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REVIEW

Using Monoclonal Antibody Therapies for Multiple Sclerosis: A Review

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Abstract: Monoclonal antibody therapies have secured an important role in the therapeutic landscape for the treatment of both relapsing and progressive forms of multiple sclerosis due to their potent efficacy, convenient dosing schedules, and well-defined side effect profiles. Each therapy has unique risks and benefits associated with its specific mechanism of action which ultimately guides clinical decision-making for individual patients. This review will summarize the mechanisms of action, evidence leading to their approval, and clinically relevant considerations for each of the current monoclonal antibody therapies approved for the treatment of multiple sclerosis.

Keywords: monoclonal antibodies, multiple sclerosis, relapsing, progressive, review

Introduction

Multiple sclerosis (MS) is a complex autoimmune disorder resulting in inflammation and demyelination of the central nervous system (CNS). Despite decades of research, there is still uncertainty about the exact pathogenesis of this disorder, likely due to the complex interaction of multiple pathologic mechanisms. While immune dysregulation appears to be the hallmark, the cause of this dysregulation is unclear. The most widely accepted hypothesis is that genetically susceptible individuals are exposed to an unknown environmental or infectious trigger which evokes an immune response that ultimately fails central and/or peripheral immune surveillance leading to autoimmunity.[1–4] This results in the establishment of a population of autoreactive CD4+ T-cells within the peripheral immune compartment that are primed to recognize myelin antigens. These autoreactive T-cells can then be activated, expand, and ultimately permeate the blood–brain barrier causing episodes of CNS demyelination via attraction and activation of a variety of other immune cells.[5–8] There also appear to be clear roles for other humoral immune cells and innate immune mechanisms in the facilitation of the CD4+ T-cell response and the direct mediation of both CNS demyelination and axonal damage.[3,4]

Complicating our understanding of MS pathophysiology is the fact that the clinical presentations and recognized phenotypes vary widely. In general, there are relapsing forms of the disease characterized by clinical attacks of neurologic dysfunction with variable recovery and progressive forms of the disease characterized by accumulation of neurologic disability. Both relapsing and progressive subtypes of MS can be active, either clinically or radiographically or inactive.[9] While the majority of MS patients exhibit a relapsing disease course, 10–15% of all MS patients exhibit a clinical course of insidious disability accumulation from the onset, termed primary

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progressive multiple sclerosis (PPMS), and approximately 50% of patients with initially relapsing disease go on to develop progressive disability without overt attacks of demyelination, termed secondary progressive multiple sclerosis (SPMS).[10] Limited research in progressive subtypes of MS suggests that T-cell and B-cell infiltration over time leads to the formation of lymphoid-like structures within the CNS. This subsequently results in widespread injury due to smoldering inflammation throughout the CNS with degeneration of both the white and gray matter, independent of any infiltration of peripheral immune cells and predominantly driven by CNS microglial cells and other cellular mechanisms.[4,11,12] Additionally, this chronic inflammatory environment within the CNS appears to drive mitochondrial damage and impair remyelination of denuded axons, both of which lead to a chronic "energy deficit" that promotes and accelerates neurodegeneration.[13]

While the complex interaction of humoral and innate immune mechanisms of disease in MS has hindered our fundamental understanding of the disease, it has also offered a variety of potential therapeutic targets to modify the disease course. This led to the development and subsequent US Food and Drug administration (FDA) approval of 22 different disease modifying therapies (DMTs) for MS with at least 11 different mechanisms of action. Of these, monoclonal antibody (mAb) therapies have gained particular interest due to their potent efficacy, predictable side effect profiles, and more recently their potential benefit in progressive forms of MS. This review will highlight the current FDA-approved mAb therapies for MS and review their mechanisms of action, clinical indications, common side effects, and the clinically relevant considerations for their use (Table 1).

Discussion

Natalizumab (Tysabri®)

Natalizumab is a humanized mAb that targets the α_4 subunit of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins present on circulating lymphocytes and monocytes, preventing their binding to endothelial receptors and subsequently inhibiting their crossing of the blood–brain barrier.[14,15] In two landmark randomized, placebo-controlled trials, natalizumab was shown to demonstrate clear and dramatic reduction in clinical relapse activity, probability of sustained disability progression, and new MRI T2 hyperintense lesions.[14,16] These data ultimately led to the FDA approval of natalizumab for relapsing forms of MS in late 2004.

Dosing, Adverse Reactions, Monitoring

Natalizumab is administered intravenously (IV) at a dose of 300mg monthly. It is generally very well tolerated and in fact, based on both anecdotal experience and the initial controlled trial of natalizumab for MS, many patients

Table 1 Monoclonal Antibody Therapies for Multiple Sclerosis

Name	MOA	Route & Frequency	Adverse Effects	Monitoring
Natalizumab	α_4 integrin inhibitor-prevents transmigration of lymphocytes into CNS	IVMonthly	**Common**: infusion reactions **Serious**: PML	**Pre**: JCV, latent infection screening **During**: JCV, sx/MRI findings of PML **Post**: monitor for rebound DA
Alemtuzumab	Anti-CD52-depletes B- & T-cells	IV Two annual cycles	**Common**: infusion reactions, infections, secondary autoimmunity **Serious**: ITP, renal failure, malignancy, stroke, PE, MI	**Pre**: CBC, CMP, UA, TSH, ECG baseline skin exam **During**: CBC, CMP, UA, TSH, HPV, annual skin exams, sx of PML & renal failure **Post**: CBC, CMP, UA, TSH, HPV, annual skin exams for 2 years
Rituximab (off-label)	Anti-CD20 -depletes B-cells	IV Every 6 months	**Common**: infusion reactions, infections **Serious**: opportunistic infections	**Pre**: Latent infection screening, baseline immunoglobulins **During**: annual immunoglobulins **Post**: none
Ocrelizumab				
Ofatumumab		SQ Monthly		

Abbreviations: MOA, mechanism of action; CNS, central nervous system; IV, intravenous; SQ, subcutaneous; PML, progressive multifocal leukoencephalopathy; ITP, immune thrombocytopenia; PE, pulmonary embolism; MI, myocardial infarction; JCV, John Cunningham virus; sx, symptoms; MRI, magnetic resonance imaging; DA, disease activity; CBC, complete blood count; CMP, complete metabolic profile; UA, urinalysis; TSH, thyroid stimulating hormone; ECG, echocardiogram; HPV, human papilloma virus.

report a sense of improved well-being on the medication.[15] In the AFFIRM trial, the most common adverse events were infusion-related reactions, with headache, fatigue, and arthralgias being reported in 38%, 27%, and 19% of patients, respectively. There was no difference in the rate of infections between natalizumab and placebo.[14] However, in the SENTINEL trial, there were 2 cases of fatal progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab and interferon beta-1a and then a third case in a patient with Crohn's disease treated with natalizumab.[16] These events led to the brief withdrawal of natalizumab from the market in February 2005 and then return in 2006 with the addition of an FDA recommended "black box warning" about the risk of PML and restricted distribution of the medication under the TOUCH Prescribing Program.

Current monitoring parameters for natalizumab include screening for latent infections (tuberculosis and hepatitis), baseline brain MRI imaging prior to initiation of therapy, monitoring for hypersensitivity reactions during and for one hour post-infusions, and assessing for signs/symptoms of hepatotoxicity, meningitis/encephalitis, acute retinal necrosis, and PML during therapy as well as periodic MRIs to assess for radiographic signs of PML.[17,18]

Clinical Considerations

Based on the results of the clinical trials referenced above, natalizumab has been widely prescribed as a highly effective medication to prevent MS relapses and disability progression. However, the black box warning for PML has prompted justifiable concern among many prescribers. Further studies examined the real-world incidence of natalizumab-associated PML as well as potential methods to predict and reduce risk. Multiple studies have shown the overall incidence of PML in natalizumab-treated patients to be between 2.1 and 4.22 per 1000 patients.[19,20] However, the risk seems to be strongly associated with several risk factors with the presence of anti-JC virus antibodies (JCV+), prior immunosuppressant (IS) use, and duration of natalizumab therapy being the highest risk factors.[19–21] For example, in JCV negative patients, the risk of PML is between 0.07 and 0.09 per 1000 patients (0.007–0.009%).[19,21] Comparatively, in JCV+ patients, the cumulative incidence of PML after 6 years was 2.7% in patients with prior IS use and 1.7% in those without prior IS use.[21] In addition, several studies have shown that the JCV antibody index value is an important determinant of risk. In JCV+ patients without prior IS, 89.9% of those who developed PML had an index value >1.5. Conversely, only 1.7% had an index value of ≤0.9.[20,22]

Based on these data, clinical practice has evolved to incorporate JCV antibody and index testing both before and during treatment with many clinicians electing to avoid this therapy in JCV+ patients, particularly those with prior IS use. However, others have sought for alternative means to reduce risk given the potent efficacy of natalizumab with the only potentially modifiable risk factor being the duration of exposure to natalizumab. This led to the exploration of what has come to be known as "extended interval dosing" (EID) in which natalizumab is given less frequently than the FDA-approved 28-day dosing interval. First, multiple investigators examined whether the efficacy of natalizumab was maintained with less frequent dosing and all found that extending the dosing interval from every 4 weeks to between 5 and 8 weeks did not decrease the clinical or radiographic efficacy of the medication.[23–25] Building on these findings, investigators examined whether EID could decrease the risk of PML in JCV+ patients. A large retrospective cohort study of >35,000 JCV+ natalizumab-treated patients from the TOUCH database demonstrated that EID during the last 18 months of recorded infusion history resulted in a 94% relative risk reduction (RRR) compared to SID and there were zero cases of PML in 815 patients who were treated with EID for their entire infusion history.[23] This compelling evidence has led to many practitioners to incorporate EID into their patients on natalizumab.

Another consideration in the use of natalizumab is what has been termed the "rebound effect" used to describe an increased risk of relapse or severe clinical and/or radiologic worsening associated with discontinuation of the medication. This has been reported in roughly 20–40% of patients with abrupt discontinuation of natalizumab.[26–28] Multiple cases of severe "rebound" relapses associated with large number of new T2 lesions, hospitalization, significant disability worsening, and even death in patients after discontinuing natalizumab have been reported.[27,29–31] The main risk factors for "rebound" relapses seem to be short-duration of natalizumab exposure, higher baseline EDSS and EDSS worsening while on natalizumab and there is some data to suggest a high-dose methylprednisolone protocol after discontinuation may mitigate this risk.[28,30,32]

One of the commonly encountered scenarios for abrupt discontinuation of natalizumab is unexpected pregnancy. Although there is no data to show a risk of teratogenesis with natalizumab, there is some limited animal data showing a small increased risk of miscarriage and fetal harm and thus natalizumab is not generally recommended in pregnancy.[17] However, because of the risk of rebound, many providers choose to continue natalizumab in pregnancy, particularly in individuals with high MS disease activity before pregnancy. The only well-known human fetal risks are infant pancytopenia when exposed to natalizumab at >30 weeks, so many MS pregnancy experts agree it is reasonable to continue natalizumab during pregnancy in select patients through the 30th week of pregnancy and then screen for hyperbilirubinemia, liver dysfunction, and pancytopenia upon delivery.[33]

Finally, it has been reported that approximately 6% of patients treated with natalizumab develop persistently positive antibodies against the mAb medication over time.[34] Persistent antibody positivity has been associated with more severe and persistent infusion reactions as well as an increased risk of clinical relapse, MRI activity, and disability progression.[34,35] Therefore, many providers consider checking for anti-natalizumab antibodies in patients with severe or persistent infusion reactions or breakthrough disease activity.

In summary, natalizumab is a highly efficacious therapy for relapsing MS that is generally very well tolerated with very few risks. However, the small but critical risk of PML in JCV+ patients on prolonged natalizumab therapy is critical to address and monitor in all patients treated with natalizumab.

Alemtuzumab (Lemtrada®)

Alemtuzumab is a humanized mAb that targets the CD52 receptor present on circulating lymphocytes resulting in depletion and eventual repopulation of both B-cell and T-cell populations. In two 2012 phase-3 randomized controlled trials, alemtuzumab showed superiority compared to interferon beta-1a for first-line and second-line treatment of what was previously termed "relapsing remitting multiple sclerosis" (RRMS) (CARE-MS I and CARE-MS II, respectively), leading to its FDA-approval for relapsing forms of MS in November 2014.[36–38]

Dosing, Adverse Reactions, Monitoring

Alemtuzumab is given intravenously, 12 mg daily for 5 consecutive days followed 12 months later by 12mg daily for 3 days. Subsequent treatment courses of 12mg daily for 3 days may be used if needed for breakthrough disease activity. Before starting alemtuzumab, screening for latent infections including tuberculosis and hepatitis is recommended with subsequent infectious disease consultation if needed. Antiviral prophylaxis for herpetic viral infections after alemtuzumab administration is also required for at least 2 months or until CD4+ lymphocyte count is ≥200/mm3, whichever occurs later.[39]

During clinical trials and in subsequent long-term safety data, alemtuzumab was found to have multiple important and clinically relevant adverse reactions. Infusion reactions (headache, rash, fever, etc.) occurred in >90% of patients and can be mitigated somewhat by premedicating with steroids and antihistamines/antipyretics.[36,40] Infections were also common, occurring in close to 70% of patients. Most infections were mild to moderate with only 2% of patients having serious infections.[33,36] The most widely known and serious adverse effect of alemtuzumab therapy is secondary autoimmunity. Clinical autoimmune disease developed in up to 48% of patients with an additional 14% of patients developing sustained novel autoantibodies without clinical disease. Thyroid disease was the most common, occurring in 41% of patients, but autoimmune hepatitis, renal disease, and hematologic disease (thrombocytopenia, neutropenia, and hemolytic anemia) have also been reported.[40,41] While very rare, there have also been cases of thyroid malignancy, Castleman's disease, acalculous cholecystitis, and vascular complications (ischemic stroke, hemorrhagic stroke, pulmonary embolism, alveolar hemorrhage, myocardial infarction) which led to FDA-mandated modifications to the alemtuzumab risk evaluation and mitigation strategy (REMS) program.[41–44]

Due to the variety and seriousness of the adverse reactions outlined above, there is monitoring needed before, during, and after alemtuzumab therapy. Baseline complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis (UA), thyroid stimulating hormone (TSH), echocardiogram (ECG), and skin exam are required prior to initiation of therapy. After initiation, CBC, CMP, and UA are recommended to be followed monthly, TSH every 3 months, and HPV screening and skin exams annually. All of these should be followed until

48 months or longer after the last infusion. Monitoring for signs/symptoms of infection, including PML, and signs of nephropathy should also be performed during therapy.[39]

Clinical Considerations

Alemtuzumab, along with cladribine, mitoxantrone, and hematopoietic stem cell transplant (HSCT), are considered "immune reconstitution therapies" for MS, meaning that their mechanisms of action exert significant effects on the body's innate and adaptive immune systems inducing long-standing immune modulating effects which result in potentially prolonged or permanent resolution of autoimmunity. In long-term safety and efficacy data, 88% of patients required only 2 or 3 cycles of alemtuzumab over a 7-year period to prevent relapses or disability progression.[40]

This potent efficacy and durable benefit of alemtuzumab give it a unique place among available MS therapies. However, the potential side effects, long-term risks, and monitoring requirements of this medication have limited its use by many providers for early or "minimally symptomatic" MS. Although this class of medications does have more frequent and severe side effects upfront, many specialists view this as "front-loaded" risk, which for some patients may outweigh the long-term risks of potentially decades of treatment with other DMTs. In addition, some investigators are looking for unique ways to mitigate the potential side effects of alemtuzumab. Since alemtuzumab induces long-term lymphocyte suppression with imbalanced reconstitution of B- and T-cells (a postulated mechanism for secondary autoimmunity), one group has reported complete success in mitigating secondary autoimmunity by using intermittent, low-dose rituximab when CD19+ B-cells return to 40–50% of their baseline levels.[45,46]

Overall, alemtuzumab is a highly efficacious MS therapy, even in patients with highly active disease at baseline, with durable prevention of relapses and disability accumulation. However, the high incidence of potentially serious side effects, most notably secondary autoimmunity, has resulted in caution and careful selection of patients who may benefit from this therapy.

Anti-CD20 Therapies

Although MS is traditionally considered a T-cell-mediated autoimmune disorder as described above, multiple B-cell targeted therapies (rituximab, ocrelizumab, and ofatumumab) have demonstrated high efficacy in suppression of inflammatory disease activity in RRMS in Phase II and Phase III clinical trials. As there is no known pathologic autoantibody associated with MS, it is postulated that the antibody-independent effects of B-cells including cytokine secretion, antigen presentation, meningeal lymphoid structure inhibition, and other immunomodulatory mechanisms likely explain the efficacy of B-cell depletion in RRMS.[43,44]

Rituximab, ocrelizumab, and ofatumumab are all monoclonal antibodies targeting the CD20-receptor present on B-cells. CD20 is a cell-surface antigen expressed on most B cells but is not present on most hematopoietic stem cells, plasmablasts, and plasma cells.[47] As a result, B-cell depletion with anti-CD20 mAb therapies results in rapid reduction in the "antigen-educated" B cells from peripheral circulation while largely preserving immunoglobulin production capabilities by sparing plasma cells. After depletion, B-cells are slowly replaced primarily by "naïve" B cells from lymphoid organs and bone marrow which is one plausible explanation for the continued efficacy of anti-CD20 therapies, even after reconstitution of B-cells.[48]

Rituximab (Rituxan® and Biosimilars (Riabni®, Ruxience®, and Truxima®))

Rituximab (RTX) is a chimeric human-murine mAb that was the first monoclonal anti-CD20 therapy FDA-approved for use in human disease but remains off-label for use in the treatment of MS in the United States. Although initially approved for oncologic and rheumatologic indications, it first demonstrated efficacy in a Phase I trial for RRMS in 2008 showing dramatic reduction in contrast enhancing MRI lesions and annualized relapse rates (ARR).[49] Many subsequent Phase II trials and population-based studies have replicated these results in larger populations of RRMS patients, leading to widespread use of rituximab worldwide for relapsing forms of MS.[48,50–52] RTX has also been studied in PPMS. The OLYMPUS trial did not show a statistically significant reduction in disability progression overall; however, subgroup analysis did show benefit for patients <51yo and/or those with contrast enhancing lesions on their study-baseline MRI.[53]

Ocrelizumab (Ocrevus®)

Ocrelizumab (OCR) is a humanized anti-CD20 mAb that is the only FDA-approved therapy for the treatment of both RRMS and PPMS. The OPERA I and II trials were Phase III RCTs comparing OCR to interferon (IFN) beta-1a for RRMS. They demonstrated clear superiority of OCR to IFN beta-1a with a near 50% relative reduction

in ARR, 95% relative reduction in enhancing lesions, and 40% relative reduction (4.5% absolute risk reduction) in disability progression at 12-weeks.[54] The ORATORIO trial was a Phase III RCT comparing OCR to placebo for patients with PPMS over nearly 2 years. It showed statistically significant reductions in 24-week confirmed disability progression (CDP), walking speed degradation, and brain volume loss compared to placebo.[55]

Ofatumumab (Kesimpta®)

Ofatumumab (OFA) is a full-humanized anti-CD20 mAb that was recently approved for the treatment of RRMS. The ASCLEPIOS I and II studies were Phase III RCTs comparing OFA to teriflunomide, showing clear superiority over teriflunomide with a greater than 50% relative reduction in ARR and approximately 4% absolute reduction in 3- and 6-month CDP.[56] OFA has not been studied in PPMS.

Dosing, Adverse Reactions, Monitoring

Although all the anti-CD20 therapies have the same mechanism of action (MOA), their routes of administration and dosing regimens differ. Since it is used off-label for MS, RTX dosing and interval strategies have been adopted and modified based on its use for oncologic and rheumatologic indications. RCTs for RTX primarily used a regimen of 1000mg IV twice 2 weeks apart followed by 1000mg every 24 weeks. However, many groups in Europe use a simplified dosing strategy of 500mg IV every 6 months since a similar degree of CD19+ B-cell suppression at 6 months has been observed with this regimen.[51] OCR is dosed as 600mg IV every 6 months with the first dose divided into two 300mg doses given 2 weeks apart.[57] OFA is dosed at 20mg subcutaneously (SQ) at Weeks 0, 1, and 2 followed by 20mg SQ monthly, starting at Week 4.[58]

All anti-CD20 therapies share the most common adverse effect of mild to moderate infusion/injection site reactions (such as fever, flushing, chills, fatigue, headache, etc.) which typically improve after the first infusions or injections.[53,56] For the IV infusion therapies, these can largely be mitigated by pre-medication with IV methylprednisolone and oral antihistamines and oral acetaminophen prior to infusions. Similar pre-medications had only limited benefit for OFA and are rarely needed in practice.[58]

Other common adverse reactions include an increased susceptibility to infection, typically non-serious respiratory and urinary tract infections, without a statistically significant difference in severe infections compared to immunomodulatory or placebo arms. However, serious infections, including opportunistic infections, have been reported in anti-CD20 therapies and it may be that RCTs have too-short follow-up to identify this risk in the long term. Of particular interest currently is the risk of contracting COVID-19 and subsequently the risk of serious infection. While data is still early and limited by small numbers, there does appear to be a 2–3 fold increased risk of contracting COVID-19 in MS patients on anti-CD20 agents and a similarly increased risk of hospitalization and severe COVID infection compared to other DMTs.[59–61] This trend was also seen in alemtuzumab treated patients, though even more limited by small numbers.[59]

It should also be mentioned that none of the anti-CD20 therapies appear to have an increased risk of malignancy. Although there was an imbalance in breast cancer incidence in OCR treated patients in the ORATORIO primary progressive trial, that risk was still within the expected incidence of the general population and long-term safety data beyond the RCTs for OCR and >20 years of real-world RTX experience have not shown an increased risk of any type of malignancy.[52] Patients should follow standard malignancy screening guidelines based on age and other risk factors.

Similarly, anti-CD20 therapies share recommendations for monitoring due to their shared MOA. All require screening for active hepatitis B infection due to the risk of latent viral reactivation with B-cell depletion. Additionally, all require testing for quantitative serum immunoglobulins prior to initiating therapy. This is due to increased risk of hypogammaglobulinemia in patients with baseline low gamma globulin levels as well as conflicting data regarding the risk of development of hypogammaglobulinemia with long-term anti-CD20 therapy.[51] It is also recommended to screen for other latent infections in high-risk populations. During therapy, yearly quantitative immunoglobulin testing is recommended along with screening for recurrent infections.

Clinical Considerations

The anti-CD20 therapies have become attractive to patients and providers alike due to their potent efficacy along with their favorable safety profiles, minimal monitoring requirements and attractive dosing intervals. However, there remain some important clinical considerations in using these therapies to treat both relapsing and progressive forms of MS.

The first and foremost consideration is whether individual MS patients are likely to benefit from anti-CD20 therapy. In patients with active relapsing MS or with new/contrast enhancing lesions on MRI, these therapies are very likely to have substantial benefits as shown by the patients included in the RCTs leading to their FDA-approval (or off-label use for RTX). However, in older patients (>50yo) without any active disease, the risk–benefit ratio is unclear. This was born out by the subgroup analyses of OLYMPUS trial for RTX in PPMS and the ORATORIO trial for OCR in PPMS.[53,55]

A second issue in patients on or about to start anti-CD20 therapies is how to approach vaccinations, which is particularly important amid the current COVID pandemic. In general, the National Multiple Sclerosis Society (NMSS) recommends that adults with MS get vaccinations according to standard vaccine guidelines and that live or live-attenuated vaccines should be avoided in patients on DMTs.[62] However, for anti-CD20 therapies, the NMSS recommends administration of the final dose of any required live or live-attenuated vaccines at least 4 weeks before and any required non-live vaccines at least 2 weeks before starting an anti-CD20 therapy.[62] For those patients already on anti-CD20 therapy or for patients who have active disease requiring urgent initiation of DMT, the NMSS recommends getting vaccinations 12 weeks or more after OCR/RTX doses but does not provide any clear guidance for timing in those on OFA. In stable patients on OFA, it may be reasonable to pause therapy to get the vaccine and resume OFA 2–4 weeks after getting fully vaccinated.[63] These recommendations are supported by several recent publications showing both the diminished response to vaccinations in patients on anti-CD20 therapies as well the preservation of a clinically meaningful vaccine response, even in patients with complete B-cell depletion.[64–66]

Conclusion

In the last two decades, monoclonal antibody therapies have revolutionized our treatment of both relapsing and progressive MS by providing therapeutic options that target specific mechanisms of disease activity in the complex pathogenesis of MS. While debate remains about the particular place of each of these agents in the MS treatment paradigm, particularly using these therapies early as "induction" agents or later as "escalation" therapies after failing less efficacious agents, natalizumab, alemtuzumab, and all the anti-CD20 mAbs are each highly effective therapies for relapsing MS with unique benefits and risks that warrant evaluation with each MS patient individually. Ocrelizumab is the only FDA-approved medication for PPMS with a modest reduction in disability progression compared to placebo, though many would assume similar benefits for all anti-CD20 therapies. Further study is needed for all these therapies to understand their effects on MS patients with progressive disease and long-term safety data. Additionally, head-to-head clinical trials are needed to further delineate comparative effectiveness of each of these therapies.

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