Monoclonal antibodies in neuro-ophthalmology

Caroline C. Keehn[1], Arman Yazdian[1], Patrick J. Hunt[1], Pamela Davila-Siliezar[2], Noor A. Laylani[2], Andrew G. Lee[1,2,3,4,5,6,7,8]

Access this article online

Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/sjopt.sjopt_256_23

Abstract:

Neuro-ophthalmologic diseases include a broad range of disorders affecting the afferent and efferent visual pathways. Recently, monoclonal antibody (mAb) therapies have emerged as a promising targeted approach in the management of several of these complex conditions. Here, we describe the mechanism-specific applications and advancements in neuro-ophthalmologic mAb therapies. The application of mAbs in neuro-ophthalmologic diseases highlights our increasing understanding of disease-specific mechanisms in autoimmune conditions such as neuromyelitis optica, thyroid eye disease, and myasthenia gravis. Due to the specificity of mAb therapies, applications in neuro-ophthalmologic diseases have yielded exceptional clinical outcomes, including both reduced rate of relapse and progression to disability, visual function preservation, and quality of life improvement. These advancements have not only expanded the range of treatable neuro-ophthalmologic diseases but also reduced adverse events and increased the response rate to treatment. Further research into neuro-ophthalmologic disease mechanisms will provide accurate and specific targeting of important disease mediators through applications of future mAbs. As our understanding of these diseases and the relevant therapeutic targets evolve, we will continue to build on our understanding of how mAbs interfere with disease pathogenesis, and how these changes improve clinical outcomes and quality of life for patients.

Keywords:

Biologicals, giant cell arteritis, myasthenia gravis, neuromyelitis optica, thyroid eye disease

[1]Department of Ophthalmology, Baylor College of Medicine, [2]Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, [3]Department of Ophthalmology, The University of Texas MD Anderson Cancer Center, Houston, [5]Department of Ophthalmology, University of Texas Medical Branch, Galveston, [6]Department of Ophthalmology, Texas A and M College of Medicine, Bryan, Texas, [4]Departments of Ophthalmology, Neurology, and Neurosurgery, Weill Cornell Medicine, New York, [7]Department of Ophthalmology, University of Buffalo, Buffalo, NY, [8]Department of Ophthalmology, The University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Address for correspondence:
Dr. Andrew G. Lee, Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, 6560, Fannin St., Ste. 450, Houston 77030, Texas, USA.
E-mail: aglee@houstonmethodist.org

Submitted: 15-Oct-2023
Revised: 12-Nov-2023
Accepted: 14-Nov-2023
Published: 29-Mar-2024

History of Development

Monoclonal antibody (mAb) therapy has only recently been harnessed for disease management. However, in this short time, these customizable pharmaceuticals have proven to be uniquely effective in treating a variety of difficult oncologic and autoimmune diseases. Dr. Edward Jenner was the first to document the use of antibodies through immunization by inoculating a patient with small pox pustular fluid in 1796.[1] Nearly 200 years later, in 1975, the hybridization of murine myeloma cells and splenic B lymphocytes was used to mass-produce clones of a single antibody. These mass-produced mAbs became the first generation of customizable immunologic therapies.[2]

Soon after clinical use of mAbs began, patients developed human anti-murine antibodies and anaphylactic reactions. These events drove the development of chimeric mAbs followed by humanized mAbs, wherein the crystallizable fragment (Fc) of human antibodies replaced that of murine origin, and murine protein loops were incorporated into human immunoglobulins, respectively. Many modern mAbs are made entirely of human proteins by recombinant DNA methods, eliminating the risk of adverse reactions to murine components.[3] Common mAb suffixes, such as -omab, -ximab, -zumab, and -umab, are used to differentiate their origins among murine, chimeric, humanized, and human, respectively [Table 1].[4]

Pharmacology and Function

Immunoglobulin (Ig) G is currently the only Ig used in mAb therapy, despite the existence of four other types of Igs: IgM, IgD, IgE, and IgA. The stability and pharmacokinetics of IgG are the best suited for mAb functions.[5] Four isotypes or subtypes of IgG Ig exist, IgG1, IgG2, IgG3, and IgG4. These isotypes activate complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) to varying extents.

How to cite this article: Keehn CC, Yazdian A, Hunt PJ, Davila-Siliezar P, Laylani NA, Lee AG. Monoclonal antibodies in neuro-ophthalmology. Saudi J Ophthalmol 2024;38:13-24.

Table 1: Substems and stems that comprise the monoclonal antibody names found within this review

Prefix	Target substem	Meaning	Source substem	Meaning	Stem	Meaning
Varies	-ci-	Cardiovascular	-u-	Human	-mab	Monoclonal antibody
	-l-	Immunomodulating	-xi-	Chimeric		
	-li-					
	-tu-	Tumor	-zu-	Humanized		
	-tum-					

Note that the nomenclature continues to be updated and that these conventions represent the time during which the discussed antibodies were named

IgG antibodies consist of two heavy and two light chains, both of which contain constant and variable domains. The Fc region of Ig is made of only heavy chains. This portion determines the effector function of the mAb through its ability to bind to the Fc gamma receptor (FcγR). When a mAb binds to the FcγR of immune cells, CDC and ADCC become activated.[3,6,7] The complementarity-determining region (CDR) is found within the antigen-binding fragment and directly binds to a pathogen's epitope. The CDR can be altered to recognize and bind any epitope, providing high specificity and affinity for a given target. The CDR allows mAbs to target-specific cells or markers while eliminating the risk of additional, unintended interactions.[3]

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease defined by clinical symptoms corresponding to demyelinating lesions which are disseminated in space and time, within the brain, optic nerve, and spinal cord.[8] The onset of MS typically occurs between 20 and 40 years of age and can present with neurological symptoms ranging anywhere from isolated incontinence or nystagmus to a simultaneous constellation of symptoms. Clinical symptoms of MS are the result of myelin destruction and axonal damage within a localized region of the central nervous system (CNS). Lesions most often affect the brainstem, cerebellum, spinal cord, and optic nerve, as well as periventricular and juxtacortical areas of the brain.[9-11]

MS manifests as a variety of neuro-ophthalmologic symptoms, which can be categorized into afferent or efferent symptoms and signs.[10] The most common ophthalmologic presentation of MS is optic neuritis (ON), defined as inflammation of the optic nerve. In patients with MS, ON is most often unilateral and begins with declining vision over the first 7–10 days from symptom onset and typically plateaus by 2 weeks. Other common symptoms of ON are pain, particularly in eye movements, visual acuity and visual field loss, reduced contrast sensitivity, and an ipsilateral relative afferent pupillary defect in the affected eye. Typically, the optic nerve appears normal (retrobulbar ON), but optic disc edema may also occur. Because they are relatively uncommon in MS-related ON, bilateral ON and optic disc edema should prompt consideration for alternative antibody-mediated ON (e.g., neuromyelitis optica spectrum disorder [NMOSD] and myelin oligodendrocyte glycoprotein antibody-associated disease [MOGAD] ON). Patients with ON typically recover over several weeks to months from onset.[10,12]

Lesions of the efferent visual pathway (e.g., brainstem or cerebellum) in MS can produce diplopia or oscillopsia. The most common efferent presentation of MS is an internuclear ophthalmoplegia (INO) from a demyelinating lesion of the medial longitudinal fasciculus (MLF). The MLF contains nerve fibers that facilitate CNVI communication with CNIII for conjugate horizontal movement. Demyelination and inflammation at the MLF cause impaired adduction of the eye ipsilateral to the lesion and a dissociated horizontal nystagmus of the contralateral eye during abduction. Other less common efferent manifestations of MS include other ocular motor cranial neuropathies from fascicular involvement in the brainstem or new-onset nystagmus. Rarely, MS can also present with uveitis (e.g., pars planitis) or periphlebitis.[11]

The revised McDonald criteria for MS, last updated in 2017,[13] include radiographic lesions on magnetic resonance imaging (MRI) of the brain and spinal cord and clinical symptoms and signs of dissemination in time and space. MS is typically divided into four subcategories based on a pattern of relapse and disease progression.[14,15] These subtypes, relapse-remitting, primary progressive, secondary progressive, and clinically isolated syndrome (CIS), were established in 2013 after the revision of the previous subcategorization.[14,16] Criteria for the (CIS) subtype include imaging and clinical history consistent with a first-time attack where MRI and historical evidence of previous demyelinating episodes is lacking. In primary progressive MS, patients do not show acute exacerbations, instead, gradual, continuous decline in neurological function is observed. The most common of the subtypes, relapsing-remitting MS, is defined by acute exacerbations of new or worsening symptoms with or without complete recovery between events. This disease course can convert to the fourth subtype, secondary progressive MS, wherein patients experience a continuous neurological decline, with or without exacerbations.[14,15,17]

Currently, the pathogenesis of MS appears to be multifactorial and the clinical course is quite variable.[13] Proposed environmental risk factors for MS include obesity, smoking, Epstein–Barr virus exposure, gut microbiome composition, serum Vitamin B levels, and serum Vitamin D levels.[8,18] The latter has been shown to have an inverse correlation with latitude, in the context of MS risk factors.[8] The non-modifiable risk factors are genetic and include female sex, as well as the presence of human leukocyte antigen (HLA)-DR15 on CD4+ T cells and HLA-A3 and HLA-B7 on CD8+ T cells.[18,19] In contrast, HLA-A2 on CD8+ T cells appears to be protective against developing MS.[19]

Several cell types and their products have been identified for their pro- and anti-inflammatory roles in MS disease. Immune dysregulation in MS is believed to be mediated primarily by T cells.[18] Peripherally, CD4+ T cells are exposed to self-antigens of the CNS, resulting in T lymphocyte recruitment to the CNS.[8,18] Several studies have identified aberrant T regulatory cells (Treg) in MS as possible culprits in peripheral T-cell self-antigen recognition. Aberrant Tregs are unable to produce an appropriate amount of their anti-inflammatory products, interleukin (IL)-10 and transforming growth factor (TGF)-β.[18,20] As a result, myelin-reactive CD4+ cells cannot be suppressed peripherally.[18] T lymphocyte infiltration into the CNS requires interactions with endothelial cellular adhesion molecules, such as lymphocytic integrin α4β1 (very late antigen-4 or VLA4) and endothelial vascular cell adhesion molecule 1 (VCAM-1), to bypass the blood brain barrier (BBB).[21,22] Several CNS self-antigens have been identified as targets of these aberrant T cells in various diseases including myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG).[23-25] On aberrant T-cell recognition of CNS self-antigen, macrophages, and microglia are activated, further propagating localized myelin destruction, axonal damage, and BBB disruption. Myelin damage then triggers Th1 and Th17 pro-inflammatory cell activation. Th1 and Th17 continue to propagate the pro-inflammatory state by releasing interferon (IFN)-γ and IL-17, respectively. Despite the prominent role of CD4+ in MS, CD8+ T cells are found in greater numbers at the site of acute inflammation.[8,18] These CD8+ T cells, which are found at the lesion and within cerebrospinal fluid (CSF), appear to have an oligoclonal expansion which suggests antigen-driven selection. Finally, these cells propagate inflammation by producing granzyme B, IFN-γ, and IL-17.[26] In contrast to an increase in pro-inflammatory cells, anti-inflammatory cells, Th2 and Th9, appear to have low serum counts in states of acute MS exacerbations.[27]

The most well-understood role of B cells in MS is the production of antibodies to self-antigens, such as anti-MBP antibody, which are released during myelin destruction. This proposed mechanism is supported by the fact these antibodies exhibit clonotypic expansion seen in the CNS and CSF.[18,28,29] Alternatively, peripheral memory B cells may be aberrant and trigger MS by presenting a self-antigen to autoreactive CD4+ T cells.[30] Evidence of other B-cell roles in MS, including antibody-independent mechanisms, is supported by B-cell depletion through Rituximab, resulting in reduced rates of relapse. Despite B-cell depletion, abnormal antibodies in the CSF persisted.[31] This reduced relapse rate secondary to B cell depletion may be attributed to a lack of circulating B cell inflammatory products, TNF-α, IL-6, and granulocyte-macrophage colony-stimulating factor.[32,33] B regulatory (Breg) cells, which produce anti-inflammatory IL-10, TGF-β, and IL-35, also appear to be reduced in MS.[28]

Treatment of MS includes acute treatment (intravenous steroids) to accelerate recovery time and chronic disease-modifying therapy (DMT) to reduce disease relapse. High-dose, short-term, IV methylprednisolone is the first-line treatment of acute MS attacks. Because this treatment period is short, infection risk is lower compared to risk during chronic glucocorticoid use. Plasma exchange serves as second-line therapy when patients do not respond appropriately to IV methylprednisolone.

Traditional DMT for MS includes injectable recombinant human IFNβ-1a/b and glatiramer acetate and oral medications such as dimethyl fumarate and cladribine.[34] Although these are effective in reducing the number of lesions, relapse rate, and progression to disability, they are limited in their ability to target key players of MS disease progression.

Natalizumab is a humanized, second-generation mAb that targets the lymphocyte-endothelial cell interaction, preventing transcytosis.[21] This mAb is the first in the class of selective adhesion molecule inhibitors. Natalizumab specifically targets α1 β4 integrin on lymphocytes, thereby preventing transcytosis through interaction with VCAM-1 on endothelial cells. Without lymphocyte transcytosis, inflammation is reduced and new lesions are prevented.[35] Natalizumab significantly reduces both the rate of MS relapse and disease progression.[36]

The most common adverse effects of natalizumab include infusion-related symptoms, infections, arthralgias, gastroenteritis, depression, and rash. Although rare, the risk of progressive multifocal leukoencephalopathy (PML), a potentially fatal disease caused by JC virus reactivation, is associated with the use of natalizumab.[37] A prospective study designed to evaluate the long-term safety of natalizumab reported <0.5% of patients developed PML and most patients tolerated natalizumab well throughout the 10-year period.[38] Ofatumumab, ocrelizumab, and rituximab are all CD20+ B-cell-depleting mAbs used in MS management. Ocrelizumab and ofatumumab were approved by the United States Food and Drug Administration (FDA) for the management of MS in 2017 and 2020, respectively. Rituximab has been used as an off-label therapy for MS before the approval of other B-cell-depleting therapies.[39,40]

Neuromyelitis Optica Spectrum Disorder

NMOSD is an antibody-mediated autoimmune disease of the CNS, preferentially affecting the optic nerve and spinal cord.[41] Recently, an antibody found in the serum of patients with NMOSD was identified as aquaporin-4 (AQP4)-IgG antibody. The AQP4 auto-antibody targets a specific water channel found in high concentrations at astrocytic end-feet and ependymal cells of the CNS.[42] Although this antibody is quite specific for NMOSD, diagnosis of NMOSD can be made in the absence of AQP4-IgG when appropriate clinical criteria are met (seronegative NMOSD). There are six core clinical criteria for the overall diagnosis of NMOSD: ON, acute myelitis, area postrema syndrome (APS), symptomatic narcolepsy or acute diencephalic syndrome with consistent imaging, or symptomatic cerebral syndrome with consistent

imaging. Diagnosis of NMOSD with AQP-4 IgG can be made when at least one of the six core clinical criteria is met, and serology is positive for AQP-4 IgG. In cases of NMOSD without AQP-4 IgG, at least two of the six core clinical criteria must be met as a result of one or more clinical attacks. One of the two clinical criteria must be either ON, acute myelitis with longitudinally extensive transverse myelitis (LETM), or APS.[43] In both cases, alternative diagnoses must be ruled out as well.[44]

Since identifying NMOSD as a separate disease from MS, several revisions to the clinical manifestations have been published.[45] In contrast to MS, NMOSD often involves a long spinal cord segment and LETM, evident on T2 weighted spinal MRI.[46,47] Other sites of inflammation characteristic of NMOSD correspond to areas where AQP-4 has the highest concentration, such as the optic nerve and area postrema.[48] The involvement of the area postrema presents with either intractable hiccups or vomiting, these clinical symptoms favor NMOSD over MS, as this involvement is consistent with APS.[49] Other clinical presentations that favor diagnosis of NMOSD over MS include new onset narcolepsy, thermal dysregulation, and autonomic dysregulation such as bradycardia or hypotension. These symptoms may correspond to inflammation of the hypothalamus and can be confirmed through MRI.[50,51] Finally, ON in NMOSD is often unilateral, however, rapidly sequential or simultaneously bilateral ON is highly suggestive of this disease.[52] Brain imaging of patients with NMOSD often does not show demyelinating lesions. Instead, the spinal cord and optic nerve, if involved, may be the only sites of radiologically evident inflammation.[53]

NMOSD predominantly occurs in females between 30 and 55 years of age.[54,55] Patients commonly present with a relapsing course, but monophasic disease courses have been reported.[46,56] The presence of AQP4-IgG is associated with a greater risk of relapse compared to those seronegative for AQP4-IgG.[45] Other epidemiologic risk factors include Asian descent and elder patients of African descent.[55,57] Importantly, treating a patient with NMOSD during or after pregnancy can be especially challenging, as many DMTs, including methotrexate, azathioprine, and mycophenolate are contraindicated in pregnant patients. This creates an increased dependence on mAbs for the treatment of pregnant patients. Although direct clinical trial data demonstrating the safety and efficacy of mAbs in treating pregnant patients is limited, several reports demonstrate positive outcomes when taking rituximab during pregnancy.[58-60] Larger studies are necessary to fully understand the safety and efficacy of mAb treatment in pregnant patients with NMOSD.

The discovery of AQP4-IgG shifted our understanding of NMOSD from a demyelinating disease to an astrocytopathy with consequential myelin and neuronal dysfunction.[61] Histologically, CNS lesions are characterized by perivascular complement, IgG, and IgM deposition in a rosette pattern with hyalinized vessels. Cellular components include neutrophils, eosinophils, macrophages, and microglia.[62]

B cells play a major role in the initiation and maintenance of NMOSD. Evidence suggests initial AQP4-IgG production occurs through peripheral B cells, as these antibodies are found in both CSF and serum in the majority of cases.[63,64] These peripheral cells are phenotypically AQP4-IgG secreting plasmablasts, and are stimulated in response to IL-6.[24,65] AQP4-IgG is believed to enter the CNS through either a damaged BBB or circumventricular organs, where the BBB is absent, but AQP4 is still expressed.[63] Once beyond the BBB, AQP4-IgG binds to the AQP channel on astrocytes. Before astrocytes die in response to events following AQP4-IgG binding, they play a crucial role in initiating the complement cascade.[66] Notably, plasmablasts found within the CNS also exhibit clonal expansion, suggesting CNS AQP4 antigen-driven selection. Further, CNS-infiltrating eosinophils release IL-6, which further stimulates AQP4-IgG production by local plasmablasts.[65,67] In addition to auto-antibody production, B cells are crucial to the maintenance of NMOSD through their role as antigen-presenting cells within the CNS.[24]

T cell contribution to NMOSD also begins peripherally, as AQP4-specific CD4+ T cells are required for the production of AQP4-IgG.[63] A growing body of research indicates AQP4 stimulation through AQP4-IgG drives the production of the pro-inflammatory cell, Th17.[68] Pro-inflammatory cytokines IL-6, IL-17, and IL-21 are produced by Th17 as a result. IL-17 facilitates BBB damage, leading to endothelial activation and further neutrophil/lymphocyte transmigration.[69] IL-6 within the CNS shifts the balance between Treg and inflammatory T cells toward AQP4-specific CD4+ T cell production, further feeding the ongoing cycle of inflammation.[68]

The role of innate immunity in NMOSD begins after AQP4-IgG binds to AQP4 on astrocytes. Astrocytes produce large quantities of C3 in response to bound AQP4-IgG, thus triggering the start of CDC. C3 then activates microglia by binding to its C3a receptor.[66] Microglia produce C1q, which contributes to disease propagation in two ways. The first is through axonal damage and subsequent neurodegeneration which occurs independent of the complement cascade. The second is through the classical complement pathway during which C1q binds to IgG or IgM antigen-antibody complexes, resulting in membrane attack complex (MAC) formation.[66,70] Other products of complement activation, C3a, and C5a, contribute to BBB permeability and act as chemokines for several granulocytes. Eosinophil and neutrophil recruitment by their chemokines, including C5a and C3a, allows ADCC to begin.[66] These granulocytes bind the Fc region of AQP4-IgG, causing degranulation and neuronal damage, leading to the formation of characteristic NMOSD lesions. Results of complement and antibody involvement in NMOSD are evident in histology through vascular fibrosis and hyalinization as well as perivascular immune and complement deposition.[71]

Classes of mAbs used in the long-term management of NMOSD include complement inhibitors (eculizumab), B cell and precursor B cell inhibitors (e.g., rituximab, ublituximab, and inebilizumab), and IL-6 inhibitors (e.g., tocilizumab

and satralizumab).[58,68] Complement inhibitors as well as B cell and precursor B cell inhibitors are discussed in other sections of this review. Tocilizumab and satralizumab are humanized IL-6 inhibitors approved as long-term therapies for patients with NMOSD. Both mAbs bind to the IL-6 cytokine, blocking its ability to trigger downstream inflammatory mechanisms.[68] Satralizumab works specifically by antagonizing and internalizing IL-6, reversing external expression of the receptor, and has been shown to have a greater affinity to IL-6 compared to tocilizumab.[72]

Satralizumab is now the first IL-6 receptor (IL-6R) antagonist FDA approved for the treatment of NMOSD.[73] Clinical trials reported a significant reduction in relapses compared to placebo and no anaphylactic reactions, opportunistic infections, or deaths. Overall, patients tolerated satralizumab well in these studies.[74,75]

Common adverse events include nasopharyngitis, headaches, upper respiratory infections, gastritis, rash, arthralgias, and fatigue. Contraindications to satralizumab include hypersensitivity reaction to the medication, active hepatitis B, and active or latent TB infections. Patients must be screened for these infections before starting therapy. Liver enzymes, platelet count, and neutrophil count should be monitored during early treatment.[76]

Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease

MOGAD is an antibody-mediated demyelinating disease of the optic nerves, brain, and spinal cord.[77] MOGAD was recently recognized as separate from MS and NMOSD after the characterization of the responsible antigen-antibody interaction in 2007.[78,79] MOGAD is characterized by IgG antibodies against the oligodendrocyte surface antigen, MOG.[80]

MOGAD affects both the pediatric and adult populations at relatively equal rates, with one study showing a predilection for pediatric populations. However, clinical presentation and incidence of MOG-IgG seropositivity differs among these populations. In addition, this disease affects men and women at equal rates.[81,82] The clinical course of MOG begins with acute onset of unilateral or bilateral symptoms of ON, altered mental status as a result of acute disseminated encephalomyelitis, and/or symptoms of transverse myelitis including incontinence, sexual dysfunction, or limb weakness.[77] Symptoms progress in severity until peaking after several days. Recovery from these episodes can take weeks to months. Relapse episodes are typical and the risk of relapse is greater in adult patients compared to pediatric patients.[83,84] Current diagnostic criteria suggest some MOGAD patients may also meet the criteria for the syndrome of NMOSD without AQP4-IgG, defined as transverse myelitis and ON with or without other CNS region involvement.[85]

Diagnostic criteria differ depending on the presence of MOG-IgG. For patients strongly positive for MOG-IgG, the presence of at least one of six core clinical demyelinating events must also be present. In cases where MOG-IgG is present but does not meet strongly positive criteria, an additional supportive MRI finding and seronegative AQP4-IgG test are required for diagnosis.[86]

The pathogenic mechanism of MOGAD has not been clearly defined. However, postinfection autoimmunity, by a pathogen yet to be identified, is believed to contribute to onset.[87] The MOG antigen in humans likely contributes to myelin maintenance and cell-to-cell communication, although this has not been formally established.[88] Th17 cytokine and chemokines present in MOGAD indicate a possible role for Th17, Th1, Treg, and B cells in MOGAD pathogenesis.[89]

DMTs are reserved for patients with relapsing MOGAD.[90] mAb therapies have not been approved for MOGAD maintenance as of the date of this manuscript's writing. However, off-label use of tocilizumab, an IL-6 inhibitor, and rituximab, a CD20+ B cell antagonist, are not uncommon in MOGAD. Rituximab appears to be less effective as a DMT of MOGAD, as relapses have been reported in roughly half of patients using this DMT.[91] Other B cell-depleting therapies, such as the CD19+ antagonist inebilizumab, are being considered for future studies, but are expected to have similar results. Rozanolixizumab is another mAb being considered for future management in MOGAD. Rozanolixizumab works by blocking the neonatal Fc receptor and facilitates pathogenic antibody degradation. The randomized clinical control trial for its use in MOGAD is currently underway.[77] Several small case-series have reported clinical and radiological evidence of complete MOGAD relapse prevention on tocilizumab. These results help clinicians and scientists better understand the role of IL-6 in MOGAD and offer an optimistic future of relapse prevention in MOGAD.[92]

Giant Cell Arteritis

Giant cell arteritis (GCA) is a chronic granulomatous inflammatory disease that primarily affects large-and medium-sized arteries and is the most prevalent systemic vasculitis, presenting most often in patients 50 years of age or older.[93,94] The symptoms of GCA typically fluctuate throughout a patient's presentation and are highly variable, with different patients presenting with different timelines and collections of symptoms.

Due to this symptomatic variability, the diagnosis of GCA is based on laboratory results in concert with clinical presentation and temporal artery ultrasound or biopsy confirmation. Diagnosis of GCA is suspected in any patient over 50 years of age with elevated erythrocyte sedimentation rate (ESR) and/or elevated C-reactive protein (CRP) and one or more of the following symptoms: Headache, abrupt onset of visual deficits, including permanent monocular vision loss, jaw claudication, constitutional symptoms (ex . fever, and chills), and other signs of vascular abnormality (e.g., tenderness to palpation of the temporal artery, asymmetric blood pressure, decreased pulse amplitude, limb claudication, vascular bruits, and vascular

nodules). Any patient who meets these criteria should be evaluated further with temporal artery biopsy, or more recently, temporal artery color Doppler ultrasound (CDUS).[95] A positive temporal artery biopsy result includes a thickened arterial wall replete with CD4+ T lymphocytes and macrophages, which form granulomatous giant cell bodies.[96] Evidence of a thickened dark arterial wall, corresponding to mural edema on the temporal artery ultrasound (the "halo sign)" also can confirm the diagnosis of GCA.[97] It is important to note that patients with GCA are at high risk of vision loss and that any patient who meets diagnostic criteria should be evaluated by an ophthalmologist early in the diagnostic process.[98]

Due to the high risk of vision loss in any patient with suspicion of GCA, high-dose glucocorticoids should be immediately initiated without waiting for histological or ultrasonic confirmation. Although never directly studied in a clinical trial, glucocorticoids have shown remarkable efficacy in preventing GCA-related vision loss.[99,100] However, glucocorticoid use is also associated with adverse effects,[101] and is contraindicated in patients with osteoporosis, diabetes, hypertension, and glaucoma.[102] For this reason, alternative immune-modulating therapies have been used to decrease reliance on glucocorticoids while maintaining remission of disease.

Tocilizumab is a mAb therapy against IL-6R that has shown remarkable efficacy in promoting remission of GCA while reducing the need for glucocorticoid therapy.[103,104] Though often used as adjunct therapy with glucocorticoids, tocilizumab has also shown efficacy as a monotherapy following the tapering of glucocorticoids. Treatment paradigms typically last 12–18 months before cessation of therapy. If the goal of complete remission without glucocorticoid use is not met, however, the therapy can be continued. Notably, there are no large trials that have tested the effects of long-term tocilizumab exposure. In short-term trials, reported adverse effects associated with tocilizumab include opportunistic infections, neutropenia, abnormal liver function tests, and increased serum cholesterol.[105] However, a systematic review found no significant increase in adverse effects when compared to placebo controls.[106] Importantly, blockade of the IL-6R pathway results in a pharmacologic depression of ESR and CRP values. Thus, patients undergoing tocilizumab treatment must be evaluated clinically and with CDUS to detect signs of GCA recurrence.[102] Due to the limited number of clinical trials of tocilizumab in patients with GCA, additional research is essential for understanding how to best incorporate this mAb therapy into the long-term care of patients with GCA.[106]

Thyroid Eye Disease

Thyroid eye disease (TED) is an autoimmune, antibody-mediated disease of the orbital tissue that most commonly occurs in association with Graves' disease, though it also infrequently occurs in patients with other thyroid diseases, including Hashimoto's thyroiditis.[107-109] The initiating events of TED are not well characterized. However, one of the early steps in the pathogenesis of this disease is the production of autoantibodies against the thyroid stimulating hormone receptor (TSHR), which is expressed by the thyroid gland, but also within the cell membranes of orbital fibroblasts and adipocytes.[110] The activity of TSHR is tightly linked to the insulin-like growth factor 1 receptor (IGF-1R), which is activated on autoantibody binding of TSHR. This subsequent activation of TSHR/IGF-1R drives an expansion of orbital fibroblasts and adipocytes. These activated fibroblasts secrete hyaluronic acid and other glycosaminoglycans, which causes fluid to accumulate within the cells of the orbit.[111] This cellular expansion and fluid accumulation, as well as accompanying inflammatory processes, drive an increase in pressure behind the eye. Consequently, the eyeball is pushed forward, causing proptosis and disrupting venous drainage, thereby worsening the fluid accumulation within the orbit. Sustained pressure and ocular displacement result in extraocular muscle dysfunction, leading to diplopia, as well as dry eye, conjunctivitis, blurring of vision, periorbital edema, optic nerve compression, and orbital pain.[112]

The majority of patients with TED can be diagnosed clinically by the combination of the hallmark ocular symptoms of the disease (i.e., proptosis, periorbital edema) and hyperthyroidism. The diagnosis of hyperthyroidism/Graves' disease can be confirmed by measuring the levels of TSH, free T4, total T3, and by testing for the presence of anti-TSHR antibodies. Subsequent diagnosis of TED can be confirmed through eye examination and demonstration of periorbital edema, sometimes extending to chemosis, failure of eyelid apposition, decreased ocular range of motion, dysconjugate gaze during extraocular movements, and proptosis confirmed by exophthalmometer measurement (>24 mm).[113]

Traditional treatment options for TED focus on reducing inflammation while ameliorating the symptoms of the disease. These included glucocorticoids combined with artificial tears with selenium supplementation. These options provided only little relief and minimal effect on the pathogenesis of the disease.

Teprotumumab is a human mAb recently approved by the FDA that disrupts the pathogenesis of TED by binding to IGF-1R, thereby inhibiting the downstream signal transduction pathway. This inhibition is sufficient to halt the mechanisms that drive TED, and ultimately leads to apoptosis of aberrant orbital fibroblasts and adipocytes, thereby reversing the pathogenesis of disease and reducing the accompanying proptosis. This approach has been shown to affect measurable improvements in proptosis in nearly 80% of patients taking this medication. Moreover, these effects have been shown to persist for at least 1 year after cessation of treatment.

Adverse events reported during the clinical trials of teprotumumab included muscle spasms, nausea, alopecia, diarrhea, and fatigue. More serious but less common events included hearing loss and Hashimoto's encephalopathy.

Overall, teprotumumab was well tolerated, with only a small fraction of the patients halting the clinical trials early due to adverse events.[114] Continued use of teprotumumab in the general public, combined with close observation by the treating clinical teams, will allow us to better understand the risks and benefits of use as this medication becomes more widely used in the population of patients with TED.

Myasthenia Gravis

Myasthenia gravis (MG) is an acquired chronic autoimmune antibody-mediated neuromuscular disorder that affects voluntary muscles. It is classically characterized by the production of autoantibodies that block acetylcholine receptors (AChRs) at the postsynaptic neuromuscular junction, reducing the number of functional receptors on the muscle membrane. The antibodies also cause complement-mediated membrane damage and expedite acetylcholine (ACh) degradation.[115] Subsequently, this interferes with the binding of ACh to the receptor, leading to inadequate nerve stimulation of muscle fibers and impaired muscle contraction.

MG is commonly diagnosed based on examination and history and supported by laboratory and electrophysiologic evidence. Patients experience muscle weakness commonly involving facial and extraocular muscles. Patients often describe a weakness that is worse on activity and markedly improved with rest. Along with the extraocular muscles, levator palpebrae superioris and orbicularis oculi are also commonly affected.[116] Progressive or recurrent variable and fatiguable ptosis and diplopia are commonly among the first signs of disease and are a presenting symptom in over 50% of patients. In over 20% of patients, MG remains confined to the extraocular muscles (ocular MG),[117] often mimicking ocular nerve palsy or INO.[116]

To confirm the diagnosis of MG, pharmacologic testing (e.g., edrophonium test or Tensilon test) involves administering edrophonium chloride to inhibit the degradation of ACh at the neuromuscular junction. A positive test can be described as an observable improvement in levator palpebrae superioris muscle function postinjection. Another electrophysiologic diagnostic test is repetitive nerve stimulation, which tracks action potentials from muscles after receiving nerve stimulation. A positive result in this test is a progressive decline in compound muscle action potential amplitude with each subsequent nerve stimulation.[115] A sleep/rest test, during which ocular muscle function is tested on waking or after resting the muscles of the eyelid, shows improved muscle function following rest in those patients with MG.[118] Finally, an ice test is highly specific for MG, where a positive test shows improvement in ptosis after an ice pack is applied to the eyelid.[119]

Serum antibody testing can also be used to support a diagnosis of MG. These autoantibodies are directed against AChRs at the neuromuscular junction. A subset of patients also have antibodies against muscle-specific kinase (MuSK) at the neuromuscular junction. In patients who are negative for anti-AChR antibodies, MuSK antibody testing can provide serological evidence of MG diagnosis.

Medical management of MG often involves the use of acetylcholinesterase inhibitors like pyridostigmine. These drugs work by decreasing the breakdown of ACh, extending its availability at the neuromuscular junction. Consequently, this improves the frequency of ACh binding to its receptors, enhancing muscle contraction. In addition to this treatment, corticosteroids have been utilized as an adjunct to suppress the immune system and reduce the production of anti-AChR autoantibodies. Plasmapheresis is another method of slowing the progression of disease, especially during acute exacerbations or in patients with severe symptoms that do not respond well to corticosteroids or other immunosuppressive treatments.[120] Surgical treatment of symptomatic MG patients includes thymectomy, leading to clinical improvement of symptoms in over 70%–80% of patients.[117,121]

In recent years, mAbs, including rituximab and eculizumab, have become a valuable addition to the treatment armament for MG. Rituximab binds to CD20 on the surface of B-cells, marking them for immune-mediated destruction, thereby reducing the number of circulating B-cells, and subsequently, the levels of anti-AChR autoantibodies. Greater than 70% of patients reported only minimal MG symptoms and no need for rescue treatment over a 4-month period after a single dose of rituximab.[122] Moreover, along with a significant reduction in antibody levels, rituximab also reduces the long-term need for prednisone use. However, rituximab use is relatively contraindicated in patients with a high risk of infection or heart failure, as well as in patients who are pregnant or breastfeeding. Rituximab use has also been associated with various side effects including infusion reactions, anemia, increasing the risk of reactivation of latent infections such as tuberculosis and viral hepatitis, and opportunistic infections. Rare cases of secondary Ig deficiency and reversible encephalopathy syndrome have also been reported.[123]

The anti-AChR autoantibodies characteristic of MG activate the complement system, resulting in complement-mediated damage to the neuromuscular junction. Eculizumab inhibits the complement system by binding to the C5 protein, preventing it from propagating the complement cascade and thus preventing immune-mediated destruction of AChRs. In 2017, the U.S. FDA approved eculizumab as a treatment option for adult patients with refractory MG who tested positive for anti-AChR antibodies.[124] Clinical trials of eculizumab reflected improvement in both the overall quality of life and the severity of MG symptoms including diplopia, ptosis, and proximal muscle weakness. Eculizumab has been noted to have various side effects including headache, diarrhea, arthralgia, and increased susceptibility to meningococcal and other systemic encapsulated bacterial infections.[125] Appropriate vaccination against these pathogens is useful in improving the long-term safety profile of eculizumab treatment.

Immune Checkpoint Monoclonal Antibody-related Adverse Effects in Neuro-ophthalmology

Although the majority of mAbs discussed in this special issue are used to directly treat neuro-ophthalmic diseases, additional classes of mAbs affect ocular health indirectly through their adverse effects in the orbit. Immune checkpoint inhibitors (ICIs) are a class of immunomodulatory antibodies that are leveraged against cancers, including advanced malignancies, by exogenously enhancing the activity of the immune system. The two major targets of ICIs are the programmed cell death receptor 1 (PD-1)/PD ligand 1 pathway and the cytotoxic T-lymphocyte-associated antigen 4 pathway.[126] Although these therapies have shown an incredible ability to fight previously untreatable cancers, their use is occasionally accompanied by immune-related adverse events (irAEs), which can be so severe as to be life-threatening.[127,128] These irAEs typically arise within the gastrointestinal, dermatological, hepatic, and endocrine systems. However, ocular side effects have also been reported.[126,129-133] The immune system enhancing mechanisms that provide the anti-cancer effects associated with these drugs are thought to be the same mechanisms that drive irAEs, though aberrant expression of these pathways in cells outside of the immune system may also play an important role in mediating the associated irAEs.[134]

Neurological syndromes that include ocular symptoms have been reported following ICI therapy use. These include MG following ipilimumab and nivolumab use. This presentation included symptoms of light sensitivity, blurred vision, diplopia, fatiguing ptosis, ophthalmoplegia, and weakness in orbicularis oculi. Although there was variability in the timing of irAE presentation and the symptoms involved, all reported patients demonstrated the hallmark diagnostic features of MG, including positive anti-AhR binding antibodies.[135,136] Similarly, patients have presented with varied forms of the Miller Fisher variant (MFV) of Guillain–Barré syndrome following pembrolizumab,[129,132] ipilimumab,[131] and nivolumab[131,133] therapy. In these patients, ophthalmoplegia is a core symptom. However, some patients additionally presented with nonfatiguing ptosis, and weakness of facial muscles, including orbicularis oculi. Interestingly, though one of these patients was found to be anti-GQ1b-positive,[129] the majority of reported cases have been found to be negative for anti-GQ1b antibodies.[131-133] This suggests that the immunological mechanisms that underlie canonical MFV may be distinct from those that drive the MFV-like symptoms observed following ICI treatment.

Isolated ocular symptoms have also been reported in response to ICI use. These include blepharitis, conjunctivitis, episcleritis, retinitis, scleritis, and uveitis.[126,137-139] Fortunately, presentations of these adverse ocular effects are uncommon, and mild cases, such as those previously reported, resolve with cessation of the ICI and symptomatic treatment under the supervision of an ophthalmologist. Importantly, more severe cases may necessitate higher levels of care, beginning with high-dose oral corticosteroids.[137]

It is essential for any clinician who is prescribing ICIs to be aware of the potential side effect profile of the given therapy and to remain vigilant for any early symptoms of irAEs. Recruitment of specialist care teams that correspond to the specific irAE may be necessary.[126,130] In addition, care teams should adopt a low threshold for pausing or stopping ICI therapy when suspicious of irAE development. Importantly, patients have shown remarkable response rates to ICIs even when these therapies have been given at different doses or given along differing timelines. This includes durable responses to therapy even after the treatment has stopped. Thus, it is best to continue ICI therapy slowly while monitoring and treating the developing irAEs without fear of losing the dose-responsivity of the ICI. The decision to pause or stop the therapy should be made in conjunction with the patient and should be based on the nature and severity of the irAEs, as well as the responsivity of the cancer to the ICI therapy.[126] It is also important to remember that alternative ICIs, even those that target the same pathway, may provide the same anti-cancer effects while avoiding the same irAEs.[140]

Future Directions

This is an exciting time of discovery and development in the field of mAb therapy. The prior decade has witnessed a boon in both the interest and acceptance of mAb therapies, causing antibody-based therapy to become one of the fastest-growing therapeutic options in the world. There now exist over 160 mAb-based therapies approved worldwide against targets that treat diseases such as cancers, autoimmune diseases, and infections, including SARS-CoV-2.[141,142] The majority of these have been approved in the past 10 years. The next decade will be characterized by a better understanding of the pharmacological mechanisms that underlie mAb therapy. These advances will be driven, in part, by the advancement of general basic scientific approaches, including next-generation sequencing, and artificial intelligence-based bioinformatic analysis. However, specific advances in the development of antibody therapies, including the development of mRNA-encoded antibodies will also continue to drive the field toward novel therapies.[142]

In addition, we will likely see a continued surge in the clinical acceptance of these medicines. There are currently over 7000 clinical trials being conducted in the United States that involve the use of mAbs as a therapy for human disease. More than 180 of these are in the final phase (Phase 4) of testing before widespread clinical use.[143] With 122 mAb therapies already approved by the FDA, the field of clinical mAb use has the potential to double in size within the coming decade.[142] These and similar initiatives will undoubtedly identify formulations and targets that minimize disease burden in patients. However, this work will also illuminate the gaps in the field that currently hinder forward progress. One such gap is the continued presence of irAEs that plague some patients under antibody treatment regimens. These can be so severe as to compromise the health of patients and often necessitate cessation of

antibody treatment.[126-128] Already, the management of the more common side effects, including thyroid dysfunction and dermatological rashes, is becoming standardized.[126] With increased focus on alleviating these irAEs, combined with the increased number of patients treated with mAb therapies, we expect a deeper understanding of the mechanisms that underlie irAEs, thereby driving a greater ability to minimize and prevent these adverse symptoms.

Conclusion

In the relatively brief time that mAbs have been in clinical use, they have shown an incredible ability to halt pathogenic mechanisms, decrease symptom burdens, and decrease patients' reliance on additional therapies, many of which carry with them their own risk of adverse effects. The clinical benefit of mAb use has become evident within the field of ophthalmology, but also within other varied fields, including neurology, rheumatology, and oncology. Increased interest in these biological therapies will continue to drive the development of novel mAb-based therapies. In addition, increased clinical use of mAbs, combined with careful observation of intended response rates, and adverse effects, will continue to shape our understanding of how mAbs disrupt mechanisms of disease, and how these tools can be best utilized to foster the health of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kaunitz JD. Development of monoclonal antibodies: The dawn of mAb rule. Dig Dis Sci 2017;62:831-2.
2. Köhler G, Milstein C. Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion. Eur J Immunol 1976;6:511-9.
3. Castelli MS, McGonigle P, Hornby PJ. The pharmacology and therapeutic applications of monoclonal antibodies. Pharmacol Res Perspect 2019;7:e00535.
4. World Health Organization (WHO). International Nonproprietary Names (INN) for Biological and Biotechnological Substances (A Review). World Health Organization; 2014. p. 8-10.
5. Buss NA, Henderson SJ, McFarlane M, Shenton JM, de Haan L. Monoclonal antibody therapeutics: History and future. Curr Opin Pharmacol 2012;12:615-22.
6. Geng X, Kong X, Hu H, Chen J, Yang F, Liang H, *et al.* Research and development of therapeutic mAbs: An analysis based on pipeline projects. Hum Vaccin Immunother 2015;11:2769-76.
7. Bayer V. An overview of monoclonal antibodies. Semin Oncol Nurs 2019;35:150927.
8. Liu R, Du S, Zhao L, Jain S, Sahay K, Rizvanov A, *et al.* Autoreactive lymphocytes in multiple sclerosis: Pathogenesis and treatment target. Front Immunol 2022;13:996469.
9. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, *et al.* Assessment of lesions on magnetic resonance imaging in multiple sclerosis: Practical guidelines. Brain 2019;142:1858-75.
10. Frohman EM, Frohman TC, Zee DS, McColl R, Galetta S. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol 2005;4:111-21.
11. Costa Novo J, Felgueiras H. Neuro-ophthalmologic manifestations of multiple sclerosis other than acute optic neuritis. Mult Scler Relat Disord 2021;48:102730.
12. Kaur P, Bennett JL. Optic neuritis and the neuro-ophthalmology of multiple sclerosis. Int Rev Neurobiol 2007;79:633-63.
13. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
14. Klineova S, Lublin FD. Clinical course of multiple sclerosis. Cold Spring Harb Perspect Med 2018;8:a028928.
15. Krajnc N, Bsteh G, Berger T, Mares J, Hartung HP. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: An overview with emphasis on pregnancy, vaccination, and risk management. Neurotherapeutics 2022;19:753-73.
16. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, *et al.* Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014;83:278-86.
17. Tarlinton RE, Martynova E, Rizvanov AA, Khaiboullina S, Verma S. Role of viruses in the pathogenesis of multiple sclerosis. Viruses 2020;12:643.
18. Van Kaer L, Postoak JL, Wang C, Yang G, Wu L. Innate, innate-like and adaptive lymphocytes in the pathogenesis of MS and EAE. Cell Mol Immunol 2019;16:531-9.
19. Fogdell-Hahn A, Ligers A, Grønning M, Hillert J, Olerup O. Multiple sclerosis: A modifying influence of HLA class I genes in an HLA class II associated autoimmune disease. Tissue Antigens 2000;55:140-8.
20. Dong C. Cytokine regulation and function in T cells. Annu Rev Immunol 2021;39:51-76.
21. Khoy K, Mariotte D, Defer G, Petit G, Toutirais O, Le Mauff B. Natalizumab in multiple sclerosis treatment: From biological effects to immune monitoring. Front Immunol 2020;11:549842.
22. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: From physiology to disease and back. Physiol Rev 2019;99:21-78.
23. Corbali O, Chitnis T. Pathophysiology of myelin oligodendrocyte glycoprotein antibody disease. Front Neurol 2023;14:1-14.
24. Bennett JL, O'Connor KC, Bar-Or A, Zamvil SS, Hemmer B, Tedder TF, *et al*. B lymphocytes in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm 2015;2:e104.
25. Kuhlmann T, Ludwin S, Prat A, Antel J, Brück W, Lassmann H. An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol 2017;133:13-24.
26. Salou M, Garcia A, Michel L, Gainche-Salmon A, Loussouarn D, Nicol B, *et al.* Expanded CD8 T-cell sharing between periphery and CNS in multiple sclerosis. Ann Clin Transl Neurol 2015;2:609-22.
27. Matsushita T, Tateishi T, Isobe N, Yonekawa T, Yamasaki R, Matsuse D, *et al.* Characteristic cerebrospinal fluid cytokine/chemokine profiles in neuromyelitis optica, relapsing remitting or primary progressive multiple sclerosis. PLoS One 2013;8:e61835.
28. Claes N, Fraussen J, Stinissen P, Hupperts R, Somers V. B Cells are multifunctional players in multiple sclerosis pathogenesis: Insights from therapeutic interventions. Front Immunol 2015;6:642.
29. Krumbholz M, Derfuss T, Hohlfeld R, Meinl E. B cells and antibodies in multiple sclerosis pathogenesis and therapy. Nat Rev Neurol 2012;8:613-23.
30. Jelcic I, Al Nimer F, Wang J, Lentsch V, Planas R, Jelcic I, *et al.* Memory B cells activate brain-homing, autoreactive CD4(+) T cells in multiple sclerosis. Cell 2018;175:85-100.e23.
31. Piccio L, Naismith RT, Trinkaus K, Klein RS, Parks BJ, Lyons JA, *et al.* Changes in B- and T-lymphocyte and chemokine levels with rituximab treatment in multiple sclerosis. Arch Neurol 2010;67:707-14.
32. Mauri C, Bosma A. Immune regulatory function of B cells. Annu Rev Immunol 2012;30:221-41.
33. Shen P, Fillatreau S. Antibody-independent functions of B cells: A focus on cytokines. Nat Rev Immunol 2015;15:441-51.
34. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: A review. JAMA 2021;325:765-79.
35. Hutchinson M. Natalizumab: A new treatment for relapsing remitting multiple sclerosis. Ther Clin Risk Manag 2007;3:259-68.
36. Pucci E, Giuliani G, Solari A, Di Pietrantonj C, Simi S, Minozzi S, *et al*. Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst Rev 2009;1:1-107.

37. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.
38. Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, *et al.* Efficacy and safety of natalizumab in multiple sclerosis: Interim observational programme results. J Neurol Neurosurg Psychiatry 2014;85:1190-7.
39. Lin M, Zhang J, Zhang Y, Luo J, Shi S. Ocrelizumab for multiple sclerosis. Cochrane Database Syst Rev 2022;5:CD013247.
40. Ligi A, Amos M, Althoff E. FDA Approves Novartis Kesimpta® (ofatumumab), the First and only Self-Administered, Targeted B-cell therapy for Patients with Relapsing Multiple Sclerosis. Novartis; 2020. Available from: https://www.novartis.com/news/media-releases/fda-approves-novartis-kesimpta-ofatumumab-first-and-only-self-administered-targeted-b-cell-therapy-patients-relapsing-multiple-sclerosis. [Last accessed on 2023 Nov 29].
41. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-15.
42. Mader S, Brimberg L. Aquaporin-4 water channel in the brain and its implication for health and disease. Cells 2019;8:90.
43. Wingerchuk DM, Lucchinetti CF. Neuromyelitis optica spectrum disorder. N Engl J Med 2022;387:631-9.
44. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.
45. Pandit L, Asgari N, Apiwattanakul M, Palace J, Paul F, Leite MI, *et al.* Demographic and clinical features of neuromyelitis optica: A review. Mult Scler 2015;21:845-53.
46. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53:1107-14.
47. Chandrasekar S, John J, Satapathy AK. Longitudinally extensive transverse myelitis: One disease, variable outcomes-a case series. J Neurosci Rural Pract 2022;13:339-42.
48. Romeo AR, Segal BM. Treatment of neuromyelitis optica spectrum disorders. Curr Opin Rheumatol 2019;31:250-5.
49. Shosha E, Dubey D, Palace J, Nakashima I, Jacob A, Fujihara K, *et al.* Area postrema syndrome: Frequency, criteria, and severity in AQP4-IgG-positive NMOSD. Neurology 2018;91:e1642-51.
50. Kanbayashi T, Shimohata T, Nakashima I, Yaguchi H, Yabe I, Nishizawa M, *et al.* Symptomatic narcolepsy in patients with neuromyelitis optica and multiple sclerosis: New neurochemical and immunological implications. Arch Neurol 2009;66:1563-6.
51. Suzuki K, Nakamura T, Hashimoto K, Miyamoto M, Komagamine T, Nagashima T, *et al.* Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: A case report and literature review. Arch Neurol 2012;69:1355-9.
52. Sellner J, Boggild M, Clanet M, Hintzen RQ, Illes Z, Montalban X, *et al.* EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol 2010;17:1019-32.
53. Matthews L, Marasco R, Jenkinson M, Küker W, Luppe S, Leite MI, *et al.* Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution. Neurology 2013;80:1330-7.
54. Ransohoff RM. Illuminating neuromyelitis optica pathogenesis. Proc Natl Acad Sci U S A 2012;109:1001-2.
55. Papp V, Magyari M, Aktas O, Berger T, Broadley SA, Cabre P, *et al.* Worldwide incidence and prevalence of neuromyelitis optica: A systematic review. Neurology 2021;96:59-77.
56. Etemadifar M, Dashti M, Vosoughi R, Abtahi SH, Ramagopalan SV, Nasr Z. An epidemiological study of neuromyelitis optica in Isfahan. Mult Scler 2014;20:1920-2.
57. Cabrera-Gómez JA, Kurtzke JF, González-Quevedo A, Lara-Rodríguez R. An epidemiological study of neuromyelitis optica in Cuba. J Neurol 2009;256:35-44.
58. Zhu W, Zhang Y, Wang Z, Fu Y, Yan Y. Monoclonal antibody-based treatments for neuromyelitis optica spectrum disorders: From bench to bedside. Neurosci Bull 2020;36:1213-24.
59. Das G, Damotte V, Gelfand JM, Bevan C, Cree BA, Do L, *et al.* Rituximab before and during pregnancy. Neurol Neuroimmunol Neuroinflammation 2018;5:e453.
60. Ringelstein M, Harmel J, Distelmaier F, Ingwersen J, Menge T, Hellwig K, *et al.* Neuromyelitis optica and pregnancy during therapeutic B cell depletion: Infant exposure to anti-AQP4 antibody and prevention of rebound relapses with low-dose rituximab postpartum. Mult Scler 2013;19:1544-7.
61. Kawachi I, Lassmann H. Neurodegeneration in multiple sclerosis and neuromyelitis optica. J Neurol Neurosurg Psychiatry 2017;88:137-45.
62. Popescu BF, Lucchinetti CF. Pathology of demyelinating diseases. Annu Rev Pathol 2012;7:185-217.
63. Papadopoulos MC, Verkman AS. Aquaporin 4 and neuromyelitis optica. Lancet Neurol 2012;11:535-44.
64. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, *et al*. A serum autoantibody marker of neuromyelitis optica: Distinction from multiple sclerosis. Lancet 2004;364:2106-12.
65. Chihara N, Aranami T, Sato W, Miyazaki Y, Miyake S, Okamoto T, *et al.* Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc Natl Acad Sci U S A 2011;108:3701-6.
66. Chen T, Lennon VA, Liu YU, Bosco DB, Li Y, Yi MH, *et al.* Astrocyte-microglia interaction drives evolving neuromyelitis optica lesion. J Clin Invest 2020;130:4025-38.
67. Vaknin-Dembinsky A, Brill L, Orpaz N, Abramsky O, Karussis D. Preferential increase of B-cell activating factor in the cerebrospinal fluid of neuromyelitis optica in a white population. Mult Scler 2010;16:1453-7.
68. Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: From pathophysiology to therapeutic strategies. J Neuroinflammation 2021;18:208.
69. Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, *et al.* Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. Nat Med 2007;13:1173-5.
70. Lucchinetti CF, Mandler RN, McGavern D, Bruck W, Gleich G, Ransohoff RM, *et al*. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002;125:1450-61.
71. Lucchinetti CF, Guo Y, Popescu BF, Fujihara K, Itoyama Y, Misu T. The pathology of an autoimmune astrocytopathy: Lessons learned from neuromyelitis optica. Brain Pathol 2014;24:83-97.
72. Traboulsee A, Greenberg BM, Bennett JL, Szczechowski L, Fox E, Shkrobot S, *et al.* Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: A randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol 2020;19:402-12.
73. Heo YA. Satralizumab: First approval. Drugs 2020;80:1477-82.
74. Fung S, Shirley M. Satralizumab: A review in neuromyelitis optica spectrum disorder. CNS Drugs 2023;37:363-70.
75. Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, *et al.* Trial of satralizumab in neuromyelitis optica spectrum disorder. N Engl J Med 2019;381:2114-24.
76. Yamamura T, Weinshenker B, Yeaman MR, De Seze J, Patti F, Lobo P, *et al.* Long-term safety of satralizumab in neuromyelitis optica spectrum disorder (NMOSD) from SAkuraSky and SAkuraStar. Mult Scler Relat Disord 2022;66:104025.
77. Sechi E, Cacciaguerra L, Chen JJ, Mariotto S, Fadda G, Dinoto A, *et al.* Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): A review of clinical and MRI features, diagnosis, and management. Front Neurol 2022;13:885218.
78. Liu A, Bryant A, Jefferson A, Friedman D, Minhas P, Barnard S, *et al.* Exploring the efficacy of a 5-day course of transcranial direct current stimulation (TDCS) on depression and memory function in patients with well-controlled temporal lobe epilepsy. Epilepsy Behav 2016;55:11-20.
79. O'Connor KC, McLaughlin KA, De Jager PL, Chitnis T, Bettelli E, Xu C, *et al.* Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. Nat Med 2007;13:211-7.
80. Johns TG, Bernard CC. The structure and function of myelin oligodendrocyte glycoprotein. J Neurochem 1999;72:1-9.
81. de Mol CL, Wong Y, van Pelt ED, Wokke B, Siepman T, Neuteboom RF, *et al.* The clinical spectrum and incidence of anti-MOG-associated

acquired demyelinating syndromes in children and adults. Mult Scler 2020;26:806-14.
82. O'Connell K, Hamilton-Shield A, Woodhall M, Messina S, Mariano R, Waters P, *et al.* Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK. J Neurol Neurosurg Psychiatry 2020;91:1126-8.
83. Dubey D, Pittock SJ, Krecke KN, Morris PP, Sechi E, Zalewski NL, *et al.* Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody. JAMA Neurol 2019;76:301-9.
84. Cobo-Calvo A, Ruiz A, Rollot F, Arrambide G, Deschamps R, Maillart E, *et al.* Clinical features and risk of relapse in children and adults with myelin oligodendrocyte glycoprotein antibody-associated disease. Ann Neurol 2021;89:30-41.
85. Neuromyelitis Optica Spectrum Disorder. Siegel Rare Neuroimmune Association; 2023. Available from: https://wearesrna.org/living-with-myelitis/disease-information/neuromyelitis-optica-spectrum-disorder/diagnosis/. [Last accessed on 2023 Nov 29].
86. Banwell B, Bennett JL, Marignier R, Kim HJ, Brilot F, Flanagan EP, *et al.* Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol 2023;22:268-82.
87. Marignier R, Pittock SJ, Paul F, Kim HJ, Bennett JL, Weinshenker BG, *et al.* AQP4-IgG-seronegative patient outcomes in the N-MOmentum trial of inebilizumab in neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2022;57:103356.
88. Tanaka K, Kezuka T, Ishikawa H, Tanaka M, Sakimura K, Abe M, *et al.* Pathogenesis, clinical features, and treatment of patients with myelin oligodendrocyte glycoprotein (MOG) autoantibody-associated disorders focusing on optic neuritis with consideration of autoantibody-binding sites: A review. Int J Mol Sci 2023;24:13368.
89. Kaneko K, Sato DK, Nakashima I, Ogawa R, Akaishi T, Takai Y, *et al.* CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: A cross-sectional study and potential therapeutic implications. J Neurol Neurosurg Psychiatry 2018;89:927-36.
90. Huda S, Whittam D, Jackson R, Karthikeayan V, Kelly P, Linaker S, *et al.* Predictors of relapse in MOG antibody associated disease: A cohort study. BMJ Open 2021;11:e055392.
91. Barreras P, Vasileiou ES, Filippatou AG, Fitzgerald KC, Levy M, Pardo CA, *et al.* Long-term effectiveness and safety of rituximab in neuromyelitis optica spectrum disorder and MOG antibody disease. Neurology 2022;99:e2504-16.
92. Elsbernd PM, Hoffman WR, Carter JL, Wingerchuk DM. Interleukin-6 inhibition with tocilizumab for relapsing MOG-IgG associated disorder (MOGAD): A case-series and review. Mult Scler Relat Disord 2021;48:102696.
93. González-Gay MA, García-Porrúa C. Systemic vasculitis in adults in Northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. Medicine (Baltimore) 1999;78:292-308.
94. Kermani TA, Schäfer VS, Crowson CS, Hunder GG, Gabriel SE, Matteson EL, *et al.* Increase in age at onset of giant cell arteritis: A population-based study. Ann Rheum Dis 2010;69:780-1.
95. Narváez J, Estrada P, Vidal-Montal P, Nolla JM. Performance of the new 2022 ACR/EULAR classification criteria for giant cell arteritis in clinical practice in relation to its clinical phenotypes. Autoimmun Rev 2023;22:103413.
96. Cavazza A, Muratore F, Boiardi L, Restuccia G, Pipitone N, Pazzola G, *et al.* Inflamed temporal artery: Histologic findings in 354 biopsies, with clinical correlations. Am J Surg Pathol 2014;38:1360-70.
97. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med 1997;337:1336-42.
98. Bilton EJ, Mollan SP. Giant cell arteritis: Reviewing the advancing diagnostics and management. Eye (Lond) 2023;37:2365-73.
99. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. Ophthalmology 1993;100:550-5.
100. Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology 2003;110:1204-15.
101. Yasir M, Goyal A, Sonthalia S. Corticosteroid Adverse Effects. 1st ed. Treasure Island, FL: StatPearls Publishing LLC; 2023.
102. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, *et al.* 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19-30.
103. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, *et al.* Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317-28.
104. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, *et al.* Tocilizumab for induction and maintenance of remission in giant cell arteritis: A phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:1921-7.
105. Salvarani C, Muratore F. Treatment of Giant Cell Arteritis. UpToDate; 2023. Available from: https://www.uptodate.com/contents/treatment-of-giant-cell-arteritis?search=giant cell arteritis&topicRef=8242&source=see_link. [Last accessed on 2023 Oct 10].
106. Antonio AA, Santos RN, Abariga SA. Tocilizumab for giant cell arteritis. Cochrane Database Syst Rev 2022;5:CD013484.
107. Alajmi S, Alshehri S, Ekhzaimy A. Graves' ophthalmopathy in the setting of primary hypothyroidism. Cureus 2022;14:e24954.
108. Bartalena L, Pinchera A, Marcocci C. Management of graves' ophthalmopathy: Reality and perspectives. Endocr Rev 2000;21:168-99.
109. Kiran Z, Rashid O, Islam N. Typical graves' ophthalmopathy in primary hypothyroidism. J Pak Med Assoc 2017;67:1104-6.
110. Davies TF. The thyrotropin receptors spread themselves around. J Clin Endocrinol Metab 1994;79:1232-3.
111. Brenner-Gati L, Berg KA, Gershengorn MC. Thyroid-stimulating hormone and insulin-like growth factor-1 synergize to elevate 1,2-diacylglycerol in rat thyroid cells. Stimulation of DNA synthesis via interaction between lipid and adenylyl cyclase signal transduction systems. J Clin Invest 1988;82:1144-8.
112. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, *et al.* Graves' disease. Nat Rev Dis Primers 2020;6:52.
113. Wiersinga WM. Management of graves' ophthalmopathy. Nat Clin Pract Endocrinol Metab 2007;3:396-404.
114. Nie T, Lamb YN. Teprotumumab: A review in thyroid eye disease. Drugs 2022;82:1663-70.
115. Noel ME, Jirawuthiworavong GV, Yen MT, Thyparampil P, Marcet MM, Burkat CN. Myasthenia Gravis. EyeWiki; 2023. Available from: https://eyewiki.aao.org/Myasthenia_Gravis. [Last accessed on 2023 Oct 08].
116. Nair AG, Patil-Chhablani P, Venkatramani DV, Gandhi RA. Ocular myasthenia gravis: A review. Indian J Ophthalmol 2014;62:985-91.
117. Sommer N, Melms A, Weller M, Dichgans J. Ocular myasthenia gravis. A critical review of clinical and pathophysiological aspects. Doc Ophthalmol 1993;84:309-33.
118. Scherer K, Bedlack RS, Simel DL. Does this patient have myasthenia gravis? JAMA 2005;293:1906-14.
119. Movaghar M, Slavin ML. Effect of local heat versus ice on blepharoptosis resulting from ocular myasthenia. Ophthalmology 2000;107:2209-14.
120. Kumar R, Birinder SP, Gupta S, Singh G, Kaur A. Therapeutic plasma exchange in the treatment of myasthenia gravis. Indian J Crit Care Med 2015;19:9-13.
121. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, *et al.* Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375:511-22.
122. Piehl F, Eriksson-Dufva A, Budzianowska A, Feresiadou A, Hansson W, Hietala MA, *et al.* Efficacy and safety of rituximab for new-onset generalized myasthenia gravis: The RINOMAX randomized clinical trial. JAMA Neurol 2022;79:1105-12.
123. Banerjee S, Adcock L. Rituximab for the Treatment of Myasthenia Gravis: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. CADTH Rapid Response Report Summary with Critical Apprais; 2018. p. 1-41.
124. Vanoli F, Mantegazza R. Current drug treatment of myasthenia gravis. Curr Opin Neurol 2023;36:410-5.
125. Dhillon S. Eculizumab: A review in generalized myasthenia gravis. Drugs 2018;78:367-76.

126. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, *et al.* Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper. Ann Oncol 2016;27:559-74.
127. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, *et al.* Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. J Clin Oncol 2017;35:785-92.
128. Gaudy-Marqueste C, Monestier S, Franques J, Cantais E, Richard MA, Grob JJ. A severe case of ipilimumab-induced guillain-barré syndrome revealed by an occlusive enteric neuropathy: A differential diagnosis for ipilimumab-induced colitis. J Immunother 2013;36:77-8.
129. Hunt PJ, Keys PH, Dalal S, Boardman D, Davila-Siliezar P, Laylani N, *et al*. GQ1b Seropositive Guillain-Barré/Miller Fisher Overlap Syndrome After Pembrolizumab Treatment. J Neuroophthalmol 2023;0:1–2. https://doi.org/10.1097/WNO.0000000000001976.
130. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, *et al.* Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015;26:2375-91.
131. Baird-Gunning JJ, Weerasinghe D, Silsby M, Gawarikar Y, Carlino MS, Smith JL, *et al.* Miller fisher syndrome associated with immunotherapy for metastatic melanoma. Neurohospitalist 2018;8:191-3.
132. Green KE, Levine AM, Ward JH, Kaufman DI. GQ1b-seronegative miller fisher syndrome associated with pembrolizumab. J Neuroophthalmol 2019;39:394-6.
133. McNeill CJ, Fehmi J, Gladwin J, Price C. A rare case of Miller Fisher variant of Guillain-Barré Syndrome (GBS) induced by a checkpoint inhibitor. BMJ Case Rep 2019;12:e229443.
134. Zhao J, Bang S, Furutani K, McGinnis A, Jiang C, Roberts A, *et al.* PD-L1/PD-1 checkpoint pathway regulates hippocampal neuronal excitability and learning and memory behavior. Neuron 2023;111:2709-26.e9.
135. Johnson DB, Saranga-Perry V, Lavin PJ, Burnette WB, Clark SW, Uskavitch DR, *et al.* Myasthenia gravis induced by ipilimumab in patients with metastatic melanoma. J Clin Oncol 2015;33:e122-4.
136. Loochtan AI, Nickolich MS, Hobson-Webb LD. Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve 2015;52:307-8.
137. Postow MA. Managing Immune Checkpoint-Blocking Antibody Side Effects. Am Soc Clin Oncol Educ B 2015;1:76-83.
138. Robinson MR, Chan CC, Yang JC, Rubin BI, Gracia GJ, Sen HN, *et al.* Cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma: A new cause of uveitis. J Immunother 2004;27:478-9.
139. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, *et al.* Pembrolizumab versus Ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521-32.
140. Nakamagoe K, Yamada T, Okune S, Moriwaki T, Tamaoka A. Fisher syndrome as an immune-related adverse event after using pembrolizumab but not nivolumab. Acta Neurol Belg 2021;121:1381-2.
141. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, *et al.* Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA 2021;325:632-44.
142. Lyu X, Zhao Q, Hui J, Wang T, Lin M, Wang K, *et al.* The global landscape of approved antibody therapies. Antib Ther 2022;5:233-57.
143. Available from: https://clinicaltrials.gov/search?term=monoclonal antibody&aggFilters=phase:4. [Last accessed on 2023 Nov 29].