TIMELINE

Treatment of multiple sclerosis — success from bench to bedside

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Abstract | The modern era of multiple sclerosis (MS) treatment began 25 years ago, with the approval of IFNβ and glatiramer acetate for the treatment of relapsing–remitting MS. Ten years later, the first monoclonal antibody, natalizumab, was approved, followed by a third important landmark with the introduction of oral medications, initially fingolimod and then teriflunomide, dimethyl fumarate and cladribine. Concomitantly, new monoclonal antibodies (alemtuzumab and ocrelizumab) have been developed and approved. The modern era of MS therapy reached primary progressive MS in 2018, with the approval of ocrelizumab. We have also learned the importance of starting treatment early and the importance of clinical and MRI monitoring to assess treatment response and safety. Treatment decisions should account for disease phenotype, prognostic factors, comorbidities, the desire for pregnancy and the patient's preferences in terms of acceptable risk. The development of treatment for MS during the past 25 years is a fantastic success of translational medicine.

Multiple sclerosis (MS) is an inflammatory and neurodegenerative demyelinating disease of the CNS, the onset of which usually occurs in young adulthood. The aetiology of MS is multifactorial and involves the interaction of genetic and environmental factors in a complex manner. The history of MS treatment is an excellent example of successful translation of research into therapeutic approaches and improvements in clinical outcomes. Approval of the first treatments for MS in the 1990s changed attitudes towards the condition and triggered 25 years of intense therapeutic development that has resulted in multiple therapeutic options that can substantially reduce the impact of MS on the lives of many patients (FIG. 1).

In this Timeline article, we look back at the major developments in the treatment of MS over the 25 years since approval of the first drug. We first consider relapsing–remitting MS (RRMS), in which the greatest progress has been made, before discussing progressive MS, treatment for which has proved more elusive. Finally, we consider the current situation with respect to the multitude of treatment options available, and the practical implications for clinical practice.

Therapies for relapsing–remitting MS

Injectables. Injectables were the first type of disease-modifying therapy developed for the treatment of RRMS. Three preparations of IFNβ were the first of these drugs to be approved in 1993 (REFS[1–3]). The exact therapeutic mechanism of IFNβ remains unknown, but the overall effect of this cytokine is an anti-inflammatory, regulatory response. Glatiramer acetate, another injectable that is composed of four amino acids, also produces an anti-inflammatory effect[4,5]. In clinical trials, these injectable drugs consistently reduced the annual relapse rate (aRR) in patients with RRMS by one-third when compared with a placebo, and modestly reduced the time to an increase in disability assessed with the Expanded Disability Status Scale (EDSS)[1–3,5]. Head-to-head trials have shown that the efficacy of all these injectable drugs is similar[6,7]. Serious adverse effects that compromise safety (such as fulminant hepatitis or pulmonary arterial hypertension) are rare with injectables, but these therapies commonly create tolerability issues, particularly flu-like symptoms for IFNβ and injection site reactions for all[1–3,5,8,9].

The most important contribution of these drugs has been a change in attitudes towards MS, which had previously not been a focus of research. The first well-designed clinical trials of injectables revealed that the natural history of MS could be modified with treatment; the term disease-modifying therapy consequently entered the arena. Furthermore, use of these drugs led to the discovery that their therapeutic effects could be monitored with MRI.

Recent advances in this group of drugs include new formulations that have reduced the necessary dosing frequency. For example, pegylated IFNβ-1a can be administered fortnightly instead of weekly, and glatiramer acetate 40 mg can be administered three times weekly instead of daily[10,11]. In addition, in April 2015, the first generic version of daily glatiramer acetate was approved by the FDA, and in February 2018, the generic version of three-times-weekly glatiramer acetate was also released to the market[12].

The first monoclonal antibody. Monoclonal antibodies are currently used to treat many autoimmune neurological disorders, including MS and neuromyelitis optica spectrum disorders (NMOSDs)[13,14]. The first to be used in MS was natalizumab, a humanized monoclonal antibody that binds to α-4 integrin, a component of very late antigen 4 (VLA4), which is present on lymphocytes. Natalizumab prevents the interaction between VLA4 and its endothelial ligand vascular cell adhesion molecule, thereby preventing lymphocytes from crossing the blood–brain barrier.

After 10 years of using injectables with a one-size-fits-all approach, natalizumab represented a considerable change in efficacy: trials showed that it reduced the aRR by almost 70% and reduced confirmed worsening on the EDSS by 40%[15]. However, a substantial increase in the risks became evident with the first two cases of natalizumab-associated progressive multifocal leukoencephalopathy (PML), a serious and potentially fatal opportunistic JC virus CNS infection[16,17]. To date, >700 patients who were treated with natalizumab

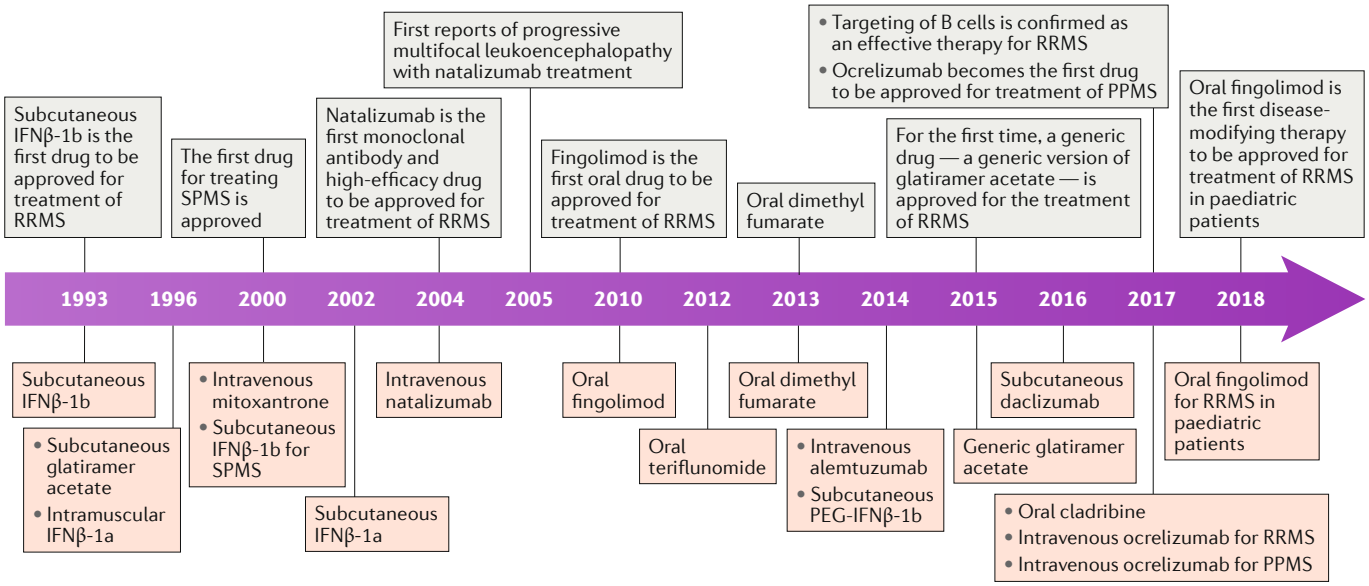

Fig. 1 | **Timeline of developments in the treatment of multiple sclerosis.** Important milestones in the development are shown in green boxes, and drugs approved by the FDA (or the European Medicines Agency for subcutaneous IFNβ for secondary progressive multiple sclerosis (SPMS) and oral cladribine) are shown in orange boxes. MS, multiple sclerosis; PEG, polyethylene glycol; PPMS, primary progressive MS; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive MS.

have developed PML. The anti-JC virus index, measured in the blood[18], is now used to stratify an individual's risk of natalizumab-associated PML, illustrating how biomarkers can facilitate treatment decisions and monitoring, although evidence that risk stratification has reduced the incidence of PML is not available because appropriate studies have not been conducted[19]. Another safety concern with natalizumab relates to discontinuation of natalizumab therapy, which can produce a rebound of disease activity. A treatment withdrawal strategy should, therefore, be planned in advance[20–22].

The arrival of oral treatments. Fingolimod, an analogue of sphingosine 1-phosphate (S1P) that acts as an S1P antagonist, was the first oral drug to be approved for the treatment of RRMS[23,24]. In May 2018, the FDA extended the approval of fingolimod to use in children aged 10 years or older[25]. Fingolimod prevents T cells from leaving the secondary lymph organs because this move depends on the S1P receptor 1 (S1P1); this effect results in a decrease in the number of circulating lymphocytes. In placebo-controlled clinical trials, fingolimod (0.5 mg once daily) reduced the aRR by approximately 50%, reduced disability accumulation by one-third (reaching statistical significance in one of the two trials) and had a marked impact on various MRI outcomes, including brain atrophy[23,24]. A head-to-head trial showed that fingolimod was also superior to intramuscular IFNβ (REF.[23]).

Some safety concerns are associated with fingolimod, and some adverse effects might be explained by non-selective modulation of S1P3, S1P4 and S1P5. Heart rate should be monitored for at least 6 hours after administration of the first dose of fingolimod to detect symptomatic bradycardia or conduction block, which occur in ~2% of patients[23,24]. Rare instances of opportunistic infections and PML have also occurred[26]. As with natalizumab, fingolimod withdrawal can result in a transient increase in disease activity, in some cases well beyond a simple return to the previous level of inflammatory activity[27]. Caution is needed with unexpected pregnancies because major fetal malformations have been reported in association with natalizumab use[28].

The concerns with fingolimod are expected to be addressed to some extent by a new drug, ozanimod, which is in clinical development. Ozanimod is a selective modulator of S1P1 and S1P5 receptors. Results of the phase III studies RADIANCE and SUNBEAM, which compared two doses of ozanimod with IFNβ-1a treatment, were presented in 2017 (REFS[29,30]). A consistent decrease in the aRR with ozanimod compared with that seen with IFNβ-1a was reported, but no effect on confirmed disability progression was seen. Ozanimod has a shorter half-life than fingolimod, and lymphocyte recovery is faster after its discontinuation. However, some adverse effects, such as first-dose bradycardia and conduction block, were still seen, probably because the S1P receptors that mediate these effects in cardiac myocytes are S1P1 (REFS[29,30]).

Teriflunomide, the second oral drug to be approved by the FDA, was approved in September 2012, 2 years after approval of fingolimod. Teriflunomide is an active metabolite of leflunomide that inhibits the proliferation of blasting B and T cells. Three randomized placebo-controlled trials in RRMS demonstrated that teriflunomide (once daily) improves disability, aRR and MRI markers of disease[31–33]. A randomized trial in which teriflunomide (14 mg) was compared with subcutaneous IFNβ-1a in RRMS demonstrated that their efficacies were similar[34]. Teriflunomide reduced aRR by one-third and reduced confirmed 12-week worsening of disability by almost 30% in both placebo-controlled phase III trials conducted. Adverse events with teriflunomide include diarrhoea, nausea, hair thinning and increased levels of liver enzymes (an increase of ~7%). Frequent monitoring of serum transaminase levels is therefore mandatory in Europe during the first 6 months of treatment. On the basis of animal studies in which fetal malformations were associated with teriflunomide administration to pregnant rats and rabbits, special caution with unexpected pregnancy is also warranted. If treatment termination is required, a washout treatment with

cholestyramine or activated charcoal is needed[31,32,34].

Fumaric acids have been used for decades to treat psoriasis, and in March 2013, the third oral treatment to be approved for the treatment of RRMS was the second-generation fumaric acid, dimethyl fumarate. Preclinical studies demonstrated that dimethyl fumarate has immunomodulatory and antioxidant properties[35]. The immunomodulatory properties probably relate to the fact that the drug induces a shift in the cytokine profile of T helper (T_H) cells from pro-inflammatory (T helper 1 (T_H1) cells) to anti-inflammatory (T helper 2 (T_H2) cells)[35]. In two pivotal phase III studies in patients with RRMS, dimethyl fumarate led to a statistically significant 50% reduction in the aRR and reduced the risk of 12-week confirmed EDSS progression over 2 years by 35% compared with the placebo; this reduction of risk was statistically significant in one of the two trials[36,37].

No increased risk of malignancy or serious infection has been observed with the use of dimethyl fumarate; however, rare instances of PML have occurred[26], usually associated with grade 3 lymphopenia (<500 cells/mm^3). Therefore, lymphocyte count needs to be monitored every 3–6 months, and treatment interruption should be considered if lymphocyte counts are <500 cells/mm^3 for more than 6 months. Caution is required, however, because PML has occurred in the setting of mild lymphopenia, probably as a result of low $CD4^+$ and $CD8^+$ cell counts[38]. Facial flushing (and occasionally flushing of the neck and chest) with redness, itching and warmth of the skin, and gastrointestinal adverse events tend to occur early during treatment and might lead to treatment discontinuation[39].

The oral drug most recently added to therapeutic options for RRMS is cladribine, which was approved in June 2017 by the European Medicines Agency (EMA) for annual administration of short-duration courses for 2 years. Cladribine is a prodrug, and intracellular phosphorylation is required to convert it to an active purine nucleoside analogue. The prodrug is resistant to degradation by adenosine deaminase and can enter cells via purine nucleoside transporters. Once within the cell, cladribine undergoes initial phosphorylation by deoxycytidine kinase (DCK) to become the active drug, 2-chlorodeoxyadenosine triphosphate. To inactivate the cladribine-derived triphosphate nucleotides and prevent their intracellular accumulation, which leads to apoptosis, dephosphorylation by 5′-nucleotidase (5′-NTase) is required. In comparison with other cell types, resting and activated lymphocytes have high levels of DCK but low levels of 5′-NTase[40], so cladribine accumulates to toxic levels and persistently decreases lymphocyte numbers as a result of apoptosis in actively proliferating and resting lymphocyte subpopulations[41].

The safety and efficacy of oral cladribine versus placebo in RRMS have been assessed in one phase III study, in which the drug reduced the aRR by 55% and the 3-month sustained progression of disability by 30%[42–44]. The efficacy of cladribine has been confirmed by the assessment of several MRI outcomes, including atrophy[45]. In the 2-year extension of this trial, cladribine produced a durable significant effect: ~75% of patients remained relapse-free despite receiving a placebo during the extension period. Treatment with cladribine tablets beyond the initial 2-year treatment period was not associated with any further clinical improvement[44].

In another study, the ability of cladribine monotherapy to prevent conversion from a first clinical demyelinating event to clinically definite MS was evaluated[46]. The trial was terminated early, but relative to placebo, cladribine was associated with a 65% risk reduction in the time to conversion to clinically definite MS[46]. The most commonly reported adverse event was mild to moderate lymphopenia, together with an increased risk of herpes zoster virus infection. PML has not been reported in patients with MS who are treated with cladribine tablets, although rare instances of the infection have occurred with other cladribine preparations for conditions other than MS[41]. A few patients who took cladribine had solid malignancies, but none of these cancers could be unequivocally attributed to cladribine therapy; all cancers were thought to be unrelated to the treatment[47].

The most recent milestone in oral treatments was the completion of the first prospective randomized clinical trial performed in children and adolescents with MS[48]. In this trial, comparison of fingolimod with IFNβ-1a clearly demonstrated superiority of fingolimod without major differences from the established safety profile of this drug.

New monoclonal antibodies. Following the success of natalizumab, further monoclonal antibodies were developed for the treatment of RRMS. In November 2014, alemtuzumab was launched into the market after its FDA approval. Alemtuzumab is a humanized monoclonal antibody against CD52, a receptor that is present on lymphocytes, monocytes and other immune and non-immune cells[49,50]. Alemtuzumab should be administered daily for 5 consecutive days, and treatment should be repeated 12 months later for 3 consecutive days. Following administration, the numbers of B cells return to normal within 7 months, whereas the numbers of T cells remain low for longer. In two phase III trials in which alemtuzumab was compared with an active comparator (subcutaneous IFNβ-1a) in treatment-naive or treatment-experienced patients, alemtuzumab significantly reduced the aRR by 55% in both studies and reduced confirmed disability worsening by 40%, which reached statistical significance in one trial[49–51]. The efficacy is long-lasting: for >70% of patients who received two courses of alemtuzumab treatment, efficacy was maintained up to year five without additional treatment[52].

Adverse events include infusion reactions secondary to cytokine release syndrome, herpetic infections that can be mitigated by prophylactic treatment with acyclovir for 1 month after each infusion, and secondary autoimmunity, including thyroid disorders (in >30% of patients), thrombocytopenia (1–3% of patients) and glomerulonephritis (<1% of patients), which tend to develop 2–3 years after the first dose of alemtuzumab (although they can develop later). Necessary safety monitoring includes a monthly assessment of complete blood counts and creatinine levels, and urinalysis for 5 years after the first infusion. Thyroid function tests should be performed every 3 months[49,50]. Human papilloma virus (HPV) infections, including cervical dysplasia, have been described, so annual HPV screening with cervical cytology is required (and is compulsory in Europe), especially for women who have not previously received the HPV vaccination. Rare instances of listeria meningitis have been reported, as have cases of acute pneumonitis or pericarditis that resulted from the release of cytokines[53,54].

Daclizumab is a humanized monoclonal antibody that is administered subcutaneously once per month. This drug was released in May 2016, although safety concerns led to its withdrawal in March 2018. Daclizumab modulates IL-2 signalling by binding to the IL-2 receptor subunit-α (also known as CD25). This binding seems to induce immune tolerance through the expansion of immunoregulatory $CD56^{bright}$ natural killer cells and the reduction of early T cell activation[55]. In a phase III trial, daclizumab significantly decreased the aRR

by 45% compared with IFNβ-1a, and had significant effects on several MRI secondary end points. No significant effect was observed on the accumulation of disability[56].

The adverse effects of daclizumab include hepatic damage, skin abnormalities, lymphadenopathy and infections. In trials, elevated levels of liver function markers were observed in patients receiving daclizumab, and one patient died because of autoimmune hepatitis[57]. This death resulted in the requirement for a warning on the box when the drug was approved by the FDA in May 2016. However, the death of another patient from liver injury (fulminant liver failure), four cases of serious liver injury and 12 reports of serious inflammatory brain disorders, including encephalitis and meningoencephalitis, led to the withdrawal of daclizumab from the market by the manufacturer, and in March 2018, the European Medicines Agency (EMA) recommended immediate suspension of its use.

B cells and monoclonal antibodies. Evidence that B cells are involved in the activation of pro-inflammatory T cells, secretion of pro-inflammatory cytokines and the production of autoantibodies led to the development of another generation of monoclonal antibodies that are targeted to these cells. Such antibodies are the CD20-binding antibodies rituximab and ocrelizumab, which deplete mature B cell pools. Positive results from clinical trials of these agents strongly suggest that B cells have an unexpectedly central role in MS pathogenesis.

Despite a positive phase II study, phase III trials of rituximab for RRMS were never undertaken[58]. However, two phase III trials of ocrelizumab in RRMS have been conducted, in which ocrelizumab was administered via intravenous infusion every 24 weeks. This treatment reduced the aRR by 45% and reduced disability progression by 40% compared with subcutaneous IFNβ-1a[59]. Analysis of brain volume loss and other MRI outcome measures also favoured ocrelizumab treatment.

In these trials, ocrelizumab was not associated with an increased risk of serious infections. However, the first case of carryover PML was reported in 2017 in a patient who had previously been treated with natalizumab for >2 years; this patient developed PML 1 month after having received the first dose of ocrelizumab[60]. PML has also occurred in patients receiving treatment with rituximab in the context of rheumatological or lymphoproliferative disorders, with a frequency of one per 32,000 treated patients[61]. Although these treatments are fairly new, targeting of CD20 has already become a widely used treatment strategy owing to its efficacy in different MS phenotypes and NMOSDs[14,59,62]. Ocrelizumab was approved by the FDA in March 2017 and by the EMA in November 2017, but it remains unavailable in many countries. Consequently, off-label use of rituximab is common practice[63,64].

Therapies for progressive MS

The trials discussed above were performed in patients with RRMS and might have included patients who had entered the secondary progressive phase of MS, although this clinical form has not usually been specified in the inclusion criteria. Specific trials have therefore been needed to determine whether drugs used in RRMS or other drugs are effective in progressive forms of the disease. The oldest trials in progressive MS were based on phenotype definitions that are now outdated[65], and these trials produced no positive results. Similarly, trials of various drugs for secondary progressive MS since the turn of the century have been negative; drugs tested include dirucotide, immunoglobulins, lamotrigine, dronabinol (which was also tested in primary progressive MS) and cladribine (a subcutaneous formulation in secondary and primary progressive MS)[66–70].

The modern era of trials in secondary and primary progressive MS could be said to have started in the mid-1990s with randomized trials of injectable drugs[71] that were approved for use in RRMS at the time. The results in patients with secondary progressive MS were mixed but predominantly negative, and the results were clearly negative in patients with primary progressive MS[72,73]. On the basis of its immunosuppressant properties, the cancer drug mitoxantrone was also tested in patients with secondary progressive MS and primary progressive MS in a study published in 2002 and was shown to effectively decrease relapse counts and disability progression[74]. The results of the above-mentioned trials led to an indication for use of the two formulations of IFNβ that are administered subcutaneously[71,75] and of mitoxantrone[74] in a subset of patients with secondary progressive MS whose disease is worsening and who exhibit evidence of inflammatory activity. No indication was approved for the treatment of primary progressive MS.

Subsequent large, well-performed trials of fingolimod in primary progressive MS[76] and natalizumab in secondary progressive MS[77] have produced largely negative results. The results of the natalizumab trial were disappointing (although a beneficial effect on upper limb function was observed), as an earlier phase II trial had indicated that this antibody might be beneficial[78].

More success has been seen in trial results that have become available in the past year or two. A phase III trial of ocrelizumab produced positive results in primary progressive MS[62], extending the relevance of B cells to the pathogenesis of the progressive condition as well as RRMS. Ocrelizumab reduced the risk of confirmed disability progression at 3 months by 24%; positive secondary outcomes included effects on walking ability (measured with the timed 25-foot walk) and changes in brain volume and T2 lesion volume[62].

Most recently, a phase III trial of siponimod versus placebo in secondary progressive MS met its primary end point: confirmed disability progression at 3 months was reduced by 21%. Several MRI secondary end points, including changes in brain volume and T2 lesion volume, were also met, but full results await publication[79,80]. Furthermore, positive results of a phase II trial of statins in secondary progressive MS, in which the primary outcome was brain volume change, await confirmation in a planned phase III trial[81]. In primary progressive MS, presented results of a phase II trial of the phosphodiesterase inhibitor ibudilast indicate that the primary end point (brain volume change) was met, but full results are yet to be published[82].

The EMA and FDA have recently approved ocrelizumab, which will become the first drug that is licensed for the treatment of primary progressive MS. The dosage and frequency of administration will probably mirror those used in RRMS, as will safety monitoring measures. The EMA indication includes patients with "early primary progressive MS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity", such that only a subset of patients will benefit, although interpretation of this indication could be diverse. As is the situation in RRMS, since the results of the ocrelizumab trial have been known to the global MS community, a growing number of patients with progressive forms of MS (probably including secondary progressive MS) who exhibit a variable degree of clinical and/or MRI activity have been prescribed rituximab off-label.

After decades of failed attempts, we now have the first drug ever to be marketed for the

treatment of primary progressive MS in the form of ocrelizumab, and if submitted and approved by the regulatory agencies, siponimod could join subcutaneous INFβ and mitoxantrone as an option for secondary progressive MS and would be the first oral drug for the treatment of this condition. Although the effects of these drugs are modest, approval of the first drug for primary progressive MS could change attitudes towards progressive MS, similar to the change that was seen in RRMS in the late 1990s.

A paradigm change in MS management

The development of so many effective therapeutics for MS has created a scenario that challenges both the clinical neurologist and the patient. Inevitably, these therapeutic advances have developed alongside shifts in the way patients with MS are managed in terms of how involved patients are in the therapeutic decision-making process and in terms of the design of new treatment algorithms and therapeutic strategies[83–86]. This change in treatment paradigm calls for personalized precision medicine[87].

Unfortunately, no biomarkers can currently facilitate the identification of the best treatment for a particular patient at a specific time point[88]. Therefore, the decision of when and how to treat patients still relies on disease characteristics and the preferences of patients and neurologists.

In addition, individual patient particularities are essential when discussing treatment indications for the first time[13]. As a simplified example, for a young female with mild disease (a low relapse rate without brainstem or spinal cord lesions) who has a short-term desire to become pregnant, clinicians might want to offer a conservative escalation strategy and start with an injectable therapy (IFNβ or glatiramer acetate) to provide a reasonable chance of curbing disease evolution with a good safety profile, including risks for pregnancy. Conversely, for a young female with a short-term desire to become pregnant but who has severe disease (many relapses with gadolinium-enhancing and/or infratentorial lesions), an induction strategy that starts with a highly efficacious drug might be more appropriate despite the more unfavourable safety profiles of these drugs and the need to postpone pregnancy until the disease is controlled.

If an escalation strategy is chosen, strict monitoring of disease activity with clinical and radiological parameters is mandatory for deciding whether treatment needs to be changed and when best to make this change[89]. With induction therapy, monitoring of treatment response is also important, but the risks associated with most available high-efficacy treatments must be considered. Patients should be informed of and adhere to strategies proposed by the regulatory agencies to mitigate the risks[13]. Accordingly, the patient needs to be involved in an optimized, shared decision-making process[83].

Conclusions

The MS treatment pipeline has changed greatly over the past 25 years (FIG. 1). Not only are a great number of new treatment options available, but high-efficacy therapeutic drugs have also emerged[90], and breakthroughs are finally being made in the treatment of progressive MS. Despite all this progress, research into novel treatments, such as the histamine receptor antagonist GSK239512 (REF.[91]) and cell-based therapies[92], is ongoing. The treatment pipeline is therefore expected to evolve further, and new insights will need to be incorporated into the daily management of patients with MS. In the meantime, research towards achieving truly personalized medicine should be a priority so that better tools are available for making therapeutic decisions when clinicians discuss treatment options with patients[93,94].

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Author contributions
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Competing interests
M.T. has received compensation for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen, Genzyme, Merck-Serono, Novartis, Roche, Sanofi-Aventis and Teva. A.V.-J. has received speaking honoraria and consulting fees from Novartis, Roche and Sanofi-Aventis. J.S.-G. has received compensation from Almirall (speaking honoraria and consulting services), Biogen, Genzyme, Novartis and Merck (travel expenses and accommodation, speaking honoraria and participation in advisory boards), Celgene (travel expenses and accommodation and participation in advisory boards), Teva (speaking honoraria, travel expenses and accommodation) and Roche (travel expenses and accommodation).