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Monoclonal Antibody Therapies for Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder

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Considerable progress has been made in treatments for multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) over the last several decades. However, the present treatments do not show satisfactory efficacy or safety in a considerable proportion of patients, who experience relapse or disability progression despite receiving treatment and suffer from side effects, which can be severe. Improvements in the understanding of the pathophysiologies of MS and NMOSD have led to numerous therapeutic approaches being proposed and developed. Monoclonal antibodies (mAbs) are receiving increasing attention because of their specificity of action and likelihood of high efficacy with fewer side effects. Many mAbs have been evaluated, and some have been approved for MS or NMOSD treatment. This article reviews the use of mAbs for treating MS and NMOSD, including summarizing their mechanisms of action, efficacy, and safety profiles.

Key Words multiple sclerosis, neuromyelitis optica spectrum disorder, monoclonal antibody, treatment, efficacy, safety.

INTRODUCTION

There has been considerable progress in treatments for multiple sclerosis (MS) in recent years. Interferon (IFN) β-1b was first introduced in 1993, and subsequent novel medications in injectable and oral formulations have progressed rapidly to provide broader treatment options. However, the efficacy and safety profile of the existing medications are still not satisfactory, with patients experiencing relapse or disability progression despite receiving treatment and suffering from side effects, which can be severe.

Only a few maintenance therapy options are available for neuromyelitis optica spectrum disorder (NMOSD), and no drug has been approved by the US Food and Drug Administration (FDA) for such maintenance therapy. Immunosuppressants such as azathioprine and mycophenolate mofetil are widely used. However, these immunosuppressants do not show satisfactory efficacy, and have possible risk of side effects related to their broad inhibition of the immune system.[1] Rituximab is a monoclonal antibody (mAb) targeting CD20 and is known to be the most efficacious therapeutic options currently available, but some patients still experience relapse despite receiving treatment with rituximab and appropriate monitoring.[2]

mAbs are generally preferred when target specificity and high treatment efficacy are considered.[3] These antibodies (Abs) bind to antigens in specific ways that allow them to mediate their effects on very specific pathways, and they can neutralize or inhibit key immune-related factors in the pathomechanism of the disease. The specificity of mAbs means that they tend to have fewer off-target effects, drug–drug interactions, and side effects.[4] Improve-

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ments in the understanding of the pathomechanisms of MS and NMOSD has resulted in mAbs becoming available for more-specific targets.

Among the mAbs developed for MS and NMOSD, natalizumab and alemtuzumab were approved by the FDA for maintenance therapy for MS. Daclizumab was approved in 2016 but later withdrawn after reports of meningoencephalitis 2 years later. No drug has been approved for NMOSD by the FDA, although rituximab is widely used and recommended as an efficacious and safe therapy.[5]

This article reviews the mAbs used for treating MS and NMOSD. Among the mAbs that have been studied, those approved by the FDA or that have shown positive results in phase-2 or phase-3 trials are discussed, and their mechanisms of action, efficacy, and safety profiles are summarized.

NATALIZUMAB

Natalizumab (Tysabri®) is a humanized mAb against the α4 subunit of α4β1 and α4β7 integrins, which are adhesion molecules present on the surface of all leukocytes except neutrophils. Natalizumab reduces inflammation in the CNS by blocking the binding of integrins to endothelial receptors and the subsequent passage of immune cells through the blood–brain barrier.[6] Natalizumab was initially approved for relapsing-remitting multiple sclerosis (RRMS) in 2004 by the FDA based on the results of two phase-3 studies (AFFIRM and SENTINEL),[7,8] but it was taken off the market in 2005 after the occurrence of three cases of progressive multifocal leukoencephalopathy (PML): one in a Crohn's disease patient and two in MS patients.[9-12] It was introduced into the market again in 2006 after data collected in postmarketing observational studies (TYGRIS) provided evidence of improvement in patient health and quality of life through reductions in the annualized relapse rate (ARR) and the number of new T2-weighted and enhanced lesions in brain MRI scans.

Efficacy for MS

In the phase-3 AFFIRM study, 942 RRMS patients were assigned to receive intravenous natalizumab (300 mg) (*n*=627) or placebo (*n*=315) every 4 weeks for more than 2 years.[7] Natalizumab reduced the risk of sustained progression of disability by 42% over 2 years, the rate of clinical relapse at 1 year by 68%, and the accumulation of new or enlarged MRI lesions by 83% over 2 years. The natalizumab group had 92% fewer lesions than the placebo group at both 1 and 2 years.

The phase-3 SENTINEL study included 1,171 RRMS patients who had experienced at least one relapse during the 12-month period before randomization despite receiving intramuscular IFNβ-1a therapy.[8] Intravenous infusion of natalizumab (300 mg) (*n*=589) or placebo (*n*=582) was performed every 4 weeks for up to 116 weeks in combination with the continuation of IFNβ-1a. The relative risk of sustained disability progression was reduced by 24% in the combination-therapy group. The cumulative probability of progression at 2 years was 23% with combination therapy and 29% with IFNβ-1a alone. Combination therapy was also associated with a lower ARR over a 2-year period than IFNβ-1a alone (0.34 vs. 0.75) and with fewer new or enlarged lesions (0.9 vs. 5.4).

The efficacy and safety of natalizumab in secondary progressive multiple sclerosis (SPMS) were evaluated in the phase-3, randomized, double-blind, multicenter ASCEND trial.[13] Patients who had a score on the Expanded Disability Status Scale (EDSS) of 3.0−6.5 and disability progression unrelated to relapse during the year prior to enrollment were included. Treatment with intravenous natalizumab (300 mg, every 4 weeks) (*n*=440) did not significantly reduce disability progression compared with placebo (*n*=449) (44% vs. 48%). However, natalizumab showed a significant benefit in the nine-hole peg test, which is a prespecified component of the primary endpoint.

Safety profile

Natalizumab is highly efficacious as a maintenance therapy for MS, but safety issues have limited its use and imposed a requirement for strict clinical surveillance of patients receiving this treatment. PML is one of the greatest concerns and requires close observation. Some postmarketing safety red flags have also been noted, which has led to greater attention being given to severe liver failure and lymphoma.[14]

The open label, prospective, observational STRATA study[15] enrolled 1,094 RRMS patients that had previously participated in the AFFIRM,[7] SENTINEL,[8] GLANCE,[16] or STARS study. The patients received a median of 56 infusions, and 16% reported at least one serious adverse event (AE) other than MS relapse, including infection and infestation (4%), gastrointestinal disorders (2%), and neoplasms (2%). In the TOP study, which was another large 10-year prospective open-label postmarketing study, 2.6% of 4,821 natalizumab-treated subjects experienced serious AEs that were definitely or possibly related to the treatment.[17] The most-common serious AE was infection (1.9%), with serious hypersensitivity reaction having an incidence of 0.5%. Malignancies of 12 different types occurred in 0.5% of the patients.[14]

The incidence of natalizumab-associated PML was reported to be 4.20 per 1,000 treated patients.[18] At present, the risk factors for PML in patients on natalizumab are previous or concomitant immunosuppression, long duration of exposure to natalizumab (particularly more than 24 doses), and a high level of anti-JCV Ab in the serum or plasma.[19] It was

recommended that patients at a low risk of PML (less than 0.09%) should receive routine assessment for MS disease activity when selecting and refining disease-modifying therapy, as well as PML surveillance. Patients at a higher risk (more than 0.09%) should undergo intensive monitoring with more-frequent MRI and Ab index assessments.[20]

Several studies have shown that discontinuation of natalizumab therapy can aggravate the disease activity.[21-23] For postnatalizumab therapy, fingolimod is the most-studied agent and has a relapse rate higher than that of natalizumab but lower than before natalizumab initiation.[24] Rituximab or alemtuzumab could also be a suitable option.[25-27]

ALEMTUZUMAB

Alemtuzumab (Lemtrada®) is a humanized IgG1 mAb against CD52, which is a glycoprotein expressed on the surface of CD4+ and CD8+ T lymphocytes, B lymphocytes, monocytes, natural killer (NK) cells, dendritic cells, and polymorphonuclear neutrophils.[28] While the exact function of CD52 is not fully known, it is speculated to work as an anti-adhesion molecule and enable lymphocytes to move freely.[29] Although the mechanism of therapeutic action of alemtuzumab has not been fully elucidated, it is thought to destroy CD52-expressing T and B lymphocytes via both Ab-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) toward the target, leading to the modulation of the immune system as a result of the depletion and repopulation of lymphocytes.[30] Alemtuzumab was approved for RRMS therapy by the FDA in 2014.

Efficacy for MS

The phase-2 CAMMS223 trial involved 334 treatment-naïve early RRMS patients with a disease duration of no more than 36 months and at least 2 exacerbations.[31] Patients were randomized to receive subcutaneous IFNβ-1a (44 μg three times weekly) or alemtuzumab. Alemtuzumab was infused intravenously at 12 or 24 mg/day for 5 consecutive days, and administration was repeated for 3 consecutive days after 12 and 24 months at the discretion of the physician based on CD4+ counts. The rate of sustained accumulation of disability was reduced in the alemtuzumab group compared with IFNβ-1a (9.0% vs. 26.2%), while the mean EDSS score improved by 0.39 in the alemtuzumab group and worsened by 0.38 in the IFNβ-1a group. The ARRs (0.10 vs. 0.36, respectively) and the MRI lesion burden were reduced more in the alemtuzumab group than in the IFNβ-1a group (-16.4% vs. -13.3% from baseline). During months 12–36 the brain volume increased in the alemtuzumab group by 0.9% while it decreased in the IFNβ-1a group by 0.2%.

The phase-3 CARE-MS I[32] and II[33] clinical trials compared alemtuzumab with subcutaneous IFNβ-1a (44 μg three times weekly). In both studies, alemtuzumab (12 mg/day) was infused intravenously for 5 consecutive days followed by additional infusions 12 months later for 3 consecutive days. CARE-MS I included treatment-naïve RRMS patients, while CARE-MS II included RRMS patients who had a clinically inadequate response to previous therapy. The total of 1,191 included patients comprised 563 in CARE-MS I (376 and 187 in the alemtuzumab and IFNβ-1a groups, respectively) and 628 in CARE-MS II (426 and 202, respectively). In the CARE-MS I study, the alemtuzumab group showed a 54.9% lower rate of patients experiencing relapse (22% vs. 40%), a higher rate of relapse-free patients at 2 years (78% vs. 59%), and a lower rate of sustained accumulation of disability (8% vs. 11%). In the CARE-MS II study, the rate of patients who experienced relapse was lower in the alemtuzumab group (35% vs. 51%), showing a 49.4% improvement, the rate of relapse-free patients at 2 years was higher (65% vs. 47%), and the rate of patients with sustained accumulation of disability was lower (13% vs. 20%).

Efficacy for NMOSD

A case-series study that investigated three NMOSD patients treated with alemtuzumab did not produce favorable findings.[34]

Safety profile

AEs associated with the use of alemtuzumab in the previous studies (CAMMS223 and CARE-MS I and II) and their follow-ups could be classified into several groups: infusion-related symptoms, infections, malignancy, and secondary autoimmunity.[35,36] Infusion-related symptoms including rash (41–92%), headache (43–61%), and pyrexia (17–38%) were common, and could be reduced by premedication with methylprednisolone or by adjusting the infusion rate.[36] Infections including upper respiratory infection (URI) (12.5–18%), urinary tract infection (UTI) (12–22%), and herpes simplex/herpes zoster (3–13%) were mostly mild or moderate due to preservation of the innate immune system, with a decreasing rate over time.[35] Most of the secondary autoimmune problems were related to the thyroid, such as hyperthyroidism (5–15%), hypothyroidism (5–7%), and thyroiditis (2–4%). Idiopathic thrombocytopenic purpura occurred in 1–3% of the patients, and in one case this was fatal. Twenty-nine patients were diagnosed with a malignancy, six of whom had thyroid carcinomas. The other malignancies occurring in multiple patients were basal-cell carcinoma (n=6), breast cancer (n=5), and malignant melanoma (n=4). PML has not been reported in MS patients treated with alemtuzumab, but has been reported in lung transplant and leukemia patients.[37,38]

Concerns about possible side effects of alemtuzumab such as stroke and heart attack have recently been raised due to cases reportedly occurring within 48 hours of its infusion. The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) advised that the use of alemtuzumab should be restricted as a temporary measure, with it only being started in adults with RRMS that is highly active despite receiving treatment with at least two disease-modifying therapies, or where other disease-modifying therapies cannot be used.[39]

DACLIZUMAB

Daclizumab is a humanized IgG1 mAb that binds to the α subunit of the high-affinity interleukin (IL) 2 receptor. IL-2 signaling is required for clonal expansion of activated T lymphocytes. The immunological effect of daclizumab is known to be associated with 1) blockage of T-lymphocyte activation, expansion, and survival, 2) up-regulation of CD56+ NK cells, 3) a reversible decrease in circulating regulatory T lymphocytes whose expansion is dependent on IL-2, and 4) a reduction in proinflammatory lymphoid tissue inducers, which are thought to contribute to the formation of cortical lesions.[40-42]

MS trials have used three forms of daclizumab: intravenous daclizumab (Zenapax®), subcutaneous daclizumab formulation 1 (DAC-SQ1; Penzberg®), and the daclizumab beta or daclizumab high-yield form (DAC-β or DAC-HYP; Zinbryta®). Daclizumab was initially developed as an intravenous medication and used for protecting against transplant organ rejection, T-lymphocyte leukemia, and severe uveitis.[43-46] DAC-SQ1 (used in the phase-2 CHOICE study) and DAC-HYP (a monthly subcutaneous injection that showed good efficacy for MS in larger phase-2 and phase-3 studies) were approved for treating relapsing MS in 2016. However, in March 2018 the EMA recommended the immediate suspension of daclizumab following 12 reports of serious inflammatory brain diseases (e.g., encephalitis and meningoencephalitis), and the company voluntarily withdrew its marketing.[42]

Efficacy for MS

The first pivotal clinical trial of daclizumab in MS was the CHOICE study. This phase-2, randomized, double-blind, placebo-controlled study investigate the DAC-SQ1 subcutaneous formulation of daclizumab.[47] In total, 230 patients with either RRMS or SPMS who were previously taking IFNβ (intramuscular IFNβ-1a, subcutaneous IFNβ-1a, or subcutaneous IFNβ-1b) were randomized to receive as an add-on drug either high-dose daclizumab (2 mg/kg every 2 weeks; *n*=75) or low-dose daclizumab (1 mg/kg every 4 weeks; *n*=78), or placebo (*n*=77) for 24 weeks. The adjusted mean numbers of new or enlarged enhanced lesions were reduced by 72.2% and 24.6% in the high-dose and low-dose daclizumab add-on groups (to 1.32 and 3.58, respectively) compared with the placebo group (4.75).

The SELECT trial was another phase-2 study in which only RRMS patients (*n*=621) were randomized to receive DAC-HYP at either 150 mg (*n*=208) or 300 mg (*n*=209), or placebo (*n*=204) every 4 weeks for 52 weeks.[48] Overall, 76% of the patients were treatment-naïve. The ARR was lower in the 150-mg daclizumab group (0.21, 54% reduction) and the 300-mg daclizumab group (0.23, 50% reduction) than in the placebo group (0.46). More patients were relapse-free in the 150-mg daclizumab (81%) and 300-mg daclizumab (80%) groups than in the placebo group (64%).

The SELECTION study was a 1-year double-blind extension of the SELECT trial in which placebo-treated patients were randomized (1:1) to receive DAC-HYP at 150 or 300 mg. The daclizumab-treated patients either continued the treatment with daclizumab or underwent a 24-week washout period followed by reinitiation of daclizumab at their previous dose.[49] Among the 567 patients who completed the SELECT trial, 517 (91%) entered the SELECTION study and were assigned to treatment initiation (*n*=170), continuous treatment (*n*=173), or washout and reinitiation (*n*=174). The primary endpoints were the safety and immunogenicity of DAC-HYP, and the secondary endpoint was the durability of the treatment effect. In the continuous-treatment group, the ARR, the numbers of new enhanced lesions, and the proportion of patients with confirmed disability progression remained constant; however, there were fewer new or enlarged T2-weighted lesions during the second year. In the washout-and-reinitiation group, the serum level of DAC-HYP and the number of $CD56^{bright}$ NK cells returned to their pretreatment states during the washout period. However, the ARR and the numbers of new enhanced lesions and new or enlarged T2-weighted lesions remained constant.

The SELECTED study was a single-arm, open-label extension study of the SELECT and SELECTION studies, and it found that the ARR analyzed at 6-month intervals was 0.15 for weeks 97−120 and 0.15 for weeks 121−144.[50] In the third year, the adjusted mean number of new or enlarged T2-weighted lesions was 1.26 (range=0.93−1.72), and the mean and median annualized changes in brain volume were -0.32% and -0.34%, respectively.

The phase-3 DECIDE study involving 1,841 RRMS patients compared DAC-HYP (150 mg every 4 weeks) with intramuscular IFNβ-1a (30 μg once weekly) for up to 144 weeks.[51] Daclizumab reduced the ARR (0.22 vs. 0.39, 45% reduction)

and the number of new or enlarged T2-weighted lesions over 96 weeks (4.3 vs. 9.4, 54% reduction). At week 144 the estimated incidence of disability progression confirmed at 12 weeks was 16% with daclizumab and 20% with IFNβ-1a, however, the difference was not statistically significant (p= 0.16).

Safety profile

The safety profile of daclizumab in patients with RRMS was analyzed in a study that integrated three clinical studies (SELECT, DECIDE, and OBSERVE) and their extension studies.[48,51,52] In total, 2,236 patients covering 5,214 patient-years were included from the 3 completed and 3 ongoing studies. The cumulative incidence rates of any AE and any serious AE other than MS relapse were 84% and 16%, respectively. The incidence of AEs remained stable during the maximum follow-up period of 6.5 years. Hepatic AEs (16%) and elevations of the serum transaminase level (10%) were important safety concerns related to daclizumab treatment, but most of them were asymptomatic and self-limiting. The cumulative incidence rates of cutaneous, infectious, and gastrointestinal AEs were 33%, 59%, and 25%, respectively. During the SELECTION study, one patient in the washout-and-reinitiation group died due to autoimmune hepatitis after the reinitiation of 300-mg DAC-HYP.[49]

Daclizumab-induced meningoencephalitis is characterized by dysregulation of the immune response. A report that analyzed 7 of 12 cases found that 6 of them fulfilled the DRESS diagnostic criteria (drug reaction with eosinophilia and systemic symptoms). Biopsies revealed the pronounced infiltration of inflammatory cells, consisting of lymphocytes, plasma cells, and eosinophils.[42,53] Although not fully understood, the causative mechanism of the disease is considered to be an imbalance between the decrease in regulatory T lymphocytes and the increase in $CD56^{bright}$ NK cells, which may lead to a paradoxical inhibition of autoregulatory mechanisms.[40-42]

RITUXIMAB

Rituximab (Rituxan®, MabThera®) is a murine/human chimeric mAb against CD20 that is expressed on both immature and mature B lymphocytes.[54] CD20 is believed to suppress the apoptotic death of CD20-expressing B lymphocytes under normal conditions, and rituximab induces both ADCC and CDC of CD20-expressing B lymphocytes. Although data from prospective randomized controlled studies are not available for rituximab in NMOSD, data obtained in retrospective studies and a meta-analysis revealed an evident clinical benefit.[55] Evidence obtained in retrospective, observational studies has led to rituximab being incorporated into treatment guidelines and recommendations.[5,56] Recent studies are focused on the use of rituximab for treating MS.

Efficacy for MS

While there has been no double-blind, phase-3 study of rituximab in MS, numerous phase-2 and phase-1 studies have demonstrated its efficacy. In the phase-2 double-blind HERMES trial, RRMS patients were infused with 1,000 mg of rituximab or placebo on days 1 and 15.[57] Compared with the placebo group (n=35), the rituximab group (n=69) showed reductions in the total numbers of enhanced lesions and the numbers of new enhanced lesions at weeks 12, 16, 20, and 24, and these results were sustained for 48 weeks. The number of patients who experienced relapse was reduced in the rituximab group at week 24 (14.5% vs. 34.3%) and at week 48 (20.3% vs. 40.0%).

A retrospective uncontrolled observational multicenter study identified MS patients treated with rituximab in the Swedish MS registry.[58] Among 822 rituximab-treated patients with MS, those with RRMS (n=557), SPMS (n=198), and primary progressive multiple sclerosis (PPMS) (n=67) were included, and they were treated with 500 or 1,000 mg of intravenous rituximab every 6−12 months for 21.8±14.3 months (mean±SD). Enhanced lesions were present in 26.2% of the patients at baseline, whereas only 4.6% of patients displayed enhanced lesions during treatment. The ARRs during the study period were 0.044, 0.038, and 0.015 in the RRMS, SPMS, and PPMS patients, respectively. The median EDSS score remained unchanged in RRMS, at 2, and increased by 0.5 in SPMS (from 5.5 to 6.0) and by 1.0 in PPMS (from 5.0 to 6.0).

In a rituximab add-on study of breakthrough RRMS, 30 patients who had experienced relapse within the previous 18 months despite treatment with an injectable disease-modifying agent and with at least 1 enhanced lesion on any 1 of 3 pretreatment MRI scans received intravenous rituximab (375 mg/m^2 weekly) 4 times.[59] Gadolinium-enhanced lesions were reduced after rituximab treatment, with the proportion of MRI scans clear of enhanced lesions increasing from 26% to 74%. The median number of enhanced lesions was reduced from 1.0 to 0, and the mean number was reduced from 2.81 to 0.33 per month after treatment, representing a 88% reduction. The Multiple Sclerosis Functional Composite scores improved, whereas the EDSS scores remained stable.

A recent meta-analysis of 15 studies involving 946 patients found that rituximab treatment was associated with decreases in the mean ARR and EDSS score of 0.80 and 0.46, respectively.[60] The likelihood of patients experiencing relapse after starting rituximab therapy was only 15%.

In the OLYMPUS study, 439 PPMS patients received in-

fusions with intravenous rituximab (1,000 mg) or placebo during weeks 0, 2, 24, 26, 48, 50, 72, and 74.[61] The time to confirmed disease progression (CDP) did not differ significantly between rituximab and placebo (30.2% vs. 38.5% at week 96). From baseline to week 96, the rituximab group showed a smaller increase in the T2-weighted lesion volume, whereas the brain volume changes were not significantly different to those in the placebo group.

Efficacy for NMOSD

While there have been no large-scale prospective double-blind study, numerous open-label, uncontrolled, observational studies have found rituximab to be one of the most-effective treatment options for NMOSD.[2,62-65] In a recent meta-analysis of 26 studies with 577 patients, among whom 75.4% were seropositive for anti-AQP4 Ab, rituximab therapy resulted in reductions of ARR and the EDSS score by mean difference ratios of -1.56 and -1.16, respectively. A relapse-free state was reached by 330 of 528 patients (62.9%).[66]

Safety profile

A meta-analysis of 15 studies of rituximab for RRMS investigated AEs in 253 out of 946 patients treated with rituximab, and found 75 (29.6%) AEs,[60] none of which were severe. Another meta-analysis of studies of rituximab for NMOSD found AEs in 95 of 577 (16.46%) rituximab-treated patients.[66] Twelve of those patients experienced severe AEs, comprising severe pneumonia (n=5), transitory hyperpyrexia (n=2), septicemia (n=2), severe allergic reaction (n=1), urogenital infection (n=1), and seborrheic dermatitis (n=1). Five patients died from pneumonia (n=2), urogenital infection and thrombosis (n=1), bone marrow transplantation (n=1), and cardiac and respiratory failure due to extensive myelitis reaching the medulla oblongata (n=1).

Between 1997 and 2009, 118 cases in which rituximab was associated with reactivation of hepatitis B virus (HBV) were reported to the FDA MedWatch Database.[67] In 2013, boxed warnings were added to the product labels for rituximab and ofatumumab that identified these agents as being associated with a high risk of HBV reactivation.[68] The European Association for the Study of the Liver recommended that Abs against hepatitis B core antigen should be tested for before initiating treatment with rituximab, with prophylactic antiviral therapy given during treatment and for a prolonged period afterward if necessary.[69]

PML associated with rituximab has been reported not in patients with MS or NMOSD but in patients with lymphoma, rheumatoid arthritis (RA), and lupus who received other immunosuppressive treatments in addition to rituximab.[70-72] However, long-term treatment with rituximab has recently been reported to be associated with the risk of a hypo-IgG status and a reduction in antitetanus IgG in NMOSD patients, which indicates the need to monitor total and specific IgG levels before and during treatment with rituximab.[73]

OCRELIZUMAB

Ocrelizumab (Ocrevus®) is a humanized IgG1 anti-CD20 mAb that causes depletion of CD20+ B lymphocytes via ADCC and CDC, and plays a greater role of the former mechanism related to a higher affinity for FcγRIII receptors on NK cells. Since ocrelizumab contains more human-derived polypeptides than does rituximab, it is expected to cause fewer allergic reactions or neutralizing Ab responses compared with rituximab.[74] Ocrelizumab was approved by the FDA for treating relapsing MS and PPMS in 2017.[75]

Efficacy for MS

A phase-2 trial assigned RRMS patients at a 1:1:1:1 ratio to receive a low dose (600 mg on days 1 and 15) or a high dose (2,000 mg on days 1 and 15) of ocrelizumab, intramuscular IFNβ-1a, or placebo.[76] Enhanced lesions were reduced by 89% and 96% and the ARR was reduced by 86% and 73% in the low-dose and high-dose ocrelizumab groups, respectively, after 24 weeks.

In 2 identical phase-3 trials that tested ocrelizumab in relapsing MS patients (OPERA I and II), 821 and 835 patients were randomized to receive intravenous ocrelizumab (600 mg every 24 weeks) or subcutaneous IFNβ-1a (44 μg 3 times weekly).[77] The first two doses of ocrelizumab were separated by a 2-week interval. In the ocrelizumab group, the ARR over 96 weeks was 46−47% lower in the ocrelizumab group, while the CDP at 12 and 24 weeks was 40% lower. CD19+ B lymphocytes remained depleted throughout the 96-week investigation. The mean numbers of enhanced lesions and new or enlarged T2-weighted lesions were reduced by 94−95% and 77−83%, respectively. In a recent study analyzing the previous phase-2 and the two OPERA studies, ocrelizumab consistently showed a rapid efficacy onset for both clinical and MRI measures of acute disease activity (as early as 4 weeks after treatment initiation).[78]

The efficacy of ocrelizumab for PPMS was also tested in the ORATORIO study.[79] This study assigned 732 patients to receive intravenous ocrelizumab (600 mg) (n=488) or placebo (n=244) every 24 weeks for at least 120 weeks and until a prespecified number of confirmed progressions in EDSS had occurred. In weeks 12 and 24, the relative risk reductions in EDSS progression were 24% (32.9% vs. 39.3%) and 25% (29.6% vs. 35.7%), respectively, in the ocrelizumab group compared with the placebo group. By week 120, the worsen-

ing of performance in the timed 25-foot walk had decreased (38.9% vs. 55.1%) and the mean total volume of T2-weighted hyperintensities had reduced (mean changes of -3.4% vs. 7.4%) in the ocrelizumab group. The percentage of brain volume loss from weeks 24 to 120 was also reduced (-0.90% vs. -1.09%).

Safety profile

The phase-2 study found serious AEs in 2 of 54 (4%) patients in the placebo group, 1 of 55 (2%) in the 600-mg ocrelizumab group, 3 of 55 (5%) in the 2,000-mg ocrelizumab group, and 2 of 54 (4%) in the IFNβ-1a group.[76] One patient in the 2,000-mg group died at week 14 from sudden delirium and status epilepticus, followed by systemic inflammatory response syndrome; however, it was unclear if this was related to the ocrelizumab treatment.

In the OPERA I and II studies, any serious AEs occurred in 6.9−7.0% of patients in the ocrelizumab group and in 7.8−9.6% of those in the IFNβ-1a group, while neoplasms occurred in 0.5% and 0.2%, respectively.[77] The ORATORIO study of PPMS patients found no clinically significant difference between groups in the rates of serious AEs and serious infections. However, neoplasms occurred in 2.3% and 0.8% of patients in the ocrelizumab and placebo groups, respectively.[79]

OFATUMUMAB

Ofatumumab (Arzerra®) is a fully human IgG1 mAb targeting CD20. It binds to a small-loop epitope of CD20 close to the cell surface, efficiently inducing ADCC and CDC even when there is a low expression of CD20.[80,81] Intravenous ofatumumab was approved for treating chronic lymphocytic leukemia.[82] Two phase-3 studies [ASCLEPIOS I (NCT02792218) and ASCLEPIOS II (NCT02792231)] are currently recruiting relapsing MS patients.

Efficacy for MS

In a small phase-2, 48-week dose-escalation study, 38 RRMS patients received 2 intravenous doses ofatumumab (100, 300, or 700 mg) (*n*=8, *n*=11, and *n*=7, respectively) or placebo (*n*=4, *n*=4, and *n*=4, respectively) separated by 2 weeks.[83] At week 24 the patients received the alternate treatment. Ofatumumab treatment induced a profound selective reduction in CD19+ B lymphocytes. The intravenous ofatumumab resulted in a huge reduction (>99%) in the rate of formation of new MRI lesions during the first 24 weeks at all doses and significant reductions in new enhanced lesions, total enhanced lesions, and new and/or enlarged T2-weighted lesions.

In the phase-2b, 48-week MIRROR study, RRMS patients (*n*=232) received subcutaneous ofatumumab (3, 30, or 60 mg) every 12 weeks (*n*=34, *n*=32, and *n*=34, respectively), 60 mg of ofatumumab every 4 weeks (*n*=64), or placebo (*n*=67) over a 24-week treatment period.[82] The cumulative number of new enhanced lesions was reduced by 65% in all of the ofatumumab groups compared with the placebo group between weeks 0 and 12. CD19+ B lymphocytes were depleted in a dose-dependent manner.

Safety profile

The most-common AE in the phase-2 study was infusion-related rash.[83] Two patients discontinued treatment due to infusion reactions that occurred after their first infusion of ofatumumab, such as rash, bronchospasm, cough, edema, erythema, nasal congestion, and pruritus. Serious AEs were reported in two patients during the first 24 weeks (influenza and headache), but neither was related to the ofatumumab treatment. During the second period, one serious AE in a patient with anemia caused by prolonged menstrual bleeding was reported.

During the three periods (weeks 0−12, 12−24, and 24−48) of the MIRROR study, AEs occurred in 50−74% of patients in the ofatumumab group and 53−64% of those in the placebo group.[82] The most-common AEs were injection-related reactions (52% and 15% of AEs in the ofatumumab and placebo groups, respectively). The incidence rates of serious AEs were 3%, <1%, 4%, and <1% during weeks 0−12, 12−24, and 24−48 and the individualized follow-up phase, respectively. Opportunistic infection or hepatitis B reactivation was not reported. The treatment was discontinued because of AEs in eight patients, mostly due to infusion-related reactions (*n*=2) and decreased IgG (*n*=2).

INEBILIZUMAB

Inebilizumab is a humanized IgG1 mAb against CD19 expressed on B lymphocytes. Compared with CD20, CD19 is expressed on a broader range of B-lymphocyte types, from earlier to later stages of the development and maturity of B lymphocytes.[84,85] Inebilizumab induces the depletion of B lymphocytes and is believed to be efficacious for B-lymphocyte-related malignancies, such as B-lymphocyte non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and autoimmune diseases.[74]

Efficacy for MS

Only one phase-1 study using inebilizumab in RRMS has been reported.[86] That study randomized 28 patients to receive inebilizumab (*n*=21; 2 intravenous doses on days 1 and 15 of 30, 100, or 600 mg, or a single subcutaneous dose on day 1 of

60 or 300 mg) or a matching placebo (n=7). They were followed up for at least 24 weeks or until the CD19+ B-lymphocyte count had recovered to at least 80 cells/μL. B-lymphocyte counts were completely depleted at all doses. Over 24 weeks, inebilizumab reduced the number of cumulative new enhanced lesions (0.1 vs. 1.3) and new or newly enlarged T2-weighted lesions (0.4 vs. 2.4) compared with placebo.

Efficacy for NMOSD

The multicenter, randomized, double-blind placebo-controlled phase-2/phase-3 N-MOmentum study assigned 230 NMOSD patients to intravenous inebilizumab (300 mg on days 1 and 15) (n=174) or placebo (n=56).[87] AQP4 Ab seropositivity occurred in 91.2% of the patients: 91.4% and 90.0% in the inebilizumab and placebo groups, respectively. The randomized controlled period for each participant was up to 197 days or until the occurrence of an adjudicated attack. This was followed by an open-label period of at least 1 year. The randomized controlled period was discontinued before complete enrollment because the efficacy had been clearly demonstrated. Twenty-one (12%) patients in the inebilizumab group and 22 (39%) in the placebo group experienced relapse (hazard ratio=0.272). Throughout the study period (i.e., randomized and open-label periods), inebilizumab reduced the risk of NMOSD attacks by 77.3% relative to placebo, the risk of worsening disability by 63%, and new MRI lesions by 43%.

Safety profile

Serious AEs occurred in three patients treated with inebilizumab in the phase-1 study of RRMS: pyrexia, UTI, and mixed-drug intoxication.[86] The last case resulted in death, but this was not related to inebilizumab. Infusion-/injection-related reactions occurred in 6 of 15 patients receiving intravenous inebilizumab, 2 of 5 patients receiving intravenous placebo, and 1 of 6 patients receiving subcutaneous inebilizumab.

In the N-MOmentum study, AEs occurred in 72% and 73% of patients in the inebilizumab and placebo groups, respectively,[87] with these being serious in 5% and 9% of patients. No serious AE was reported in more than one patient. Two deaths occurred during the open-label period. One patient in the placebo group died from pneumonia. The other deceased patient was in the inebilizumab group: she received 300 mg of inebilizumab on days 1 and 15 and an additional 300 mg at the beginning of the open-label period. On day 9 of the open-label period, she experienced weakness and aphasia with neurological decline and seizures, suffered respiratory arrest, and died of cardiopulmonary complications of mechanical ventilation. A clear diagnosis was not made, but the differential diagnosis included PML, acute disseminated encephalomyelitis, and atypical NMOSD attack.

UBLITUXIMAB

Ublituximab is a novel glycoengineered chimeric IgG1 mAb against CD20 that is currently being investigated in the phase-3 ULTIMATE study for MS. It is designed to have a low fucose content in its Fc region, leading to enhanced affinity for FcγRIIIa (CD16) and facilitating more-efficient NK-cell-mediated ADCC.[88] One particular benefit is that it has a short infusion time of 1−2 hours.

Efficacy for MS

A phase-2 study of relapsing MS enrolled 48 patients, and ublituximab was infused on days 1 and 15 and during week 24.[89] The optimal dose was determined by comparing the efficacy of B-lymphocyte depletion and the safety and tolerability (450 or 600 mg over an infusion time of 1−4 hours). The median amount of B-lymphocyte depletion was more than 99% at week 4 (the primary analysis point), and this was maintained at weeks 24 and 48, with no significant differences between the cohorts. A particularly interesting finding was that the T lymphocytes showed a population shift toward naïve and regulatory phenotypes. Reductions were observed in enhanced T1-weighted lesions (by 100% at weeks 24 and 48) and the mean T2-weighted lesion volume (by 8% and 10% at weeks 24 and 48, respectively). The ARR was 0.07 for all patients, and sustained disability progression was not observed in any patients.

Efficacy for NMOSD

The efficacy of ublituximab in acute relapse of AQP4-IgG-seropositive NMOSD has also been investigated in an open-label phase-1b trial.[90] The five included NMOSD patients comprised four with transverse myelitis and one with optic neuritis. On days 1−5 of admission the patients received 1,000 mg of intravenous methylprednisolone, and a single dose of 450 mg of ublituximab was infused within 5 days of relapse onset. The median EDSS scores decreased from 6.5 at admission to 4.0 at the 90-day follow-up. Two patients did not achieve complete B-lymphocyte depletion and exhibited relapses within 3 months.

Safety profile

No serious AEs (including opportunistic infections) occurred in the phase-1b study of NMOSD, but one patient experienced transient leukopenia.[90]

ECULIZUMAB

Eculizumab (Soliris®) is a humanized IgG2/IgG4-hybrid mAb against C5 (complement component 5) that prevents its cleavage into C5a (a potent chemoattractant and activator of neutrophils) and C5b (which coordinates the formation of the membrane attack complex C5b-9 on the cell surface).[91,92] The C5b-9 complex has a strong potential to destroy target cell membranes. Eculizumab has been approved for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.[74]

Efficacy for NMOSD

The findings of an open-label longitudinal study suggested that eculizumab was effective in 14 female NMOSD patients who showed AQP4-IgG positivity.[93] Eculizumab at a dose of 600 mg was infused weekly for 4 weeks, followed by a 900-mg dose in the fifth week and then a dose of 900 mg every 2 weeks for 48 weeks. Only two patients experienced possible clinical attacks during 12 months of treatment. The median ARR decreased from 3 (range=2−4) before treatment to 0 (range=0−1) during treatment. No patient exhibited worsened disability, and the median EDSS score improved from 4.3 (range=1.0−8.0) before treatment to 3.5 (range=0−8.0) during treatment.

A recent randomized, double-blind, time-to-event trial (the PREVENT study) assigned 143 AQP4-IgG-seropositive NMOSD patients to receive either intravenous eculizumab (900 mg weekly for 4 weeks, followed by 1,200 mg every 2 weeks) (*n*=96) or matched placebo (*n*=47).[92] The continuation of immunosuppressive therapy at a stable dose was permitted. The trial was stopped after 23 of the 24 prespecified adjudicated relapses occurred due to the uncertainty in estimating when the final event would occur. Adjudicated relapses were experienced by 3 patients (3%) in the eculizumab group and 20 (43%) in the placebo group. The adjudicated ARRs were 0.02 and 0.35 in the eculizumab and placebo groups, respectively, while the mean EDSS score decreased by 0.18 in the eculizumab group and increased by 0.12 in the placebo group.

Safety profile

One of the 14 NMOSD patients in the first study experienced meningococcal sepsis and sterile meningitis 2 months after starting the treatment, but resumed treatment after making a full recovery.[93] Since eculizumab inhibits assembly of the C5b-9 complex, the risk of infection by polysaccharide-encapsulated bacteria such as meningococcus, pneumococcus, or *Haemophilus influenzae* is known to increase, and meningococcal vaccination at least 2 weeks before starting eculizumab treatment is highly recommended.[74,94]

In the PREVENT study, AEs including URI and headache were more common in the eculizumab group,[92] while nasopharyngitis, nausea, and diarrhea were also common. Serious AEs occurred in 26% of eculizumab-group patients and 28% of placebo-group patients. There was one death from pulmonary emphysema in the eculizumab group.

TOCILIZUMAB

Tocilizumab (Actemra®, RoActemra®) is a humanized IgG1 mAb directed against the IL-6 receptor (IL-6R), which exists in both soluble and membrane-bound forms. IL-6 is a pleiotropic cytokine that has both proinflammatory and anti-inflammatory functions. It promotes the differentiation of B lymphocytes into plasma cells, activates cytotoxic T lymphocytes, and regulates bone homeostasis. As with other proinflammatory cytokines, IL-6 is implicated in Crohn's disease and RA.[95,96] In NMOSD, IL-6 promotes the differentiation of inflammatory Th17 cells and plasmablasts, leading to production of pathogenic Abs. It also increases the permeability of the blood–CNS barrier, allowing Abs and proinflammatory cells to infiltrate the CNS.[97] Tocilizumab binds to soluble and membrane-bound IL-6R and inhibits their signal transmission. The level of IL-6 in cerebrospinal fluid was reported to be significantly higher in NMOSD,[98] and tocilizumab has recently been suggested as a treatment option for NMOSD.

Intravenous tocilizumab is approved and has demonstrated efficacy and safety in patients with RA. Subcutaneous tocilizumab has demonstrated efficacy with a safety profile similar to that of intravenous tocilizumab, and has been approved by the FDA for the same disease.[99]

Efficacy for NMOSD

There have been no large or randomized controlled clinical trials of tocilizumab in MS or NMOSD. However, some case reports and case series have suggested that tocilizumab reduces the relapse rate and possibly ameliorated neurological disability in NMOSD.[100-104] Most of the reported patients exhibited resistance to previous medications, and tocilizumab was considered to be an alternative second-line treatment.

A case-series study of the long-term safety and efficacy of tocilizumab (at dose of 6−8 mg/kg) included eight highly active AQP4-IgG-seropositive NMOSD patients whose disease had been refractory despite previously taking other medications, including rituximab.[105] The follow-up period was 30.9± 15.9 months after switching to tocilizumab. Two of the eight patients received add-on therapy with temporary monthly high-dose corticosteroid or azathioprine. Tocilizumab treat-

ment reduced the median ARR (from 4.0 to 0.4) and the median EDSS score (from 7.3 to 5.5), and the number of patients with active MRI lesions decreased from six to one. Three patients were relapse-free during treatment with tocilizumab. Five patients experienced a total of eight relapses, with half of them occurring during the first 2.5 months of treatment. Five attacks were associated with the administration of tocilizumab being delayed by more than 40 days, and six attacks were associated with the tocilizumab dose being reduced from 8 to 6 mg/kg. The AQP4-IgG titers and pain levels were also reduced.

Safety profile

In the case-series study of NMOSD, the AEs included elevation of the cholesterol level (*n*=6), infection (*n*=4), deep-vein thrombosis (*n*=1), and neutropenia (*n*=1).[105] The main AEs associated with tocilizumab—previously found during its use for RA—are infusion-related reactions and infection, similar to those of other mAbs. Multiple colon ulcers and diverticulitis, which can cause intestinal perforation, have been reported in RA patients.[106,107] One case report suggested that tocilizumab treatment for RA could trigger the onset of MS.[108]

SATRALIZUMAB

Satralizumab is a humanized IgG2 mAb targeting IL-6R. It was designed to improve the pharmacokinetics of tocilizumab (another mAb against IL-6R) by applying so-called Ab recycling technology,[109] and increases the dissociation of tocilizumab from IL-6R in the endosome in an acidic environment at pH 6.0 while maintaining its binding affinity to IL-6R in plasma at pH 7.4. The pH-dependent dissociation of IL-6R in the endosome leads to lysosomal degradation of the previously bound IL-6R, while releasing the free Ab back into the plasma to bind another IL-6R molecule.

Efficacy for NMOSD

The phase-3 SAkuraSky study evaluated the efficacy and safety of satralizumab (120 mg) in NMOSD as an add-on drug to oral immunosuppressive drugs, including azathioprine, mycophenolate mofetil, and/or corticosteroids.[110] Satralizumab (120 mg) (*n*=41) or placebo (*n*=42) was administered subcutaneously at weeks 0, 2, and 4, and every 4 weeks thereafter.[110] This intervention reduced the overall risk of relapse in the treated group by 62%: by 79% and 34% among AQP4-Ab-positive and -negative patients, respectively. In the satralizumab group, 88.9% and 77.6% of the patients were relapse-free at 48 and 96 weeks, respectively; these proportions were 66.0% and 58.7% in the placebo group.

The SAkuraStar study also compared satralizumab with placebo in NMOSD patients.[111] Satralizumab (120 mg) (*n*=63) or placebo (*n*=32) was administered subcutaneously at weeks 0, 2, and 4, and every 4 weeks thereafter. A reduction of 55% in the risk of relapse was shown for satralizumab versus placebo. In the satralizumab group, 76.1% and 72.1% of the patients were relapse-free at 48 and 96 weeks, respectively, compared with 61.9% and 51.2% in the placebo group. In particular, the reduction was 74% in patients with NMOSD and AQP4-Ab seropositivity. At 48 and 96 weeks, 82.9% and 76.5% of the patients taking satralizumab were relapse-free, respectively, compared with 55.4% and 41.1%, in the placebo group.

Safety profile

In the SAkuraSky study, a rates of AEs and serious AEs were similar in the treatment and placebo groups.[110] Meanwhile, in the SAkuraStar study, the rates of AEs, serious AEs, and serious infections in the treatment group (92.1%, 19.0%, and 9.5%, respectively) were similar to those in the placebo group (75.0%, 15.6%, and 9.4%).[111] Severe AEs were more common in the satralizumab group (27.0% and 6.3%, respectively). However, these AEs were distributed in different system organ classes and had small numbers in each category, making interpretation difficult. One patient in each group withdrew from the study treatment due to an AE.

OPICINUMAB

Opicinumab is a fully humanized mAb against leucine-rich repeat and Ig domain-containing protein-1 (LINGO-1), which is a CNS-specific protein that has a single transmembrane structure and is expressed in neurons and oligodendrocytes.[112] In neurons, LINGO-1 works as an essential coreceptor of the Nogo receptor complex that mediates the inhibition of axonal growth due to regulatory factors present in myelin.[113] By inhibiting LINGO-1, oligodendrocyte precursor cells can differentiate into mature oligodendrocytes and allow for the remyelination of damaged plaques.[114]

Efficacy for MS

Opicinumab was evaluated in the phase-2 RENEW study as an add-on therapy in patients with optic neuritis.[114] After treatment with intravenous methylprednisolone (1 g/day for 3–5 days), intravenous opicinumab (100 mg/kg, *n*=33) or placebo (*n*=36) was infused once every 4 weeks (six doses), and patients were followed up until week 32. The opicinumab group showed improvement in full-field visual evoked responses of 9.1 ms at week 32 in the prespecified per-protocol analyses; however, no significant improvement was found in the intention-to-treat analysis.

The phase-2 SYNERGY study evaluated the efficacy of the coadministration of opicinumab and intramuscular IFNβ-1a in relapsing MS.[115] Patients were randomized at a 1:2:2:2:2 ratio to receive opicinumab at 3 mg/kg (*n*=45), 10 mg/kg (*n*=95), 30 mg/kg (*n*=94), or 100 mg/kg (*n*=92), or placebo (*n*=93). Confirmed disability improvement, as measured by the timed 25-foot walk, nine-hole peg test, and 3-s paced auditory serial addition test over 72 weeks was seen in 49% of patients in the placebo group and in 47%, 63%, 65%, and 40% of those in the 3-, 10-, 30-, and 100-mg/kg opicinumab groups, respectively. A linear dose–response relationship in the probability of confirmed disability improvement was not seen (linear trend test: p=0.89).

An additional study (the AFFINITY study) is underway, which is investigating patients who responded better in the SYNERGY study and includes those with disease activity lasting less than 21 years and who meet protocol-defined MRI criteria for magnetization transfer ratios and diffusion-tensor imaging.[116]

Safety profile

Opicinumab is well tolerated, with the reported AEs being similar in opicinumab and placebo groups. However, some mild hypersensitivity reactions have been reported.[4]

In the SYNERGY study, AEs occurred in 85% of patients assigned any dose of opicinumab and 85% of those assigned placebo.[115] Influenza-like illness, MS relapse, and headache were the most-common AEs. Serious AEs included UTI (in 1% of patients in the placebo group), suicidal ideation and intentional overdose (in 1% of those in the 30-mg/kg opicinumab group), bipolar disorder (in 1% of those in the 100-mg/kg opicinumab group), and hypersensitivity (in 4% of those in the 100-mg/kg opicinumab group).

CONCLUSIONS

Considering that mAbs have a highly specific mechanism of action, these Abs could be promising treatment options with excellent efficacy and safety profiles for patients with MS or NMOSD, especially among those who show poor responses to the present treatments. Promising results have been obtained for several mAbs in clinical trials, and these are expected to receive approval and be used in real-world applications.

Most clinical studies have been performed in adult patients with RRMS or in AQP4-IgG-seropositive NMOSD patients, and data on new treatments are too scarce or not satisfactory for pediatric patients or patients with progressive MS or AQP4-IgG-seronegative NMOSD. In addition, long-term efficacy and safety data are not yet available. Although mAbs function via a specific mechanism of action, long-term suppression or modulation of the immune system may cause various side effects, some of which might be unexpected and serious. Indeed, safety issues have arisen even for previously approved drugs, as described in this review. The excessive cost of new drugs could be another barrier to their utilization.

Regarding that the treatment decisions for each patient must include overall assessments of therapeutic efficacy and effectiveness, long-term safety and tolerability, monitoring, and cost-effectiveness,[117] further studies of mAbs targeting various antigens related to the pathogenesis and recovery of MS and NMOSD are needed.

Author Contributions

Conceptualization: Woojun Kim, Ho Jin Kim. Data curation: Woojun Kim. Funding acquisition: Ho Jin Kim. Investigation: Woojun Kim. Methodology: Woojun Kim. Project administration: Woojun Kim, Ho Jin Kim. Resources: Woojun Kim, Ho Jin Kim. Supervision: Ho Jin Kim. Validation: Woojun Kim, Ho Jin Kim. Writing—original draft: Woojun Kim. Writing—review & editing: Woojun Kim, Ho Jin Kim.

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Conflicts of Interest

Kim W reports no financial disclosures. Kim HJ received a grant from the National Research Foundation of Korea; received consultancy/speaker fees from Alexion, Celltrion, Eisai, HanAll BioPharma, Merck Serono, Novartis, Sanofi Genzyme, Teva-Handok, and Viela Bio; serves on a steering committee for MedImmune/Viela Bio; is a co-editor for the *Multiple Sclerosis Journal* and an associated editor for the *Journal of Clinical Neurology*.

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