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REVIEW ARTICLE

Monoclonal Antibodies for Multiple Sclerosis: An Update

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Abstract
The use of monoclonal antibodies in multiple sclerosis (MS) patients is in a transitional period. Studies regarding well-established, effective antibodies such as natalizumab and alemtuzumab focus more and more on long-term efficacy and safety, risk management, and treating complications. Primary progressive MS, a disease that was long considered to be unmodifiable, is currently in focus following ocrelizumab being approved as the first drug with a proven beneficial effect on the disease course. Conversely, post-marketing safety mechanisms have also proven to function as daclizumab has been suspended after a series of relevant serious adverse events. Currently, new therapies are emerging that promise more convenience and an improved safety profile (ofatumumab) or remyelinating potential with clinical improvement (opicinumab). While it is very unlikely that monoclonal antibodies will ever cure MS, they have become very valuable therapeutic tools to better patient outcomes. This review focuses on developments of monoclonal antibodies used in the past, present, and near future in MS patients.

Key Points

Monoclonal antibodies have changed the way we approach treatment of multiple sclerosis (MS) as they specifically target molecules that are key in the pathogenesis of MS.

Currently, there is a wide range of therapeutic options for MS and new treatments on the horizon need to prove additional benefit, e.g., remyelination, clinical improvement, a better safety profile, and/or cost effectiveness.

Treatment safety is as important as efficacy, especially for long-term use of monoclonal antibodies in MS, which markedly impact immune system functionality.

1 Introduction

Multiple sclerosis (MS) is the most frequent autoimmune inflammatory disease of the central nervous system (CNS). Worldwide, some 2.5 million people are afflicted; it is the commonest cause of neurological disability in young adults [1]. MS takes either a relapsing or progressive course. The disease most likely results from a complex interplay of genetic, environmental, and immunological factors that determine individual susceptibility. The past 25 years have witnessed gratifyingly successful clinical drug developments so that a range of injectable and oral drugs are now available [1–3].

Monoclonal antibodies revolutionized the treatment of both relapsing and, very recently, progressive MS. All of the currently licensed antibodies have proven their efficacy in phase III studies, especially in the relapsing MS form in which they are used when the disease is highly active. None of these biological drugs are licensed in Europe for the use in mild to moderate, less active disease, stressing not only their potency but also the associated relevant risks. While the labels for these agents are broader in the USA and Australia, for example, most neurologists would in practice concur with this approach [4, 5]. Since each licensed drug is currently in a different post-marketing phase, recent studies have concentrated on distinct treatment-relevant aspects. Furthermore, post-marketing safety mechanisms have also proven to be operative as one monoclonal antibody (daclizumab) has

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recently been withdrawn and new therapies emerge promising more convenience and a potentially improved safety profile (ofatumumab) or even remyelinating potential with clinical improvement (opicinumab). Additionally, data continue to be published on how to deal with progressive multifocal leukoencephalopathy (PML) in MS patients treated with natalizumab. With regard to future drugs, two phase III studies comparing ublituximab, a monoclonal antibody targeting a unique epitope on CD20, with teriflunomide are recruiting patients with relapsing MS (ClinicalTrials.org identifiers NCT03277261 and NCT03277248), but there is no monoclonal antibody currently in late-stage clinical studies [6]. As more and more disease-modifying therapies are approved for MS patients, the idea of individualizing treatment becomes relevant [7]. Current concepts in MS therapy have been repeatedly reviewed, for example, and safety concerns been addressed [8, 9], but the complexity of the current monoclonal antibody spectrum warrants a concise overview and assessment of the recent developments.

Here we provide an update on the current status of monoclonal antibodies—licensed and unlicensed—used in the past, present, and, potentially, in the future for the treatment of MS.

The most crucial developments and aspects have been summarized in tables: Table 1 gives a concise overview over the most recent developments, Table 2 focuses on risk management and minimization, Table 3 gives a broad overview of the pivotal phase II and III trials, Table 4 summarizes the most relevant adverse effects, and Table 5 provides an overview on the reported serious adverse events.

2 Natalizumab

The monoclonal antibody natalizumab blocks leukocyte migration by binding to α-4 integrin. This mechanism leads to a marked reduction of the relapse rate in MS patients. The clinical and radiological efficacy of natalizumab has been proven both in a phase II trial published in 2003 [10] and two phase III trials published in 2006 [11] as it markedly diminished the number of new relapses as well as lesions on magnetic resonance imaging (MRI) compared to placebo. Of note, a post hoc analysis of natalizumab-treated patients revealed that 383 (64%) of 596 patients taking natalizumab and 117 (39%) of 301 taking placebo were free of disease activity, paving the way for the concept of NEDA (no evidence of disease activity) [12].

Although natalizumab is generally well-tolerated and safe, this effectiveness comes at a price: the risk of PML hangs like a sword of Damocles over the treated patients, particularly those seropositive for anti-JC (John Cunningham) virus (JCV) antibodies. Natalizumab treatment is associated with the highest risk of developing PML in JCV-seropositive patients, compared with all other medications

Table 1 Recent pivotal trials and publications on monoclonal antibodies used in multiple sclerosis patients

Monoclonal antibody	Key message	References
Natalizumab	Yearly benefit–risk re-evaluation and consideration of the anti-JCV antibody index seems crucial in clinical practice	[19]
	Natalizumab therapy is associated with higher rates of seroconversion and greater anti-JCV index variability than in patients naïve to natalizumab	[27]
	In natalizumab-associated PML, plasma exchange and corticosteroid administration should be used with caution	[34, 35]
Alemtuzumab	5-Year efficacy and safety data suggest that the annualized relapse rate stayed low and most patients showed NEDA and brain volume loss, i.e. atrophy, improved	[45, 46]
Rituximab	Significant association between presence and titers of anti-drug antibodies and incomplete B cell depletion in rituximab treatment, but not with infusion reactions, adverse reactions, or clinical outcomes	[104]
Daclizumab	Association with hepatotoxicity	[78]
	Cutaneous events	[83, 84]
	DRESS	[85]
	Encephalitides	[81, 82]
Ocrelizumab	Post-marketing data suggest beneficial influence on the relapsing disease course	[112]
Ofatumumab	Ofatumumab may suppress new brain MRI lesions compared with placebo, complete depletion was not necessary for a robust treatment effect, a conditioning dose added no benefit, and repletion occurred faster with all ofatumumab doses than previously reported with anti-CD20 therapy	[115]
Opicinumab	Remyelination in the human CNS with opicinumab might be possible	[120]
	LINGO-1 blockade does not seem to affect immune function	[122]

CNS central nervous system, *DRESS* drug reactions with eosinophilia and systemic symptoms, *JCV* John Cunningham polyomavirus, *LINGO-1* leucine-rich repeat and immunoglobulin domain-containing neurite outgrowth inhibitor receptor-interacting protein-1, *MRI* magnetic resonance imaging, *NEDA* no evidence of disease activity, *PML* progressive multifocal leukoencephalopathy

Table 2 Management and minimization of major risks related with monoclonal antibodies used in multiple sclerosis patients

Monoclonal antibody	Treatment interval	Major risks	Risk management and minimization
Natalizumab	Every 28 days	PML	Yearly benefit–risk re-evaluation, consideration of the anti-JCV antibody index, and higher-risk quarterly MRI scans
Alemtuzumab	First course 5 days; second course 3 days 1 year later	Infections, thyroid disorders, immune thrombocytopenia, nephropathy	Before treatment: Infectious risk stratification[a] Check vaccination status During treatment: Aciclovir and corticosteroid prophylaxis Monthly laboratory, quarterly clinical, and annual MRI monitoring After treatment: Monthly laboratory, quarterly clinical and annual MRI monitoring Continue laboratory monitoring until 48 months after last infusion
Rituximab	Days 1 and 15; subsequent courses every 24 weeks	Infections	Before treatment: Infectious risk stratification[a] Check vaccination status During treatment: Clinical and laboratory monitoring Consider hepatitis B reactivation prophylaxis
Daclizumab	Once a month	Hepatotoxicity (fatal cases), encephalitides	Withdrawal from market
Ocrelizumab	Days 1 and 15; subsequent courses every 24 weeks	Infections, malignancies (?), in particular breast cancer	Before treatment: Infectious risk stratification[a] Check vaccination status During treatment: Clinical and laboratory monitoring Consider hepatitis B reactivation prophylaxis Follow standard cancer screening guidelines
Ofatumumab	As yet unknown; cumulative dose of 60 mg administered over 12 weeks provided maximal benefit	Injection-related reactions, cholelithiasis, hypokalemia, angioedema, urticaria, malignant melanoma	Undetermined (drug currently not licensed for use in multiple sclerosis)
Opicinumab	As yet unknown; once every 4 weeks (total of 6 doses) in optic neuritis	As yet unknown; possible interaction with immune system	Undetermined (drug currently not licensed for use in multiple sclerosis) LINGO-1 blockade does not seem to affect immune function

JCV John Cunningham polyomavirus, *LINGO-1* leucine-rich repeat and immunoglobulin domain-containing neurite outgrowth inhibitor receptor-interacting protein-1, *MRI* magnetic resonance imaging, *PML* progressive multifocal leukoencephalopathy

[a] Screening for tuberculosis, HIV, hepatitis B, hepatitis C, varicella zoster virus, *Treponema pallidum*

approved for MS [13]. As of August 31, 2018, the total incidence of natalizumab-associated PML is 4.16 per 1000 treated patients, and as of September 05, 2018, a total of 795 natalizumab-associated cases of PML have been reported, according to the manufacturer [14].

Consequently, recent studies focused on the PML risk stratification and treatment strategies, bearing in mind that the drug was withdrawn in 2005 after the first three cases of PML and reintroduced under strict monitoring requirements 1 year later. Of note, the result of an interim safety program revealed no new safety signals [15]. Nevertheless, the PML risk should be kept in mind, especially after changing from natalizumab to a different therapy, even more than 6 months after cessation of natalizumab [16].

The pathology and pathogenesis of PML and PML–immune reconstitution inflammatory syndrome (IRIS) have already been concisely reviewed [17, 18]. Following detection of this rare but serious complication, algorithms were developed based on the identification of risk factors for PML to allow patients to be stratified according to these: in this context, clinical aspects of natalizumab treatment, the need for yearly benefit–risk re-evaluation, and consideration of the role of the anti-JCV antibody index, especially in JCV-positive patients in clinical practice, have been emphasized [19] as anti-JCV antibody levels may increase and herald development of natalizumab-associated PML [20]. In the pivotal JCV risk stratification trial, risk estimates were generated for JCV antibody index thresholds:

Table 3 Pivotal phase II and III trials of monoclonal antibodies used in multiple sclerosis patients

Monoclonal antibody	Pivotal trial	Study result	
		Primary endpoint(s)	Secondary endpoint(s)
Natalizumab	Phase II RRMS [10]	Number of new gad-enhancing lesions over 6-month treatment period *Reduction in natalizumab vs. placebo*	Number of persistent enhancing lesions; New active lesions; Total volume of enhancing lesions; and Percentage of scans showing activity *Reduction in natalizumab vs. placebo*
	Phase III RRMS (AFFIRM) [11]	Cumulative probability of sustained progression of disability *Reduction in natalizumab vs. placebo*	Reduction in the number of lesions detected by T2 MRI; and Number of lesions detected by gad-enhanced MRI *Reduction in natalizumab vs. placebo*
	Phase III SPMS (ASCEND) [37]	Sustained disability progression *No treatment effect on EDSS or the T25FW; reduced 9HPT progression* Incidence of adverse events and serious adverse events *No new safety concerns were identified*	Consistent improvement in T25FW Change in patient-reported ambulatory status as measured by the MSWS-12 Change in patient-reported manual ability based on the ABILHAND questionnaire Effect on patient-reported quality of life with the MSIS-29 physical score Change in whole-brain volume between weeks 24 and 96, and disability progression measured by EDSS *No significant differences between treatment groups in the change from baseline to year 2 were seen*
Alemtuzumab	Phase II RRMS (CAMMS223) [40]	Sustained accumulation of disability (EDSS) and the rate of relapse *Alemtuzumab reduced the risk of EDSS progression and of relapse compared with IFN-β1a*	Proportion of patients who did not have a relapse; Changes in T2 lesion burden; and Brain volume *In clinical and MRI outcomes, alemtuzumab was superior to IFN-β1a*
	Phase III RRMS (CARE-MS I) [41]	Relapse rate and time to 6-month sustained accumulation of disability *Alemtuzumab is more effective than high-dose subcutaneous IFN-β1a for reduction of rates of relapse in previously untreated patients* *No benefit in terms of disability endpoints*	Proportion of relapse-free patients, change in EDSS; Percentage change in T2 lesion volume; and Change in MSFC *Mean EDSS score improved, MSFC change and decreases in T2 lesion volume by 24 months were not significant* *Alemtuzumab reduced the proportions of patients with gad-enhancing and new or enlarging T2-hyperintense lesions, and slowed brain volume loss*
	Phase III RRMS (CARE-MS II) [42]	Relapse rate; and Time to 6-month sustained accumulation of disability *Alemtuzumab reduced the rate of relapse compared with IFN-β1a; and* *Alemtuzumab reduced the risk of sustained accumulation of disability compared with IFN-β1a*	Proportion of relapse-free patients; Changes in EDSS; T2 lesion volume; and MSFC *MSFC scores were not regarded as significantly different* *Median T2 lesion volume did not differ between groups* *Tertiary analyses suggested that, compared with IFN-β1a, alemtuzumab reduced the proportion of patients who developed new gad-enhancing lesions and new or enlarging T2 lesions* *Brain volume loss was reduced after alemtuzumab compared with IFN-β1a*

Table 3 (continued)

Monoclonal antibody	Pivotal trial	Study result	
		Primary endpoint(s)	Secondary endpoint(s)
Rituximab	Phase II RRMS (HERMES) [92]	Sum of the number of gad-enhancing lesions on serial T1-weighted MRI brain scans at weeks 12, 16, 20, and 24 *Rituximab superior to placebo*	Proportion of patients with relapses; Annualized rate of relapse; Total number of new gad-enhancing lesions observed on serial T1 MRI brain scans at weeks 12, 16, 20, and 24; and Change from the baseline lesion volume on T2 MRI scans *Rituximab superior to placebo*
	Phase II/III PPMS (OLYMPUS) [100]	Time to CDP Percentage of participants with CDP *No evidence of significant difference in time to CDP*	Change from baseline to week 96 in total volume of T2 brain lesions Change from baseline to week 96 in brain volume *Patients receiving rituximab had significantly less increase in T2 lesion volume on brain MRI scans*
Daclizumab	Phase II RRMS (SELECT) [75]	Annualized relapse rate *Annualized relapse rate was lower for patients given daclizumab HYP 150 or 300 mg than for those given placebo*	Cumulative number of new gad-enhancing lesions on brain MRI scans performed at weeks 8, 12, 16, 20, and 24 in a subset of patients Number of new or newly enlarging T2 lesions at week 52 Proportion of relapsing patients between baseline and week 52; and Quality of life, as measured by the change from baseline to week 52 in the MSIS-29 physical impact score *Daclizumab HYP reduced new multiple sclerosis lesion activity in all patients, significant improvement in the mean MSIS-29 physical score at week 52 for patients in the daclizumab HYP 150 mg group vs. those on placebo, but not for those in the 300 mg group*
	Phase III RRMS (DEFINE) [74]	Annualized relapse rate *Daclizumab superior to IFN-β1a i.m.* (intramuscular)	Mean number of new or newly enlarging T2 lesions Proportion of participants with sustained disability progression Proportion of participants relapse free at week 144 Percentage of participants with a ≥ 7.5-point worsening from baseline in the MSIS-29 Physical Impact Score *Daclizumab superior regarding mean number of new or newly enlarging T2 hyperintense lesions, proportion of relapse-free participants at week 144, and MSIS-29*

Table 3 (continued)

Monoclonal antibody	Pivotal trial	Study result	
		Primary endpoint(s)	Secondary endpoint(s)
Ocrelizumab	**Phase III RMS** (OPERA I and II) [109]	Annualized relapse rate *Ocrelizumab superior to IFN-β1a*	Time to onset of CDP Number of gad-enhancing lesions Number of new and/or enlarging T2 lesions Percentage of participants with CDI Number of T1 lesions Change from baseline in MSFC Percentage change in brain volume Change from baseline in SF-36 PCS Percentage of participants who have NEDA *Ocrelizumab superior regarding all secondary endpoints except MSFC and SF-36 in OPERA I; and* *Superior regarding all secondary endpoints except CDI and percentage change in brain volume in OPERA II*
	Phase III PPMS (ORATORIO) [110]	Time to onset of CDP sustained for at least 12 weeks *Ocrelizumab superior to placebo*	Time to onset of CDP sustained for at least 24 weeks Percentage change from baseline in T25FW Percentage change from baseline in total volume of T2 lesions Percentage change in total brain volume Change in PCS score and SF-36 Percentage of participants with at least 1 adverse event *Ocrelizumab superior regarding time to onset of CDP sustained for at least 24 weeks, percentage change from baseline in T25FW, percentage change from baseline in total volume of T2 lesions, and percentage change in total brain volume*
Ofatumumab	Phase IIb RMS (MIRROR) [115]	Cumulative number of new gad-enhancing brain lesions at week 12 *Ofatumumab superior to placebo*	Cumulative number of new gad-enhancing lesions at week 24 Cumulative number and total volume of new and new plus persisting gad-enhancing lesions New and/or newly enlarging T2 lesions, and T1 lesions at weeks 12 and 24 Proportion of patients who were relapse free from weeks 0 to 12 EDSS MSFC; and MFIS scores *Ofatumumab superior regarding secondary MRI endpoints, but not regarding clinical endpoints*
Opicinumab	Phase II ON (RENEW) [120]	Recovery of affected optic nerve conduction latency using FF-VEP vs. the unaffected fellow eye at baseline *Opicinumab not superior to placebo*	Percentage change in SD-OCT Change in SD-OCT average RGCL/IPL Change in LCLA *Opicinumab not superior to placebo*

Major trials are indicated in bold

9HPT 9 hole peg test, *CDP* Confirmed Disability Progression, *CDI* Confirmed Disability Improvement, *EDSS* Expanded Disability Status Scale, *FF-VEP* full-field visual evoked potential, *gad* gadolinium, *HYP* high-yield process, *IFN* interferon, *LCLA* low-contrast letter acuity, *MFIS* Modified Fatigue Impact Scale, *MRI* magnetic resonance imaging, *MSFC* Multiple Sclerosis Functional Composite, *MSIS-29* Multiple Sclerosis Impact Scale-29, *MSWS-12* 12-item Multiple Sclerosis Walking Scale, *NEDA* no evidence of disease activity, *ON* optic neuritis, *PCS* Physical Component Summary, *PPMS* primary progressive multiple sclerosis, *RGCL/IPL* retinal ganglion cell layer/inner plexiform retinal layer, *RRMS* relapsing-remitting multiple sclerosis, *SD-OCT* spectral-domain optical coherence tomography, *SF-36* Short Form Health Survey-36, *SPMS* secondary progressive multiple sclerosis, *T25FW* timed 25-foot walk

Table 4 Relevant serious adverse effects of monoclonal antibodies used in multiple sclerosis patients

Monoclonal antibody	Adverse effect
Natalizumab	PML
	PML with IRIS
	Hepatotoxicity
Alemtuzumab	Infections
	Infusion reaction
	Thyroid disorders
	Nephropathy
	Immune thrombocytopenia
Rituximab	Infections
	Infusion reaction
	Hepatitis B reactivation
Daclizumab	Hepatotoxicity
	Encephalitis
	Cutaneous events
	DRESS
Ocrelizumab	Infections
	Infusion reaction
	Hepatitis B reactivation
	Malignancies (breast cancer) (?)
Ofatumumab	Infections
	Infusion reaction
	Hepatitis B reactivation
Opicinumab	Specific adverse effects unknown

DRESS drug reactions with eosinophilia and systemic symptoms, *IRIS* immune reconstitution inflammatory syndrome, *PML* progressive multifocal leukoencephalopathy

natalizumab-treated patients naïve to prior immunosuppressive therapy who were anti-JCV antibody positive with an index from ≥ 0.9 to ≤ 1.5 in the first 24 months of natalizumab treatment had an estimated PML risk of 0.1 per 1000 patients, whereas those with an index > 1.5 had an estimated PML risk of 1.0 per 1000 patients [21]. The risk appears to be even higher in patients with prior exposure to immunosuppressants, approximately 4 in 1000 patients.

The blocking effect of natalizumab vanishes after approximately 8 weeks, a much shorter period than that of the other monoclonal antibodies currently used in MS patients [22]: after natalizumab treatment interruption, the earliest detectable markers (e.g., α4-integrin saturation, CD49d expression) were present by week 8, by week 12 peripheral lymphocyte counts had decreased significantly, and by week 16 all markers appeared to be similar to those observed in patients not treated with natalizumab. These constellations should be considered, especially in patients at a high risk of developing PML when switching to a different treatment option.

Still, how to switch natalizumab therapy remains a controversial topic [23], even more than a decade after licensing. A recent study suggests initiation of fingolimod within 8 weeks of natalizumab discontinuation [24]. In clinical routine, a switch from natalizumab to fingolimod within 4–6 weeks is not uncommon based on observations that with a longer interval the risk of disease recrudescence or even rebound appears to be higher. Of note, a recent performance analysis of the PML diagnostic criteria (proposed in a consensus statement from the American Academy of Neurology [25]) revealed that in natalizumab-associated PML the current case definition of PML has low sensitivity for diagnosis of natalizumab–PML in a real-world clinical setting [26].

Interestingly, natalizumab therapy has been associated with higher rates of seroconversion and greater anti-JCV index variability than those detected in patients naïve to natalizumab, and natalizumab exposure may influence the frequency of JCV antibodies [27]. Furthermore, JCV antibody positivity increases with age [28]. High natalizumab drug concentrations were not associated with the development of PML [29], but with a decrease of matrix metalloproteinase 9 [30]. L-selectin (CD62L) has been discussed [31] as a possible biomarker indicating PML risk in natalizumab-treated patients: on the one hand, an unusually low percentage of L-selectin-expressing CD4-positive T cells was highly correlated with the risk of developing PML [32], but, on the other hand, in a well-defined cohort of natalizumab-treated patients, L-selectin was not associated with PML but sensitive to sample collection [33].

With regard to handling natalizumab-associated PML, plasma exchange and corticosteroid administration should be used with caution [34, 35].

Preliminary evidence suggests that extending the dosing interval beyond 1 month may diminish the risk of developing PML [36]. A phase III trial addressing the efficacy of less frequent dosing is underway (NCT03516526).

Natalizumab failed to meet the primary composite endpoint at 2 years in a phase III trial performed in secondary progressive MS [37]. However, detailed analysis suggested a potential benefit in certain subtests, particularly for function of the upper extremities, and an extension of the study showed efficacy on the overall outcome at year 3.

Natalizumab was approved by the US Food and Drug Administration (FDA) in 2004, withdrawn in 2005, and reintroduced in 2006 under a special prescription program. The European Medicines Agency (EMA) granted a marketing authorization valid throughout the European Union (EU) in 2006.

3 Alemtuzumab

The humanized monoclonal antibody alemtuzumab selectively targets CD52, which leads to a durable depletion of T and B lymphocytes. B cells recur much faster, within a

Table 5 Severe adverse events in pivotal phase II and III trials of monoclonal antibodies used in multiple sclerosis patients

Monoclonal antibody	Pivotal trial	Design of experiment, regimen, route of administration	SAEs
Natalizumab	Phase II RRMS [10]	Randomized, double-blind trial; 3 mg of IV natalizumab per kg body weight, 6 mg/kg, or placebo every 28 days for 6 months	5 SAEs in 5 patients receiving natalizumab 3 mg/kg, and 4 SAEs in 3 patients receiving natalizumab 6 mg/kg; anaphylactoid reaction with urticaria and bronchospasm, serum sickness
	Phase III RRMS (AFFIRM) [11]	Randomized, double-blind trial; IV natalizumab 300 mg or placebo (2:1 ratio) every 4 weeks for up to 116 weeks	19% of patients receiving natalizumab; most common SAEs were MS relapse, cholelithiasis, and need for rehabilitation therapy; 2 patients died in the natalizumab group (malignant melanoma, alcohol intoxication)
	Phase III SPMS (ASCEND) [37]	Randomized, double-blind, placebo-controlled trial (part 1) with an optional 2-year open-label extension (part 2); IV natalizumab 300 mg or placebo (ratio 1:1) every 4 weeks for 2 years	20% of patients receiving natalizumab; most common SAEs were relapsing MS, urinary tract infection, pneumonia, and urosepsis
Alemtuzumab	Phase II RRMS (CAMMS223) [40]	Randomized, blinded trial; alemtuzumab 12 or 24 mg/day or IFN-β1a (ratio 1:1:1); IV alemtuzumab was given on 5 consecutive days during the first month and on 3 consecutive days in months 12 and 24, SC IFN-β1a 44 μg was administered 3 times weekly. All patients received IV methylprednisolone 1 g for 3 days at baseline and at months 12 and 24	22.2% of patients receiving alemtuzumab 12 mg and 25% of patients receiving alemtuzumab 24 mg; most relevant SAEs were hyperthyroidism, immune thrombocytopenic purpura, infections, and infusion-related events; 2 patients died in the alemtuzumab group (cardiovascular disease, immune thrombocytopenic purpura)
	Phase III RRMS (CARE-MS I) [41]	Randomized, rater-masked trial; IV alemtuzumab 12 mg/day for 5 days at baseline and 3 days at 12 months, or SC IFN-β1a 44 μg three times per week (ratio 2:1)	14% of patients receiving alemtuzumab, excluding MS relapse; most relevant SAEs were thyroid disorders, blood and lymphatic system disorders, infections, infusion-related events, and thyroid cancer; 2 patients died in the alemtuzumab group (car accident, sepsis after study)
	Phase III RRMS (CARE-MS II) [42]	Randomized, rater-masked trial; SC IFN-β1a 44 μg three times per week, IV alemtuzumab 12 mg/day, or IV alemtuzumab 24 mg/day (ratio 1:2:2). Alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. The 24 mg/day group was discontinued to aid recruitment, but data are included for safety assessments	13% of patients receiving alemtuzumab 12 mg/day and 17% receiving alemtuzumab 24 mg/day, excluding MS relapse; most relevant SAEs were thyroid disorders, blood and lymphatic system disorders, infections, infusion-related events, and neoplasms; 2 patients died in the alemtuzumab group (automobile accident, aspiration pneumonia after a brainstem relapse that occurred 1 year previously on-study)
Rituximab	Phase II RRMS [92]	Randomized, double-blind, placebo-controlled study; IV rituximab 1000 mg or placebo on days 1 and 15 (ratio 2:1)	13% of patients receiving rituximab; 1 patient with ischemic coronary artery syndrome and 1 had a malignant thyroid neoplasm; 1 patient died in the rituximab group (homicide)
	Phase II/III PPMS (HERMES) [100]	Randomized, double-blind trial; patients received IV rituximab 1000 mg or placebo (ratio 2:1) on weeks 0, 2, 24, 26, 48, 50, 72, and 74	16% of patients receiving rituximab; most common SAEs were infections; 1 patient died in the rituximab group (aspiration pneumonia)
Daclizumab	Phase II RRMS (SELECT) [75]	Randomized, double-blind trial; SC injections of daclizumab HYP 150 or 300 mg or placebo (ratio 1:1:1) every 4 weeks for 52 weeks	7% of patients receiving daclizumab HYP 150 mg and 9% receiving daclizumab 300 mg, excluding MS relapse; most relevant SAEs were infections, cutaneous events, neoplasms, ALT or AST abnormalities
	Phase III RRMS [74]	Randomized, double-blind trial; SC daclizumab HYP 150 mg every 4 weeks and intramuscular placebo once weekly or intramuscular IFN-β1a 30 μg once weekly and SC placebo every 4 weeks (ratio 1:1) for at least 96 weeks and no more than 144 weeks	15% of patients receiving daclizumab HYP 150 mg, excluding MS relapse; most common SAEs were infections, neoplasms, blood and lymphatic system disorders, cutaneous events, gastrointestinal disorders

Table 5 (continued)

Monoclonal antibody	Pivotal trial	Design of experiment, regimen, route of administration	SAEs
Ocrelizumab	Phase II RRMS [111]	Randomized, double-blind trial; IV placebo, low-dose (600 mg) or high-dose (2000 mg) ocrelizumab in two doses on days 1 and 15, or intramuscular IFN-β1a 30 μg (open-label, rater-masked control) once a week; at week 24, patients in the initial placebo, ocrelizumab 600 mg, and IFN-β1a groups received ocrelizumab 600 mg; the 2000 mg group received 1000 mg	2% of patients receiving ocrelizumab 600 mg and 6% receiving ocrelizumab 200 mg (weeks 0–24), 2% of patients receiving ocrelizumab 600 mg and 4% receiving ocrelizumab 200 mg (weeks 24–48); serious infection rates were similar in ocrelizumab and placebo patients; 1 patient in the high-dose ocrelizumab group died after DIC and MODS, the symptomatology was diagnosed as SIRS
	Phase III RMS (OPERA I and II) [109]	Randomized, double-blind, double-dummy trials; IV ocrelizumab 600 mg every 24 weeks, administered as two 300 mg infusions on days 1 and 15 for the first dose and as a single 600 mg infusion thereafter, or SC IFN-β1a at a dose of 44 μg 3 times weekly (ratio 1:1) throughout the 96-week treatment period; patients in each group received a matching SC or IV placebo	6.9% of patients receiving ocrelizumab; most relevant SAEs were neoplasms (2 cases of invasive ductal breast carcinoma, 1 case of renal cell carcinoma, and 1 case of malignant melanoma) and 5 additional cases of neoplasms during the open-label extension study (2 cases of breast cancer, 2 cases of basal cell skin carcinoma, and 1 case of malignant melanoma) and infections
	Phase III PPMS (ORATORIO) [110]	Randomized trial, event-driven, double-blind treatment for a minimum of 5 doses (120 weeks); IV ocrelizumab 600 mg (administered as two 300 mg infusions 14 days apart) or matching placebo every 24 weeks	20.4% of patients receiving ocrelizumab; most relevant SAEs were neoplasms (breast cancer in 4 patients, basal cell carcinoma in 3, and endometrial adenocarcinoma, anaplastic large-cell lymphoma, malignant fibrous histiocytoma, and pancreatic carcinoma in 1 each) and infections; 4 patients died in the ocrelizumab group due to pulmonary embolism, pneumonia, pancreatic carcinoma, and aspiration pneumonia
Ofatumumab	Phase II RRMS [114]	Randomized, double-blind trial; IV ofatumumab (100, 300, or 700 mg) or placebo 2 weeks apart	1 case of headache leading to hospitalization in the ofatumumab 300 mg group
	Phase IIb RMS (MIRROR) [115]	Randomized, double-blind study with 4 phases; patients were randomized (ratio 2:1:1:1:2) to SC placebo or ofatumumab 3, 30, or 60 mg doses every 12 weeks or 60 mg every 4 weeks	Incidences of SAEs were 3%, < 1%, 4%, and < 1% in weeks 0–2, 12–24, and 24–48 and the IFU phase, respectively. The only SAEs to occur in ≥ 1 patient during the treatment phase were IRRs, occurring in 3 patients
	Phase III RMS (NCT02792218 ASCLEPIOS I; NCT02792231 ASCLEPIOS II)	Randomized, double-blind, double-dummy, active comparator-controlled, parallel-group trial; SC ofatumumab every 4 weeks or active comparator teriflunomide orally once daily	Ongoing
Opicinumab	Phase II ON (RENEW) [120]	Randomized, double-blind trial; IV opicinumab 100 mg/kg or placebo (ratio 1:1) once every 4 weeks (6 doses) and followed up to week 32	12% of patients receiving opicinumab; 1 patient with MS relapse, 1 with optic neuritis in the fellow eye; 1 with hypersensitivity reactions, and 1 with asymptomatic increase of ALTs and ASTs
	Phase II RMS (SYNERGY) [in press]	Randomized, double-blind, dose-ranging trial; 5 parallel treatment groups of IV opicinumab (3, 10, 30, or 100 mg/kg) or placebo (ratio 1:2:2:2:2)	16% of patients receiving opicinumab; most relevant SAEs were urinary tract infection, suicidal ideation, bipolar disorder, and hypersensitivity

Major trials are indicated in bold

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *DIC* disseminated intravascular coagulopathy, *HYP* high-yield process, *IFN* interferon, *IFU* individualized follow-up, *IRRs* injection-related reactions, *IV* intravenous, *MODS* multi-organ-dysfunction syndrome, *MS* multiple sclerosis, *ON* optic neuritis, *PPMS* primary progressive multiple sclerosis, *RMS* relapsing multiple sclerosis, *RRMS* relapsing-remitting multiple sclerosis, *SAEs* serious adverse events, *SC* subcutaneous, *SIRS* systemic inflammatory response syndrome, *SPMS* secondary progressive multiple sclerosis

matter of 3 months, while peripheral blood T cells may stay at almost undetectable levels for 12–18 months. Repopulation of the immune system may reconfigure the previously deranged immune system [38, 39]. Hence alemtuzumab, like cladribine, is considered a short-pulse immune reconstitution therapy as 12 mg/day is administered intravenously for 5 days and then for 3 days 12 months later. Alemtuzumab was the first monoclonal antibody that proved its efficacy against an active comparator (high-dose interferon [IFN]-β1a) in a phase II trial [40] and two phase III trials [41, 42] regarding clinical and MRI outcomes. In a pooled post hoc analysis of the pivotal trials [43], 80% of patients that had received two annual courses of alemtuzumab were free from clinical disease activity [44]. The recently published 5-year efficacy and safety data indicated that the annualized relapse rate stayed low, most patients showed NEDA, and the extent of brain volume loss was slowed, although about 70% [CARE-MS (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis) I] and 60% (CARE-MS II) of patients did not receive an additional alemtuzumab course after their second fixed annual cycle [45, 46]. Furthermore, alemtuzumab has a beneficial effect on measures of disability improvement in patients with relapsing-remitting MS (RRMS) with inadequate response to prior therapy [47].

In comparison with other disease-modifying therapies [48], acknowledging the limitations of judging relative efficacies outside head-to-head trials, alemtuzumab and natalizumab seem to exert similar effects on annualized relapse rates in RRMS. Alemtuzumab appears to be superior to fingolimod and IFN-β in mitigating relapse activity. It has also been suggested that natalizumab is more effective than alemtuzumab in enabling recovery from disability. Collectively, the available data indicate that both natalizumab and alemtuzumab are highly effective and useful immunotherapies for MS [49]. In addition, alemtuzumab was shown in one study to be a cost-effective therapy compared with other second-line therapies [50].

Beyond the well-known adverse effects related to thyroid, platelets, and kidneys, rarer but clinically significant serious adverse events have been reported in patients during and following alemtuzumab treatment. Alemtuzumab therapy may lead to exacerbated CNS inflammation [51, 52] with tumefactive demyelination [53], acute cholecystitis [54], vasculitis [55], sarcoidosis [56–58], alopecia [59], vitiligo [60], listeria meningitis [61] and meningoencephalitis [62], warm hemolytic anemia [63], hemophagocytic lymphohistiocytosis [64], opportunistic infections [65] such as active cytomegalovirus infection [66], and acute pneumonitis and pericarditis [67]. Individual case reports need to be balanced against aggregate data from the clinical development program, which, for example, have shown that most infections associated with alemtuzumab were mild to moderate and tended to decrease in frequency over time [68]. A retrospective analysis revealed that Grave's disease due to alemtuzumab treatment requires definitive or prolonged antithyroid drug therapy [69].

When making treatment decisions in patients with highly active disease, the apparently comparable efficacy needs to be individually weighed against the risks in terms of rare but serious opportunistic infections and the more frequent secondary B cell-mediated complications noted with alemtuzumab [70]. Pharmacovigilance and infectious risk stratifications, i.e., screening for tuberculosis, HIV, hepatitis B, hepatitis C, varicella zoster virus, and *Treponema pallidum*, are fundamental before, during, and after treatment [71, 72]. Regarding risk mitigation, herpes prophylaxis with aciclovir and zoster immunization prior to treatment initiation should be performed and listeria prophylaxis with co-trimoxazole considered. In fact, blood monitoring is mandatory over a period of 48 months following the last infusion cycle.

Alemtuzumab was approved by the FDA in 2014. The EMA granted a marketing authorization valid throughout the EU in 2013.

4 Daclizumab

The humanized monoclonal antibody daclizumab high-yield process (HYP, or daclizumab β) modulates interleukin-2 signaling by binding to the α subunit of the interleukin-2 receptor (CD25), which leads to the expansion of CD56 bright natural killer (NK) cells that may silence the autoaggressive T lymphocytes [73]. In the clinical trials in relapsing MS, daclizumab reduced the annualized relapse rate and the mean number of new or newly enlarging T2 hyperintense lesions compared with IFN-β1a and placebo, respectively [74, 75]. NEDA status was achieved frequently [76] and a positive impact on cognitive functions was described [77]. This medication was licensed for the treatment of relapsing MS patients in Europe and the USA in 2016. Daclizumab was restricted following reports of serious hepatotoxicity with its use, and after reports of eight cases of serious encephalitis/meningoencephalitis from Germany and Spain, it was withdrawn from the market in March 2018 [78]. Autoimmune-mediated encephalitis [79, 80] associated with both *N*-methyl-D-aspartate (NMDA) receptor antibodies [81] and glial fibrillary acidic protein (GFAP) α immunoglobulin G (IgG) [82] have recently been reported. Initial major concerns related to cutaneous events [83, 84] and drug reactions with eosinophilia and systemic symptoms (DRESS) [85]. The story of daclizumab highlights the importance of post-marketing phase IV safety studies and registries, as rare and potentially fatal adverse effects may occur after a longer treatment duration [78].

Daclizumab was approved by the FDA and the EMA granted a marketing authorization valid throughout the EU in 2016. Both the FDA and EMA withdrew the approval in 2018.

5 Rituximab

Monoclonal antibodies depleting B cells as major mode of action have been studied in autoimmune disorders for many years. These include antibodies to either the CD19 or CD20 differentiation antigen. Among the latter, distinct, albeit closely related, epitopes on the CD20 molecule are recognized. CD20-directed monoclonal antibodies further differ in their structure (chimeric, humanized, fully human), relative potency to drive antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, route of administration (intravenous or subcutaneous), pharmacokinetics, and required infusion times [86].

Rituximab selectively depletes CD20-positive cells, i.e., B cells. Along the B cell lineage from bone marrow-resident stem cells to circulating plasma cells, CD20 is only expressed on pre-B cells, immature B cells, mature B cells, memory B cells, and a small fraction of T cells [87–89]. Therefore, rituximab therapy keeps stem cells and plasma cells intact. Thus, repopulation and immunological humoral memory allowing manufacturing of antibodies (e.g., to neutralize invading microorganisms) are maintained. After initial small case reports and uncontrolled series [90, 91], Hauser et al. [92] were the first to test this drug in MS patients in a phase II trial, with great success. To date, a number of studies are available that stress the effectiveness of rituximab in treating not only aggressive RRMS [93–97] but also a range of other autoimmune neurological diseases [98]. Furthermore, a large retrospective, observational study from Sweden provided class IV evidence that rituximab is safe in patients with MS (mean treatment duration 21.8 months with a standard deviation of 14.3 months, median of 18.4 months, and range of 0–88 months) [99]. However, a randomized controlled phase III study has not been conducted with rituximab or the already available biosimilars in MS patients to date. Therefore, official licensing of this (cost-)effective treatment in the near future is rather unlikely. Furthermore, rituximab was the first CD20-depleting therapy to also be examined in a phase II/III trial in primary progressive MS (PPMS) patients [100]. Rituximab did not meet the defined primary endpoints, but this trial cleared the way for the exploration of ocrelizumab in this disease stage as it gave valuable clues regarding its efficacy in progressive disease [101]. A retrospective subgroup analysis identified younger patients with shorter disease duration and evidence of inflammatory activity on baseline MRI as potential responders to rituximab.

Physicians using rituximab to treat patients should bear in mind that depletion of CD20-positive cells, not only with rituximab but also with ocrelizumab and ofatumumab, may lead to reactivation of hepatitis B, as observed in other indications [102], and prophylactic vaccination may be suitable [103]. Of note, a recent study showed that there is a significant association between both presence and titers of anti-drug antibodies and incomplete B cell depletion in rituximab treatment, but not with infusion reactions, adverse reactions, or clinical outcomes [104]. The adjusted odds ratio of PML in rituximab-treated MS patients is 3.22 (95% confidence interval (CI) 1.07–9.72) and the timepoint of PML onset may vary between indications [105]. Patients treated with rituximab should be screened for hypogammaglobulinemia [106] and neutropenia [107, 108] as these constellations are independent risk factors for developing infections.

6 Ocrelizumab

The humanized monoclonal antibody ocrelizumab—like rituximab, its biosimilars, and ofatumumab—selectively depletes CD20-positive B cells. To date, it is the only intravenous anti-CD20 antibody that has been tested in an extensive clinical development program, culminating in two randomized controlled phase III twin trials, one in relapsing MS [109] and one in PPMS [110], after publication of a phase II trial in relapsing MS only [111]. In relapsing MS, ocrelizumab was superior to subcutaneous IFN-β1a regarding the primary endpoint annualized relapse rate and the secondary MRI endpoints, with the exception of percentage change in brain volume in OPERA II. In progressive MS, ocrelizumab met both the primary endpoint and the secondary MRI endpoints in patients with relatively early disease defined by age (18–55 years) and disease duration (duration of MS symptoms of <15 years in patients with an Expanded Disability Status Scale (EDSS) score of >5.0 at screening or <10 years in patients with an EDSS score of ≤ 5.0 at screening): The percentage of patients with 12-week confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo, and the total volume of brain lesions decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo, while the percentage of brain volume loss was 0.90% with ocrelizumab versus 1.09% with placebo. Of note, subgroup analysis revealed that gadolinium-enhancing lesions at baseline were not associated with a better response to ocrelizumab. A subgroup analysis of patients with and without gadolinium-enhancing lesions at baseline revealed that the results were directionally consistent with the findings in the overall study population [110]. Post-marketing data have already stressed the beneficial influence on the relapsing disease course, as 66.4% in the ocrelizumab and 24.3% in the IFN-β1a groups achieved NEDA during weeks

24–96 [112]. There is an abundance of published comments and reviews regarding this therapeutic breakthrough, but follow-up safety data regarding possible adverse effects (infection reactivation, neoplasia) have been reported only at meetings to date [113]. Reassuringly, they do not indicate new safety signals. The impact of long-term and complete B cell depletion is still unknown, especially regarding the risk of malignancies (e.g., breast cancer) or infections.

The malignancy incidence observed in the clinical development program and post-marketing to date appears to be in the range of an age-matched general population, as concluded from large cancer registries.

Ocrelizumab was approved by the FDA in 2017. The EMA granted a marketing authorization valid throughout the EU in 2018.

7 Ofatumumab

After the intravenous formula raised no unexpected safety concerns in a phase II trial in 2014 [114], the subcutaneously administered anti-CD20 monoclonal antibody ofatumumab was recently assessed in MS patients in a randomized, double-blind, placebo-controlled, phase IIb multicenter study with four phases [115]: overall, ofatumumab has a high capacity to suppress new brain MRI lesions compared with placebo. Notably, complete depletion was not necessary for a robust treatment effect, a conditioning dose added no benefit, and repletion occurred faster in all ofatumumab doses than previously reported with anti-CD20 therapy. A cumulative dose of ofatumumab 60 mg administered over 12 weeks provided maximal benefit, with no additional suppression of lesions at higher cumulative doses. The prospect of an efficacious subcutaneous B cell-targeting therapy raises the possibility of self-administration and therefore improvement over intravenous administration in terms of both convenience of use and, arguably, the use of healthcare resources. It remains to be seen whether the less profound depletion and faster repletion of B cells achieved with ofatumumab will also translate into a more favorable safety profile. Currently, subcutaneous ofatumumab versus teriflunomide is being tested in two phase III randomized, double-blind, double-dummy, active comparator-controlled, parallel-group multicenter studies [ASCLEPIOS I (NCT02792218); ASCLEPIOS II (NCT02792231)]. While all CD20-depleting monoclonal antibodies therapies may target the same molecule although recognizing distinct epitopes, there are notable differences that need to be kept in mind. To date, ocrelizumab is the only CD20-depleting therapy that has proven its efficacy in phase III trials. Rituximab, on the other hand, has outstanding cost effectiveness, and the ofatumumab trials suggest that complete depletion may not be necessary when the CD20-directed monoclonal antibody is administered subcutaneously.

8 Opicinumab

The human monoclonal antibody opicinumab directed against leucine-rich repeat and immunoglobulin domain-containing neurite outgrowth inhibitor receptor-interacting protein-1 (LINGO-1) has shown remyelinating capacity in preclinical studies [116–118]. To date, two studies have been conducted in order to test whether this approach can be translated to a clinical setting. In a randomized, double-blind, placebo-controlled, multicenter phase II study in patients with a first unilateral acute optic neuritis episode (using optic neuritis as a model approach for such trials [119]), remyelination could not be confirmed in the intention-to-treat analysis. Still, results from the prespecified patient population suggest that enhancing remyelination in the human CNS with opicinumab might be possible [120] and a post hoc analysis implies that age was the strongest prespecified baseline characteristic associated with a treatment effect (with older patients responding better to therapy) [121]. In recently published preclinical and phase I studies, LINGO-1 blockade does not seem to affect immune function [122]. In a randomized, double-blind, placebo-controlled, dose-ranging phase II study (SYNERGY (NCT01864148); in press), opicinumab as an add-on therapy to intramuscular IFN-β1a showed an inverted U-shaped dose response regarding the primary endpoint (percentage of participants with confirmed improvement over 72 weeks of treatment), but the treatment effect was not statistically significant. Interestingly, patients with younger age, RRMS, shorter disease duration, lower baseline whole-brain diffusion tensor imaging radial diffusivity (DTI-RD), higher baseline thalamic volume, and higher baseline whole-brain volume seem to respond most to opicinumab in SYNERGY. All in all, further investigations are warranted to assess the remyelinating potential of this approach as remyelination is the new frontier in CNS disease, but is still difficult to assess as a clinical outcome measure [123]. In this context, MRI markers may represent promising biomarkers for both neurodegeneration and neuroregeneration, especially in progressive disease [124].

9 Infusion Management: Practical Issues Related to Monoclonal Antibodies

The increasing relevance of therapies using monoclonal antibodies warrants attention to be paid to the most common practical issues. For instance, infusion reactions tend to be more common in cell-depleting therapies (e.g., alemtuzumab [41, 42], ocrelizumab [109]) than in non-cell-depleting therapies (e.g., natalizumab [11]), which can be mitigated by prior administration of corticosteroids and antihistamines [125].

Dealing with pregnancy and breastfeeding is also an important aspect of monoclonal antibody treatment in MS [126, 127]. Of note, the rate of MS relapse decreases during pregnancy but increases 6 months postpartum [128]. According to the EMA's summary of product characteristics (SmPC) for natalizumab [129], the monoclonal antibody has shown reproductive toxicity in animal studies, but data from clinical trials, a prospective pregnancy registry, post-marketing cases, and available literature do not suggest an effect on pregnancy outcomes. Furthermore, the SmPC states that discontinuation of therapy should be considered if a woman becomes pregnant while taking natalizumab. However, this needs to be weighed against the risk of a potentially catastrophic rebound following drug cessation. As natalizumab is excreted in human milk, the SmPC states that breastfeeding should be discontinued during treatment with natalizumab. According to the EMA SmPC for alemtuzumab [130], the monoclonal antibody has shown reproductive toxicity in animal studies, but it is not known whether alemtuzumab can cause fetal harm when administered to pregnant women. Women of childbearing potential should use effective contraception when receiving a course of alemtuzumab treatment and for up to 4 months after each course of treatment. The alemtuzumab SmPC states that breastfeeding should be discontinued during each treatment course and for 4 months following the last infusion of each treatment course. According to the EMA SmPC for ocrelizumab [131], animal studies do not indicate teratogenic effects, but B cell depletion was detected in utero and reproductive toxicity was observed in pre- and post-natal development studies. Women of childbearing potential should use contraception while receiving ocrelizumab and for 12 months after the last infusion. The ocrelizumab SmPC states that women should be advised to discontinue breastfeeding during ocrelizumab therapy.

10 Conclusions

Monoclonal antibodies changed not only the way we approach treatment of MS, but also the way we evaluate new treatment options as perspectives are in a state of constant change: for example, natalizumab might not be licensed if it was introduced today, and the safety profile of daclizumab might have been evaluated differently if it had been the first highly effective treatment introduced to the market. Additionally, a monoclonal antibody (ocrelizumab) has proven that progressive disease can be modified. These perspectives together with the current developments mentioned in this article stress that treatment safety and strategies on how to deal with adverse effects are now as important as efficacy, especially when using monoclonal antibodies in MS. Currently, there is an abundance of therapeutic options targeting the immune system, but there is a lack of therapeutic algorithms. Therefore, new treatments on the horizon need to prove additional benefit, e.g., remyelination, clinical improvement, a better safety profile, and/or cost effectiveness. In addition, new markers predicting the optimal therapeutic response in individual patients related to a given drug are needed in order to lead us to personalized therapy in MS. Phase IV safety trials will also become more and more important in the future. Additionally, regarding the treatment choice for an individual patient, the emerging field of real-world data and statistical tools such as propensity matching will be increasingly relevant in the absence of head-to-head studies [132].

Compliance with Ethical Standards

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