Monoclonal Antibody Therapy in Multiple Sclerosis

Finding the forest among the trees with an update on the safety, efficacy, and mechanisms of monoclonal antibodies.

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There has been a marked increase in disease-modifying therapies for patients with multiple sclerosis (MS) over the last decade. Of these, 3 are monoclonal antibodies of diverse origin (Table) that target diverse pathways (Figure). This diversity reflects the continued growth in understanding of the complex role of the immune system in MS and our fledgling understanding of how modulating these pathways can alleviate disease. Each therapy has unique risks, many of which are not fully realized in clinical trials, as recent events have shown with daclizumab, which has been withdrawn from the market. In addition, treatment of MS has recently shifted to a focus not only on disease modification, but also on remyelination and repair.

This article updates efficacy and safety data for monoclonal antibody treatments, including an overview of current clinical trials and research that will define the next generation of monoclonal antibodies for treating patients with MS.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody targeting CD52, a cell surface marker widely expressed on mature lymphocytes. Targeting CD52 leads to depletion of circulating B and T cells with subsequent repopulation over months to years. Alemtuzumab has a different dosage schedule versus other immunotherapies; it is given in 2 short series of infusions 1 year apart, and then given again only if further disease activity occurs. In 2 phase 3 clinical trials, alemtuzumab was shown effective in preventing relapse for patients who had not been treated previously, and those who had been treated with interferon-β-1a or glatiramer acetate and still had disease progression. Although efficacy of alemtuzumab was well demonstrated, the high rate and severity of side effects are a barrier to treatment for many patients and physicians. Infusion reactions are common; infections, sometimes serious, have been noted; and most importantly, high rates of secondary autoimmunity are seen (e.g., thyroid disease, immune thrombocytopenic purpura [ITP], and antiglomerular basement membrane disease). Follow-up after 5 years provides measures of longer-term efficacy with excellent levels of patient retention. Clinical and radiographic disease activity remains low in most patients, and a substantial reduction in brain volume loss is seen in extended follow-up. Roughly two-thirds of patients did not require redosing of alemtuzumab beyond the first 2 years, and year 3 infusions had lower infusion-related events than prior years. That said, in data from 6 years of follow-up, only 50% of patients did not need to receive additional immunotherapy after the initial 2 treatments.

Additional instances of autoimmune disease and serious infections were seen in open-label follow-up and postmarketing experience. In open-label follow-up, secondary autoimmunity peaked in the third year of treatment, although cases were seen throughout the extension period. Autoimmune thyroid disease occurred in >40% of patients, and additional cases of ITP were seen in both studies. A single additional case of nephropathy occurred in open-label follow-up. Herpetic infections occurred at a rate similar to the initial trials, but complications were largely mitigated by the use of prophylactic acyclovir. In postmarketing data, more than 30 cases of listeria meningitis have been documented, with the highest preponderance in the month after infusion, which led to the formal recommendation of listeria prophylaxis in the United States in 2003. Alemtuzumab is the only other labeled monoclonal antibody (natalizumab and ocrelizumab) that has been associated with listeria meningitis.

Note: Source infixes for antibodies prior to 2010. Revised nomenclature can be found in the revised International Nonproprietary Names for Pharmaceuticals.

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Kingdom. In addition, rare side effects have been noted in postmarketing data, including acalculous cholecystitis, and a report of an acute coronary syndrome during infusion, among others. Clinicians must remain vigilant because the full spectrum of secondary effects from alemtuzumab is being uncovered.

**B-Cell Therapies**

B-cell therapies have been a growing area since the initial trial of rituximab showed effectiveness for relapsing-remitting multiple sclerosis (RRMS). Although a trial of rituximab in primary progressive disease was ultimately unsuccessful, it laid the groundwork for future trials of anti-CD20 antibodies, including ocrelizumab, the first therapy to demonstrate efficacy in primary progressive MS (PPMS). Although an approved biologic for other diseases, rituximab remains off-label for patients with MS. Nevertheless, rituximab continues to be used in many centers. A number of studies demonstrate long-term efficacy and safety of rituximab in cohort of 822 patients, as well as favorable efficacy both when switching from natalizumab compared to fingolimod and as initial therapy when compared to on-label therapies. This medication remains a viable option for treatment of persons with MS in areas where off-label use is possible and where ocrelizumab is not available.

Ocrelizumab is approved for treatment of patients with MS; it also is directed against CD20. Ocrelizumab was studied in 2 parallel trials for treatment of RRMS versus interferon-β-1a and in a placebo-controlled trial in PPMS. For RRMS, there was a 46% to 47% reduction in the primary endpoint of annualized relapse rate (ARR) in comparison to interferon-β-1a. In a trial for treatment of patients with PPMS, a 24% relative risk reduction of the 12-weeks confirmed disability progression was seen compared to placebo. Overall, ocrelizumab has been well-tolerated by patients. Serious infections were seen in trials in combination with other immunotherapies in persons with lupus and rheumatoid arthritis, leading to the suspension of those trials. These adverse results have not been mirrored in trials of ocrelizumab for treatment of patients with MS. An increased rate of breast cancer was seen in patients treated with ocrelizumab in both trials, but follow-up safety data suggest a return to expected incidence in this population. Progressive multifocal leukoencephalopathy (PML) remains a concern, but the only incidences of PML thus far have occurred in the setting of a transition from natalizumab or fingolimod.

There are 2 additional antiCD20 therapies on the immediate horizon. Ofatumumab and ublituximab are both being evaluated in phase 3 trials for RRMS. Ofatumumab is delivered as a subcutaneous injection. In a phase 2 trial, ofatumumab demonstrated efficacy in reducing enhancing lesions at 12 weeks with a variety of doses. This includes doses causing incomplete suppression of CD20 cells and partial B-cell
repopulation between doses, highlighting the uncertain target of B-cell suppression in these patients. Ublituximab was glyco-engineered for enhanced affinity to FcyRIIIa receptors, with the goal of increased antibody-dependent cellular cytolysis. It is given intravenously, as are the available on-label therapies. Because of increased potency, the infusion time required for treatment with ublituximab is decreased to 1 to 2 hours for most patients. Data from ongoing trials suggest a robust radiographic response.20

Inebilizumab, in early stages of evaluation, targets B cells and CD19 which is expressed on a wider lineage of B cells, including plasmablasts and some plasma cells that are otherwise spared by CD20 agents.21 Although targeting these cells may be efficacious for MS, it also presents a greater theoretical risk for immunoglobulin deficiencies, and it will be necessary to monitor for infectious complications.

**Daclizumab**

Used sparingly, daclizumab is an antibody directed at IL2R-α, otherwise known as CD25. This monoclonal antibody was one of the first ever used in human disease, initially for prevention of renal allograft rejection. It was later repurposed for use in patients with MS after reformulation as daclizumab high-yield process. Daclizumab demonstrated efficacy in RRMS; however, serious side effects, including fulminant autoimmune hepatitis, were seen in trials.22,23 It was available under a monitoring program for patients who had not responded to 2 other disease-modifying therapies, leading to little exposure to the therapy. Postmarketing experience in Europe led to recognition of secondary autoimmune events, including 12 cases of an inflammatory CNS condition that led to at least 3 deaths.24 Daclizumab was withdrawn from the market March 2, 2018.

The withdrawal of daclizumab presents a quandary for clinicians when transitioning patients to a new therapy. Risk of rebound is unclear, appropriate length of washout is unknown, and interactions with other disease-modifying therapies are known only at the level of case reports. Liver function needs to be monitored monthly for at least 6 months because hepatic events were observed after treatment discontinuation. Although the optimal period of washout is unknown, the opinion of the authors is to wait for 2 months or until all complications from daclizumab resolve, whichever is later.

**Natalizumab**

Natalizumab is a humanized monoclonal antibody against α4-integrin that prevents lymphocyte migration across the blood–brain barrier. It is the first monoclonal antibody approved for use in patients with MS and demonstrated efficacy versus placebo25 and in combination with interferon-β-1a versus interferon-β-1a alone.26 Although clearly effective and fast-acting, it has the highest risk of PML of all available agents. The development of the JC virus (JCV) index and a monitoring program allows for stratification based on level of titer, length of exposure, and prior immunosuppression.27 PML risk ranges from 1:10,000 in patients with low JCV titers without prior immunosuppression to as high as 1:70 in patients with high JCV titers and prior exposure to immunosuppressive agents.28

Extended interval dosing (EID) has been used in studies in an attempt to limit PML risk with natalizumab treatment, but studies assessing efficacy and safety are limited by small numbers of treated patients and varying definitions of EID. Data from the Touch Registry were used to compare safety data for standard dosing versus EID. Using varying definitions of EID, including recent use of EID, any exposure to EID, and EID since treatment initiation, Ryerson et al demonstrated a considerable decrease in the risk of PML in all definitions of EID. Cases of PML did still occur with the exception of those who underwent EID since treatment initiation. Although intriguing, this study was limited by a lack of JCV titer capture, a low number of patients who underwent EID from treatment initiation, and most importantly, a lack of corresponding efficacy data. It remains to be seen if EID of natalizumab could further reduce PML risk and maintain the same level of effectiveness.

**Remyelination Therapies**

Although disease-modifying therapies continue to increase in effectiveness in preventing new inflammatory lesions and disease progression, none has demonstrated long-term disability improvement with consistency. The field of remyelination provides an alternative avenue for treatment, focusing on the recovery of damaged white matter in the hope that this will lead to clinically significant improvement. The regulation of remyelination in MS is complex, and recent work has focused on oligodendrocyte precursor cells (OPCs) and methods of promoting differentiation into functional oligodendrocytes in areas of demyelination.

In early human studies of remyelinating agents, 2 monoclonal antibodies have had a significant role. Opicinumab is a fully humanized antibody that targets leucine-rich repeat and immunoglobulin domain-containing neurite outgrowth inhibitor receptor-interacting protein-1 (LINGO-1), which is a negative regulator of OPC differentiation into oligodendroglia.29 In a phase 2 clinical trial, treatment with opicinumab in patients with new-onset optic neuritis over 6 months with the primary endpoint of recovery of latency in visual evoked potentials using the contralateral eye as a baseline failed to reach significance compared to placebo in both intention-to-treat and prespecified per protocol analysis, although the drug was well-tolerated.31 In another phase 2 trial of opicinumab in patients with RRMS who were being treated with interferon-β-1a intramuscular injections over the course of 84 weeks, the primary endpoint was a multicomponent clinical endpoint that was not significantly different versus placebo; however, at higher doses, more responders were seen. These trials have provided...
insight for future trial design and allow for post hoc analyses that may assist in future patient selection. Another monoclonal antibody for remyelination, rituximab, has completed phase 1 trials in humans. This recombinant antibody was isolated from a patient with Waldenström's macroglobulinemia and demonstrates the ability to induce remyelination in a mouse model of demyelination. Although the mechanism of action is unknown, the beneficial effects on remyelination have been seen in multiple animal models. In a phase 1 study, it was well-tolerated and able to cross the blood–brain barrier in small amounts. Further clinical studies are necessary to determine whether this antibody can reach the CNS in sufficient amounts, and if the beneficial remyelinating effects in animal studies are mirrored in humans.

Conclusion

Monoclonal antibodies represent the most highly effective therapies, and of these, ocrelizumab is the first approved for patients with PPMS. Clinicians still must be vigilant for both known side effects and for adverse events that were not captured during initial trials. It is this vigilance that led to the recognition of an unacceptable risk of severe autoimmune disease in daclizumab and to the continued discovery of the long-term effects of alemtuzumab treatment. As more monoclonal treatments become available, close monitoring will be required as even antibodies with the same target can have significantly different safety profiles. Monoclonal antibodies have featured prominently in early trials of remyelination, and despite recent setbacks, these therapies have informed us about the potential for neurologic recovery and for future trial design.