the first treatment indicated for gait disorders in patients with EDSS 4-7. It shows an average improvement of 25% in walking speed in 37% of treated patients and a significant improvement in related symptoms.

Pain occurs in 75% of patients throughout their lives, the most common being neuropathic pain. A recent study with Sativex® in combination with the existing treatment regimen for the relief of central neuropathic pain failed to show significant results [37]. Conversely, anodal transcranial direct current stimulation has been shown to reduce pain scale scores for two months in patients with chronic neuropathic pain [38].

The impact of depression in MS patients goes beyond the level of disability and can appear early in the disease. In addition to the psychosocial component, depression has a biological burden that has been reflected in many studies through its associations with T_2 volume, regional lesions, and cerebral atrophy. In fMRI, patients with depression exhibit alterations of the amygdala and the prefrontal cortex. In a review of depression therapy in MS by Koch et al. [39], no treatment stands out (Figure).

Fatigue has many dimensions –physical and mental, central or peripheral– and a multifactorial origin is posited. There are no new data but rather published evidence that supports the conclusion that none of the treatments is effective. In this regard, the idea of seeking strategies to conserve energy is reinforced (Figure).

Symptoms related to urinary tract or digestive tract disorders are quite common in patients with long-standing disease. Urinary disturbances are mainly caused by involvement of the spinal cord, although supraspinal injuries and psychosocial factors may also be involved in their development. There are several specific diagnostic and treatment protocols for MS [40,41], in addition to more general protocols or guidelines for patients with neurogenic urinary disturbance, regardless of underlying conditions [42]. Constipation and faecal incontinence are the most common disorders of the digestive tract. For constipation, in addition to physical or pharmacological measures, educational strategies are often adopted, such as increasing physical activity, increasing fluid intake, adopting a fibre-rich diet and establishing a regular habit of going to the bathroom [43,44]. Faecal incontinence can be treated with loperamide, effective biofeedback-like stimulation techniques, or techniques or exercises to improve pelvic floor muscle strength and rectal sensory perception [43,44].

Conclusions

In terms of informing future strategies in the treatment of MS, the EAE animal model appears to be useful for the evaluation of drug mechanisms of action and for preclinical studies, despite the clinical benefits not necessarily being similar to those observed in MS. On the horizon are many drugs with different mechanisms of action, although new strategies and treatment algorithms are required, as are new biomarkers and measures of assessment of secondary progression and long-term records to assess safety [45,46]. Well-designed extended studies that appropriately mitigate confounding factors are advocated to measure the effect of long-term treatment, and the use of historical controls in future clinical trials is discouraged.

Many MS symptoms have a marked impact on the quality of life of patients. Thus, it is remarkable that no common scales quantify this impact, and a personalised treatment plan and multidisciplinary approach are favoured.

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Resumen. Los datos más relevantes presentados en la XXIX edición del Congreso del Comité Europeo para el Tratamiento e Investigación en Esclerosis Múltiple (ECTRIMS), celebrado en octubre de 2013 en Dinamarca, se han resumido en la sexta edición de la Reunión de Expertos Post-ECTRIMS celebrada en Madrid en octubre de 2013, fruto de la cual nace esta revisión, que se publica en tres partes. Esta tercera parte de la revisión Post-ECTRIMS aborda los efectos del tratamiento inmunomodulador en la historia natural de la esclerosis múltiple, con especial atención a la valoración del efecto a largo plazo y al uso de controles históricos como alternativa a los estudios aleatorizados comparados con placebo. Este artículo recoge posibles estrategias terapéuticas futuras que pasan por los modelos experimentales, y expone los ensayos clínicos en marcha y futuros tratamientos. Asimismo, resume los resultados de los últimos estudios de los tratamientos modificadores de la enfermedad y las novedades en el manejo sintomático. Brevemente, en el horizonte, hay muchos fármacos con diferentes mecanismos de acción, aunque son necesarias nuevas estrategias y algoritmos terapéuticos, biomarcadores y nuevas medidas de evaluación de la progresión secundaria, y registros a largo plazo para evaluar la seguridad. En cuanto al tratamiento sintomático de la enfermedad, se apuesta por un plan personalizado de tratamiento y una aproximación multidisciplinar, de cara a mejorar la calidad de vida de los pacientes.

Palabras clave. Anticuerpos monoclonales. Esclerosis múltiple. Fármacos orales. Tratamiento modificador de la enfermedad.