Monoclonal Antibody Therapies and Neurologic Disorders

John C. Novak, MD; Amy E. Lovett-Racke, PhD; Michael K. Racke, MD

The role of monoclonal antibody (mAb) therapies in treating medical conditions has expanded tremendously since its inception in the 1970s, and their use in neurologic conditions has increased in just the past few years. Currently, mAb treatments are being tested in conditions ranging from neuromuscular disorders to demyelinating diseases. What is now considered experimental therapy may soon become common. In addition, neurologic adverse effects have been reported during the use of mAb therapy in nonneurologic conditions that neurologists should be able to recognize. Because of the rapid increase in the use of mAb treatments, this review highlights their use in neurologic conditions and their neurologic adverse effects.

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Antibodies (Abs) are produced by B cells and share the same basic structure. The base of the Ab is composed of a constant region (Fc) that imparts the effector properties of the molecule in the immune system. This region is recognized by Fc receptors on various cell types. Therefore, the actual effect of Ab binding is determined by the cell type and the receptor binding it. The opposing end, the variable region (Fv), imparts the specificity of the molecule to bind to unique antigens (Ags). Each B-cell line produces Abs specific for 1 Ag and is, thus, considered to take part in monoclonal Ab (mAb) production. The unique Ag-binding properties of the Fv region combined with the highly conserved Fc region focuses a wide range of immune responses to a highly specific target.

PRODUCTION OF THERAPEUTIC mAb

Although the Ag that an Ab may target is unique, the method of producing various mAbs is very similar. The target Ag, or part of the Ag, is injected into a host animal that will then mount an immune response and create a pool of B cells specific to that Ag. The B cells are harvested and put into culture with myeloma cells, where the 2 cell types can be fused. After mitotic division, a hybridoma is created that can produce the desired mAb yet have the reproductive properties of the tumor cells. The result is a line of immortal mAb-producing cells that can divide in vitro to generate daughter cells and, therefore, more Abs. However, the Fc region of Abs produced in host animals, such as mice and horses, are recognized as foreign when given to humans. Consequently, an immune response can be initiated that can neutralize the treatment or even lead to a fatal anaphylactic reaction. Modern therapeutic lines of mAbs are often humanized through the use of transgenic mice that create Abs with human Fc regions. Products that use this method are identifiable as having names that end in -zumab. Another approach is to split host-derived mAbs and then combine the created Fv region with human Fc regions. The end products are considered to be chimeras and have names that end in -ximab. A third common approach is to create a fusion protein composed of a human Fc region and an Ag-specific receptor. These products may not resemble typical Abs in structure but act in a similar manner. Etanercept was one of the first approved products to use this approach, but more have since been created, and all share the -cept suffix. Despite the variety of methods used, the goal is to mass produce Abs that are specific to a desired Ag yet do not induce an immunogenic response against themselves.
The variety of targets to which they can be directed is continually expanding (Figure). This has resulted in a variety of uses, ranging from cancer treatment to autoimmune disease therapy. The mAbs mediate their therapeutic effect by targeting cells for death via Ab-induced apoptosis, Ab-dependent cell cytotoxicity, or complement-mediated cell lysis, or mAbs can physically block a receptor-ligand interaction (Table).1-13

These various mechanisms share the common goal of targeting a specific cell population or molecule relevant to disease pathogenesis. The use of these treatments in neurologic diseases is an emerging field that is the focus of this article.

NEUROLOGIC USES OF mAbs

Multiple Sclerosis

The most widely recognized use of mAbs in neurology has been in the treatment of multiple sclerosis (MS). Natalizumab is a humanized Ab directed against α4β1 integrin, a molecule believed to play a role in allowing the entry of inflammatory cells into the central nervous system. This therapy seemed promising because it reduced disability rates and magnetic resonance imaging evidence of disease.6,7 However, after 3 patients developed progressive multifocal leukoencephalopathy, it was subsequently withdrawn from the market. Its recent reintroduction allows its use in relapsing forms of MS, but only as monotherapy, and it carries an approximately 0.1% risk of having progressive multifocal leukoencephalopathy develop.14 Although natalizumab may be the only Food and Drug Administration–approved mAb therapy for MS, other therapies are being investigated. Alemtuzumab (Campath; Genzyme Corp, Cambridge, Massachusetts) is an anti-CD52 Ab that targets multiple cell types in vivo, including B cells, T cells, monocytes, and eosinophils. In a 1999 study, 125 patients with secondary progressive MS were treated with a single pulse of alemtuzumab. Magnetic resonance imaging performed up to 18 months later showed a reduction in gadolinium-enhancing lesions; however, patients still developed generalized brain atrophy and clinical disability. A more recent trial2 of alemtuzumab showed a 75% decrease in relapses and a 65% decrease in sustained accumulation of disability compared with high-dose interferon beta-1a. Six of 216 patients developed immune thrombocytopenic purpura, including 1 case of fatal intracerebral hemorrhage. Daclizumab acts to decrease T-cell proliferation by blocking a portion of the interleukin 2 receptor (CD25) on activated T cells. Two separate trials using daclizumab have shown promising results, with improved radiologic and clinical measures in treated patients.3,4 The drug was also well tolerated and is likely to be given further consideration with expanded trials. Treatment with rituximab has been shown to deplete B cells in the peripheral blood of patients with MS, but its effect in the cerebrospinal fluid may not be as robust.15,16 A recent phase 2 clinical trial15 found that gadolinium–enhancing lesions were reduced by 91% and relapses by 58% 24 weeks into the study. These trials show the potential utility of mAb therapies in the treatment of MS and may eventually offer new options for this debilitating disease.

Neuromyelitis Optica

Neuromyelitis optica (NMO), or Devic disease, is an inflammatory demyelinating condition that attacks the optic nerve and spinal cord. Autopsy evidence from several patients with NMO has implicated Ab responses in at least contributing to spinal cord tissue destruction.17 The Ab, believed to be directed against aquaporin 4, is detectable and is a reasonably sensitive diagnostic test for NMO. The theory that Ab suppression could help decrease central nervous system damage has led to the trial of rituximab as treatment for NMO. Cree et al8 reported on the use of this B-cell depleting mAb in 8 patients with NMO. They saw decreased attack frequency in all of their patients and even remarkable recovery in at least 1. This was a small and unblinded study, but several patients had failed previous therapies yet responded favorably to rituximab. This study result has yet to be confirmed, but given the lack of other effective therapies, rituximab may find a prominent role in the treatment of NMO.

Neuromuscular Diseases

Neuromuscular conditions embody another large area of autoimmune processes in which mAb therapy is being investigated. Rituximab was used in an open-label study11 of 6 patients with dermatomyositis that had been refractory
Table. Monoclonal Antibody Therapies and Current Clinical Studies Regarding Their Use in Neurologic Diseases

<table>
<thead>
<tr>
<th>Generic Drug (Trade Name)</th>
<th>Target</th>
<th>Mechanism of Action</th>
<th>Conditions</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>CD52</td>
<td>Depletes T and B cells via an unknown mechanism</td>
<td>Multiple sclerosis</td>
<td>Paolillo et al., 1999; Cole and CAMMS223 Group, 2007</td>
</tr>
<tr>
<td>Daclizumab (Zenapax)</td>
<td>IL-2 receptor</td>
<td>Blocks IL-2 receptor α chain</td>
<td>Multiple sclerosis</td>
<td>Rose et al., 2004; Bielekova and Richert, 2004</td>
</tr>
<tr>
<td>Infliximab (Remicade), etanercept (Enbrel)</td>
<td>TNF</td>
<td>Inhibits TNF-α activity</td>
<td>Dermatomyositis, polymyositis</td>
<td>Efthimiou et al., 2006</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>α4β1 Integrin</td>
<td>Blocks entry of T cells into the CNS</td>
<td>Multiple sclerosis</td>
<td>Polman et al., 2006; Miller et al., 2007</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>CD20</td>
<td>Induces cell lysis and reduces the total B-cell count</td>
<td>NMO, multiple sclerosis, immune neuropathies, dermatomyositis, MMN</td>
<td>Cree et al., 2005; Hauser et al., 2007; Levine, 2005; Dinh et al., 2007; Rüegg et al., 2004</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; IL-2, interleukin 2; MMN, multifocal motor neuropathy; NMO, neuromyelitis optica; TNF, tumor necrosis factor; TNF-R, TNF receptor.

Another area of interest in the use of mAb therapy is in peripheral neuropathy treatment. The current standard treatment for many Ab-mediated neuropathies is to give intravenous immunoglobulin, a polyclonal immunoglobulin infusion with the aim of reducing the amount of pathologic autoantibodies. Rituximab produces a similar effect by targeting the B cells that produce Abs, thereby reducing their number. Thus, it can be used in a variety of Ab-mediated conditions, and reported successes have been seen in multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, and anti–myelin-associated glycoprotein–associated neuropathy.10,11,20 Trials have been small but promising enough that the European Federation of Neurological Societies and the Peripheral Nerve Society consider the use of rituximab to be a “good practice” in patients with multifocal motor neuropathy not responding to typical treatments.21

NEUROLOGIC ADVERSE EFFECTS OF mAb USE

The ever-increasing use of mAb therapies has not been without its share of adverse effects, including unexpected neurologic toxic effects. Bevacizumab is directed at vascular endothelial growth factor and is used in the treatment of colon and renal cancers. Several incidents of a reversible posterior leukoencephalopathy have been reported after its administration and may be related to the induction of vasospasm or hypertension.12,23 Patients presented with typical symptoms of a posterior leukoencephalopathy, such as cortical blindness, decreased mental status, and seizures, and had concordant magnetic resonance imaging findings. Although the clinical presentation and diagnostics were typical, patients presented 1 to 2 weeks after infusion, and systolic blood pressures greater than 170 mm Hg were not reported. This may have delayed diagnosis in these cases and illustrates the need for neurologists to be aware of this potential adverse effect.

The TNF blocking agents were originally thought to be potential treatments for MS, but a 1999 trial of a TNF antagonist, lenenercept, was stopped early owing to increased MS exacerbation rates compared with placebo. Other anti-TNF agents, such as etanercept, infliximab, and adalimumab, are used in rheumatoid arthritis and Crohn disease but have been implicated in causing optic neuritis and even MS.25-28 Demyelination outside of the central nervous system has been seen in relation to the same anti-TNF treatments. A review by Shin et al.29 identified 15 patients in the Food and Drug Administration Adverse Event Reporting System who developed demyelinating neuropathies potentially related to treatment with one of these medications. The mechanism by which these agents may lead to Guillain-Barré syndrome–like conditions is not fully understood. The TNF antagonism may leave patients susceptible to more viral infections that could secondarily lead to Guillain-Barré syndrome–like syndromes. Another possibility is that TNF is somehow protective to myelin. Whether these agents are directly responsible or these patients are just more prone to developing demyelinating conditions is yet to be uncovered. In addition to demyelination, infliximab is believed to be responsible for the development of an axonal neuropathy in at least 2 patients receiving infliximab for gastrointestinal tract conditions.29 The time of onset varied from several days to weeks after medication infusion and argues against a di-
rect toxic effect of the medicine. This type of neuropathy has not been as widely reported as demyelinating nerve damage, and the coexistence of motor neuropathy and gastrointestinal tract abnormalities is a possibility.

Despite the ability to target specific Ags, the complete effects of mAb therapy are largely not understood. The immune system is extremely complex, and much is left to be learned about how the numerous cytokines and cell types interact. Treatment with mAbs results in therapeutic effects that last much longer than the pharmacologic half-life; likewise, many of the toxic effects seem delayed. As our knowledge of these mechanisms increases, so also may our ability to predict toxic effects. Until then, neurologists must be aware of the potential neurologic adverse effects of these agents as their use increases.

Many of the current uses of mAb are in experimental stages and, consequently, are limited to clinical trials and large academic institutions. However, their use is likely to spread as the community becomes more familiar with the effects of current therapies and as new drugs are developed. Neurologists in all settings will need to be familiar with these treatments as they gain more widespread use. The neurology community is also likely to see an increase in patients’ conditions. Much of this knowledge expands, and it will be imperative that the neurology community as a whole remain current regarding their disease activity and treatment options. Recognition of these symptoms as an adverse effect of a past treatment is important to help accurately diagnose patients’ conditions. Much of this information will likely be updated and change as knowledge expands, and it will be imperative that the neurology community as a whole remain current regarding their indications and adverse effects.

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Correspondence: Michael K. Racke, MD, Department of Neurology, The Ohio State University Medical Center, 1654 Upham Dr, Columbus, OH 43210 (Michael.Racke@osumc.edu).

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REFERENCES