Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm

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Purpose of review
The treatment of multiple sclerosis is evolving rapidly with 11 classes of disease-modifying therapies (DMTs). This article provides an overview of a new classification system for DMTs and treatment paradigm for using these DMTs effectively and safely.

Recent findings
A summary of research into the use of more active approaches to early and effective treatment of multiple sclerosis with defined treatment targets of no evident disease activity (NEDA). New insights are discussed that is allowing the field to begin to tackle more advanced multiple sclerosis, including people with multiple sclerosis using wheelchairs. However, the need to modify expectations of what can be achieved in more advanced multiple sclerosis are discussed; in particular, the focus on neuronal systems with reserve capacity, for example, upper limb, bulbar and visual function.

Summary
The review describes a new more active way of managing multiple sclerosis and concludes with a call to action in solving the problem of slow adoption of innovations and the global problem of untreated, or undertreated, multiple sclerosis.

Keywords
asynchronous progressive multiple sclerosis, multiple sclerosis is a central length-dependent axonopathy, no evident disease activity, therapeutic lag, treat-2-target

INTRODUCTION

The treatment of multiple sclerosis is evolving rapidly with 11 classes of disease-modifying therapies (DMTs). This article provides an overview of a new classification system and treatment paradigm for using these DMTs effectively and safely. To tackle more advanced multiple sclerosis, including people with multiple sclerosis using wheelchairs, we need a two pronged approach. A more aggressive approach to early and effective treatment of multiple sclerosis with defined treatment target of no evident disease activity (NEDA). In addition, we need to modify our expectation of what can be achieved in more advanced multiple sclerosis and focus on neuronal systems with reserve capacity, for example, upper limb, bulbar and visual function. The review concludes with a call to action in solving the problem with slow adoption of innovations and the global problem of untreated, or undertreated, multiple sclerosis.

NO EVIDENT DISEASE ACTIVITY AS A TREATMENT TARGET

Data shows that both relapses and ongoing focal inflammatory activity on MRI (new or enlarging T2-lesions and gadolinium (Gd)-enhancing lesions) are associated with a worse short-term to intermediate-term prognosis, contradicting natural history studies [1,2]. These observations have led to increasing adoption of NEDA as a treatment target in multiple

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KEY POINTS

- Multiple sclerosis should be treated actively using a no evident disease activity (NEDA) as a treatment target.
- Multiple sclerosis is an asynchronous progressive disease that can be explained by it being a central length-dependent axonopathy.
- Immune reconstitution therapies (IRTs) offer several advantages when treating multiple sclerosis.

sclerosis [3]. NEDA is a composite of three related measures of disease activity: no relapses, no disability progression and no MRI activity (new or enlarging T2 lesions or Gd-enhancing lesions) [3–5]. The composite emerged from post hoc analyses of phase 3 clinical trials [3–5].

NEDA is an important goal for treating individual patients, and could potentially be used as an outcome in clinical trials [6]. To adopt NEDA in day-to-day clinical practice, it is advisable to 'rebaseline' treated patients after the onset of action of the DMT been assessed. The timing of the baseline MRI is based on the pharmacodynamics of the DMT concerned [7]. Please note that recommendations for immune reconstitution therapies (IRTs formerly referred to as induction therapies) different to maintenance therapies [7]. In the case of an IRT, for example, alemtuzumab or cladribine, which are given as short courses breakthrough disease activity can be used as an indicator to retreat rather than to necessarily switch therapy. Therefore, a rebaselining MRI should be delayed until after the final initial course of therapy, for example, 2 years, or close enough to the time when a third, or subsequent course, can be administered [8,9]. The question of how many cycles need to be given before considering that a person has failed an IRT will remain a moot point until much needed long-term evidence emerges to guide us. In comparison to IRTs, disease activity on maintenance therapies, provided the patient has been adherent to treatment, is usually interpreted as a sub-optimal or non-response [1].

A major criticism of NEDA is the inclusion of nonrelapse-associated disease worsening, separate to that of incomplete recovery from relapses, as a component of the composite. Worsening disability in the absence of relapses may have little to do with ongoing focal inflammatory activity and may simply represent a dying back central axonopathy as a result of preceding focal inflammatory lesions [10▪▪,11▪]. Although some of the more effective DMTs may modify this stage of the disease, many neurologists feel uncomfortable switching, or stopping a DMT, based simply on nonrelapse-associated worsening disability [11▪].

The definition of NEDA is evolving with clinical practice. Some centres are incorporating brain atrophy and/or cerebrospinal fluid neurofilament light chain (NFL) into the composite and referring to these as NEDA-4 (brain atrophy) [12] and NEDA-5 (CSF-NFL levels) [13,14]. From a scientific perspective, including a more objective end-organ biomarker makes sense. In pivotal phase 3 studies, both focal inflammatory lesions, as measured by increased T2-lesion load over 2 years, and end-organ damage, measured using whole brain volume loss in year 2 of the studies, explain approximately 75% of the variance of disability progression over 2 years on DMT, which is better than either metric alone [15]. This is important in that some DMTs, in particular, the higher efficacy therapies, have been shown to reduce the rate of brain atrophy in treated patients [16–19].

Many commentators remain sceptical of using NEDA as a treatment target; they remain critical of the zero tolerance target. They are concerned that the majority of patients would end up being on 'more risky' high-efficacy therapies. A less aggressive approach using the Rio [20], or modified Rio [21], scores aims to allow a minimal level of disease activity (MEDA). MEDA, however, flies in the face of the science of the focal inflammatory lesion being 'bad' and is associated with poor short, intermediate and long-term outcomes. If the majority of patients end up on the so-called 'risky high-efficacy' therapies because of breakthrough disease activity, then this is what they probably need to treat their multiple sclerosis. Achieving long-term remission or, NEDA, is a well established treatment target in other autoimmune diseases, such as rheumatoid arthritis [22] and inflammatory bowel disease [23]. Patients with multiple sclerosis treated-to-target of NEDA do better than those with breakthrough disease (at a clinical or subclinical level) [12]. I would, therefore, strongly encourage neurologists to adopt NEDA as a treatment target for multiple sclerosis.

Figure 1 is a flowchart of one example of how to implement a treat-2-target of NEDA strategy. The important take-home message is that the treatment target in multiple sclerosis have moved and now require the setting of goals and the active monitoring of outcomes to achieve these goals. Finally, there is an evident need to regularly update the definition of NEDA as new technologies become available and are validated as predictors of a treatment response; I envisage the definition of NEDA changing in the near future to include more objective metrics, particularly ones measuring end-organ damage, and

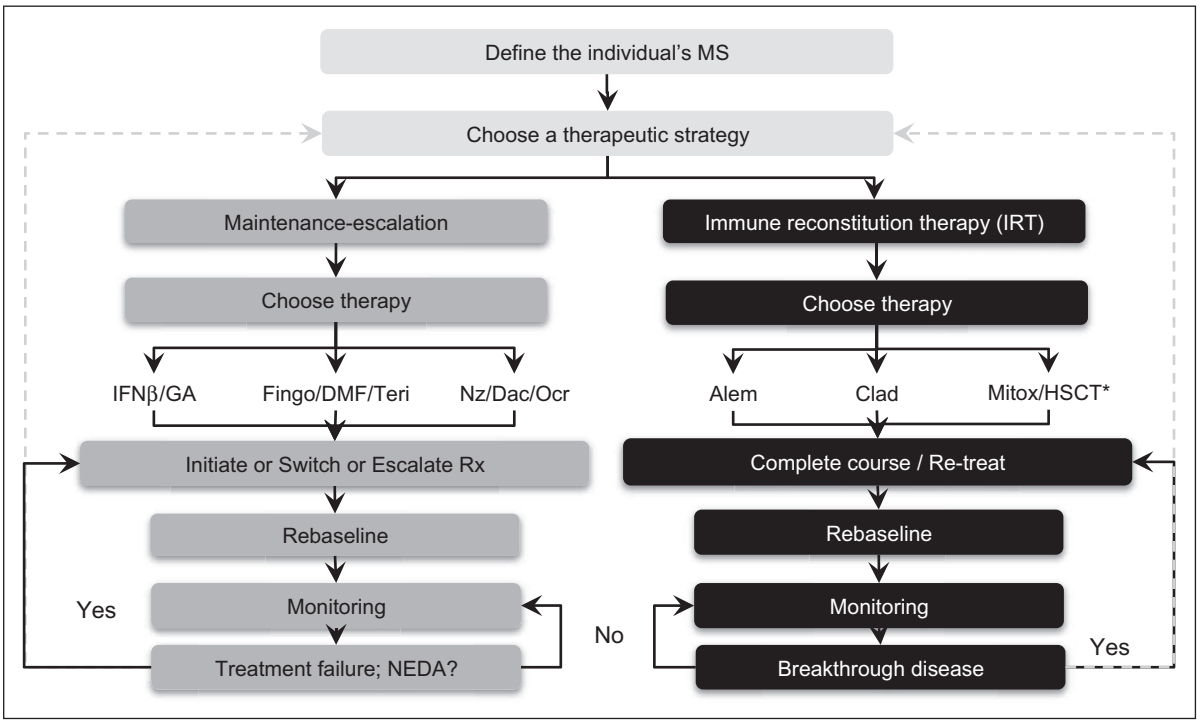

FIGURE 1. Treat-2-target algorithm of no evident disease activity in relapsing-forms of multiple sclerosis (adapted from Giovannoni *et al.* [7]). Alem, alemtuzumab; Clad, cladribine; Dac, daclizumab; DMF, dimethyl fumarate; Fingo, fingolimod; GA, glatiramer acetate; HSCT, hematopoietic stem cell transplantation; IFNβ, interferon-beta; Mitox, mitoxantrone; Nz, natalizumab; Ocr, ocrelizumab; Teri, teriflunomide.

the inclusion of patient-related outcome measures (PROMS).

DISEASE-MODIFYING THERAPIES

A detailed discussion of each individual DMT is beyond the scope of this review. Table 1 summarizes the most important attributes of each DMT. In relation to efficacy, or relative efficacy, of individual DMTs, this become less important in the context of a strategy of treat-2-target of NEDA. Choosing a DMT with a lower efficacy rate, that is, lower NEDA rate (Fig. 2), simply means that a greater proportion of treated patients will need to be switched onto higher efficacy therapies over time to achieve NEDA. In comparison, patients choosing high-efficacy therapies will have a greater chance of achieving NEDA with their initial choice of therapy. The real question that needs to be answered is, 'do patients treated with the step-care approach do worse on average than those offered rapid escalation or high-efficacy DMTs first line?' The latter of the three approaches has been referred to flipping the pyramid, that is, choosing high-efficacy therapies first line (Fig. 3). On the basis of the current evidence, one could argue 'YES.' In recent trials of alemtuzumab [16,17,24], ocrelizumab [25▪▪,26] and daclizumab [26], patients randomized to 2 years of interferon-beta-1a therapy had poorer outcomes than those receiving highly active therapy from the outset.

In relation to the conventional stepcare paradigm, patients switching horizontally in terms of efficacy from interferon-beta to glatiramer acetate, or vice-versa, that is, from one moderate efficacy DMT to another moderate efficacy DMT, did not do as well as patients switching vertically to fingolimod a highly effective DMTs [27]. Similarly, patients escalating to natalizumab, a very-high efficacy DMT, did better than patients being escalated to the less effective, but still high-efficacy, DMT fingolimod [28].

What determines what efficacy level of a DMT is appropriate depends on individual factors, for example, baseline prognostic profile, family planning, local or national treatment guidelines, socioeconomic factors, patient factors in particular comorbidities, cognitive impairment, risk aversion and lifestyle issues. The adoption rate of the rapid escalation or the flipping of the pyramid over the conventional step-care approach is highly variable across the world and even within countries. To address the variation in clinical practice and the way multiple sclerosis is treated, we launched a policy document 'Brain Health: time matters in multiple sclerosis' [29▪▪], which aims to activate

Table 1. Main attributes of licensed multiple sclerosis disease-modifying therapies

	Trade name	Mode of action	Efficacy	Class	Immuosuppression	Posology	Main AEs	NAbs	Monitoring requirements	Pregnancy	Breastfeeding	Male fertility	Vaccination	SmPC
Interferon-beta		Immunomodulatory (not immunosuppressive), pleiotropic immune effects	Moderate	Maintenance immunomodulatory	No	Variable and depends on formulation	Injection site reactions, flu-like symptoms, abnormal LFTs, lymphopaenia, leucopenia	Yes	Baseline: FBC, U&E, LFTs, TFTs, serum protein electrophoresis, renal protein. Follow-up: 1-month, 3-month, 6-month and 6-monthly FBC, U&E and LFTs. TFTs 12 monthly. NABs 12 and 24 months	Increased risk of spontaneous abortion. Initiation of treatment is not recommended during pregnancy	Safe, not contra-indicated	Safe	Safe	
IFN-beta-1b	Betaseron, Betaferon, Extavia	Continuous type 1 interferon receptor stimulation and downregulation	"	'	"	'Freeze-dried, 250 μg s.c. alt. day	"	30%	"	'	"	'	"	'
IFN-beta-1a	Avonex	Pulsatile, type 1 interferon stimulation	"	'	"	'refilled syringe, 30 μg IM weekly	"	5%	"	'	"	'	"	'
IFN-beta-1a	Rebif	Continuous type 1 interferon receptor stimulation and downregulation	"	'	"	'refilled syringe or cartridge, 22/44 μg sc TIW	"	12–25%	"	'	"	'	"	'
Peg-IFN-beta-1a	Plegridy	Pegylated (long-circulating half-life), continuous type 1 interferon receptor stimulation	"	'	"	'refilled syringe 125 μg sc 2-weekly	"	2%	"	'	"	'	"	'
Glatiramer acetate	Copaxone	Immunomodulatory (not immunosuppressive), pleiotropic immune effects	Moderate	Maintenance immunomodulatory	No	Prefilled syringe 20 mg sc daily or 40 mg sc TIW	Injection site reactions, lipoatrophy, flushing reactions	n/a	None required	No known reproductive toxicity. Generally considered to be well tolerated in pregnancy	Safe, not contra-indicated	Safe	Safe	https://www.medicines.org.uk/emc/product/183
Mitoxantrone	Novatrone	Immune depleter (topoisomerase inhibitor)	Very high	IRT (nonselective)	Yes, intermittent	12 mg/m^2 IVI 3 monthly for 2 years; maximum dose of 140 mg/m^2	Leucopenia, hair loss, nausea, vomiting, infections, cardiomyopathy, amenorrhoea	n/a	Baseline: FBC, U&E, LFTs, TFTs, serum protein electrophoresis, serum immunoglubulin levels, serology (VZV, HIV1&2, hepatitis B&C, syphilis), TB elispot and pregnancy test. Follow-up: 3-monthly (predosing) FBC, U&E and LFTs. TFTs 12 monthly.	Contra-indicated. Risk of amenorrhoea and premature menopause (fertility counselling regarding harvesting and storage of eggs)	Not recommended during treatment	Generally considered unnecessary as only a transient drop in sperm counts	Not recommended until immune reconstitution has occurred	https://www.medicines.org.uk/emc/product/1694/smpc
Natalizumab	Tysabri	Anti-VLA4, selective adhesion molecule inhibitor	Very high	Maintenance immunosuppressive	Yes, continuous	300 mg i.v. 4-weekly	Infusion reactions, progressive multifocal leucoencephalopathy (PML)	5–6%	Baseline: FBC, U&E, LFTs, JCV-serology and pregnancy test. Follow-up: LFTs 3 monthly for a year. NABs at 12 months. JCV serology 6-monthly	Available data do not suggest an effect of natalizumab exposure on pregnancy outcomes	As natalizumab is a monoclonal antibody, with only very small amounts entering the breast milk, it is considered well tolerated; that is, very low risk to baby	Safe	Humoral immune responses to recall antigens and neoantigens preserved. Live vaccines have not been studied and should, therefore, be avoided	https://www.medicines.org.uk/emc/product/222
Fingolimod	Gilenya	Selective S1P modulator, prevents egress of lymphocytes from lymph nodes	High	Maintenance immunosuppressive	Yes, continuous	0.5 mg daily p.o.	Bradycardia, hypertension, bronchospasm, lymphopaenia, abnormal LFTs, infections, basal cell carcinoma, macular oedema, opportunistic infections (PML, cryptococcosis, etc.)	n/a	Baseline: BP, FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV1 and 2, hepatitis B and C, syphilis), TB elispot, pregnancy test and ECG. Follow-up: 3-monthly FBC, U&E and LFTs. TFTs 12 monthly. OCT at 3–months for macular oedema	Contra-indicated, if a woman becomes pregnant while taking fingolimod, discontinuation of fingolimod is recommended	Not recommended; fingolimod crosses in breast milk	Well tolerated	To be avoided	https://www.medicines.org.uk/emc/product/4545
Dimethyl fumarate	Tecfidera	Pleotropic, NRF2 activation, downregulation of NFKβ	Moderate/high	Maintenance immunosuppressive	Yes, continuous	240 mg BD	Flushing, gastrointestinal symptoms (dyspepsia, cramps and diarrhoea), lymphopaenia, abnormal LFTs, proteinuria, PML	n/a	Baseline: FBC, U&E, LFTs, urine protein and pregnancy test. Follow-up: FBC and urine protein 3-monthly for a year, then 6-monthly	DMF should only be used during pregnancy if clearly needed and if the potential benefit justifies the potential undefined risk to the foetus	Well tolerated	Well tolerated	Not recommended until immune reconstitution has occurred	https://www.medicines.org.uk/emc/product/5256

Table 1 (*Continued*)

	Trade name	Mode of action	Efficacy	Class	Immuosuppression	Posology	Main AEs	NAbs	Monitoring requirements	Pregnancy	Breastfeeding	Male fertility	Vaccination	SmPC
Alemtuzumab	Lemtrada	Anti-CD52, nonselective immune deplete	Very high	IRT (nonselective)	Yes, intermittent	12 mg IVI × 5 days yr-1, 12 mg IVI × 3 days yr-2	Infusion reactions, infections, opportunistic infections, leucopoenia, secondary autoimmunity (thyroid, ITP, renal, etc.)	Low after 2 courses	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV 1and 2, hepatitis B and C, syphilis), TB elispot, pregnancy test and cervical smear. Follow-up (for 48 months after last course): monthly FBC, U&E and urine analysis and 3-monthly TFTs	Pregnancy recommended 4 months after a course of alemtuzumab	As alemtuzumab is a monoclonal antibody, with only very small amounts entering the breast milk, it is considered well tolerated; that is. very low risk to baby	Well tolerated; no evidence of sperm abnormalities	Not recommended until immune reconstitution	https://www.medicines.org.uk/emc/product/5409
Teriflunomide	Aubagio	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis), antiproliferative	Moderate	Maintenance immunomodulatory	Possible (no well defined immunosuppressive signature)	7 or 14 mg daily p.o. (7 mg dose only licensed in the USA)	Hair thinning, gastrointestinal symptoms (nausea, diarrhoea), abnormal LFTs, leucopoenia	n/a	Baseline: BP, FBC, U&E, LFTs, urine protein and pregnancy test. Follow-up: 2-weekly LFTs for 6 months and every 8 weeks thereafter. Weekly LFT monitoring is recommended for ALT elevations between two-fold and three-fold the upper limit of normal. 3-monthly FBC for 1 year followed by 6-monthly assessment thereafter	Teriflunomide may cause serious birth defects and is, therefore, contraindicated in pregnancy. Women wishing to become pregnant should undergo an accelerated elimination procedure with cholestyramine or-activated charcoal	Breast-feeding women must not receive teriflunomide as it is excreted in breast milk	Not recommended; the risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low	Inactivated neoantigen (first vaccination), or recall antigen (reexposure) well tolerated. Live attenuated vaccines should be avoided	https://www.medicines.org.uk/emc/product/5244
Daclizumab	Zinbryta	Anti-CD25 (high-affinity IL2 receptor), IL2 modulator (reduces T-reg, effector T-cell and memory B-cell function and simultaneously expands the CD56-bright NK cells)	High	Maintenance immunomodulatory	Possible	150 mg s.c. 4-weekly	Abnormal LFTs, hypersensitivity skin rash, autoimmune hepatitis, increased risk of serious infections, colitis	<2%	Baseline: FBC, U&E, LFTs, TFTs, serology (VZV, HIV 1 and 2, hepatitis B and C, syphilis), TB elispot and pregnancy test. Follow-up: monthly LFTs and 3-monthly FBC, U&E and urine analysis	Daclizumab should only be used during pregnancy only if the potential benefit justifies the potential undefined risk to the foetus	As natalizumab is a monoclonal antibody, with only very small amounts entering the breast milk, it is considered well tolerated; that is, very low risk to baby.	Likely to well tolerated	Inactivated neoantigen (first vaccination), or recall antigen (reexposure) well tolerated. Live attenuated vaccines should be avoided	https://www.medicines.org.uk/emc/product/7379
Cladribine	Mavenclad	Deoxyadenosine (purine) analogue, adenosine deaminase inhibitor, selective T-cell and B-cell depletion	High	IRT (semi-selective)	Yes, intermittent	10 mg tablets: cumulative dose of 3.5 mg/kg over 2 years. Tablets given for 4–5 days in month 1 and 2 in yr-1 and the cycle is repeated in yr-2 (8–10 days of treatment per year)	Lymphopaenia, infections (in particular, herpes, zozter)	n/a	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV 1 and 2, hepatitis B and C, syphilis), TB elispot, pregnancy test and cervical smear. Follow-up: FBC 2 and 6 months after start of treatment in each treatment year	Pregnancy is not recommended for at least 6 months after the last dose	Breast-feeding is contraindicated during treatment with cladribine and for 1 week after the last dose	Male patients must take precautions to prevent pregnancy of their female partner for at least 6 months after the last dose	Not recommended until immune reconstitution has occurred	https://www.medicines.org.uk/emc/product/8435
Ocrelizumab	Ocrevus	Anti-CD20, B-cell deplete	Very high	Maintenance immunosuppressive	Yes, continuous	Initially 300 mg IVI, followed 2-weeks later by second dose of 300 mg IVI. Subsequent dosing 600 mg IVI 6 monthly	Infusion reactions, infections, possible hypogammaglobulinaemia with prolonged use	< 1%	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV 1 and 2, hepatitis B and C, syphilis), TB elispot, pregnancy test and cervical smear. Follow-up: annual serum immunoglobulin levels	Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus	As natalizumab is a monoclonal antibody, with only very small amounts entering the breast milk, it is considered well tolerated; that is, very low risk to baby	Likely to well tolerated	To be avoided	https://www.medicines.org.uk/emc/product/8898

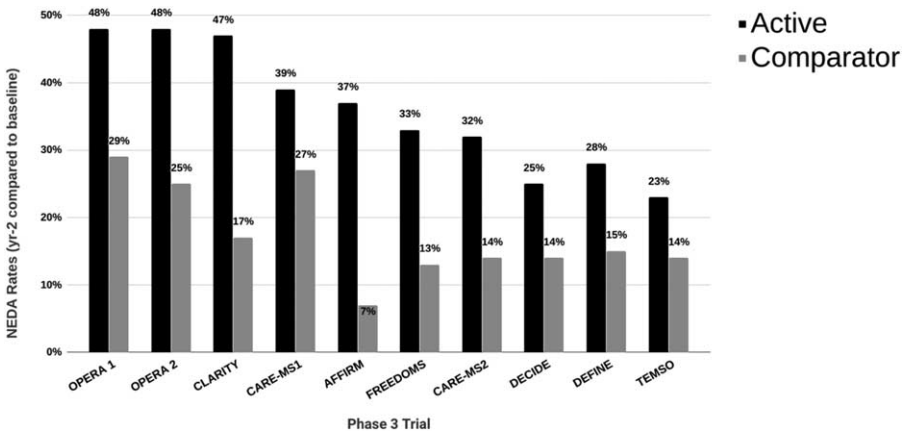

FIGURE 2. NEDA rates of disease-modifying therapies for relapsing forms of multiple sclerosis from phase 3 trials. OPERA I, ocrelizumab versus sc IFN β-1a [36]; OPERA II, ocrelizumab versus sc IFN β-1a [36]; CLARITY, cladribine tablets versus placebo [4]; CARE-MS I, alemtuzumab versus sc IFN β-1a [4,37▪▪]; AFFIRM, natalizumab versus placebo [4,5,37▪▪], FREEDOMS, fingolimod versus placebo [38]; CARE-MS II, alemtuzumab versus sc IFN β-1a [39▪▪]; DECIDE, daclizumab versus im IFN β-1a [40▪]; DEFINE, dimethyl fumarate versus placebo [41]; TEMSO, teriflunomide versus placebo [42].

the multiple sclerosis community to be more proactive in the way we manage multiple sclerosis.

In terms of the pathogenesis of multiple sclerosis, it is worth asking the question if is there anything common to the modes of action of the licensed DMTs that could explain why such disparate classes of therapies are all capable of modifying the inflammatory component of

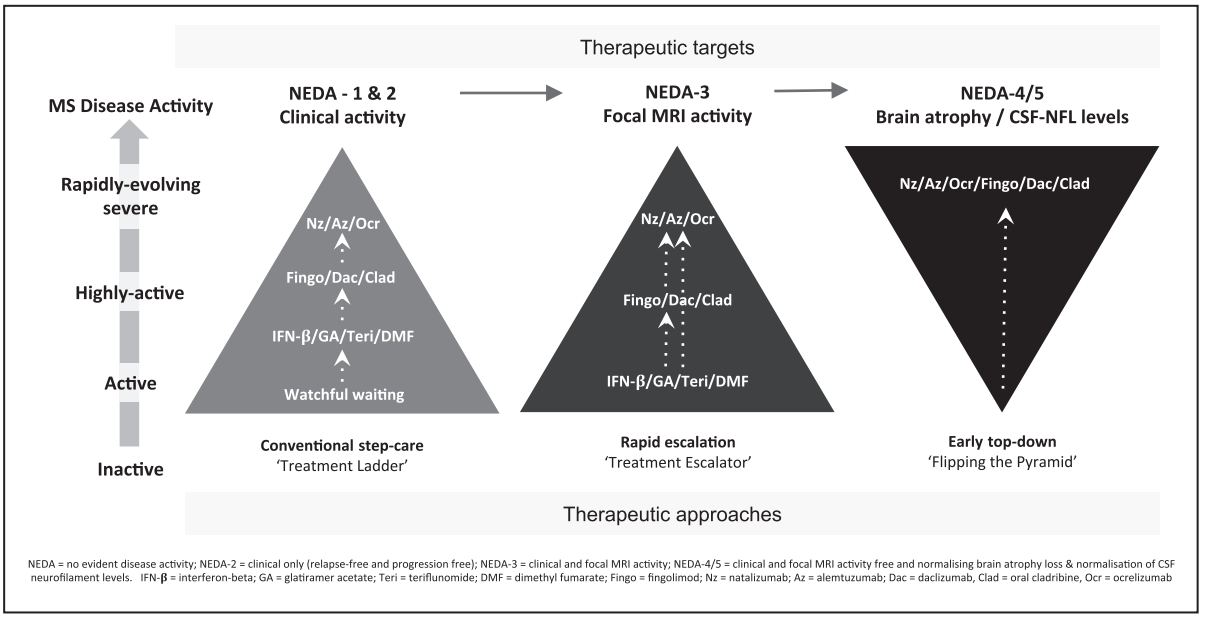

FIGURE 3. Different therapeutic approaches to the use of disease-modifying therapies in the treatment of relapsing forms of multiple sclerosis. Disease activity: active multiple sclerosis: documented clinical relapses in the last 2-years and/or the presence of Gd-enhancing lesions or increased T2 lesion load in the last 12 months. Highly active multiple sclerosis: unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with a platform therapy, or one or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. Rapidly evolving severe multiple sclerosis: two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. Therapeutic targets: NEDA, no evident disease activity; NEDA 1/2, clinical only (relapse-free and/or progression-free); NEDA-3, clinical and focal MRI activity; NEDA-4/5, clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. Az, alemtuzumab; Clad, oral cladribine; Dac, daclizumab; DMF, dimethyl fumarate; Fingo, fingolimod; GA, glatiramer acetate; IFN-β, interferon-beta; Nz, natalizumab; Ocr, ocrelizumab; Teri, teriflunomide.

Table 2. Similarities and differences between maintenance treatments and immune reconstitution therapies

	Maintenance-escalation	Immune reconstitution therapy
Duration	Continuous	Intermittent: one-off or pulsed short courses
Adherence	Variable	Likely to be high
Efficacy	Low to very high	High to very high
Reversibility	Reversible	Irreversible
Risk	Perceived to be lower risk. Risk is cumulative and increases with time	Perceived to be higher. Risk tends to be front loaded when initial immune depletion occurs
Breakthrough disease	Breakthrough disease indicates a suboptimal response. NEDA is a reliable metric to assess efficacy	Breakthrough disease not necessarily a marker of a suboptimal response, but rather an indication to retreat. NEDA unreliable metric to assess efficacy
Rebound activity	Rebound activity, that is, disease activity over an above-baseline disease activity, is relatively frequent, particularly, with the washing-out of anti-trafficking agents, for example, natalizumab and fingolimod	Rebound activity is less common, although it has been described with all IRTs
Pregnancy	Generally, not recommended as the agent is present within the body continuously. Safety of maintenance therapies in pregnancy depends on the profile of individual DMTs	Generally well tolerated after the immune system has reconstituted. Unlike the maintenance therapies, IRTs do not persist in the body continuously
Vaccinations	Variable response depending on specific DMT. For immunosuppressive therapies, live vaccines are contraindicated	After immune reconstitution, vaccines are well tolerated and effective, including live vaccinations. Most HSCT protocols recommend a re-vaccination programme
Cure	Maintenance therapies do not eliminate autoimmunity, therefore, they do not offer possibility of a cure	IRTs can induce long-term remission off DMTs and the possibility of a cure[a]
DMTs	Interferon-beta, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, daclizumab, ocrelizumab	Nonselective: mitoxantrone, alemtuzumab (anti-CD52), HSCT Semi-selective: cladribine

[a]How to define a cure in multiple sclerosis is controversial. Some commentators have recommended cumulative NEDA at 15 years or more after an IRT (3). DMTs, disease-modifying therapies; HSCT, hematopoietic stem cell transplantation; IRT, immune reconstitution therapy; NEDA, no evident disease activity.

multiple sclerosis. Baker *et al.* [30▪] have attempted this and suggest that all DMTs may be working via a common target, the memory B cell. Importantly, they highlight that antitumour necrosis alpha (anti-TNF-δ) and atacicept, which neutralizes both BAFF (B-cell activating factor) and APRIL (a B-cell proliferation-inducing ligand), expand the memory B-cell population and exacerbate multiple sclerosis disease activity [30▪]. These observations suggest that memory B cells are the most likely culprit in driving ongoing disease activity. The question is, what is unique to this population of cells?

One development that is worth highlighting is the emerging classification of DMTs into maintenance and immune reconstitution therapies (Table 2) and those that are immunomodulatory compared with those that result in immunosuppression (Fig. 4). In addition, immunosuppressive therapies can be further subdivided into those that cause prolonged compared with short-term immunosuppression, the relative attributes of which are compared in Table 3.

MAINTENANCE VERSUS IMMUNE RECONSTITUTION THERAPIES

In Fig. 1 there is a fork in relation to two treatment philosophies; maintenance-escalation versus IRTs. By definition an IRT is given as a short course, that is, as a one-off treatment in the case of HSCT or intermittently as in the case of alemtuzumab or cladribine. IRTs are not given continuously and additional courses of the therapy are only given if there is a recurrence of inflammatory activity. IRTs have the ability to induce long-term remission and in some cases potentially a cure. One could argue that none of our treatments cure multiple sclerosis, but unless we define what constitutes a cure and look for it we would not find it.

One definition, defines a multiple sclerosis cure as NEDA 15 years after the administration of an IRT [3]. The authors justify using 15 years as it is the most commonly accepted time point for defining benign multiple sclerosis and happens to be beyond median time to the onset of secondary progressive multiple sclerosis in natural history studies [31].

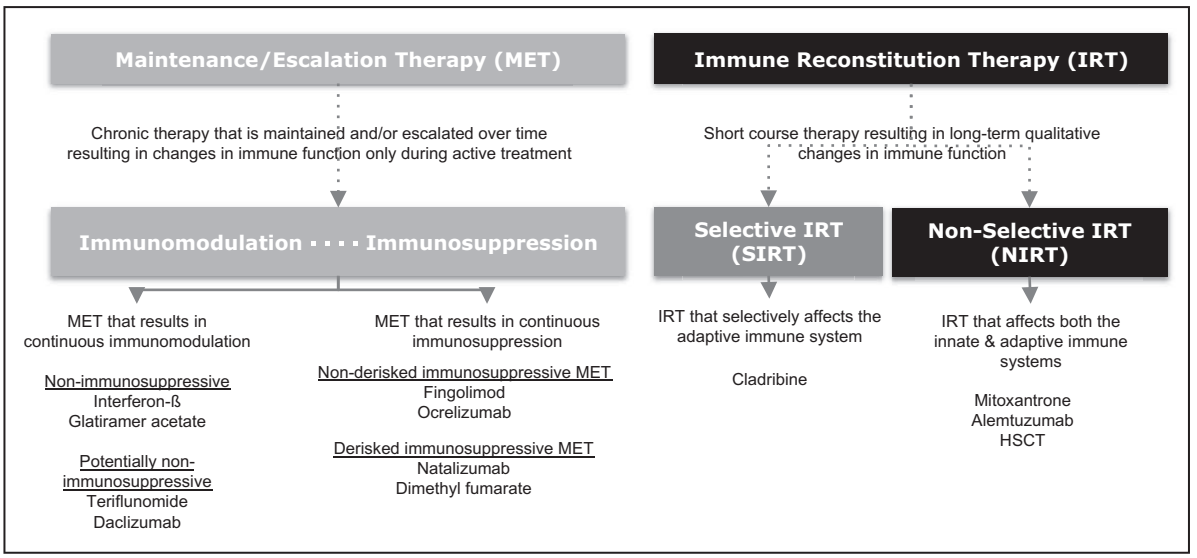

FIGURE 4. New classification of disease-modifying therapies for relapsing forms of multiple sclerosis.

In comparison, a maintenance therapy by definition is given continuously without an interruption in dosing. Although maintenance therapies have the ability to induce long-term remission, that is, NEDA, they cannot by definition result in a cure. With maintenance therapies the recurrence of, or ongoing, inflammatory activity, is an indication that there is a suboptimal response to treatment and typically results in a treatment switch. Ideally this switch should be to a more effective class of DMTs, hence the term escalation. Table 2 summarizes the main attributes of maintenance therapies and IRTs.

CONTINUOUS AND INTERMITTENT IMMUNOSUPPRESSION

Another useful way of classifying DMTs is based on whether or not they are immunosuppressive.

Table 3. Major differences between continuous and intermittent immunosuppression

	Continuous immunosuppression	Intermittent immunosuppression
Duration	Immunosuppression persistent for the duration of treatment	Short-term immunosuppression that is only present during the period of immunodepletion
Risk	Risk of complications increases with time, that is, the cumulative frequency of opportunistic infections and secondary malignancies increases with duration of treatment	Risk of complications is front-loaded and decrease with time. Once immune reconstitution occurs the risk of opportunistic infections and secondary malignancies drops
Live vaccines	Contraindicated	Generally well tolerated once immune reconstitution has occurred.
Exotic infections	Risk of potentially serious complication from exotic infections, for example, dengue and other arbovirus infections	Risk of potentially serious complications from exotic infections lower after immune reconstitution
Pregnancy	Generally, not recommended as the immunosuppressive agent is present within the body continuously. Safety in pregnancy depends on the safety profile of individual agent	Generally well tolerated after the immune system has reconstituted. The exception being delayed secondary autoimmune complications associated with alemtuzumab; these tend to be antibody-mediated disorders and the transfer of autoantibodies across the placenta can cause neonatal disease, for example, neonatal hyperthyroidism
Pharmacovigilance	Tends to be long-term	Less burden postimmune reconstitution; the exception being monitoring for secondary autoimmune complications postalemtuzumab (anti-CD52)
Examples	Natalizumab, fingolimod, dimethyl fumarate, ocrelizumab	Mitoxantrone, alemtuzumab (anti-CD52), cladribine, HSCT

Interferon-beta, glatiramer acetate, teriflunomide and daclizumab are neither generally associated with persistent lymphopaenia, blunted vaccine responses nor an overt opportunistic infection or secondary malignancy risk, which is why they are classified as immunomodulatory agents. HSCT, hematopoietic stem cell transplantation.

Broadly speaking, an immunosuppressive is any DMT that reduces the activation, or effectiveness, of the immune system. From a regulatory perspective for a drug to be classified as being immunosuppressive it should cause significant lymphopaenia, be associated with opportunistic infections, reduce the antibody response to vaccines and increase the risk of secondary malignancies. The duration and intensity of immunosuppression further determines the risks. For example, short-term or intermittent immunosuppression associated with IRTs front-loads the risks, which are substantially lower, once the immune system has reconstituted itself. In comparison, long-term continuous or persistent immunosuppression, which occurs with some of the maintenance DMTs, accumulates problems over time, in particular, opportunistic infections and secondary malignancies. Table 2 attempts to summarize the main attributes of intermittent and persistent immunosuppression. Please note live vaccines are in general contraindicated in patients on immunosuppressive therapies. In comparison, patient on IRTs who have reconstituted their immune systems are able to tolerate and respond to live vaccines. The decision to administer live vaccines in this situation needs to be balanced against the risks of the vaccine.

ADVANCED MULTIPLE SCLEROSIS

I have had several debates with a colleague about therapeutic targets and whether or not they are achievable. In general, many consider NEDA to be an unrealistic treatment target as most of our patients who achieve NEDA still have residual problems. Therein lies the problem. NEDA refers to no evidence of ongoing inflammation. NEDA does not refer to reversal of previous damage, nor does it refer to the ongoing consequences of previous damage. You can only do so much with an anti-inflammatory agent, that is, switch-off inflammation, and even then most anti-inflammatory agents do not switch-off innate immune activation within the CNS, for example, activated microglia, nor do they necessarily purge the nervous system of B cells, plasmablasts, plasma cells and their oligoclonal immunoglobulin products that are considered to plan a major role in worsening disease. In reality, we can only ask so much of our current DMTs, which is why we need combination therapy strategies to target other pathways [3,10▪▪].

I want to propose that we consider rejecting the adjective 'progressive' to describe worsening disability in multiple sclerosis. Progression is a misnomer and means improvement. I personally prefer the term 'worsening multiple sclerosis,' which captures the associated disability that comes with the later phases of the disease. As a community, we need to accept that the processes that drive neuroaxonal loss, or neurodegeneration (the pathological substrate that underlies 'worsening multiple sclerosis') as [10▪▪] being there from the beginning. This means that the neurodegenerative phase of multiple sclerosis is present from the beginning before people with multiple sclerosis (pwMS) become physically disabled.

In my opinion, multiple sclerosis is one disease and not two or three diseases. The division of multiple sclerosis into several diseases is not backed up by science, nor by any philosophical arguments. The false division of multiple sclerosis into several diseases has become counter-productive to the field of multiple sclerosis. The division of multiple sclerosis into relapsing and progressive forms was Pharma-led to get multiple sclerosis defined as an orphan disease, which allowed interferon-beta 1b to get a license in the United States based on the results of one pivotal phase 3 study.

Following the point above, the division between SPMS and PPMS is false. There is no pathological, genetic, imaging or other data that suggests these are different entities. We, therefore, should be doing trials in both populations simultaneously. Another bit of dogma that needs addressing is the proposal that more advanced multiple sclerosis has reduced inflammation, or is 'noninflammatory.' There are clinical, imaging and pathological data that shows inflammation still plays a big, and probably a major, role in advanced worsening multiple sclerosis. Therefore, not to target more advanced multiple sclerosis with an anti-inflammatory is folly and may explain why so few monotherapy neuroprotective trials have been unsuccessful. Now that ocrelizumab has been licensed for primary progressive multiple sclerosis, this may form the platform for future add-on trials [32▪▪].

It is important to acknowledge that reserve capacity in particular neuronal systems plays an important part in how multiple sclerosis worsens. Neuronal systems with reserve are more likely to be able to recover function and hence, show a treatment effect compared with neuronal systems in which reserve capacity is exhausted [10▪▪]. In the latter systems, it will simply take longer to show a treatment effect; we refer to this as therapeutic lag [10▪▪]. These observations could be explained by the length-dependent axonopathy hypothesis of worsening multiple sclerosis; that is, progressive multiple sclerosis manifests initially in pathways that have the longest axons (bladder and lower limb pyramidal function). This means that we should focus more on the arm-and-hand function as a primary outcome in pwMS who have already lost too much

function in their lower limbs (EDSS ≥6.0). Once someone with multiple sclerosis who has lost lower limb function and become a wheelchair-user, they still have neuronal systems that are potentially modifiable, for example, upper limb, bulbar and visual function. In fact, there is an extensive evidence base showing that several licensed DMTs can slow the worsening of upper limb function despite patients having advanced multiple sclerosis [10▪▪]. I feel very strongly about this point and I am keen to argue for future trials in advanced multiple sclerosis to include wheelchair users with a focus on upper limb function as the primary outcome measure. What keeps pwMS independent and functioning in society is arm and hand function.

Another trend that is beginning to emerge is the need to use combination therapies in advanced multiple sclerosis. This does not necessarily exclude using two classes of anti-inflammatory therapies, provided their mechanisms of action are complementary. There are good arguments for combining agents that targets innate immune mechanisms – for example, laquinimod, which targets activated glia [33] – with a classic anti-inflammatory targeting adaptive immune mechanisms that are presumably multiple sclerosis specific, for example, anti-B and anti-T cell-driven autommunity. However, a combination of an anti-inflammatory targeting adaptive immune responses in combination with a neuroprotective or remyelination therapy makes most sense.

We also need to tackle ageing and its impact on worsening multiple sclerosis. The evidence that early, or premature, ageing from the reduced brain, and cognitive, reserve drives worsening of multiple sclerosis in older pwMS, is in my opinion beyond doubt [10▪▪,34]. What we need is some way of dissecting-out premature ageing from multiple sclerosis-specific mechanisms. Another issue with ageing is the emergence of comorbidities as a driver of worsening multiple sclerosis, in particular, smoking, hypertension, hypercholesterolaemia, metabolic syndrome, diabetes and a sedentary lifestyle [35].

Despite the promise of treatments to modify the course of more advanced multiple sclerosis [32▪▪] we need to manage expectations. PwMS are expecting an effective treatment to restore function or return them to normal. This is not going to happen. The best we can expect is to slow down the rate of worsening disability, or flat-line disability progression, with anti-inflammatory and neuroprotective strategies. Although it is plausible that neuronal systems and pathways with reserve capacity have the capability to show improvement in function, it is unlikely to be sufficient to make predictions on future outcomes and falsely raise the hopes of pwMS. To get substantial and meaningful improvements in disability, we will need new classes of treatments, possibly not only remyelination therapies but also therapies that promote axonal sprouting, synaptogenesis and plasticity mechanisms to restore function.

CONCLUSION

Over the last 25 years, the treatment and management of multiple sclerosis has been transformed. Who would have thought that we would be targeting NEDA, and potentially end-organ damage, as a realistic treatment target for pwMS and defining a what a potential cure looks like? The multiple sclerosis community is now turning towards the challenge of slowing down disability worsening in the more advanced stages of the disease, including people in wheelchairs, and exploring add-on neuroprotective and neurorestorative therapies. Despite all the hype of the future, the biggest single problem we in the multiple sclerosis community face is the slow, and in some circumstances very low, rates of adoption of new innovations. Far too many pwMS remain untreated, or under treated, with DMTs. In many parts of the world this is simply because of economic factors and the unaffordability of high-cost innovator drugs. We need to think of creative ways on how to get people who are living in resource poor environments access to effective DMTs; this may involve compassionate-use DMT access programmes or the establishment of an evidence-based list of essential low-cost off-label DMTs.

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Conflicts of Interests

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