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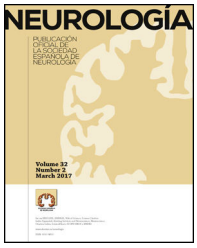

REVIEW ARTICLE

Consensus statement on the treatment of multiple sclerosis by the Spanish Society of Neurology in 2016☆

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Abstract With the advent of new disease-modifying drugs, the treatment of multiple sclerosis is becoming increasingly complex. Using consensus statements is therefore advisable. The present consensus statement, which was drawn up by the Spanish Society of Neurology's study group for demyelinating diseases, updates previous consensus statements on the disease.

The present study lists the medications currently approved for multiple sclerosis and their official indications, and analyses such treatment-related aspects as activity, early treatment, maintenance, follow-up, treatment failure, changes in medication, and special therapeutic situations.

This consensus statement includes treatment recommendations for a wide range of demyelinating diseases, from isolated demyelinating syndromes to the different forms of multiple sclerosis, as well as recommendations for initial therapy and changes in drug medication, and additional comments on induction and combined therapy and practical aspects of the use of these drugs.

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PALABRAS CLAVE
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Resumen La incorporación de nuevos medicamentos para modificar el curso de la esclerosis múltiple y la complejidad de su uso plantea la conveniencia de utilizar consensos terapéuticos. El consenso actual ha sido elaborado por el grupo de enfermedades desmielinizantes de la Sociedad Española de Neurología y actualiza consensos previamente publicados.

Se enumeran los medicamentos aprobados para la esclerosis múltiple con sus indicaciones oficiales. Se analizan aspectos relacionados con el tratamiento, como la presencia de actividad, la precocidad, el mantenimiento terapéutico, el seguimiento, el fallo terapéutico, los cambios de medicación y el tratamiento en situaciones especiales.

Se elaboran indicaciones de tratamiento desde el síndrome desmielinizante aislado a las distintas formas de esclerosis múltiple detallando recomendaciones de tratamiento inicial, cambios de medicación, con consideraciones sobre terapia combinada e inducción y aspectos prácticos del uso de medicamentos.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterised by inflammation, demyelination, glial scarring, and axonal damage leading to varying degrees of neurological impairment. MS usually affects young adults and is 2 to 3 times more frequent in women. It causes episodes of neurological dysfunction lasting a few days or weeks and known as relapses; they tend to resolve partially or completely, especially in the early stages of the disease. In a small percentage of patients (around 10%), MS leads to progressive neurological impairment without relapses.

The associated symptoms vary greatly. The first episode, known as clinically isolated syndrome (CIS), is associated with symptoms indicative of spinal cord, brainstem, or eye involvement. Although symptoms usually resolve, relapses leave permanent sequelae.

Disease progression also varies. The first stage, which usually lasts several years, is characterised by sporadic relapses. After 10 to 15 years, relapses become less frequent. Approximately half of all patients will develop progressive deterioration (this stage is called ''secondary progressive MS'').

MS has 2 distinct characteristics: autoimmune inflammation, which is typical of the initial stages and manifests as relapses and demyelinating lesions in white and grey matter on MR images; and degeneration, which is associated with irreversible damage to axons and neurons starting in the early stages of the disease and becoming more significant in later stages.

The personal and socio-economic impact of MS is considerable given its frequency, the associated disability it causes in young adults, its interference with work productivity, the associated need for care, and high treatment costs.

This document is an updated version of the 2010 consensus document published by the Spanish Society of Neurology's study group for demyelinating diseases.[1,2]

Approved drugs for multiple sclerosis

In the past 20 years, 11 drugs have been approved as MS treatments in the European Union, plus azathioprine in some individual countries including Spain.

All these drugs have had a positive impact on several clinical variables (by decreasing relapse frequency and, to a lesser extent, cumulative disability) and on MRI results. The first of these drugs, approved 20 years ago, was interferon beta 1b (Betaferon®), followed by intramuscular (IM) interferon beta 1a (Avonex®), subcutaneous (SC) interferon beta 1a (Rebif®), and glatiramer acetate (Copaxone®). Mitoxantrone (Novantrone®) was then approved, followed by the first monoclonal antibody, natalizumab (Tysabri®), a few years later. Fingolimod (Gilenya®) was the first drug to be administered orally. In 2014, the 4 most recent drugs were approved: oral drugs teriflunomide (Aubagio®) and dimethyl fumarate (Tecfidera®), monoclonal antibody alemtuzumab (Lemtrada®), and pegylated interferon beta 1a (Plegridy®). Each of these drugs was approved based on the results of clinical trials.[3–13]

They have all been proven effective for treating relapsing-remitting MS; several of these drugs are also effective against CIS given that they have been found to delay onset of further demyelinating episodes or new MRI lesions; others have been proved effective in patients with secondary progressive MS associated with relapses. According to the published clinical trials, none of these drugs has been shown to alter primary or secondary progression when MS is not associated with relapses (further explanation to follow).

Summary of official indications for treatment

Each of the approved drugs has been studied in clinical trials including patients with a certain clinical form of the disease;

approved indications are therefore limited to that specific clinical form.

Clinically isolated syndrome

The 3 types of non-pegylated interferon beta and glatiramer acetate have been studied in patients experiencing an initial demyelinating episode. These 4 drugs have been approved for CIS.

Relapsing-remitting multiple sclerosis

Glatiramer acetate, teriflunomide, dimethyl fumarate, and the 4 types of interferon beta have been approved as first-line treatments for relapsing-remitting MS. Second-line drugs natalizumab, fingolimod, and alemtuzumab may also be used in the initial stages in patients with severe forms of presentation of the disease.

Patient characteristics have changed over the years. Clinical trials were conducted in adult patients able to walk without assistance and with active forms of the disease; this concept has changed over the years, as explained in a later section.

Secondary progressive multiple sclerosis with relapses

The only drugs shown by specific clinical trials to be effective for this type of MS are interferon beta 1b and SC interferon beta 1a.[14,15] Mitoxantrone, which was approved for secondary progressive MS with inflammatory activity, is no longer used due to its toxicity.[16]

Primary progressive and secondary progressive multiple sclerosis

No treatments have been approved for these forms of MS since clinical trials conducted to date have failed to yield significant improvements.[17–19] Positive results for disability progression in a clinical trial of ocrelizumab that included patients with primary progressive MS may open the door to treatment for this variant. However, we cannot draw robust conclusions yet. The same drug was also shown to be highly effective for relapsing-remitting MS in a preliminary study.[20]

Treatment requirements

Disease activity. The purpose of treatment is to control inflammatory activity to prevent relapses and slow cumulative disability. One of the conditions for employing current drug treatments is that the disease be active. There is no universal definition of active disease and the criteria used in the main clinical trials have varied considerably, from 2 relapses in the previous 2 years (interferon beta 1b[21]) to one relapse in the preceding year (teriflunomide[22]) or active MRI lesions in the previous year (dimethyl fumarate[23]). According to the most recent description of MS courses, MS may be considered active when the patient has experienced relapses or exhibited new MRI findings in the last year.[24] Ideally, treatment for MS would deliver complete symptom control (no relapses or progression) and absence of new neuroimaging findings (stabilisation of MRI lesions), that is, 'no evidence of disease activity' (NEDA).[25]

Early treatment. The purpose of early treatment is to prevent irreversible CNS lesions and progression to disability. Numerous clinical trials have shown the benefits of early treatment compared to delayed treatment. Patients with active MS are therefore recommended to start treatment as early as possible. Likewise, evidence suggests that early treatment leads to better responses and a more favourable course of the disease.

Treatment duration. Several studies have shown that inflammatory activity reappears after treatment discontinuation; long-term treatment is therefore recommended.[26] Adherence, another important factor in treatment outcomes, has been associated with treatment success.[27]

Follow-up. Follow-up based on clinical and neuroimaging data is necessary to assess treatment effectiveness and safety. A follow-up MRI study should be conducted 6 to 12 months after treatment onset, depending on the type of drug. Subsequent MRI studies should be carried out based on each patient's characteristics; a recent consensus document recommends performing follow-up MRI scans on a yearly basis.[24] Furthermore, at least 2 follow-up visits should be scheduled in patients undergoing long-term treatment.

Treatment failure

The concept of treatment failure is key for decisions of whether to maintain treatment or change the drug when it has failed to provide the desired effects. Although this concept is referred to in the summary of product characteristics of some drugs, there is no consensus on its definition. It therefore depends on the expert opinions, which are based on assessments of clinical activity and neuroimaging findings. Several studies have assessed treatment response based on clinical data on relapses and progression and on MRI findings.[28,29]

Changes in medication. Treatment must be changed when a drug fails to achieve the desired response given a sufficient period. A number of factors must be considered when changing medication. A drug may be changed for another drug in the same group but possessing a different mechanism of action. In some cases, using second-line treatment is necessary (treatment escalation); second-line drugs have greater anti-inflammatory activity but also more severe adverse effects. Induction is another treatment strategy in which a powerful drug is administered during a limited period of time and subsequently replaced by a drug with less severe adverse effects for long-term treatment.[30]

Special situations

Aggressive onset. Patients experiencing aggressive onset show rapid deterioration of neurological function and signs of uncontrolled inflammatory activity in the form of relapses associated with multiple MRI lesions.

Paediatric patients. A significant percentage of patients develop MS in childhood. Data on treatment for this population is more limited than for adults.

Pregnancy. None of the drugs approved for MS is authorised for use during pregnancy.

Radiologically isolated syndrome (RIS) may be considered a preclinical stage of MS. Evidence is insufficient to establish treatment recommendations for this syndrome.

Proposed treatment approach

Clinically isolated syndrome

Interferon beta 1b, IM interferon beta 1a, SC interferon beta 1a, and glatiramer acetate have been shown to be superior to placebo in delaying subsequent relapses of demyelinating episodes, that is, conversion to clinically definite MS and appearance of new demyelinating lesions (definite MS according to the McDonald criteria).

The first study evaluated the efficacy of IM interferon beta 1a, followed by interferon beta 1b, SC interferon beta 1a, and lastly glatiramer acetate. These clinical trials resulted in the approval of these drugs for CIS. Teriflunomide was shown to be effective in these patients although it has yet to be approved for this indication.[31–35]

After the 2010 revision of the McDonald diagnostic criteria for MS[36] were published, the criteria used in some of the studies cited previously became obsolete. The first demyelinating episode may be classified as MS if it is associated with certain MRI findings demonstrating lesion dissemination in space and time, a diagnostic criterion for MS. If the first episode of demyelination can be diagnosed as MS, patients will be treated for relapsing-remitting MS, as described below.

There are no widely accepted criteria for determining which patients experiencing an initial episode should be treated. Current clinical trials suggest that these patients improve in terms of relapses and progression according to MR images. However, given that the risk of relapse increases with the presence of MRI findings, among other factors,[37] early treatment seems reasonable in patients at a greater risk for relapse according to clinical factors (type of involvement), paraclinical factors (IgG oligoclonal bands, number of lesions on MRI), and other prognostic factors.[38]

In some patients, short-term follow-up with MRI may be useful for early detection of new subclinical activity that may require treatment.

Relapsing-remitting multiple sclerosis

Initial treatment

Patients with a new diagnosis of MS or experiencing disease reactivation (that is, a relapse or MRI findings suggestive of MS in the previous year[24]) are candidates for any of the drugs in the group of first-line medications, all of which have a level A of evidence. All these treatments are valid options, but choosing one or another must also be based on clinical data, side effects, and such personal characteristics as age, sex, prospects for pregnancy, concomitant diseases and treatment, and patients' preferences. As previously mentioned, patients with clinically aggressive MS may benefit from initial treatment with fingolimod, natalizumab, or alemtuzumab, following the indications of the European Medicines Agency (EMA), although none of these drugs has been studied in clinical trials specifically designed for patients with these characteristics.

Changes in medication

Changes in medication due to *adverse drug reactions*: patients treated with a drug that causes significant clinical or analytical adverse effects may switch to another drug in a different pharmacological group. As a general rule, substituting a well-tolerated injectable drug for an oral drug is not recommended in patients showing no evidence of clinical or radiological activity.

Changes in medication due to *ineffectiveness*: patients with no cumulative disability who display relapses or new findings on MRI (new or expanding lesions on T2-weighted sequences or presence of gadolinium-enhancing lesions) may start treatment with another drug, whether oral or injectable, with a different mechanism of action. Though a viable option, there is little evidence on the effectiveness of switching to another first-line drug.[39]

To assess drug response, treatment must have been administered for enough time for the drug to have had clinical effects; the time depends on the type of drug and is usually between 6 and 12 months. It is essential not to delay medication changes when there is evidence that a drug is ineffective in order to minimise CNS damage due to uncontrolled activity of the disease.

When suboptimal response is accompanied by relapses affecting EDSS scores, escalation to a second-line treatment is recommended (natalizumab, fingolimod, or alemtuzumab). Choosing one drug or the other depends on a number of factors, including clinical severity, how fast the drug is expected to act, presence of anti-JC virus antibodies, and presence of comorbidities which are less compatible with some drugs. Fingolimod is frequently administered to patients bearing anti-JC virus antibodies and no comorbidities that may increase the risks associated with this drug, whereas natalizumab is the most common treatment for non-bearers. However, no comparative studies of these 2 drugs are available.

Patients treated with natalizumab must undergo a follow-up MRI scan on a yearly basis; additionally, JC-virus – negative patients will need serology tests every 6 months. Natalizumab may be a viable option in some patients with anti-JC virus antibodies; in these cases, treatment should be administered for a limited period of time (1-2 years) to reduce the risk of progressive multifocal leukoencephalopathy (PML).[40,41] In patients with anti-JC virus antibodies who meet clinical criteria to be treated with natalizumab for more than 24 months, antibody levels should be measured periodically and MRI scans should be conducted every 3 to 6 months to gauge and minimise the risk of PML (more information in the study by McGuigan et al.[42]).

When discontinuing natalizumab is being considered due to risk factors for PML, switching to fingolimod is the option supported by the most evidence. Published evidence of clinical reactivation of the disease when there are washout periods of over 3 months between drugs suggests that fingolimod should be started between 8 and 12 weeks after discontinuing natalizumab.[43,44] Although there

is no evidence of the effectiveness of dimethyl fumarate or teriflunomide when fingolimod cannot be used after natalizumab is discontinued, these drugs may constitute a viable option.

Alemtuzumab is a recently approved initial treatment in selected patients with marked inflammatory activity and who are not candidates for treatment with either natalizumab or fingolimod. Generally speaking, alemtuzumab is a second-line option, but it is also an alternative when fingolimod and natalizumab are not effective. No comparative studies of the relative effectiveness of these 3 drugs have been completed. Alemtuzumab is a powerful drug which achieves long-lasting remission periods. Its use has been associated with potentially severe autoimmune adverse events; patients treated with alemtuzumab must therefore be closely monitored with monthly analyses up to 4 years after the last dose.[45]

Second-line treatment failure

Before alemtuzumab was approved, fingolimod or natalizumab failure led to considering treatment with other unapproved drugs, for example some monoclonal antibodies with phase II evidence, such as rituximab. Patients with uncontrolled aggressive MS may benefit from mitoxantrone, classic immunosuppressants such as cyclophosphamide, or autologous stem cell transplantation (ASCT). Ocrelizumab, daclizumab, and ofatumumab may be available soon, which may change treatment recommendations.

Further considerations

Combination therapy

There is a rational basis and evidence for the effectiveness of combining drugs with different mechanisms of action in certain conditions. Although several controlled clinical trials have been conducted in patients with MS, current evidence is insufficient to recommend any drug combinations.

Induction

There is a solid theoretical basis for this treatment strategy.[30] Several treatments of this type, such as ASCT, have been completed. At present, despite having access to alemtuzumab, a drug that may be considered an induction agent,[46] evidence is insufficient to establish recommendations for this treatment strategy.

Key concepts

Lines of treatment. Lines of treatment are the different treatment options available for a disease, whether in initial or late stages. This concept is frequently used in such medical specialties as oncology. Lines of treatment in MS do not rule out the possibility of replacing first-line drugs (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate) with second-line drugs (natalizumab, fingolimod, alemtuzumab) if there are clinical indications to do so.

Therapeutic equivalences or equivalent treatment alternatives. Each drug has specific pharmacological characteristics. First- and second-line drugs are not equivalent and cannot therefore replace one another except when there are clinical indications to change the medication.

To guarantee treatment quality and equality, both MS patients and the neurologists treating them should have access to all the drugs approved by the EMA for the treatment of MS.

Clinical assessment may establish indications that are not included on drug leaflets and which may be taken from clinical consensus statements. A specialist's evaluation based on available evidence and the particularities of each case is essential for deciding which drug to administer to a specific patient.

Therapeutic algorithm

Clinically isolated syndrome

Interferon beta 1b, IM interferon beta 1a, SC interferon beta 1a, glatiramer acetate.

Relapsing-remitting multiple sclerosis

Initial treatment or first-line treatment: interferon beta 1b, IM interferon beta 1a, SC interferon beta 1a, glatiramer acetate, teriflunomide, dimethyl fumarate, pegylated interferon beta 1a.

Aggressive onset: natalizumab, fingolimod, alemtuzumab.

First-line treatment failure: change to another first-line drug or escalate to second-line drug, depending on the patient's characteristics.

Second-line treatment failure: change to another second-line drug.

When other second-line drugs also fail, other unapproved drugs may be administered (rituximab, cyclophosphamide, ASCT).

Discontinuing natalizumab: a treatment alternative should be administered 8 to 12 weeks after discontinuation.

Secondary progressive multiple sclerosis with relapses

Interferon beta 1b, SC interferon beta 1a, mitoxantrone (rarely administered due to its toxicity).

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Conflicts of interest

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References

1. García Merino A, Fernández O, Montalbán X, de Andrés C, Arbizu T. Documento de consenso de la sociedad española de neurología sobre el uso de medicamentos en la esclerosis múltiple. Escalado terapéutico. Neurología. 2010;25:378—90.
2. García-Merino A, Fernández O, Montalbán X, de Andrés C, Oreja-Guevara C, Rodríguez-Antigüedad A, et al. Documento del grupo de consenso de la Sociedad Española de Neurología sobre el uso de medicamentos en esclerosis múltiple. Neurología. 2013;28:375—8.
3. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993;43:655—61.
4. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al., The Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39:285—94.
5. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al., The Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing — remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology. 1995;45:1268—76.
6. PRISMS Study Group. Randomised double-blind placebo controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998;352:1498—504.
7. Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet. 2002;360:2018—25.
8. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899—910.
9. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362:387—401.
10. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365:1293—303.
11. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367:1087—97.
12. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829—39.
13. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon β-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13:657—65.
14. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: clinical results. Neurology. 2001;56:1496—504.
15. La Mantia L, Vacchi L, Rovaris M, di Pietrantonj C, Ebers G, Fredrikson S, et al. Interferon β for secondary progressive multiple sclerosis: a systematic review. J Neurol Neurosurg Psychiatry. 2013;84:420—6.
16. Cocco E, Marrosu MG. The current role of mitoxantrone in the treatment of multiple sclerosis. Expert Rev Neurother. 2014;14:607—16.
17. Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. Neurology. 2003;60:44—51.
18. Wolinsky JS, Naravana PA, O'Connor P, Coyle PK, Ford C, Johnson K, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol. 2007;61:14—24.
19. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized

double-blind placebo-controlled multicenter trial. Ann Neurol. 2009;66:460—71.
20. Sastre-Garriga J, Wiendl H. Highlights from the 31st ECTRIMS congress-Barcelona 2015. Mult Scler. 2016;22:7—10.
21. Betaferón ficha técnica. Available in: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000081/WC500053225.pdf. 31 January 2006.
22. Aubagio, ficha técnica. Available in: www.ema.europa.eu/docs/es_ES/document../WC500148682.pdf. 26 August 2013.
23. Tecfidera, ficha técnica. Available in: www.ema.europa.eu/docs/es_ES/document../WC500162069.pdf. 30 January 2014.
24. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83:278—86.
25. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord. 2015;4:329—33.
26. Siger M, Durko A, Nicpan A, Konarska M, Grudziecka M, Selmaj K. Discontinuation of interferon beta therapy in multiple sclerosis patients with high pre-treatment disease activity leads to prompt return to previous disease activity. J Neurol Sci. 2011;303(1—2):50—2.
27. Al-Sabbagh A, Bennet R, Kozma C, Dickson M, Meletiche D. Medication gaps in disease-modifying therapy for multiple sclerosis are associated with an increased risk of relapse: findings from a national managed care database. J Neurol. 2008; 255 Suppl. 2:S79.
28. Río J, Nos C, Tintoré M, Téllez N, Galán I, Pelayo R, et al. Defining the response to interferon-beta in relapsing-remitting multiple sclerosis patients. Ann Neurol. 2006;59:344—52.
29. Sormani MP, Río J, Tintoré M, Signori A, Li D, Cornelisse P, et al. Scoring treatment response in patients with relapsing multiple sclerosis. Mult Scler. 2013;19:605—12.
30. Rieckmann P. Concepts of induction and escalation therapy in multiple sclerosis. J Neurol Sci. 2009;277 Suppl. 1:S42—5.
31. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernández O, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet. 2001;357:1576—82.
32. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, et al., CHAMPS Study Group. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. N Engl J Med. 2000;343: 898—904.
33. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, et al., BENEFIT Study Group. Effect of early vs delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet. 2007;370:89—97.
34. Comi G, Martinelli V, Rodegher M, Moiola L, Bajenaru O, Carra A. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1503—11.
35. Miller AE, Wolinsky JS, Kappos L, Comi G, Freedman MS, Olsson TP, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:977—86.
36. Polman CH, Reingold SC, Banwell B, Clanet M, Chen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292—302.
37. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med. 2002;346:158—64.
38. Tintoré M, Rovira A, Río J, Otero-Romero S, Arrambide G, Tur C, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain. 2015;138 Pt 7:1863—74.
39. Gajofatto A, Bacchetti P, Grimes B, High A, Waubant E. Switching first-line disease-modifying therapy after failure: impact on the course of relapsing-remitting multiple sclerosis. Mult Scler. 2009;15:50—8.
40. Kappos L, Bates D, Edan G, Eraksoy M, Garcia-Merino A, Grigoriadis N, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol. 2011;10:745—58.
41. Fernández O, García-Merino A, Arroyo R, Álvarez-Cermeño JC, Arbizu T, Izquierdo G, et al. Consenso español sobre la utilización de natalizumab (Tysabri®)-2013. Neurología. 2013;28:375—8.
42. McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, Molyneux P, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry. 2016;87:117—25.
43. Cohen M, Maillart E, Tourbah A, de Sèze J, Vukusic S, Brassat D. Switching from natalizumab to fingolimod in multiple sclerosis: a French prospective study. JAMA Neurol. 2014;71:436—41.
44. Kappos L, Radue EW, Comi G, Montalban X, Butzkueven H, Wiendl H, et al. Switching from natalizumab to fingolimod: a randomized, placebo-controlled study in RRMS. Neurology. 2015;85:29—39.
45. Informe de posicionamiento terapéutico de alemtuzumab (Lemtrada®). [accessed 9 April 2015]. Available in: http://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-alemtuzumab-lemtrada.pdf
46. Coyle PK. Current evaluation of alemtuzumab in multiple sclerosis. Expert Opin Biol Ther. 2014;14:127—35.