Meeting Review

Aggressive multiple sclerosis (2): Treatment

Georgina Arrambide, Ellen Iacobaeus, Maria Pia Amato, Tobias Derfuss, Sandra Vukusic, Bernhard Hemmer, Lou Brundin and Mar Tintore for the 2018 ECTRIMS Focused Workshop Group

Abstract: The natural history of multiple sclerosis (MS) is highly heterogeneous. A subgroup of patients has what might be termed aggressive MS. These patients may have frequent, severe relapses with incomplete recovery and are at risk of developing greater and permanent disability at the earlier stages of the disease. Their therapeutic window of opportunity may be narrow, and while it is generally considered that they will benefit from starting early with a highly efficacious treatment, a unified definition of aggressive MS does not exist and data on its treatment are largely lacking. Based on discussions at an international focused workshop sponsored by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), we review our current knowledge about treatment of individuals with aggressive MS. We analyse the available evidence, identify gaps in knowledge and suggest future research needed to fill those gaps. A companion paper details the difficulties in developing a consensus about what defines aggressive MS.

Keywords: Aggressive, highly active, multiple sclerosis, disability, relapsing–remitting, treatment response

Date received: 13 November 2019; revised: 18 March 2020; accepted: 16 April 2020.

Introduction

Over the past 25 years, more than a dozen therapies have been approved by regulators for use in MS. Safety and efficacy have been demonstrated through prospective randomized controlled clinical trials, most often including subjects with relapsing forms of the disease, relatively early in the disease process, and with demonstrated inflammatory underlying disease biology. Historically, such patients have been deemed to be a subgroup that most likely benefits from treatment, and thus trial populations have been enriched to focus on these individuals. Only recently have clinical trials been successful in subjects with progressive forms of MS (pMS).

A long-recognized subgroup of patients has what might be termed aggressive MS. An aggressive disease course may manifest from onset or develop during the disease course. These patients may have frequent, severe relapses with incomplete recovery and are at risk of developing greater and permanent disability within a short time frame. Although it was not possible to come to consensus about a definition of aggressive MS at the end of the workshop, we considered radiological, clinical and biological features that might be used to obtain such a consensus. Two recent papers proposed reaching an Expanded Disability Status Scale (EDSS) ≥ 6.0 within 10 years of disease onset as aggressive MS (please refer to the companion paper for a more detailed discussion). These and several other definitions are based on relapse frequency or severity, lack of recovery, disability accrual or magnetic resonance imaging (MRI) lesions.

While it is tempting to extrapolate results from past successful clinical trials to all patients with MS when considering treatment options, data are not necessarily applicable to individuals with a more aggressive disease because of differences in underlying disease processes, demographic considerations that may have an impact on treatment outcomes, differences in comorbidities and other factors compared with the general relapsing MS trial population.

While prospective randomized clinical trial data on treatment of enriched populations of aggressive MS are largely lacking, suggestive evidence is available.
from other types of studies, including data from other relapsing inflammatory demyelinating diseases (Table 1) and data from subgroups of patients in MS clinical trials using a variety of descriptions of what is considered aggressive disease (Tables 2–4). Here, we present what is known about treatment of more aggressive forms of MS and provide suggestions for future research to fill gaps in knowledge about the best therapeutic management of these patients.

### Materials and methods

Aggressive MS, its definition and management were discussed at the 1–2 March 2018 Focused Workshop on Aggressive Multiple Sclerosis held in Brussels, Belgium, supported by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). A review of the pathology, demographic and clinical characteristics, and prognosis of aggressive MS, as well as the methods used to try to reach a consensus definition are presented in a companion article. Prior to the workshop, specific treatments or groups of treatments were assigned to different participating MS specialists who conducted a relevant literature search on PubMed including but not limited to the terms: ‘treatment x’ AND ‘multiple sclerosis’ OR ‘MS’ AND ‘aggressive’ OR ‘highly active’. The search was performed up to March 2018 with no limits on language. At the workshop, attendees (Supplemental Table 1) presented and discussed available evidence that could inform treatment options for their assigned subgroup of patients based on data derived from post hoc analyses, subgroup analyses, meta-analyses, registries, cohorts and the scarce treatment trials designed especially for aggressive MS. Subsequent to the workshop, the discussions were summarized and the references were updated using a similar literature search.

### Table 1. Treatment of severe relapse: types of patients included and definitions of relapse severity.

| Author          | Treatment | Type of inflammatory demyelinating diseases studied | Definition of severe relapse |
|-----------------|-----------|-----------------------------------------------------|-----------------------------|
| Weinshenker et al. | PLEX      | CDMS, acute transverse myelitis, acute disseminated encephalomyelitis, Marburg variant of MS, NMO, recurrent myelitis and focal cerebral demyelination | One or more of the following: coma, aphasia, acute severe cognitive dysfunction, hemiplegia, paraplegia or quadriplegia |
| Keegan et al.   | PLEX      | MS, NMO, Marburg variant of MS and ADEM            | Severe attack not defined: retrospective analysis of patients receiving PLEX for CNS demyelinating diseases between 1984 and 2000 |
| Schilling et al. | PLEX      | CIS, RRMS and NMO                                 | Corticosteroid-refractory relapses |
| Magana et al.   | PLEX      | Probable or definite MS (RR, SP, PP), NMO, LETM, recurrent ON, monophasic ON, ADEM, short TM and CIS | Corticosteroid-refractory CNS IDD |
| Llufriu et al.  | PLEX      | MS, CIS, Marburg disease, ADEM, NMO, idiopathic ON and idiopathic TM | Non-responders to corticosteroid treatment (at least one course of IV methylprednisolone 1 g/day for 3–5 days) |
| Meca-Lallana et al. | PLEX    | RRMS, CIS, recurrent myelitis, TM, LETM, ADEM, Baló’s concentric sclerosis and NMO | Corticosteroid-refractory CNS IDD |
| Mauch et al.    | IA        | RRMS, SPMS and NMO                               | Corticosteroid-unresponsive relapses |
| Schimrigk et al. | IA        | RRMS and pMS with relapses | Corticosteroid-refractory MS relapse |
| Visser et al.   | IVIg      | CDMS                                               | A relapse with $\geq$ 1-point increase in the EDSS |

PLEX: plasma exchange; CDMS: clinically definite multiple sclerosis; MS: multiple sclerosis; NMO: neuromyelitis optica; ADEM: acute disseminated encephalomyelitis; CNS: central nervous system; CIS: clinically isolated syndrome; RRMS: relapsing–remitting multiple sclerosis; RR: relapsing–remitting; SP: secondary progressive; PP: primary progressive; NMO: neuromyelitis optica spectrum disorders; LETM: longitudinally extensive transverse myelitis; ON: optic neuritis; TM: transverse myelitis; IDD: inflammatory demyelinating diseases; IA: immunoadsorption; SPMS: secondary progressive multiple sclerosis; pMS: progressive MS; IVIg: intravenous immunoglobulin; EDSS: Expanded Disability Status Scale.

*Of the 59 patients, 25 were included in the 1999 PLEX clinical trial."
### Table 2. Studies investigating the use of oral DMTs for the treatment of aggressive MS.a.

| Author          | Study and DMT | Definition(s) of aggressive MS | Disease activity outcomes | Disability outcomes | NEDA as outcome |
|-----------------|---------------|--------------------------------|--------------------------|---------------------|-----------------|
| Bar-Or J et al. | DEFINE subgroup analysis, DMFb | a. ≥ 2 relapses in the 12 months prior to study entry  
  b. T2 lesion volume ≥ median of the study population  
  c. Gd+ lesions at baseline | ARR at 2 years compared to placebo, RR (95% CI):  
  a. 0.446 (0.296–0.673)  
  b. 0.374 (0.226–0.619)  
  c. 0.321 (0.175–0.589) | CDP at 2 years, HR (95% CI):  
  a. 0.67 (0.38–1.20)  
  b. 0.58 (0.30–1.12)  
  c. 0.56 (0.25–1.26) | NA |
| Hutchinson et al. | CONFIRM subgroup analysis, DMFb | a. ≥ 2 relapses in the 12 months prior to study entry  
  b. T2 lesion volume ≥ median of the study population  
  c. Gd+ lesions at baseline | ARR at 2 years compared to placebo, RR (95% CI):  
  a. 0.664 (0.422–1.043)  
  b. 0.497 (0.302–0.819)  
  c. 0.490 (0.276–0.871) | Not analysed (non-significant results in the ITT population of the CONFIRM trial) | NA |
| Devonshire et al. | FREEDOMS subgroup analysis, fingolimod | Group E: treatment-naïve patients with rapidly evolving severe RRMS (≥ 2 relapses within the year prior to study inclusion and ≥ 1 Gd+ lesions at baseline) | ARR at 2 years compared to placebo, RR (95% CI):  
  0.33 (0.18–0.62), p = 0.0006 | CDP at 2 years, HR (95% CI):  
  0.73 (0.25–2.07), p = 0.55 | NA |
| Derfuss et al. | FREEDOMS and FREEDOMS II post hoc analysis, fingolimod | Disease activity despite previous DMTs:  
  ≥ 1 relapse in the previous year and either ≥ 1 Gd+ lesion or ≥ 9 T2 lesions at baseline, and/or as many or more relapses in the year before baseline as in the previous year | ARR at 2 years compared to placebo, RR (95% CI):  
  0.52 (0.40–0.69), p < 0.001 | CDP at 6 months, HR (95% CI):  
  0.5 (0.34–0.90), p = 0.016 | NA |
| Derfuss et al. | FREEDOMS, FREEDOMS II and TRANSFORMS pooled data, fingolimod | a. ≥ 3 relapses in the 2 years prior to study inclusion  
  b. ≥ 1 Gd+ lesions at baseline  
  c. Baseline EDSS ≥ 3.0 | ARR at 2 years compared to placebo: relative reduction of 46%–59% across the three subgroups (p < 0.001 for all comparisons)  
  ARR at 1 year compared to IM IFN-β1a: relative reduction of 39%–51% (p < 0.001 for b. and p < 0.01 for a. and c.) | NA | NA |
| Prosperini et al. | Propensity score-matched cohort study comparing natalizumab, fingolimod and self-injectables | a. Non-responders to first-line DMTs: either ≥ 2 relapses or 1 relapse associated with a residual EDSS score ≥ 2.0 in the previous year while on DMTs  
  b. HA, treatment-naïve patients: ≥ 2 relapses in the previous year and ≥ 1 Gd+ lesion on brain or spinal cord MRI | NA | NA | NEDA-3f at 2 years:  
  a. Natalizumab 67% versus fingolimod 42%, p = 0.034  
  b. Natalizumab 75% versus fingolimod 67%, p > 0.2 |

(Continued)
Table 2. (Continued)

| Author | Study and DMT | Definition(s) of aggressive MS | Disease activity outcomes | Disability outcomes | NEDA as outcome |
|--------|---------------|--------------------------------|--------------------------|--------------------|-----------------|
| Huisman et al.37 | Systematic review and meta-analysis, efficacy of fingolimod relative to DMF in a. and natalizumab in b. | a. HA RRMS: unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with ≥ 1 DMT b. RES MS: ≥ 2 disabling relapses in the past year, and ≥ 1 Gd+ lesions on MRI or increase in the T2 lesion load compared with a previous MRI | ARR at 2 years, HR (CrIs)6b: a. Fingolimod versus DMF: 0.91 (0.57–1.47); SUCRA 82.0% versus 67.9% b. Fingolimod versus natalizumab: 1.72 (0.84–3.53); SUCRA 53.4% versus 96.5% | 3-month CDP at 2 years, HR (CrIs)h: a. Fingolimod versus DMF: 0.55 (0.27–1.12); SUCRA 96.7% for fingolimod; DMF not available b. Fingolimod versus natalizumab: 1.62 (0.51–5.13); SUCRA 46.1% versus 89.0% | -- |
| Giovannoni et al.31 | CLARITY post hoc and subgroup analysis, cladribine | ≥ 2 relapses in the previous year and either ≥ 1 T1 Gd+ lesions or ≥ 9 T2 lesions on baseline MRI | NA | NA | NEDA at 96 weeks, cladribine (3.5 mg/kg) compared to placebo, OR (95% CI)k: 4.28 (3.05–6.02), p < 0.0001 |
| Giovannoni et al.32 | CLARITY post hoc and subgroup analysis, cladribine 3.5 mg/kg | Two overlapping, categorical subgroups: a. HRA: ≥ 2 relapses during the year prior to study entry, whether on DMT or not b. HRA + DAT: ≥ 2 relapses during the year prior to study entry, whether on DMT or not, and patients with ≥ 1 relapse during the year prior to study entry while on therapy with other DMTs and ≥ 1 Gd+ lesions or ≥ 9 lesions | ARR at 2 years compared to placebo, RR (95% CI): a. 0.32 (0.22–0.47) b. 0.33 (0.23–0.48) Cumulative new Gd+ lesions, RR (95% CI): 0.087 (0.052–0.144) 0.077 (0.046–0.128) | 6-month CDP, HR (95% CI): a. 0.18 (0.08–0.44) b. 0.18 (0.07–0.43) | Proportion of patients achieving NEDA, OR (95% CI): a. 8.02 (3.93–16.35) b. 7.82 (4.03–15.19) |

DMT: disease-modifying treatment; MS: multiple sclerosis; NEDA: no evidence of disease activity; DMF: dimethyl fumarate; Gd+: gadolinium-enhancing; ARR: annualized relapse rate; RR: risk ratios; 95% CI: 95% confidence intervals; CDP: confirmed disability progression; HR: hazard ratios; NA: not assessed; ITT: intention-to-treat analysis; RRMS: relapsing–remitting multiple sclerosis; EDSS: Expanded Disability Status Scale; IFN: interferon; IM: intramuscular; HA: highly active; MRI: magnetic resonance imaging; RES: rapidly evolving severe; SUCRA: surface under the cumulative ranking curve; OR: odds ratio; HRA: high relapse activity; DAT: disease activity on treatment.

*Results shown when available.

bResults for DMF TID were similar (data not shown).

**≥ 1.0-point increase in the EDSS in patients with a baseline score ≥ 1.0, or a ≥ 1.5-point increase in patients with a baseline score of 0, sustained for 12 weeks.

†Results for fingolimod 0.5 mg. Results for fingolimod 1.25 mg were similar (data not shown).

‡Time to disability progression confirmed after 3 months: increase in 1-point on the EDSS from baseline, or 0.5 points if the EDSS score was ≥ 5.5.

§Absence of clinical relapses, disability worsening and radiological activity.

∥Credible intervals (CrIs) used instead of CIs. CrIs assume the true value of the point estimate is within 95% of the range, whereas CIs assume that, if the analysis was replicated 100 times, 95% of the CIs would include the true value of the parameter.

#HRs < 1 favour fingolimod and > 1 favour the comparator.

&6-month confirmed disability progression also available for subgroup b. comparison, with similar results to 3-month CDP.

No relapses, no 3-month sustained change in EDSS and no T1 Gd+ or active T2 lesions. Time to NEDA not specified.

©Similar results at 24 and 48 weeks and with cladribine 5.25 mg/kg.
Table 3. Studies investigating the use of monoclonal antibodies for the treatment of aggressive MS.

| Author           | Study and DMT                                                                 | Definition(s) of aggressive MS                                                                 | Disease activity outcomes                                      | Disability outcomes       | NEDAs as outcome |
|------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------|--------------------------|-------------------|
| Kappos et al.33  | AFFIRM post hoc analysis, natalizumab                                        | ⩾ 2 relapses in the year before study entry and ⩾ 1 Gd+ lesion at study entry                    | ARR at 3 months, compared to placebo, RR (95% CI): 0.32 (0.15–0.69), p < 0.01    | NA                       | NA                |
| Havrdova et al.34| AFFIRM post hoc analysis, natalizumab                                        | ⩾ 2 relapses in the year before study entry and ⩾ 1 Gd+ lesion at study entry                    | NA                                                              | NA                       | Absence of disease activity over 2 years compared to placebo, % absolute difference (95% CI): 48.5 (36.0–61.0), p < 0.0001 |
| Hutchinson et al.35 | AFFIRM and SENTINEL post hoc analysis, natalizumab               | 1. ⩾ 3 relapses in the year prior to screening  
2. ⩾ 9 lesions at baseline  
3. ⩾ 1 Gd+ lesions at baseline  
   a. Natalizumab versus placebo  
   b. Natalizumab plus IFN-β1a versus IFN-β1a alone | ARR at 2 years, RR (95% CI): a. 0.20 (0.10–0.42), p < 0.001  
                                                                                         b. 0.41 (0.25–0.68), p < 0.001  
                                                                                         a. 0.33 (0.26–0.42), p < 0.001  
                                                                                         b. 0.41 (0.35–0.49), p < 0.001  
                                                                                         a. 0.28 (0.21–0.39), p < 0.001  
                                                                                         b. 0.30 (0.23–0.40), p < 0.001 | 12-week CDP at 2 years, HR (95% CI): a. 0.29 (0.11–0.77), p = 0.012  
                                                                                         b. 0.55 (0.23–1.29), p = 0.168  
                                                                                         a. 0.56 (0.42–0.75), p < 0.001  
                                                                                         b. 0.72 (0.56–0.92), p = 0.008  
                                                                                         a. 0.48 (0.31–0.75), p < 0.001  
                                                                                         b. 0.59 (0.40–0.87), p = 0.007 | NA |
| Hutchinson et al.35 | AFFIRM subanalysis, natalizumab                                                 | ⩾ 2 relapses in the year prior to study entry and ⩾ 1 Gd+ lesion at study entry                   | ARR over 2 years, % reduction compared to placebo, RR (95% CI): 81\% (0.28 vs 1.46), p < 0.001 | 12-week CDP at 2 years, HR (95% CI): 0.47 (0.24–0.93), p = 0.029 | NA |
| Hutchinson et al.35 | SENTINEL subanalysis, natalizumab                                             | ⩾ 2 relapses in the year prior to study entry and ⩾ 1 Gd+ lesion at study entry                   | ARR over 2 years, % reduction natalizumab + IFN-β1a versus IFN-β1a alone: 76\% (0.28 vs 1.16), p < 0.001 | 12-week CDP at 2 years, HR (95% CI): 0.39 (0.21–0.74), p = 0.004 | NA |
| Lorscheider et al.38 | Registry of the Swiss Federation for Common Tasks of Health Insurances, patients on natalizumab and fingolimod | ⩾ 1 relapse in the year before switching from IFN-β or glatiramer acetate to natalizumab or fingolimod | Natalizumab compared to fingolimod over a 2-year period, HR (95% CI) for a., and RR (95% CI) for b.:  
Relapse-free patients: 0.5 (0.4–0.8), p < 0.001  
ARR: 0.5 (0.3–0.8), p = 0.001 | Compared to fingolimod, HR (95% CI): 12-month CDP: 0.9 (0.5–1.5), p = 0.62e  
12-month disability improvement: 1.8 (1.1–2.7), p = 0.01f | NA |

(Continued)
### Table 3. (Continued)

| Author          | Study and DMT                                                                 | Definition(s) of aggressive MS                                                                 | Disease activity outcomes                                                                 | Disability outcomes                                                                 | NEDA as outcome                                                                 |
|-----------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Curti et al.39  | Hospital-based multi-centric study with prospectively collected data, natalizumab and fingolimod | a. Unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with ≥ 1 DMT, or b. Patients with a rapidly evolving severe course: ≥ 2 disabling relapses in the past year and ≥ 1 Gd+ lesions on MRI or significant increase in T2 lesion load compared with a previous MRI | Natalizumab compared to fingolimod over a 2-year period: ARR, multivariate OR (95% CI): 0.52 (0.26–1.04), p=0.06 New/enlarging T2 lesions, mean (SD): 0.17 (0.62) versus 0.63 (1.46), p=0.003 Gd+ lesions, mean (SD): 0.02 (0.13) versus 0.00 (0.00), NA | Compared to fingolimod over a 2-year period, (%) for CDP, OR (95% CI) for CDR: CDP: 9.0% versus 6.7%, p=0.62 CDR: 3.76 (1.07–13.22), p=0.03 | Compared to fingolimod, NEDA after 2 years of treatment, (%): 39.0% versus 22.0%, p=0.04 |
| Cobo-Calvo et al.40 | Hospital-based study with prospectively collected data, natalizumab | ≥ 2 relapses and disability progression ≥ 1 point during the year before natalizumab initiation sustained for at least 6 months  
  a. After 1 year of treatment  
  b. During the second year  
  c. After 2 years of treatment | Freedom from clinical activityi, n (%)  
  a. 49/70 (70.0%)  
  b. 42/56 (75.0%)  
  c. 31/56 (55.4%) | Freedom from radiological activity, n (%):  
  a. 59/70 (84.3%)  
  b. 50/52 (96.2%)  
  c. 44/52 (84.6%) | Freedom of disease activityk, n (%):  
  a. 43/70 (61.4%)  
  b. 38/52 (73.1%)  
  c. 25/52 (48.1%) |
| Coles et al.41  | CAMMS223 post hoc and subset analysis, alemtuzumab                           | > 2 relapses in the year prior to inclusion                                                      | ARR, at 36 months, compared to SC IFN-β1a^jk, RR (95% CI): 0.203 (0.098–0.420), p<0.0001 6-month CDP^m,n, at 36 months, alemtuzumab compared to SC IFN-β1a, HR (95% CI): 0.340 (0.128–0.905), p=0.031 SRD (HR): 5.906 | Clinical disease activity (relapses and CDP) at 36 months, compared to SC IFN-β1a, HR (95% CI): 0.240 (0.127–0.454), p<0.0001 | Disease-free at last follow-up after one cycle: 4 Two remained disease-free for 25 and 33 months but required a second cycle of alemtuzumab, after which they remained disease-free at last follow-up |

Le Page et al.42 | Study (type) n=8 RRMS, n=8 SPMS, alemtuzumab, either during mitoxantrone treatment or ≥ 12 months after mitoxantrone withdrawal | RRMS before treatment: mean (range) ARR of 2.9 (1–5), and EDSS worsened by 2.2 (0–5) points, and a mean number of Gd+ lesions > 15 (2 to > 20) | Disease activity: One switched to glatiramer acetate after a mild relapse and one active lesion at 18 months follow-up | EDSS improvement after first alemtuzumab cycle: 1.9 (0–4.0) points One patient had a sustained improvement for 2 years but then worsened progressively without any MRI activity | Disease-free at last follow-up after one cycle: 4 Two remained disease-free for 25 and 33 months but required a second cycle of alemtuzumab, after which they remained disease-free at last follow-up |

(Continued)
Table 3. (Continued)

| Author                  | Study and DMT                      | Definition(s) of aggressive MS                                      | Disease activity outcomes                                                                 | Disability outcomes                                                                 | NEDA as outcome |
|-------------------------|------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------|
| Turner et al. [43]      | OPERA I and OPERA II subgroup analysis, ocrelizumab | 1 relapse in the year prior to randomization and ≥ 9 T2 lesions or ≥ 1 T1 Gd+ lesion at baseline | ARR over 2 years, % reduction compared to SC IFN-β1a: 68% (p < 0.001) Gd-enhancing lesions over 2 years, reduction compared to IFN β1a sc: 98% (p < 0.001) New or enlarging T2 lesions over 2 years, reduction compared to SC IFN-β1a: 80% (p < 0.001) | 12-week CDP at 2 years, % reduction compared to SC IFN-β1a: 53% (p = 0.035) | NA              |
| Durozard et al. [44]    | French retrospective multicentre study, off-label rituximab | Refractory RRMS: ≥ 1 T1 Gd+ lesion and/or new T2 lesions despite treatment with fingolimod, natalizumab, mitoxantrone, cyclophosphamide or alemtuzumab | ARR, rituximab compared to previous immunosuppressive treatment, median (range): 0 (0–1.87) versus 0.6 (0–3.8), p < 0.0001 Gd+ lesions before versus after switching to rituximab, %: 72% versus 8%, p < 0.0001 | EDSS, rituximab compared to previous immunosuppressive treatment, median (range): 4.0 (0–7.5) versus 4.5 (0–7.0), p < 0.0001 | NEDA at the last clinical evaluation while on rituximab, n (%): 35/50 (approximately 70%) |

MS: multiple sclerosis; DMT: disease-modifying treatment; NEDA: no evidence of disease activity; Gd+: gadolinium-enhancing; ARR: annualized relapse rate; RR: rate ratio; 95% CI: 95% confidence interval; IFN: interferon; CDP: confirmed disability progression; HR: hazard ratio; MRI: magnetic resonance imaging; OR: odds ratio; SD: standard deviation; CDR: confirmed disability regression; SRD: sustained reduction in disability; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale.

aNo relapses, no progression of disability (sustained for 12 weeks), no Gd+ lesions and no new or enlarging T2-hypointense lesions.
bSimilar results for 24-week CDP at 2 years.
cMean (SD) number of relapses in the year prior to inclusion after matching: 2.8 (2.0) for natalizumab and 2.7 (3.1) for fingolimod.
dAfter propensity score matching.
eIncrease in ≥ 1.5 points from an EDSS score of 0, ≥ 1.0 point from an EDSS score of 1.0–5.5, or ≥ 0.5 point from an EDSS score of ≥ 6.0.
fDecrease in ≥ 1 EDSS step or 0.5 steps if baseline EDSS ≥ 6.0.
gIncrease in ≥ 1.0 points if baseline EDSS score < 5.5 or ≥ 0.5 point if baseline EDSS ≥ 5.5, confirmed at 6 months.
hDecrease in ≥ 1 point if baseline EDSS ≤ 5.5 or ≥ 0.5 points if baseline EDSS ≥ 5.5, confirmed at 6 months.
iNo relapses or increase in disability.
jAbsence of both new lesions and Gd+ lesions.
kNo relapses, no increase in disability and absence of both new lesions and Gd+ lesions.
lResults at 24 months were similar.
mPooled 12 and 24 mg analysis.

n≥ 1.0-point increase in EDSS score if the baseline EDSS score was > 0, or ≥ 1.5 increase if the baseline EDSS score was 0, sustained for a 6-month period. Results for CDP sustained for 3 months were similar.

oDecrease in EDSS score by ≥ 1 point, sustained for a consecutive 6-month period, for patients with a baseline EDSS score ≥ 2.0; given patients with a baseline EDSS score of 0 are not accessible for SRD; in accordance to a previous study, only patients with an EDSS score ≥ 2.0 at baseline were included in the analysis.

p24-week CDP: 50% (p = 0.082).
qOf fingolimod, natalizumab, mitoxantrone, cyclophosphamide or alemtuzumab as treatments prior to rituximab, only the first three DMTs were included in the analysis after patient selection.
rGd+ lesions on first MRI after rituximab initiation.
| Author           | Study                                      | Definition(s) of aggressive MS                                                                 | Disease activity outcomes                                                                 | Disability outcomes                                                                 | NEDA as outcome |
|------------------|--------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------|
| Fagius et al.    | Case series Mobilization: CP (2 g/m²) and G-CSF (5 μg/kg). Conditioning: BEAM for all except a boy who received CP 50 mg/kg daily for 4 days | Early, malignant MS: frequent (≥ 4/year) and severe (EDSS ≥ 6.0) relapses, disease duration or duration of aggressive disease ≤ 1.5 years, and clearly documented recent improvement periods indicative of non-reversible damage of the CNS | Relapses in patient-months: Before aHSCT: 61 relapses in 82 patient-months After aHSCT: one relapse in 289 patient-months | Median (range) EDSS Before aHSCT: 7.0 (3.5–8.0) Improvement after aHSCT: 3.5 (1.0–7.0) | NA              |
| Atkins et al.    | Multi-centric, single-group Phase 2 trial Mobilization: CP (4.5 g/m²) and filgrastim (10 μg/kg/day for 10 days) Conditioning: busulfan every 6 hours for 16 doses, CP (50 mg/kg/day for 4 days), and rabbit ATG (1.25 mg/kg/day for 4 days). | Multiple early relapses, early development of sustained disability measured by EDSS affecting motor control with cerebellar or pyramidal functional system scores ≥ 3.0 within 5 years of disease onset, evidence of ongoing clinical disease activity despite ≥ 1 year of DMT or immunosuppressive treatment and EDSS of 3.0–6.0 with a cerebellar or pyramidal functional system score ≥ 3.0 | With up to 13 years of follow-up after aHSCT: No relapses occurred No Gd+ or new T2 lesions were seen on 314 MRIs | With up to 13 years of follow-up after aHSCT: 70% of patients had no disability accrual 35% had a sustained improvement of their EDSS score | Primary outcome: activity-free survival at 3 years; incidence with person-time in years (95% CI): 69.6 (46.6–84.2) |
| Nash et al.      | Phase 2, multicentre high-dose immunosuppression and autologous transplantation for MS (HALT-MS) clinical trial Mobilization: filgrastim (16 μg/kg/day for 4 days) Conditioning: BEAM, rabbit ATG (2.5 mg/kg/day for 2 days) and filgrastim (5 μg/kg/day for 14 days and tapering over 2 weeks) | EDSS 3.0–5.5 at baseline and disease duration < 15 years, with failure of DMT | Relapse-free survival: 86.9 (69.5–94.7)% MRI activity-free survival: 86.3 (68.1–94.5)% | Progression-free survival: 91.3 (74.7–97.2)% Disability improvement, median (IQR) EDSS change: −0.5 (−1.5 to 0, p = 0.001) in patients who completed the study No treatment-related mortality | Primary endpoint: event-free survival evaluated through 5 years after aHSCT, Kaplan–Meier (95% CI): 69.2 (50.2–82.1)% |
| Mancardi et al.  | ASTIMS, multicentre, randomized, Phase 2 study to assess the effect of aHSCT versus mitoxantrone on disease activity in MS Mobilization: CP (4 g/m² in 1 day) and filgrastim (5 mg/kg until completion of the stem cell harvest Conditioning: BEAM and rabbit ATG (3.75 mg/kg/day for 2 days) | SPMS or RRMS that accumulates disability between relapses, with a documented worsening during the last year, in spite of conventional therapy and presence of ≥ Gd+ lesions on MRI, and EDSS score between 3.5 and 6.5 | Primary endpoint: cumulative number of new T2 lesions in the 4 years after randomization, compared to mitoxantrone (n = 17); RR (95% CI): 0.21 (0.10–0.48), p = 0.00016 Zero Gd+ lesions at 4 years: aHSCT 100% versus mitoxantrone 56%, p = 0.029 ARR (RR, 95% CI): 0.36 (0.15–0.88), p = 0.026 | Disability accrual at 4 years: aHSCT 57% versus mitoxantrone 48%, p = 0.50 | NA              |

(Continued)
| Author            | Study                                                                 | Definition(s) of aggressive MS                                                                 | Disease activity outcomes                                                                 | Disability outcomes                      | NEDA as outcome |
|-------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------|-----------------|
| Muraro et al.49   | Long-term, multicentre, observational, retrospective cohort study of patients who received aHSCT between January 1995 and December 2006 | At the time of aHSCT, 171 of 281 patients (60.9%) had received ≥ 2 DMTs. The most represented subtype was SPMS (186 of 281 patients, 66.2%), and the median EDSS score was 6.5 (range, 1.5–9.0) | NA                                                                                       | Progression-free survival\(^{a}\) at 5 years, \(n = 231\), Kaplan–Meier (95% CI) | NA              |
| Sormani et al.50   | Meta-analysis of 15 studies including 764 patients from 1995 to 2016 | Median (range) follow-up time of 41.7 (24–80.4) months. Baseline EDSS \((p < 0.001)\), disease duration \((p = 0.08)\) and the proportion of patients with pMS \((p < 0.001)\) were lower in reports > 2005. In total, 14 out of 15 studies were open-label uncontrolled studies, 1 study was the experimental arm of a randomized study; 5 studies were retrospective and 10 were assessed prospectively | ARR (11 of 15 studies), pooled estimate rate post-transplant (95% CI) 0.037 (0.028–0.047) | Rate of disease progression, pooled estimate rate (95% CI) 17.1 (9.7–24.5)% at 2 years 23.3 (16.3–31.8)% at 5 years At 2 years in studies with less RRMS, 24.8 (16.7–32.9)% versus 7.8 (1.3–14.2)% in studies with more RRMS TRM, pooled estimate rate (95% CI): By year of transplant: 0.3 (0–2.0)% > 2005 versus 3.6 (2.2–6.0)% \(p = 0.014\) By phenotype: 1.0 (0.4–2.6)% if higher proportion of RRMS versus 3.4 (1.9–6.0)% if lower proportion of RRMS | NEDA (5 of 15 studies), proportion (range) 83 (70–92)% at 2 years 67 (59–70)% at 5 years |

\(a\)BEAM dose not specified.
\(^{b}\)Either ≥ 2 disabling relapses in the year before enrolment, 3 disabling relapses in the 2 years before enrolment or deterioration of the EDSS in the 18 months before enrolment (1.0 point if EDSS ≤ 5.0 or 0.5 points if EDSS > 5.5).
\(^{c}\)No relapses, new or Gd+ lesions and sustained progression of EDSS.
\(^{d}\)≥ 2 relapses over 18 months while on DMT and associated with a ≥ 4-week sustained EDSS increase (1.0 for EDSS 3.0–3.5 or 0.5 for EDSS 4.0–5.5).
\(^{e}\)Three deaths occurred during follow-up at 2.5, 3.5 (MS-related) and 4.5 years (cardiorespiratory arrest).
\(^{f}\)Survival without death or disease activity (disability progression, relapse or new lesions on MRI).
\(^{g}\)One step of EDSS or 0.5 when EDSS is between 5.5 and 6.5.
\(^{h}\)IFN β or glatiramer acetate or immunosuppressive therapy.

Progression: increase in 1 point in the EDSS score confirmed at 12 months (0.5 points if the baseline EDSS score was ≥ 5.5) compared with the pre-treatment baseline, which was defined as the last assessment before mobilization of peripheral blood stem cells (for peripherally mobilized autologous grafts) or before immunosuppressive conditioning (for bone marrow autologous grafts).
strategy. Gaps in knowledge were identified, and strategies for future research to better understand treatment of aggressive MS were discussed.

Results

Acute treatment

Relapses, including frequency, duration and severity, are clinical indicators of MS disease activity. While usually self-limiting, some relapses can be disabling and recovery can be incomplete, resulting in long-term accumulating disability. Clinical trials of agents for treating relapsing forms of MS (rMS) have examined the impact of treatment on relapse rate, but few have examined the impact on shortening the duration or reducing the severity of a relapse. Trials assessing relapse treatments often have heterogeneous inclusion criteria, including patients with differing MS phenotypes and sometimes different demyelinating diseases (Table 1).

High-dose corticosteroids. High-dose intravenous (IV) or oral corticosteroids are the first-line treatment for relapses in MS. Corticosteroids are believed to have an impact on MS relapses by exerting a rapid immunosuppressant effect. Data indicate that IV or oral corticosteroids decrease the severity of relapses as measured by the EDSS or the Kurtzke Functional System Scale and speed patient recovery in rMS, but evidence of its effect on relapses in pMS is very limited.

Plasmapheresis and immunoadsorption. Plasma exchange (PLEX) has been used for patients with persistently severe neurological deficits, although definitions of severity vary among studies. Evidence of usefulness of PLEX in MS arises largely from a randomized, sham-controlled, double-masked trial in patients with severe attacks of inflammatory demyelinating diseases (not all with MS) who failed to recover after IV high-dose methylprednisolone treatment. Moderate or greater improvement occurred in 42.1% of courses of active treatment with PLEX compared to 5.9% of courses of sham treatment \( (p = 0.011) \). Initiation of treatment within the first 20 days of an attack was one of the factors associated with moderate or marked improvement, and a beneficial effect was also observed with treatment within the first 20–60 days in some cases. In general, clinical improvement was seen after three PLEX treatments, and continuing improvement was observed as late as 6 months after the completion of PLEX in treatment responders. Only anecdotal evidence exists for a role of PLEX in corticosteroid-refractory superimposed relapses in secondary progressive MS (SPMS).

MRI predictors of response to PLEX include the presence of gadolinium-enhancing (Gd+) lesions and lesions with mass effect, according to results from an exploratory analysis of 153 patients with central nervous system inflammatory demyelinating diseases. Conversely, a smaller observational, pilot study, including 15 patients with different demyelinating diseases, showed no significant association between the degree of resolution of the radiological activity and the clinical response to PLEX.

In contrast to PLEX, immunoadsorption (IA) removes antibodies and immune complexes while avoiding plasma product substitution. Similarly to PLEX, results from retrospective studies suggest that IA might be most effective after three such procedures in MS patients with corticosteroid-refractory relapses. Moderate to marked improvement from attack-related disability as measured by the EDSS can be observed in approximately 70% of cases, including a subset of patients with pMS and relapses. However, its widespread use is limited and this procedure is not approved in some countries.

Intravenous immunoglobulin. Evidence of the effect of intravenous immunoglobulin (IVIg) on relapses in aggressive MS is very limited. A small, randomized, double-blind, placebo-controlled pilot study in 19 MS patients compared the efficacy of IVIg given with IV corticosteroids to IV corticosteroids alone to promote recovery from moderate to severe relapses. The primary outcome was the EDSS level at 4 weeks. No statistically significant differences were found in the median change in EDSS \( (p = 0.81) \). Furthermore, the median time to improvement of at least one point on the EDSS was 14 days in both groups \( (p = 0.95) \).

Based on these published results, limited evidence appears to support the use of PLEX and IA for corticosteroid-refractory MS relapses. However, IVIg appears to have no effect in severe relapses (Table 1).

Disease-modifying treatments

Tables 2–4 summarize the different studies assessing treatment in patients with aggressive MS. Definitions used in the cited studies for aggressive rMS vary from exclusively clinical or radiological to combinations of both. Many of these studies compare disease-modifying treatments (DMTs) to placebo or to first-line treatments. In the following text, we focus on studies with drug–drug comparisons; studies assessing naïve
patients who started a high-efficacy DMT and studies assessing patients who switched from first-line to high-efficacy DMT or from one high-efficacy DMT to another. Of note, there are no specific studies on treatment for aggressive pMS.

Importantly, although not available at the time of the workshop, data since have shown a superiority of monoclonal antibodies (Mabs) over oral DMTs. Most of said studies were not included in this review because: (1) they do not assess patients with aggressive MS, (2) it is impossible to determine if the included subjects have aggressive MS according to the baseline characteristics or (3) they do include a subgroup with aggressive MS but it is not evaluated individually.

**Oral and intravenous DMTs.** Dimethyl fumarate (DMF) was assessed in a subgroup analysis of patients with high clinical or radiological activity in the DEFINE and CONFIRM trials. However, results were not compared to other DMTs in this analysis.

Fingolimod has been compared to other DMTs and showed a greater effect on the annualized relapse rate (ARR) compared with interferon (IFN)-β1a in β show a greater effect on the annualized relapse rate. Fingolimod has been compared to other DMTs and were not compared to other DMTs in this analysis.

Conversely, a study based on a national registry using propensity score matching in patients switching to second-line DMTs after breakthrough disease while on IFN-β or glatiramer acetate did demonstrate natalizumab was more effective than fingolimod in reducing the number of relapses and improving disability. Although the selection criteria for this study did not restrict patient selection to cases with highly active disease, the mean (SD) number of relapses in the year prior to inclusion was 2.8 (2.0) for patients switching to natalizumab and 2.7 (3.1) for patients switching to fingolimod, which might be considered a relatively high relapse rate for included subjects. Another hospital-based study also demonstrated natalizumab was superior to fingolimod in inducing regression of disability and NEDA at 2 years. There were, however, no significant differences between medications when comparing the clinical components of NEDA individually. These results could be due to the small sample size after propensity score matching and dropouts in the fingolimod group due to breakthrough disease.

Post hoc subgroup analyses of the CLARITY clinical trial in patients with high disease activity compared cladribine to placebo. A recent analysis suggested that patients with highly active MS have a better response to cladribine than those with a milder disease course. This analysis classified patients into two overlapping, categorical subgroups: the high relapse activity (HRA) and the HRA plus disease activity on treatment (HRA + DAT) subgroups. During cladribine treatment, the ARR was lower in HRA versus non-HRA patients and in HRA + DAT versus non-HRA + DAT patients, although without reaching statistical significance. Similarly, the risk of new Gd+ lesions decreased slightly in patients with a more active disease.

A prospective hospital-based study assessed 70 patients with highly active MS treated with natalizumab, of whom 97.1% had received a previous DMT. The proportion of patients free of clinical and overall disease activity was 60.0%–70.0% at 1 year but decreased to approximately 50.0% after 2 years. Conversely, freedom from radiological activity was consistently high throughout the study period.

Alemtuzumab has been compared to IFN-β1a in a post hoc and subset analysis of the CAMMS223 trial. Results favoured alemtuzumab in patients with frequent relapses. In a single small study of alemtuzumab as rescue therapy after mitoxantrone in patients with rMS and SPMS, some subjects showed EDSS improvement and NEDA.
Finally, ocrelizumab has shown increased treatment benefits relative to IFN-β1a by reducing disease activity and disability progression in a subgroup of rMS patients with highly active disease. Similarly, rituximab has proven effective in patients with rMS with persistent disease activity despite treatment with other high-efficacy DMTs, such as fingolimod, natalizumab or mitoxantrone (Tables 2 and 3).

**Autologous haematopoietic stem cell transplantation.** Autologous haematopoietic stem cell transplantation (aHSCT) is used to induce long-term immunosuppression and immune reconstitution in aggressive forms of MS. To date in MS, it has been mostly used as an escalation therapy approach when more than one first- or second-line DMTs has failed.

Early evidence on the efficacy of aHSCT came as small case series showing a significant improvement in EDSS and reduction in number of relapses. Results from two Phase 2 clinical trials (one including both rMS and pMS patients and one with rMS patients only) support the efficacy of aHSCT in patients with high clinical activity. In these studies, two-thirds of subjects were free of disease activity at 3 and 5 years and no treatment-related mortality was reported in one of the trials. Another Phase 2 trial compared aHSCT and mitoxantrone in rMS and pMS patients with high clinical and radiological activity, using cumulative number of new T2 lesions after 4 years as primary endpoint. Compared to mitoxantrone, aHSCT reduced the number of new T2 lesions by 79.0% and also had an effect on Gd+ lesions and ARR, but no difference was found in disability progression. A long-term, multicentre, observational, retrospective cohort of rMS and pMS patients who received aHSCT showed that the overall 5-year probability of progression-free survival was 46.0%, and the size effect was greater in RRMS than in SPMS patients. Importantly, factors increasing the risk of overall worse survival after aHSCT are older age, pMS, more than two previous DMTs and a high EDSS.

These findings are supported by a meta-analysis evaluating the rate of disease progression and NEDA after aHSCT. At 5 years, the pooled rate of progression was 23.3% and NEDA was observed in 67.0% of patients. In general, progression-free survival in patients has increased in studies post-2005, in younger patients with EDSS  ≤ 5.5 and in rMS. Finally, when aHSCT is compared to first- and second-line DMTs tested in Phase 3 trials, NEDA at 2 years was greater in patients undergoing aHSCT than in those receiving placebo or DMTs. However, these results should be interpreted with caution due to the absence of direct comparisons. aHSCT is still considered experimental in MS, with a need to demonstrate a sound risk/benefit profile in a well-defined target population (Table 4).

**Mitoxantrone.** The efficacy of mitoxantrone has been assessed against methylprednisolone or placebo in studies, including both RRMS and SPMS. One of the rare trials including a well-defined highly active population studied the effect of short-term immunosuppression with mitoxantrone in patients with aggressive RRMS, defined as ≥ 2 relapses or an EDSS increase ≥ 2 points in the 12 preceding months, ≥ 1 Gd-enhancing lesion and baseline EDSS between 2.5 and 5.0. The time to worsen by ≥ 1 point in EDSS at 3 months was delayed in patients who received mitoxantrone plus methylprednisolone for 6 months before switching to IFN-β, compared to patients receiving IFN-β alone. Nevertheless, use of mitoxantrone has declined due to serious adverse events and it should be considered only in individual cases.

**Special situations and populations**

**Pregnancy.** Pregnancy risks should be discussed with patients and spouses before starting any DMT. Information on treatment of patients with highly active MS during pregnancy is limited. Most data come from studies and observations on individuals with a broad spectrum of MS phenotypes and severities. Therapies which can be administered throughout pregnancy or those which are stopped at conception but have lasting effects throughout pregnancy should be considered.

Immune reconstitution treatments administered in short courses, such as alemtuzumab, cladribine and probably rituximab, offer a window of opportunity in patients with aggressive MS planning a pregnancy (typically 4–6 months after the last dose, with some authors suggesting 1 month in the case of rituximab). To minimize the risk of recurrent disease activity in patients stable while using natalizumab, continuing treatment until the beginning of the third trimester or throughout pregnancy should be considered, as the haematological changes reported in exposed newborns are temporary and not clinically relevant. In the rare occurrence of aggressive MS developing in a pregnant woman, natalizumab or anti-CD20 therapies might be considered, but evidence of their safety and efficacy in such a situation is scant. This is an area for future research. Fingolimod is...
contraindicated not only due to the risk of recurrent disease activity after stopping treatment, but mainly due to the increased risk of major birth defects in exposed infants.61

After delivery, early reintroduction of DMTs is advisable if prior therapies do not have long-lasting therapeutic effects.62,63 In case of relapses, PLEX has been used successfully during pregnancy,64 but caution should be used since it can aggravate IRIS-like phenomena following natalizumab discontinuation.65,66 There is no specific evidence supporting the use of IA or IVIg as alternatives to PLEX in pregnant women with highly active MS.

Children. Severe relapses in children with MS have been treated with repeated corticosteroid boluses, PLEX, IVIg, rituximab and cyclophosphamide with varying degrees of benefit.67–69 However, inclusion of patients with demyelinating diseases other than MS cannot be ruled out in some of these studies, so their relevance to a paediatric MS population may be limited.

A retrospective single-centre study identified paediatric patients with highly active disease according to the definition in German guidelines70 (≥ 1 attack within the previous year and ≥ 9 T2 lesions or ≥ 1 Gd+ lesion while under first-line DMT. At diagnosis, ≥ 2 attacks and EDSS worsening within the last 12 months and ≥ 1 Gd+ lesion or a significant increase in T2 lesions within the last 6–12 months). The 12-month period before and after treatment initiation with natalizumab or fingolimod was studied. After 1 year of treatment, relapse rate was reduced by 95.2% in natalizumab-treated patients and 75.0% in fingolimod-treated patients. Significant reductions were also observed in MRI parameters of disease activity. When compared to a historical cohort of patients with mild-to-moderate disease activity treated with first-line therapies, patients on natalizumab or fingolimod had a 44.0% reduction in mean EDSS.71

Other than these, there are no treatment studies specifically addressing highly active disease in children. Nevertheless, most children present with a higher disease activity than adults and can be considered as having aggressive MS simply by their natural history. In the PARADIGMS clinical trial72 in paediatric MS, fingolimod was associated with a lower ARR (relative difference of 82.0%) and with less accumulation of MRI-detected brain lesions than IM IFN-β1a. Evidence relating to the use of rituximab in children is minimal and not focused in highly active MS.73

In summary, children with aggressive MS could benefit from initiating a more efficacious DMT from the start.69,74 Such a strategy takes the generally higher disease activity in this population into account, but it will have to be prospectively studied. The long-term impact of such therapies in children, including clinical and immunological developmental milestones, remains unknown.

Senior patients. There are no data regarding DMT in senior patients (> 65 years of age at time of treatment) with aggressive MS. In this age group, the safety and tolerability of highly effective DMTs in very active cases may be affected by MS- and age-related comorbidities.10,75–77 Given that senior patients are usually excluded from clinical trials, encouraging their representation in prospective trials would increase the available evidence but, to date, real-world data (registries, observational cohorts) may be the best source of information for this patient group.

How to manage and prevent complications of high-efficacy treatments
Risk-minimizing strategies before, during and after treatment with high-efficacy DMTs are reviewed in detail elsewhere.78 It is important to note that the time frame to implement such strategies is likely narrower in patients with aggressive MS. In addition, the occurrence and management of adverse events may be different for aggressive and non-aggressive MS depending on the comorbidities that may be associated with more severe MS and the adverse event profile of individual treatments. A list of some adverse events related to the immunosuppressive effects of these DMTs is shown in Supplemental Table 2.

Beyond treatment-related AEs, all patients should receive vaccinations as indicated in their respective regions, with special considerations depending on the type of vaccination and the MS treatment plan. A 4 to 6-week interval is typically recommended between administration of live-attenuated vaccines and initiation of high-efficacy treatments.79,80 Until new data emerge supporting the safety of live-attenuated vaccines in patients treated with immunosuppressive therapies, such vaccines are contraindicated during therapy and for a variable period after treatment termination, usually ranging from 2 to 6 months.81 Data support the effectiveness of vaccinations (sometimes reduced compared to placebo) during treatment with natalizumab, fingolimod or DMF, indicating that inactivated, subunit and toxoid vaccines can be administered in such cases.81
Achievements, gaps in knowledge and future perspectives

Considering available evidence to date regarding treatment in patients with aggressive MS, direct data are limited. The PLEX randomized, sham-controlled trial for severe attacks and the mitoxantrone and methylprednisolone randomized multicentre study in rMS were the only trials we identified that included patients with an aggressive disease. However, the former was not limited to patients with MS and the latter included patients with different MS phenotypes.

Therefore, many open issues remain. An important limitation to address the questions on treatment is the lack of a unified definition of aggressive MS. Before any consensus on treatment of aggressive MS can be obtained, it will be particularly important to develop a unified definition of aggressive disease. To the extent possible, paraclinical and clinical biomarkers may aid stratify the more severe cases of both relapsing and pMS phenotypes. As mentioned before, two studies have recently proposed EDSS ≥ 6.0 at 10 years as a definition of aggressive MS, but this proposal needs to be validated in other cohorts or registries. In addition, it is important to assess whether other biomarkers of aggressive disease (i.e. potentially neurofilament light chain levels, atrophy measures) may have an added value to NEDA-3 and other scores of breakthrough disease.

Open issues also remain regarding treatment of severe attacks: does oral methylprednisolone act as quickly and effectively as the IV form when an equivalent dose is used? Is 1 g/day the best dose in these cases? When should treatment be escalated to PLEX? Can natalizumab or anti-CD20 Mabs be used as treatments of severe attacks?

Concerning the use of DMTs, an escalation paradigm does not appear to be a good option in patients with aggressive MS. Based on current data, their window of therapeutic opportunity is narrow, as response to DMTs is better early in the disease course and in younger patients with minimal disability. Rather than escalating, starting a high-efficacy treatment in these instances would likely be a better option to limit the possibilities of breakthrough disease. Nevertheless, the evidence for conducting such approach is limited because pivotal trials were not focused in patients with aggressive MS. As for the post hoc analyses from the DMTs pivotal clinical trials, they are limited to comparisons with placebo or self-injectables, short term and underpowered to demonstrate any significant differences among DMTs in the more aggressive subpopulations. In the case of aHSCT, the most recent studies show that highly active patients with rMS are good candidates for this treatment, but such studies lack active comparators.

Consequently, more rigorous prospective studies are needed to confirm which treatments are the best option for patients with aggressive MS. Examples include the ongoing trials comparing aHSCT to high-efficacy treatments in patients with breakthrough disease despite first- or second-line DMTs. When considering a trial design for aggressive MS, a first step would be to consider the features that best define this phenotype early in the disease course to inform the inclusion criteria. A second step would consist in identifying a medium-term (2–3 years) endpoint related to, for example, EDSS 6.0 at 10 years, sensitive enough to occur frequently in the control group. The next steps would be selecting the active comparator the control group will receive and hypothesizing the expected reduction in outcome events with the more efficacious DMT. It is then that the sample size can be calculated. Finally, a decision on performing a conventional clinical trial or a pragmatic trial can be made according to the sample size.

It is important to consider that head-to-head comparative studies require very large sample sizes to demonstrate the differential efficacy and safety using the current outcome measures. Conducting pragmatic trials is a different approach that evaluates the effectiveness of an intervention in the real-world setting. These trials are designed to test interventions in the full spectrum of everyday clinical settings to maximize applicability and generalizability. Pragmatic trials measure mostly patient-centred outcomes, whereas conventional trials focus on measurable symptoms or biomarkers. Examples of such trials are TREAT-MS and DELIVER-MS, which compare two treatment paradigms: early highly effective therapy versus escalation of therapy. However, these two trials are not designed specifically for aggressive MS.

In addition, evidence from long-term follow-up of patients included in clinical trials and large, real-world cohorts assessing different subgroups of patients with MS, including pMS and special populations with aggressive MS, may provide useful data when controlled trials are not feasible.

Finally, we are aware that limitations on treatment access to highly efficacious DMTs vary widely from country to country, mostly due to financial restrictions. We hope papers such as this one may help MS specialists provide information about the usefulness
of starting a highly efficacious DMT in patients with aggressive MS to their local regulatory agencies.

Acknowledgements
The authors thank ECTRIMS for financial and administrative support of the focused workshop that served as the basis for this paper and all workshop attendees (Supplemental Table 2) for their participation. All attendees had the opportunity to review and comment upon an advanced draft of the manuscript prior to submission. They also thank Dr Stephen C. Reingold for assistance with manuscript writing and editing, supported by ECTRIMS.

Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: G.A. has received compensation for consulting services or participation in advisory boards from Sanofi, Merck and Roche; research support from Novartis; travel expenses for scientific meetings from Novartis, Roche and Stendhal; and speaking honoraria from Sanofi and Merck. E.I. has honoraria for advisory boards or lecturing for Sanofi Genzyme and Merck outside the submitted work. M.P.A. has received research grants and personal fees as a speaker and member of advisory boards by Biogen, Sanofi Genzyme, Merck Serono, Novartis, Roche and Teva outside the submitted work. T.D. reports grants from Novartis and Biogen. His institution received financial support from Novartis, Biogen, Roche, Merck Serono, Celgene, Sanofi Genzyme, MedDay, GeNeuro, Mitsubishi Pharma and Actelion for his activities as steering committee or advisory board member or consultant. S.V. has received grants, personal fees and non-financial support from Biogen, Celgene, Genzyme, Novartis, Teva outside the submitted work. B.H. has served on scientific advisory boards for Novartis and as DMSC member for AllergyCare and TG therapeutics, he or his institution have received speaker honoraria from Desitin, holds part of two patents: one for the detection of antibodies against KIR4.1 in a subpopulation of MS patients and one for genetic determinants of neutralizing antibodies to interferon. L.B. has received honoraria for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Sanofi Aventis and Teva Pharmaceuticals. M.T. has received research grants and compensation for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Sanofi Aventis and Teva Pharmaceuticals. M.T. is the co-editor of Multiple Sclerosis Journal—ETC.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The workshop on which the manuscript is based was supported in its entirety by the European Committee on Treatment and Research in Multiple Sclerosis (ECTRIMS).

ORCID iDs
Georgina Arrambide https://orcid.org/0000-0002-2657-5510
Tobias Derfuss https://orcid.org/0000-0001-8431-8769
Sandra Vukusic https://orcid.org/0000-0001-7337-7122
Bernhard Hemmer https://orcid.org/0000-0001-5985-6784
Mar Tintore https://orcid.org/0000-0001-9999-5359

Supplemental material
Supplemental material for this article is available online.

References
1. Tintore M, Vidal-Jordana A and Sastre-Garriga J. Treatment of multiple sclerosis – success from bench to bedside. Nat Rev Neurol 2019; 15(1): 53–58.
2. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler 2018; 24(2): 96–120.
3. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 90(17): 777–788.
4. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017; 376(3): 209–220.
5. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): A double-blind, randomised, phase 3 study. Lancet 2018; 391(10127): 1263–1273.
6. Rush CA, MacLean HJ and Freedman MS. Aggressive multiple sclerosis: Proposed definition and treatment algorithm. Nat Rev Neurol 2015; 11(7): 379–389.
7. Iacobaeus E, Arrambide G, Amato MP, et al. Aggressive Multiple Sclerosis (1): Towards a
definition of the phenotype. *Mult Scler* 2020; 26: 1031–1044.

8. Tintore M, Arrambide G, Otero-Romero S, et al. The long-term outcomes of CIS patients in the Barcelona inception cohort: Looking back to recognize aggressive MS. *Mult Scler*. Epub ahead of print 15 October 2019. DOI: 10.1177/1352458519877810.

9. Malpas CB, Manouchehrinia A, Sharmin S, et al. Aggressive form of multiple sclerosis can be predicted early after disease onset. *Mult Scler* 2019; 25: 605–607.

10. Magliozzi R, Howell OW, Nicholas R, et al. Inflammatory intrathecal profiles and cortical damage in multiple sclerosis. *Ann Neurol* 2018; 83(4): 739–755.

11. Zhang T, Tremlett H, Zhu F, et al. Effects of physical comorbidities on disability progression in multiple sclerosis. *Neurology* 2018; 90(5): e419–e427.

12. Bevan C and Gelfand JM. Therapeutic management of severe relapses in multiple sclerosis. *Curr Treat Options Neurol* 2015; 17(4): 345.

13. Le Page E, Veillard D, Laplaud DA, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): A randomised, controlled, double-blind, non-inferiority trial. *Lancet* 2015; 386(9997): 974–981.

14. Filippini G, Brusaferri F, Sibley WA, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev* 2000; 4: CD001331.

15. Weinshenker BG, O’Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 1999; 46(6): 878–886.

16. Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: Predictors of response. *Neurology* 2002; 58(1): 143–146.

17. Schilling S, Linker RA, Konig FB, et al. Plasma exchange therapy for steroid-unresponsive multiple sclerosis relapses: Clinical experience with 16 patients. *Nervenarzt* 2006; 77(4): 430–438.

18. Magana SM, Keegan BM, Weinshenker BG, et al. Beneficial plasma exchange response in central nervous system inflammatory demyelination. *Arch Neurol* 2011; 68(7): 870–878.

19. Llufríu S, Castillo J, Blanco Y, et al. Plasma exchange for acute attacks of CNS demyelination: Predictors of improvement at 6 months. *Neurology* 2009; 73(12): 949–953.

20. Zettl UK, Hartung HP, Pahnke A, et al. Lesion pathology predicts response to plasma exchange in secondary progressive MS. *Neurology* 2006; 67(8): 1515–1516.

21. Linker RA, Chan A, Sommer M, et al. Plasma exchange therapy for steroid-refractory superimposed relapses in secondary progressive multiple sclerosis. *J Neurol* 2007; 254(9): 1288–1289.

22. Meca-Lallana JE, Hernandez-Clares R, Leon-Hernandez A, et al. Plasma exchange for steroid-refractory relapses in multiple sclerosis: An observational, MRI pilot study. *Clin Ther* 2013; 35(4): 474–485.

23. Mauch E, Zwanzger J, Hettich R, et al. Immunoadsorption for steroid-unresponsive multiple sclerosis-relapses: Clinical data of 14 patients. *Nervenarzt* 2011; 82(12): 1590–1595.

24. Schimrigk S, Faisj S, Kohler W, et al. Escalation therapy of steroid refractory multiple sclerosis relapse with tryptophan immunoadsorption – observational multicenter study with 147 patients. *Eur Neurol* 2016; 75(5–6): 300–306.

25. Visser LH, Beekman R, Tijssen CC, et al. A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with i.v. methylprednisolone in the treatment of relapses in patients with MS. *Mult Scler* 2004; 10(1): 89–91.

26. Bar-Or A, Gold R, Kappos L, et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: Subgroup analyses of the DEFINE study. *J Neurol* 2013; 260(9): 2297–2305.

27. Hutchinson M, Fox RJ, Miller DH, et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: Subgroup analyses of the CONFIRM study. *J Neurol* 2013; 260(9): 2286–2296.

28. Devonshire V, Havrdova E, Radue EW, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of the FREEDOMS study. *Lancet Neurol* 2012; 11(5): 420–428.

29. Derfuss T, Bergvall NK, Sfikas N, et al. Efficacy of fingolimod in patients with highly active relapsing-remitting multiple sclerosis. *Curr Med Res Opin* 2015; 31(9): 1687–1691.

30. Derfuss T, Ontaneda D, Nichols J, et al. Relapse rates in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of pooled data from three phase 3 trials. *Mult Scler Relat Disord* 2016; 8: 124–130.

31. Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: A post-hoc
and subgroup analysis. *Lancet Neurol* 2011; 10(4): 329–337.

32. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. *Mult Scler* 2018; 24(12): 1594–1604.

33. Kappos L, O’Connor PW, Polman CH, et al. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. *J Neurol* 2013; 260(5): 1388–1395.

34. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: A retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol* 2009; 8(3): 254–260.

35. Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: Subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 2009; 256(3): 405–415.

36. Prosperini L, Sacca F, Cordioli C, et al. Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis. *J Neurol* 2017; 264(2): 284–294.

37. Huisman E, Papadimitrioupolou K, Jarrett J, et al. Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. *BMJ Open* 2017; 7(3): e013430.

38. Lorschieder J, Benkert P, Lienert C, et al. Comparative analysis of natalizumab versus fingolimod as second-line treatment in relapsing-remitting multiple sclerosis. *Mult Scler* 2018; 24(6): 777–785.

39. Curti E, Tsantes E, Baldi E, et al. The real-world effectiveness of natalizumab and fingolimod in relapsing-remitting multiple sclerosis. An Italian multicentre study. *Mult Scler Relat Disord* 2019; 33: 146–152.

40. Cobo-Calvo A, Bau L, Matas E, et al. Effectiveness of natalizumab in patients with highly active relapsing remitting multiple sclerosis. *Eur Neurol* 2015; 73(3–4): 220–229.

41. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: Post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurol* 2011; 10(4): 338–348.

42. Le Page E, Deburghgraeve V, Lester MA, et al. Alemtuzumab as rescue therapy in a cohort of 16 aggressive multiple sclerosis patients previously treated by Mitoxantrone: An observational study. *J Neurol* 2015; 262(4): 1024–1034.

43. Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol* 2019; 266(5): 1182–1193.

44. Durozard P, Maarouf A, Boutiere C, et al. Efficacy of rituximab in refractory RRMS. *Mult Scler* 2019; 25(6): 828–836.

45. Fagius J, Lundgren J and Oberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation. *Mult Scler* 2009; 15(2): 229–237.

46. Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: A multicentre single-group phase 2 trial. *Lancet* 2016; 388(10044): 576–585.

47. Nash RA, Hutton GJ, Rake MK, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology* 2017; 88(9): 842–852.

48. Mancardi GL, Sormani MP, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A phase II trial. *Neurology* 2015; 84(10): 981–988.

49. Muraro PA, Pasquini M, Atkins HL, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. *JAMA Neurol* 2017; 74(4): 459–469.

50. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. *Neurology* 2017; 88(22): 2115–2122.

51. Sormani MP, Muraro PA, Saccardi R, et al. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. *Mult Scler* 2017; 23(2): 201–204.

52. Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: A randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; 62(2): 112–118.

53. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: A placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; 360(9350): 2018–2025.

54. Edan G, Comi G, Le Page E, et al. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: A 3-year randomised trial. *J Neural Neurosurg Psychiatry* 2011; 82(12): 1344–1350.

55. Dobson R, Dassan P, Roberts M, et al. UK consensus on pregnancy in multiple sclerosis: ‘Association of British Neurologists’ guidelines. *Pract Neurol* 2019; 19(2): 106–114.
56. Rog D, Oh J, Chambers C, et al. Pregnancy outcomes in patients with RRMS treated with alemtuzumab from the clinical development program. *Mult Scler J* 2017; 23(3 Suppl.): 375–376.

57. Hellwig K, Ciplea AI, Thiel S, et al. Alemtuzumab and pregnancy – a case series from the German MS and Pregnancy Registry. *Mult Scler J* 2017; 23(3 Suppl.): 133.

58. Coyle PK. Management of women with multiple sclerosis through pregnancy and after childbirth. *Ther Adv Neurol Disord* 2016; 9(3): 198–210.

59. Langer-Gould AM. Pregnancy and family planning in multiple sclerosis. *Continuum* 2019; 25(3): 773–792.

60. Haghikia A, Langer-Gould A, Rellensmann G, et al. Natalizumab use during the third trimester of pregnancy. *JAMA Neurol* 2014; 71(7): 891–895.

61. EMA. Updated restrictions for Gilenya: Multiple sclerosis medicine not to be used in pregnancy, https://www.ema.europa.eu/en/documents/press-release/updated-restrictions-gilenya-multiple-sclerosis-medicine-not-be-used-pregnancy_en.pdf (2019, accessed 25 November 2019).

62. Vukusic S, Durand-Dubief F, Benoit A, et al. Natalizumab for the prevention of post-partum relapses in women with multiple sclerosis. *Mult Scler* 2015; 21(7): 953–955.

63. Portaccio E, Moiola L, Martinelli V, et al. Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: II: Maternal risks. *Neurology* 2018; 90(10): e832–e839.

64. Cox JL, Koepsell SA and Shunkwiler SM. Therapeutic plasma exchange and pregnancy: A case report and guidelines for performing plasma exchange in a pregnant patient. *J Clin Apher* 2017; 32(3): 191–195.

65. Lenhard T, Biller A, Mueller W, et al. Immune reconstitution inflammatory syndrome after withdrawal of natalizumab? *Neurology* 2010; 75(9): 831–833.

66. Papeix C, Depaz R, Tourbah A, et al. Dramatic worsening following plasma exchange in severe post-natalizumab withdrawal multiple sclerosis relapse. *Mult Scler* 2011; 17(12): 1520–1522.

67. Makhani N, Gorman MP, Branson HM, et al. Cyclophosphamide therapy in pediatric multiple sclerosis. *Neurology* 2009; 72(24): 2076–2082.

68. Hanumanthe SB, Francisco C, Hart J, et al. Biopsy-supported tumefactive demyelination of the central nervous system in children. *J Child Neurol* 2016; 31(14): 1528–1533.

69. McGinley M and Rossman IT. Bringing the HEET: The argument for high-efficacy early treatment for pediatric-onset multiple sclerosis. *Neurotherapeutics* 2017; 14(4): 985–998.

70. Huppke P. S1-Leitlinie 022/014: Pädiatrische Multiple Sklerose. *AWMF Online*, http://www.awmf.org/leitlinien/detail/ll/022-014.html (2016, accessed 25 November 2019).

71. Huppke P, Huppke B, Ellenberger D, et al. Therapy of highly active pediatric multiple sclerosis. *Mult Scler* 2019; 25(19): 72–80.

72. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med* 2018; 379(11): 1017–1027.

73. Beres SJ, Graves J and Waubant E. Rituximab use in pediatric central demyelinating disease. *Pediatr Neurol* 2014; 51(1): 114–118.

74. Chitnis T, Ghezzi A, Bajer-Kornek B, et al. Pediatric multiple sclerosis: Escalation and emerging treatments. *Neurology* 2016; 87(9 Suppl. 2): S103–S109.

75. Marrie RA. Comorbidity in multiple sclerosis: Implications for patient care. *Nat Rev Neurol* 2017; 13(6): 375–382.

76. Kowalec K, McKay KA, Patten SB, et al. Comorbidity increases the risk of relapse in multiple sclerosis: A prospective study. *Neurology* 2017; 89(24): 2455–2461.

77. McKay KA, Tremlett H, Fisk JD, et al. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology* 2018; 90(15): e1316–e1323.

78. Winkelmann A, Loebermann M, Reisinger EC, et al. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol* 2016; 12(4): 217–233.

79. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; 58(3): e44–e100.

80. Esposito S, Bonanni P, Maggi S, et al. Recommended immunization schedules for adults: Clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (W Aidid). *Hum Vaccin Immunother* 2016; 12(7): 1777–1794.

81. Epstein DJ, Dunn J and Deresinski S. Infectious complications of multiple sclerosis therapies: Implications for screening, prophylaxis, and management. *Open Forum Infect Dis* 2018; 5(8): ofy174.
82. Corboy JR, Weinshenker BG and Wingerchuk DM. Comment on 2018 American Academy of Neurology guidelines on disease-modifying therapies in MS. Neurology 2018; 90(24): 1106–1112.

83. Massey JC, Sutton JJ, Ma DDF, et al. Regenerating immunotolerance in multiple sclerosis with autologous hematopoietic stem cell transplant. Front Immunol 2018; 9: 410.

84. Boesen F, Norgaard M, Trenel P, et al. Longer term effectiveness of inpatient multidisciplinary rehabilitation on health-related quality of life in MS patients: A pragmatic randomized controlled trial – The Danish MS Hospitals Rehabilitation Study. Mult Scler 2018; 24(3): 340–349.

85. Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci 2011; 13(2): 217–224.

86. Ontaneda D, Tallantyre E, Kalincik T, et al. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. Lancet Neurol 2019; 18(10): 973–980.