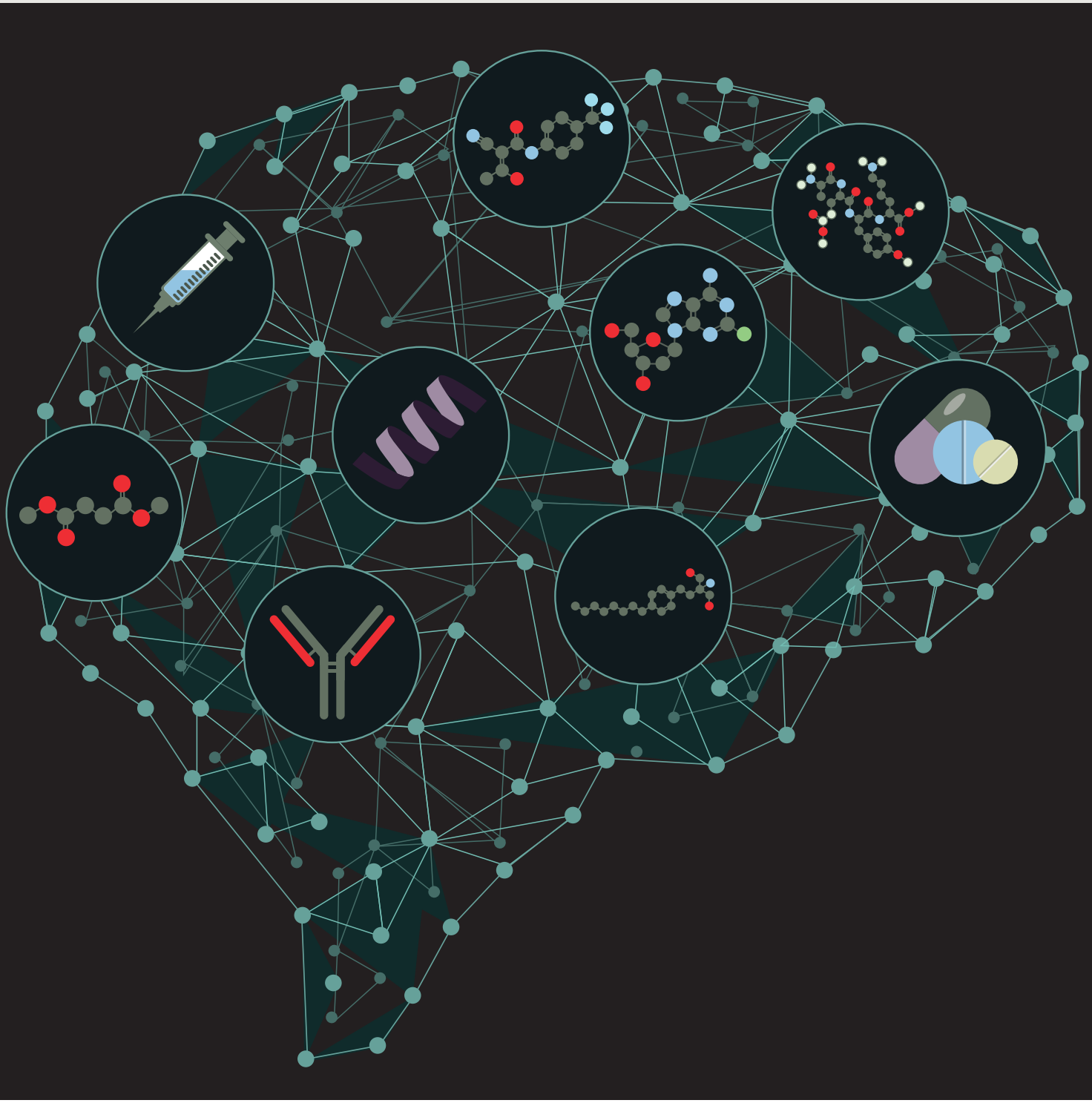
nature MILESTONES

December 2018
http://www.nature.com/collections/ms-milestone

Treatment of multiple sclerosis



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TREATMENT OF MULTIPLE SCLEROSIS — A TIMELINE

1993 — **The dawn of the therapeutic era in MS** (MILESTONE 1)
An appreciation that aberrant immunological responses were important in multiple sclerosis led to the development and approval of interferon-β-1b. Glatiramer acetate and additional formulations of interferon-β soon followed, and these injectable therapies were the mainstays of multiple sclerosis therapy for a decade.

2004 — **The first monoclonal antibody therapy** (MILESTONE 2)
A new therapeutic option became available with the approval of natalizumab, which reduces migration of lymphocytes across the blood–brain barrier by inhibiting the interaction between the α4β1 integrin on lymphocytes with VCAM1 on vascular endothelial cells.

2005 — **The risk of natalizumab-associated PML is revealed** (MILESTONE 3)
After its approval in 2004, natalizumab was withdrawn from the market in 2005 owing to two cases of progressive multifocal leukoencephalopathy that were associated with the treatment. The therapy was reintroduced — with improved safety warnings — in 2006, and subsequent research has led to ongoing refinement of approaches to risk stratification.

2010 — **Oral drugs expand therapeutic options** (MILESTONE 4)
Three oral therapies for relapsing–remitting multiple sclerosis were approved between 2010 and 2013: fingolimod, teriflunomide and dimethyl fumarate. These three molecules all inhibit the immune activation in the brain that is characteristic of the disease. The option to use oral, rather than injectable, therapies reduced the burden of treatment.

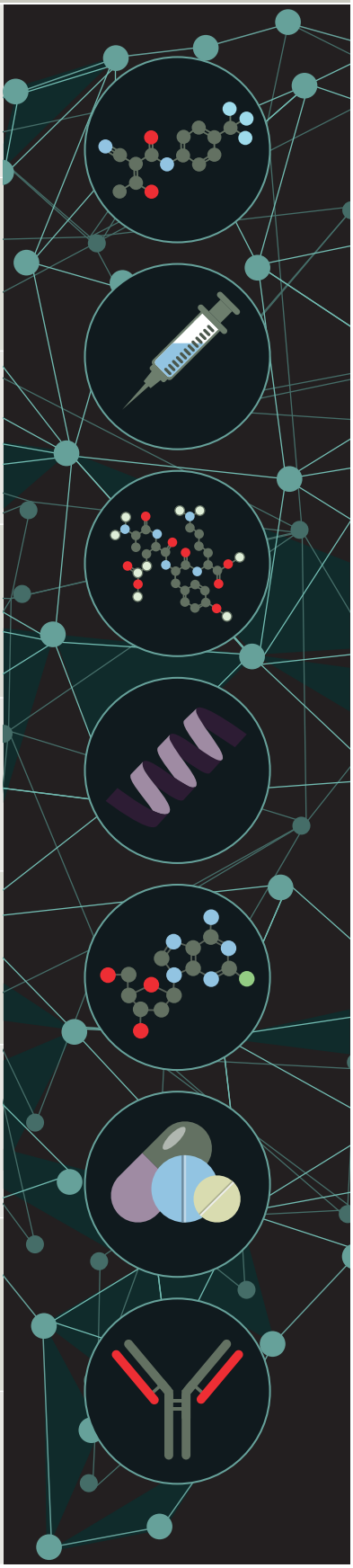
2014 — **Highs and lows with second-generation monoclonal antibodies** (MILESTONE 5)
Alemtuzumab and daclizumab, which both suppress the immune system but via different mechanisms, were approved for the treatment of relapsing–remitting multiple sclerosis in 2014 and 2016, respectively. However, in 2018, daclizumab was withdrawn from the market owing to concerns of serious adverse effects.

2014 — **More treatments create clinical dilemmas** (MILESTONE 6)
As the therapeutic options for multiple sclerosis increased, several clinical dilemmas arose, and clinicians had to start making decisions about which therapy to use, when to treat patients, and when and how to switch medications in patients with a suboptimal response. These clinical dilemmas continue today, but treatment strategies continue to be refined.

2017 — **The story of cladribine reaches its climax** (MILESTONE 7)
After a long and, at times, uncertain route to regulatory approval, oral cladribine was approved for treatment of relapsing–remitting multiple sclerosis in 2017. It is currently the only oral drug that has the potential for pulsed immune reconstitution, and its mechanism of action differs from that of other current treatments for multiple sclerosis.

2017 — **Targeting B cells leads to breakthrough therapy** (MILESTONE 8)
As B cells emerged as key players in the multiple sclerosis disease process, anti-CD20 antibodies that deplete circulating B cells were tested in patients with relapsing–remitting and progressive multiple sclerosis. The results were groundbreaking.

2018 — **Progressive and aggressive MS — new frontiers emerge** (MILESTONE 9)
The huge progress made in the treatment of relapsing–remitting multiple sclerosis in the past 25 years has not been replicated for progressive or aggressive forms of multiple sclerosis. However, the latest trials in these areas have provided breakthroughs, laying the foundations for another successful 25 years of MS treatment.



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MILESTONE 1

The dawn of the therapeutic era in MS

The therapeutic era in multiple sclerosis (MS) began with the approval of interferon-β-1b (IFNβ-1b) by the FDA for the treatment of relapsing–remitting multiple sclerosis (RRMS) in 1993. Glatiramer acetate and additional formulations of IFNβ soon followed, and these injectable therapies were the mainstays of MS therapy for the following decade.

For more than a century, a limited understanding of the pathological mechanisms of MS in combination with the highly variable course of the disease hindered the development of treatments. In the late 1980s, however, an increased appreciation that aberrant immunological responses were associated with exacerbation of the disease sparked an interest in the potential of immunomodulatory therapies for MS. In addition, the development of MRI facilitated assessment of potential therapies by enabling brain and spinal cord lesions to be monitored non-invasively over time.

Therapeutic development focused on interferons — cytokines released in response to pathogens — on the basis of the hypothesis that MS is caused or exacerbated by viral infection. The first such therapies to be trialled were based on IFNγ, but it quickly became clear that this cytokine exacerbates relapses in patients with MS. Consequently, attention turned to IFNα and IFNβ, which were known to be inhibitors of IFNγ.

Evidence suggested that the safety profile of IFNβ was superior to that of IFNα. Isoforms of IFNβ that were derived from mammals (IFNβ-1a) and bacteria (IFNβ-1b) were tested in patients with RRMS in several small trials. These studies, although inconclusive, showed promise of therapeutic efficacy.

In 1993, a landmark multicentre, randomized, double-blind, placebo-controlled trial that included 372 patients with RRMS demonstrated that subcutaneous injection of IFNβ-1b significantly reduced annual relapse rates. The highest dose of IFNβ-1b reduced the number of annual relapses by 34% compared with placebo at 2 years. These results demonstrated the first successful modification of the disease course of MS, although IFNβ-1b had no detectable effect on disability progression.

Subsequent trials of IFNβ-1a did reveal an effect on disability progression in RRMS. A study published in 1996 showed that intramuscular IFNβ-1a not only reduced annual relapse rates by 18% compared with placebo, but also reduced sustained disability progression, measured with the Expanded Disability Status Scale (EDSS), after 2 years. Some uncertainty remained owing to early termination of the trial, the small number of patients included and the small, delayed effect, but a large double-blind, placebo-controlled study of subcutaneous IFNβ-1a in 560 patients with RRMS mitigated these concerns in 1998. In this trial, the time to sustained disability progression was significantly increased in patients who received IFNβ-1a compared with individuals who received placebo. This effect was in addition to a 27–33% reduction in relapse rate, depending on the dose.

> “success with injectable therapies in the 1990s transformed attitudes towards MS treatment”

In the midst of the interferon trials, glatiramer acetate became the second injectable therapy to be approved for RRMS in 1997. Glatiramer acetate is a mixture of peptides composed of four amino acids. The peptides are thought to mimic myelin basic protein and competitively inhibit the interaction between immune cells and myelin.

Following promising results in a pilot study of glatiramer acetate, a landmark trial published in 1995 showed that subcutaneous glatiramer acetate reduced annual relapse rates in patients with RRMS by 29% compared with placebo. Measurement of disability with the EDSS showed that glatiramer acetate reduced the chance of disability progression and increased the chance of disability improvement.

The success with injectable therapies in the 1990s transformed attitudes towards MS treatment. Previously, treatment had focused on symptomatic therapy, but the new drugs demonstrated that the disease course is amenable to therapeutic modification. Furthermore, the strong safety profiles of IFNβ and glatiramer acetate mean that these first injectable agents remain a crucial part of the clinician's toolbox for MS treatment today.

Charlotte Ridler, Associate Editor,
Nature Reviews Neurology

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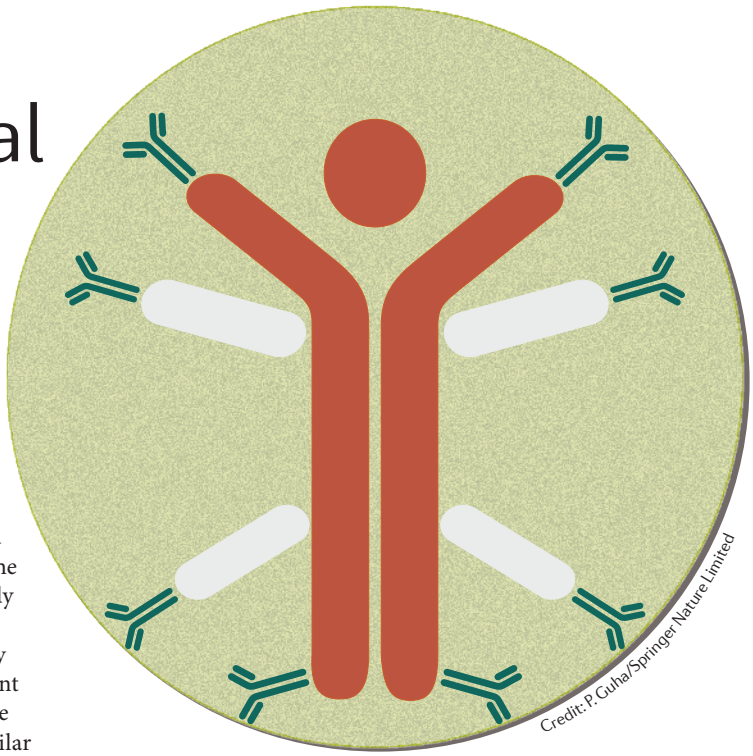
MILESTONE 2

The first monoclonal antibody therapy



Although the injectable therapies (interferon-β (IFNβ) and glatiramer acetate; MILESTONE 1) for multiple sclerosis (MS) were groundbreaking, they were only moderately effective, reducing the annual rate of relapse by approximately one-third. In addition, approximately one-third of patients who receive IFNβ do not respond at all to the treatment. Consequently, efforts continued after their approval to develop more effective treatments, and subsequent work led to the development of the first monoclonal antibody for MS, natalizumab.

The development of natalizumab stemmed from investigations into the therapeutic mechanism of action of IFNβ. Its overall effect is anti-inflammatory, but its exact mechanism of action remains unknown. It is thought to act, in part, by reducing lymphocyte migration across the blood–brain barrier, an important early step in the formation of the inflammatory brain lesions that characterize MS.

While seeking to identify the receptors that mediate attachment of circulating leukocytes to the endothelium in rats with experimental autoimmune encephalomyelitis (EAE; a commonly used animal model of MS), Ted Yednock and colleagues found that their binding was inhibited by antibodies against α4β1 integrin (also known as VLA4), but not by antibodies against various other adhesion receptors. When tested in vivo, the antibody against α4β1 integrin prevented accumulation of leukocytes in the rat CNS and the development of EAE.

The mechanism of action of the antibody was found to be inhibition of the interaction of α4β1 integrin on the surface of lymphocytes with vascular cell adhesion molecule 1, a receptor on the surface of vascular endothelial cells in the brain and spinal cord. Blockade of this interaction reduces the adhesion of lymphocytes and their migration into areas of inflammation.

The work of Yednock and colleagues had been preceded in 1986 by FDA approval of the first ever monoclonal antibody treatment, muromonab-CD3 (anti-CD3), a mouse antibody for the prevention of transplant rejection. This work paved the way for development of a similar therapy to treat MS. However, muromonab-CD3 induced counter-productive immune responses owing to patients producing antibodies against the mouse antibody. For this reason, the antibody that was developed to target α4β1 integrin in MS was a humanized monoclonal antibody — natalizumab.

Results from the initial clinical trials of natalizumab were published in two papers in 1999. These studies indicated that natalizumab was safe and well-tolerated. Among patients with active relapsing–remitting MS or secondary progressive MS, the mean number of new active lesions detected over the first 12 weeks was significantly lower for patients who received natalizumab (1.8) than for those who received placebo (3.6). Similarly, the number of new gadolinium-enhancing lesions was lower (a mean of 1.6 versus 3.3).

Given the promising short-term effects in these initial studies, longer clinical trials were started. Similar results were reported in 2003 in a trial with 213 participants who received natalizumab or placebo every 28 days for 6 months. In 2006, results of a phase III trial that included 942 people who received natalizumab or placebo for more than 2 years showed that natalizumab reduced the relapse rate at 1 year by 68% and the risk of sustained progression of disability by 42% over 2 years compared with placebo.

> “natalizumab reduced the relapse rate at 1 year by 68% and the risk of sustained progression of disability by 42% over 2 years”

In 2005, reports emerged of three patients who had developed progressive multifocal leukoencephalopathy (PML) while receiving natalizumab treatment. These reports led to temporary withdrawal of natalizumab administration until the risks were understood and recommendations were made for their management (MILESTONE 3).

The development of natalizumab had a positive effect on MS treatment and preceded development of further, more effective antibody therapies (MILESTONE 5, 8). However, the only approved therapies at the time required injection, and efforts continued to find suitable drugs for oral administration.

Katharine Barnes, Managing Editor, *Nature Protocols*

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MILESTONE 3

The risk of natalizumab-associated PML is revealed

FDA approval of natalizumab for treatment of multiple sclerosis (MS) in November 2004 was accelerated on the basis of 1-year results from two randomized, placebo-controlled, phase III clinical trials — the AFFIRM and SENTINEL trials (MILESTONE 2). However, in February 2005, natalizumab was withdrawn from the market and ongoing trials were terminated following reports of progressive multifocal leukoencephalopathy (PML) in two patients who had received natalizumab in the SENTINEL trial.

PML is a rare but potentially fatal demyelinating brain disorder caused by the polyomavirus JC virus. The disorder most commonly occurs in people with HIV infection, but has also been reported in patients receiving long-term immunosuppression. JC virus is ubiquitous in the human population and usually infects children and adolescents asymptomatically before becoming latent. It almost never causes disease in immunocompetent individuals. Natalizumab is thought to increase the risk of PML infection by preventing lymphocytes from adhering to the endothelium of the blood–brain barrier, thereby reducing their migration from the blood into the CNS and suppressing T cell-mediated immune responses in the brain.

In June 2006, the FDA approved the reintroduction of natalizumab as monotherapy for relapsing–remitting MS. This reintroduction required revised labelling and improved safety warnings to highlight the potential risk of PML and, in the USA, adherence to a special programme that restricted availability of natalizumab to authorized centres and required ongoing evaluation of patients during treatment to minimize the risks. Subsequently, much research has been carried out to examine the risk of PML with natalizumab treatment, leading to stringent management strategies.

> “clinical vigilance is crucial for early detection of PML”

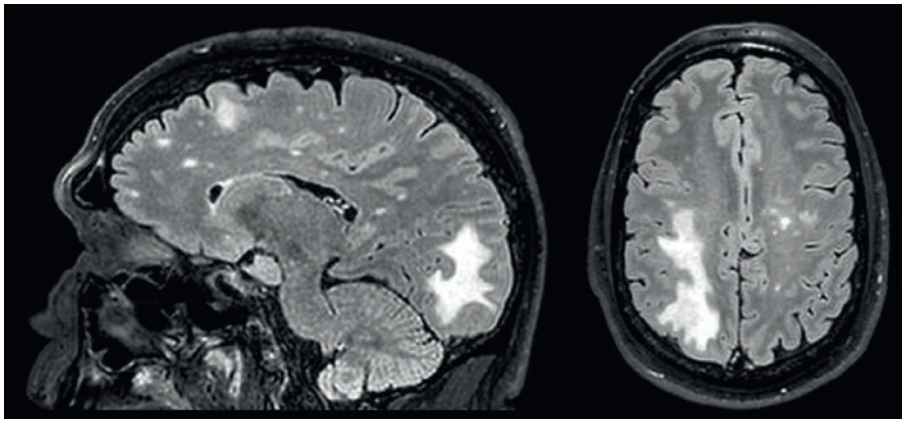
Patient monitoring has shown that the global incidence of PML in individuals with MS who have received natalizumab in the post-marketing setting is ~4.2 per 1,000 patients, and the survival rate is ~70–75%. The median time from treatment initiation to onset of PML symptoms has been estimated at 25 months (range 6–80 months). However, PML can also occur up to 6 months after cessation of natalizumab.

The main identified risk factors for natalizumab-associated PML are positivity for anti-JC virus antibodies in the serum, previous exposure to immunosuppressants and longer natalizumab therapy. Conversely, several factors have been associated with improved survival and outcomes from natalizumab-associated PML, including younger age, lower JC virus viral load and more localized brain involvement detected with MRI at diagnosis. In addition, extending the time between doses of natalizumab has been suggested as a way to reduce the risk of PML, but further studies are needed to confirm this hypothesis.

No direct antiviral treatment against JC virus is available, so clinical vigilance is crucial for early detection of PML in patients who are receiving natalizumab. Research since the introduction of natalizumab has led to several recommendations for patient monitoring to improve the safety of the antibody. Before treatment, patients can be stratified for risk of PML by use of the JC virus antibody index in anti-JC virus antibody-positive patients with no prior immunosuppression, although there is currently no evidence as to whether this measure reduces the incidence of PML. Once treatment has started, patients should be closely monitored for new neurological symptoms, such as cognitive and behavioural changes, retrochiasmatic visual disturbance, hemiparesis and seizures. Consequently, regular clinical and MRI monitoring are essential. Assessment of JC virus antibody serology status every 6 months, or more frequently in patients who have previously been exposed to immunosuppressants, has been recommended. Similarly, MRI screening every 3–4 months has been recommended for patients at high risk of PML (those who are seropositive for anti-JC virus antibodies and those whose duration of natalizumab treatment is >18 months) and annually for anti-JC virus seronegative patients.

Despite the safety concerns, natalizumab is an effective treatment for relapsing–remitting MS and remains an important option. Insight into the causes and risk factors has enabled management of the risks, but refinement of stratification protocols and research into new biomarkers continue. Furthermore, subsequent development of new MS treatments, including further antibody therapies, has provided alternative options when the risks of PML are high.

Rebecca Kelsey, Senior Editor, Nature Reviews



MRI scans from a patient with progressive multifocal leukoencaphalopathy. Courtesy of Avindra Nath, National Institute of Neurological Disorders and Stroke, USA.

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MILESTONE 4

Oral drugs expand therapeutic options

The treatment of relapsing–remitting multiple sclerosis (RRMS) made a leap forward in 2010 with the introduction of the first of three currently used oral therapies. Relative to the previous first-line treatments — inteferon-β (IFNβ) and glatiramer acetate (MILESTONE 1) — these therapies were similarly or more effective and expanded the options for the route of treatment administration.

Three oral therapies for RRMS were approved between 2010 and 2013: fingolimod, teriflunomide and dimethyl fumarate (DMF). These three molecules have distinct modes of action, but all three inhibit the immune activation in the brain that is characteristic of patients with RRMS and causes relapses. In 2016, these three drugs together accounted for nearly 40% of the market for MS therapies.

Fingolimod was discovered through chemical derivatization of myriocin, a fungal metabolite with immunosuppressant properties. Studies in animal models, particularly models of graft-versus-host disease, suggested that fingolimod acts differently from classical immunosuppressants. Subsequent work showed that it is an antagonist of the sphingosine 1-phosphate (S1P) receptor, which is highly expressed in numerous cell types including leukocytes. Fingolimod causes T cells to be sequestered in the lymph nodes, thereby reducing the number of circulating T cells and, consequently, the extent of T cell migration into the CNS.

Two phase III clinical trials published in 2010 demonstrated the efficacy of fingolimod. In the 24-month, double-blind FREEDOMS study, fingolimod reduced the annual relapse rate by ~60% compared with placebo, and in the 12-month, double-blind TRANSFORMS study, fingolimod reduced the annual relapse rate by ~50% compared with IFNβ. In both studies, fingolimod reduced the number of new or enlarged lesions visible on MRI scans. Importantly, in the FREEDOMS study, fingolimod also reduced the probability of disability progression. The reduced number of circulating lymphocytes was associated with a slightly increased risk of some viral infections in both studies.

The second oral therapeutic to be approved by the FDA, teriflunomide, is the active metabolite of leflunomide, a therapy for rheumatoid arthritis that has been in use since 1998. It inhibits the proliferation of rapidly dividing cells, such as T cells, by reducing their capacity to synthesize pyrimidine. In two key phase III, placebo-controlled trials in MS, known as TEMSO and TOWER, teriflunomide significantly reduced relapse rates, MRI evidence of disease activity and disability progression. Mean reductions in lymphocyte count with teriflunomide were small in these studies, and infection rates did not differ between patients treated with teriflunomide and those treated with placebo.

> “oral therapies have transformed the treatment of RRMS”

Within months of FDA approval of teriflunomide, a third oral therapy — DMF — was added to the list. DMF is a fumaric acid ester; similar molecules are known immunosuppressants and were being used in topical formulations for the treatment of psoriasis. DMF reduces the number of circulating T cells, particularly $CD8^+$ T cells, thereby suppressing immune responses. The phase III CONFIRM and DEFINE studies compared the effects of DMF with those of placebo over 2 years of treatment. In both studies, DMF treatment reduced the annual relapse rates and the number of new or enlarged lesions on MRI scans. In the DEFINE study, DMF also reduced the rate of disability progression. Lymphocyte counts were reduced in patients who were treated with DMF, but infection rates did not differ between the drug-treated and placebo-treated patients.

These three oral therapies have transformed the treatment of RRMS. The option to use oral, rather than injectable, therapies for equal or greater therapeutic benefit reduced the burden of treatment, thereby increasing both patient satisfaction and compliance.

Megan Cully, Senior Editor,
Nature Reviews Drug Discovery

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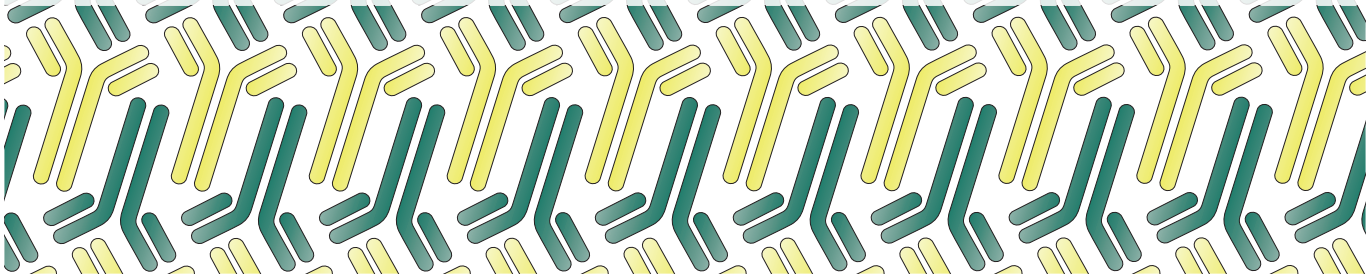
MILESTONE 5

Highs and lows with second-generation monoclonal antibodies



Credit: S. Fenwick/Springer Nature Limited

Following the eventual success of natalizumab therapy for multiple sclerosis (MS; MILESTONE 3), alemtuzumab and daclizumab — two second-generation monoclonal antibodies — were approved for treatment in 2014 and 2016, respectively, although the success of daclizumab did not last.

While natalizumab prevents lymphocytes from crossing the blood–brain barrier (MILESTONE 2), the second-generation antibodies each have different biological actions. Alemtuzumab binds to CD52 on mature lymphocytes and depletes circulating T cells and B cells, which are subsequently repopulated spontaneously. This process can lead to lasting changes in adaptive immunity. Daclizumab targets CD25, the α-subunit of the high-affinity IL-2 receptor. Treatment with daclizumab reduces IL-2 signalling through this receptor and increases signalling at the intermediate-affinity IL-2 receptor. As a result, numbers of $CD56^{bright}$ natural killer cells increase and numbers of lymphoid tissue inducer cells decrease, thereby reducing immune responses.

In 2012, two clinical trials demonstrated the efficacy of alemtuzumab treatment for patients with relapsing–remitting MS (RRMS). In the CARE-MS I trial, patients with previously untreated RRMS were randomly allocated to receive alemtuzumab (12 mg daily for 5 days at baseline and for 3 days at 12 months) or interferon-β-1a (IFNβ-1a; 44 μg three times per week). Over 2 years, fewer patients in the alemtuzumab group than in the IFNβ-1a group experienced a relapse. However, alemtuzumab offered no benefit over IFNβ-1a in terms of sustained accumulation of disability.

In the CARE-MS II trial, alemtuzumab was compared with IFNβ-1a in patients with RRMS who had experienced a relapse while receiving a standard disease-modifying therapy. Among patients in the alemtuzumab group, the annual relapse rate was 49.4% lower than in the IFNβ-1a group, and sustained accumulation of disability was 42% lower. Secondary autoimmunity was the main adverse effect of alemtuzumab therapy, but this effect could be managed effectively to reduce the risk. Thus, alemtuzumab was approved for treatment in 2014.

In 2013, the randomized, double-blind, placebo-controlled SELECT trial of daclizumab in patients with RRMS was published. In this trial, patients received daclizumab (150 mg or 300 mg) or placebo every 4 weeks for 1 year. The annual relapse rate was lower in patients who received daclizumab (either dose) than in those who received placebo.

The subsequent SELECTION study was a multicentre, randomized, double-blind trial to assess the safety and immunogenicity of extended treatment with daclizumab in patients with RRMS. The conclusions were that adverse events and immunogenicity did not increase in the second year of continuous treatment with daclizumab relative to the first. In a further trial published in 2015, daclizumab was compared with IFNβ-1a. Daclizumab treatment resulted in a lower annual relapse rate than IFNβ-1a treatment.

> “fewer patients in the alemtuzumab group than in the IFNβ-1a group experienced a relapse”

On the basis of these trial results, daclizumab was approved for the treatment of RRMS in 2016, with a contraindication for patients with pre-existing hepatic disease or impairment (owing to observations in clinical trials that levels of liver enzymes were elevated in patients receiving daclizumab, and to the death of one patient from autoimmune hepatitis).

However, in 2016 and 2017 reports of immune-mediated adverse reactions in the CNS, including encephalitis and meningoencephalitis, started to emerge. Given the seriousness of these immune-mediated events and a high likelihood that they were linked to or caused by daclizumab, the drug was withdrawn from the market with immediate effect in March 2018.

Isobel Leake, Senior Editor, Nature Reviews

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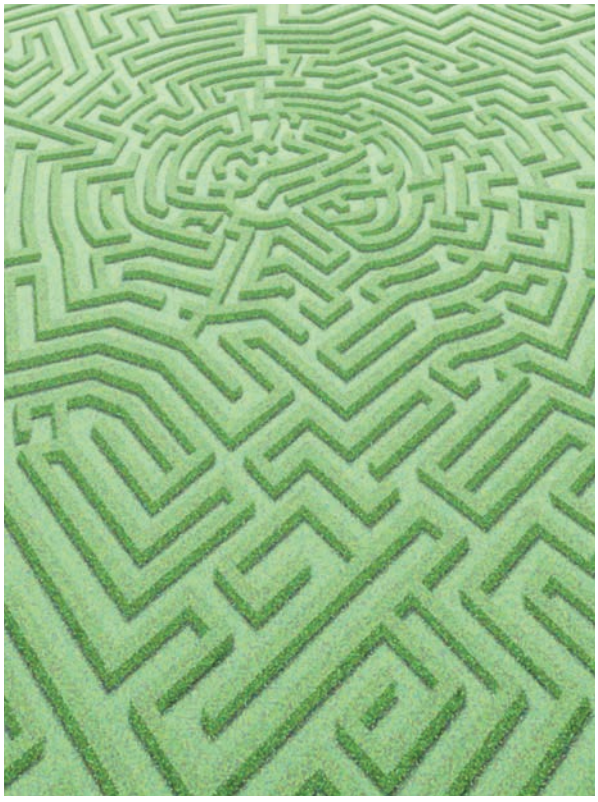
MILESTONE 6

More treatments create clinical dilemmas

With the introduction of several disease-modifying therapies (DMTs) for relapsing–remitting multiple sclerosis (MS), the decision of which treatment to use became increasingly complex. The choice between injectable therapies (MILESTONE 1), monoclonal antibodies (MILESTONE 2, 5) and oral drugs (MILESTONE 4) with different efficacies and risks meant clinicians had to start making decisions about which treatment is appropriate, when to commence treatment, and when and how to switch treatments if the clinical response is suboptimal. Each aspect has a dilemma to address for each patient.

Difficulty in selecting the initial therapy for a specific patient with MS comes from uncertainty about the relative efficacies of the DMTs and about how a patient will respond to a particular DMT. Trial results show that some DMTs have a higher efficacy than others; for example, natalizumab is more effective than interferon-β (IFNβ) (MILESTONE 2). However, few DMTs have been compared in head-to-head trials and the relative efficacies of DMTs remain controversial, posing a conundrum for clinicians. Analysis of real-world data can inform treatment decisions, but individual treatment responses cannot be accounted for.

> “the relative efficacies of DMTs remain controversial, posing a conundrum for clinicians”



Credit: V. Summersby/Springer Nature Limited

Consensus has not been reached on how to identify patients who will benefit most from a particular DMT. Some patients respond well to the traditional first-line therapies (IFNβ-1a and glatiramer acetate; MILESTONE 1), whereas others do not and require more potent second-line treatments, such as natalizumab, fingolimod or alemtuzumab. However, these second-line DMTs are typically associated with severe adverse effects, which might preclude their use in some patients.

Consequently, the clinician is faced with a difficult choice. Initial therapy with first-line treatments with the option to escalate to second-line treatments is initially safer, but risks a suboptimal response that allows disease progression. By contrast, initial therapy with a second-line treatment is more likely to induce remission, but could have serious adverse consequences.

Guidelines recommend that the choice of initial therapy be based on a dialogue between patient and clinician and that it takes into account disease severity, patient lifestyle factors and the toxicity and efficacy of available drugs. These factors enable the risk–benefit ratio to be established before therapy is commenced.

Another difficulty that has arisen as a result of the approval of several DMTs is pressure on clinicians to make an early diagnosis. Studies of multiple DMTs have consistently shown that treatment of MS early in the disease course, and even in patients who do not fulfil the entire diagnostic criteria for MS (such as those with clinically isolated syndrome), is associated with better long-term outcomes than later treatment. This finding drives clinicians to make an early diagnosis. As a consequence, misdiagnosis of MS is a risk, occurs regularly and can lead to initiation of unnecessary or incorrect treatments that can have serious adverse effects and can be financially costly.

Finally, as the therapeutic armamentarium for MS has grown, treatment switching to improve a patient's clinical response or to improve tolerability has become an option, but is challenging in clinical practice. Switching therapies has been shown to reduce disease activity in patients with breakthrough disease, although precisely when a patient is deemed to be non-responsive to a particular DMT is a matter of debate. Indeed, even defining a lack of response to DMTs is difficult, as many patients receiving treatment for MS have some disease activity, and several different sets of criteria for a suboptimal treatment response — largely based around MRI activity or clinical findings — have been proposed. Moreover, selecting the appropriate treatment to switch to is complicated by the uncertainty over the relative efficacies of DMTs, and escalation to a treatment of higher efficacy is often associated with more-severe adverse effects.

These clinical dilemmas continue today, and their importance is reflected in the 2018 publication of the ECTRIMS/EAN and the AAN guidelines for the treatment of MS. With more experience, treatment strategies are likely to be refined, and such a range of treatment options presents an opportunity for personalized therapy.

Louise Adams, Associate Editor, *Nature Reviews Disease Primers*

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MILESTONE 7

The story of cladribine reaches its climax

In June 2017, the European Medicines Agency (EMA) approved oral cladribine for the treatment of relapsing–remitting multiple sclerosis (RRMS). However, cladribine is not a new drug, and its efficacy in RRMS had already been demonstrated in 2010, but safety concerns prevented its approval. The eventual approval was a landmark because cladribine is the most effective of the oral therapies and is the only oral option for pulsed immune reconstitution, which otherwise requires monoclonal antibodies. Additionally, cladribine's mechanism of action differs from that of other current MS treatments that target lymphocyte function.

Cladribine, or 2-chloro-2′-deoxyadenosine, is a synthetic adenosine analogue that is activated in cells when it is phosphorylated by deoxycytidine kinase. The triphosphorylated active form is cytotoxic, resistant to breakdown by adenosine deaminase and disrupts DNA synthesis and repair, thereby inducing apoptosis. In most cell types, the drug is inactivated through dephosphorylation by 5′-nucleotidase, but in lymphocytes, and particularly B cells, the kinase:phosphatase ratio is high, so the drug remains active and preferentially depletes these cells, leaving other cell types unaffected.

In 2010, the efficacy of oral cladribine for the treatment of RRMS was tested in the 96-week phase III CLARITY trial. Patients with RRMS were randomly assigned to receive placebo or cladribine at a dose of 3.5 mg/kg or 5.25 mg/kg body weight administered over 1–2 weeks at the start of each year. Cladribine at both doses reduced the annual relapse rate at 96 weeks by more than 50% compared with placebo, increased the proportion of patients who were relapse-free (~79% versus 61%) and reduced the risk of 3-month sustained progression of disability by >30% and the mean lesion number detected by MRI by >70%.

Despite these highly encouraging clinical benefits, development of solid tumours, as well as the expected adverse effects of lymphopenia and infections, in a small number of cladribine-treated patients meant that approval for cladribine was denied by the FDA and EMA and the drug did not come to market (although ongoing trials were completed). However, concerns about the safety of cladribine have since been ameliorated by a meta-analysis in which the cancer risk associated with cladribine was found to be similar to that associated with other disease-modifying drugs.

In 2014, the results of the 96-week phase III ORACLE MS trial were reported. This trial tested the effect of cladribine on the time to conversion from a first demyelinating event to clinically definite MS. The trial was terminated early, but both 3.5 mg/kg and 5.25 mg/kg cladribine increased the time to MS diagnosis and reduced numbers of MRI lesions compared with placebo. Importantly, adverse events occurred at a similar rate in all patient groups, confirming the safety of cladribine.

> "cladribine has finally arrived as an effective and unique oral therapy for MS"

In 2018, the results of the CLARITY Extension study were published. In this study, patients from the placebo group in the original CLARITY trial received low-dose cladribine, whereas recipients of cladribine in the original trial were randomly assigned to receive cladribine or placebo. This study design enabled assessment of the effects of long-term cladribine treatment and early versus late treatment, and of the durability of cladribine's clinical effects. Long-term dosing did not increase efficacy, but later treatment was associated with a shorter time to first relapse. Crucially, among patients who received cladribine in CLARITY but placebo in CLARITY Extension, the proportion who were free from relapses and disease progression was unchanged, indicating a durable clinical response.

The short duration of cladribine dosing in the 1-year treatment cycles (allowing haematological recovery during the rest of the year), together with the durable clinical response, suggests that cladribine has potential as an induction therapy. The durability of cladribine's clinical effects also suggests that it 'resets' the immune system, thereby enabling long-lasting disease remission without the need for maintenance therapy.

Despite a long and, at times, uncertain route to regulatory approval, cladribine has finally arrived as an effective and unique oral therapy for MS.

Grant Otto, Associate Editor, Nature Reviews

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MILESTONE 8

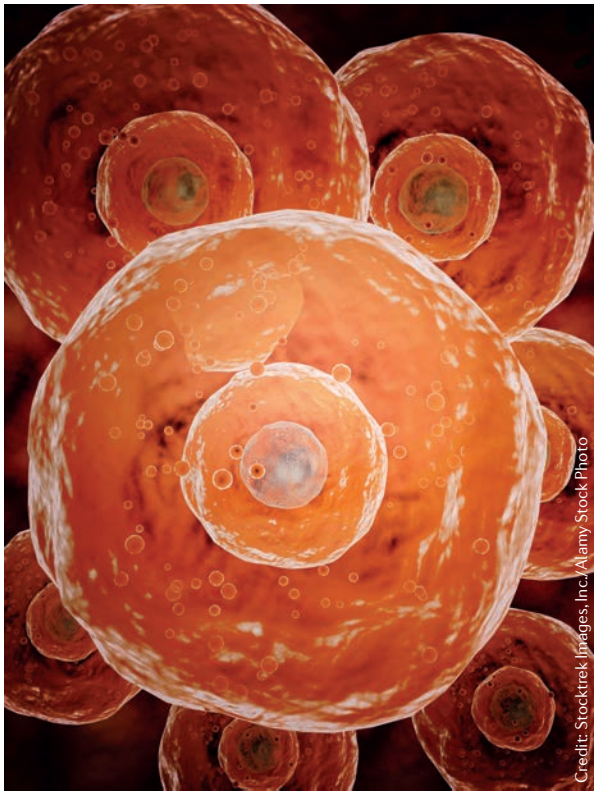
Targeting B cells leads to breakthrough therapy

Traditionally, T cell-mediated neuroinflammation has been considered central to the pathogenesis of multiple sclerosis (MS). Over the past few years, however, B cells have also emerged as key players in the MS disease process and are providing an important focus for the development of new disease-modifying therapies for both relapsing and progressive forms of the condition.

In MS, the inflammatory environment in the brain is thought to promote the proliferation, maturation and survival of B cells — effects mediated by trophic factors such as BAFF (B cell-activating factor of the TNF family) and APRIL (a proliferation-inducing ligand). B cells can produce both pro-inflammatory and anti-inflammatory cytokines, but their pro-inflammatory function seems to predominate in MS. B cells also produce immunoglobulin that forms oligoclonal bands in the cerebrospinal fluid — one of the principal diagnostic features of MS.

Several established MS therapies, including interferon-β (IFNβ), natalizumab and fingolimod, have been found to exert their beneficial effects partially through modulation of B cell function. In light of this knowledge, the B cell-specific monoclonal antibodies rituximab and ocrelizumab have recently been tested in MS. These antibodies selectively deplete circulating B cells by targeting the CD20 antigen, which is expressed on developing and mature B cells.

Rituximab was the first anti-CD20 monoclonal antibody to be licensed for use in humans, and has been approved for the treatment of various conditions, including non-Hodgkin lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis. In 2008, a phase II placebo-controlled trial of rituximab in patients with relapsing–remitting MS (RRMS) was published. Over the 48-week study period, patients who received rituximab experienced fewer relapses and had fewer gadolinium-enhancing lesions in the brain than those who received placebo.



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> “the efficacy of anti-CD20 B cell-depleting therapies in RRMS and PPMS represents a breakthrough”

Despite the early promise of rituximab, no phase III trials of this drug in patients with MS have yet been published. Consequently, rituximab is not approved by the FDA for the treatment of MS, although it is frequently prescribed off-label for this indication.

The year 2017 saw the publication of OPERA I and OPERA II, two pivotal phase III trials that tested the efficacy and safety of ocrelizumab versus IFNβ-1a in patients with RRMS. The trials had identical designs but were conducted at different locations. Both trials showed that ocrelizumab was more effective than IFNβ-1a at reducing MS disease activity and progression over a 96-week period. A third phase III trial, ORATORIO, demonstrated the benefits of ocrelizumab in patients with primary progressive MS (PPMS; MILESTONE 9).

On the basis of the OPERA I, OPERA II and ORATORIO data, the FDA approved ocrelizumab for the treatment of RRMS and PPMS in March 2017, and the European Medicines Agency followed suit in November 2017.

In all three phase III trials of ocrelizumab, the overall safety profile of the treatment was good. However, in comparison with IFNβ-1a in OPERA I and OPERA II and with placebo in ORATORIO, ocrelizumab treatment was associated with a slight increase in the risk of neoplasms. Furthermore, although no cases of progressive multifocal leukoencephalopathy (PML; MILESTONE 3) occurred in the trials, some cases of PML associated with ocrelizumab therapy have been reported since its approval. For these reasons, ongoing monitoring of the real-world safety of ocrelizumab is needed.

Despite these potential drawbacks, the efficacy of anti-CD20 B cell-depleting therapies in RRMS and PPMS represents a breakthrough. By taking the first steps into previously uncharted territory, this development has further expanded the therapeutic options for RRMS.

Heather Wood, Chief Editor,
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MILESTONE 9

Progressive and aggressive MS — new frontiers emerge

The huge progress made in the treatment of relapsing–remitting multiple sclerosis (RRMS) in the past 25 years has not been replicated for progressive forms of multiple sclerosis (MS) or for aggressive MS that does not respond to disease-modifying therapies (DMTs). However, progress has been made in the past 2–3 years, making these areas the new frontiers.

Progressive MS is characterized by accumulation of disability without relapses. In primary progressive MS (PPMS), this disease course occurs from the onset, whereas in secondary progressive MS (SPMS) this course follows a relapsing–remitting phase.

After years of failure to develop treatments for progressive MS, a major breakthrough was seen in 2017 when ocrelizumab was approved as the first treatment for PPMS.

The approval of ocrelizumab for PPMS was based on results of the ORATORIO trial, published in 2017. In this trial, 732 patients with PPMS received either ocrelizumab or placebo every 24 weeks for at least 120 weeks. Relative to placebo, ocrelizumab reduced 12-week and 24-week disability progression and slowed brain atrophy. Ocrelizumab also reduced brain lesion volume relative to baseline. Given that ocrelizumab depletes B cells (MILESTONE 8), its efficacy in PPMS implicates B cells in the pathophysiology of progressive disease, forming the basis for testing and development of other B cell-targeted therapy in this context.

A lack of therapeutic options in SPMS also looks likely to end following the EXPAND study, a phase III trial of siponimod. Siponimod is a sphingosine 1-phosphate (S1P) receptor inhibitor that acts similarly to fingolimod (MILESTONE 4) in preventing egress of lymphocytes from lymphoid tissue and reducing migration of peripheral lymphocytes into the CNS. In EXPAND, 1,645 patients with SPMS were randomly assigned to receive 2 mg of oral siponimod or placebo once per day for up to 3 years. Treatment with siponimod led to a 21% reduction in the relative risk of 3-month confirmed disability progression. The safety profile was good, so the trial suggests that siponimod could be a useful treatment in SPMS.

Aggressive MS is not well defined, but can be described as highly active disease that causes early and rapid progression of disability. One treatment with potential in aggressive MS and progressive MS is autologous haematopoietic stem cell transplantation (aHSCT).

> “the trials … demonstrate the encouraging steps taken towards treatments for the most disabling forms of MS”

This procedure, first developed to treat haematological malignancies, involves extraction of haematopoietic stem cells (HSCs) from the patient, followed by suppression or ablation of the immune system and subsequent replacement of the HSCs to enable immune reconstitution. Safety concerns have meant that aHSCT has only been used as a rescue therapy after other options have been exhausted. However, safety has improved in the latest studies, and the efficacy is striking.

In a study published in 2016, immunoablation and aHSCT in 24 patients drastically affected MS disease activity. During follow-up (median 6.7 years), no patients had relapses and no new lesions were detected with MRI. One patient died, highlighting the remaining risks, but mortality was much lower than in many previous studies. Similarly, in the HALT-MS study published in 2017, high-dose immunosuppression followed by aHSCT in 24 patients resulted in freedom from disease activity in 70% of patients over a median follow-up period of 62 months. No unexpected adverse events were reported.

Finally, in a study of long-term outcomes, almost half of 281 patients who underwent aHSCT for MS were free of disease progression at 5 years. Mortality was again lower than in many previous studies, at 2.8%. Importantly, almost 80% of patients in this study had progressive MS.

Together, the trials in progressive and aggressive MS demonstrate the encouraging steps taken towards treatments for the most disabling forms of MS. These steps lay the foundations for a second 25 years of MS treatment that is as successful as the first.

Ian Fyfe, Senior Editor,
Nature Reviews Neurology

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