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Neurological Complications of Therapeutic Monoclonal Antibodies: Trends from Oncology to Rheumatology

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Abstract

Purpose of Review This review is to describe the scope of neurological complications associated with monoclonal antibody-based therapies, applied across medical specialties, to demonstrate the common and rare neurological syndromes that may be encountered in clinical practice according to the therapeutic agent being receive, and to explain appropriate work-up, diagnosis, and management of drug complications, as supported by the literature.

Recent Findings The number of commercially available, evidence-based therapeutic monoclonal antibodies continues to expand. In oncology, immune checkpoint inhibitors are particularly important, as a wide range of central and peripheral nervous system complications are described. In rheumatology, anti-TNF alpha drugs remain associated with demyelinating syndromes.

Summary The number of therapeutic monoclonal antibodies encountered in practice continues to grow, as does the number of described neurological complications. Recognition of a possible drug complication is key, as these are typically complex patients at risk of other causes of neurological injury. Identification of a complication of therapy often leads to intervention and a change in management.

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Introduction

The use of therapeutic monoclonal antibodies continues to expand across many medical subspecialties. In the last decade, the number of available drugs has greatly increased. Often, these medications are well tolerated, and the development of this class of drugs has clearly led to great strides in the treatment of a broad spectrum of disorders.

Therapeutic monoclonal antibodies are not without risk, however. Among the possible complications of therapy are neurological manifestations. These complications may be encountered by neurologists either in the ambulatory clinic setting or in the inpatient consultative environment. Further, these complications run a broad clinical spectrum. They may range from mild and self-limiting to the point that the patient's ongoing management is not changed. On the other end of the spectrum, these complications may be profoundly severe and necessitate intensive care admission. Neurologically speaking, central and peripheral nervous system localizations are possible.

The recognition of these complications is important for a number of reasons. Patients receiving these drugs are often medically complex, with other reasons for neurological injury. For example, patients with malignancy will often have metastatic disease or radiation complications on the differential diagnosis. Patients with rheumatologic disease are at risk of other autoimmune neurological complications in the absence of these treatments. Therefore, a grasp of the breadth of

possible drug complications may help guide appropriate work-up. Further, because many of these syndromes are immune-mediated, treatments with various forms of immunotherapy may be indicated and improve outcomes. This underscores the importance of timely recognition and treatment.

The number of medications in this class is vast, and the spectrum of described neurological complications is far-reaching. Therefore, the focus of this review will be on key drugs whose complications are more commonly encountered. The majority of syndromes described here are immune-mediated. Table 1 briefly details each of the medications discussed, including the medications' uses and potential neurologic complications.

It is important to note that these drugs have immunomodulatory effects. Patients are at risk of opportunistic infections. These infections may cause neurological presentations, including tuberculosis, progressive multifocal leukoencephalopathy, and others. Less immune surveillance predisposes towards malignancy, and some drugs may predispose to conditions such as lymphoma which can also affect the nervous system. These infectious and malignant possibilities should remain on the differential diagnosis when a monoclonal antibody has been employed.

Monoclonal Antibodies: Biology and History

Antibodies or immunoglobulins are produced by B cells. They are composed of two heavy chains and two light chains. The heavy chain present will differentiate among the IgA, IgE, IgG, and IgM subtypes of immunoglobulins. IgG predominates in the body and functions in the secondary phase of the immune response. IgG is typically the structural basis for therapeutic monoclonal antibodies [1, 2].

While the number of commercially available therapeutic monoclonal antibodies has exploded over the past several years, this technology is not especially new. In 1975, Kohler and Milstein published what is known as the hybridoma technique. This mouse-derived technology later yielded a Nobel Prize [3]. Later, hybridized (containing both mouse and human-derived elements) and humanized monoclonal antibodies became feasible, as well. The first commercially available monoclonal antibody was muromonab, a monoclonal antibody directed against CD3 for use in the renal transplant population. Daclizumab, also developed for use in transplant, was the first humanized monoclonal antibody made available, in 1997 [4, 5].

The market for therapeutic monoclonal antibodies is massive. Between 2008 and 2013, the sales generated grew from approximately 39 billion dollars to 75 billion dollars, reflecting a 90% increase in sales [6••]. The figure of 75 billion dollars reflects approximately half of all pharmaceutical sales in the year 2013. Approximately 10 metric tons of monoclonal

antibody was produced by industry in 2013. By November 2014, 47 different monoclonal antibodies had been approved for use in the USA [6••].

Monoclonal Antibodies in Oncology

Ipilimumab

Immune checkpoint molecules are involved in the maintenance of immunologic homeostasis and prevent the development of autoimmunity and promote self-tolerance [7]. Cytotoxic lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PD-1) are both inhibitory molecules that have been translated into clinical uses [8]. CTLA-4 is an immunoglobulin on the surface of T cells and transmits an inhibitory signal to the T cell. Ipilimumab is a fully human monoclonal antibody against CTLA-4 binding which causes deactivation of the inhibitory signal of the T cell [9]. Ipilimumab is associated with substantial survival advantage over cytotoxic chemotherapy in metastatic melanoma [10, 11]. Combination therapy for melanoma with ipilimumab and nivolumab leads to a higher response rate and longer time to progression than either agent alone [12]. Ipilimumab also improves recurrence-free survival in patients with resected stage III melanoma [13].

Immune-related adverse events from immune checkpoint inhibitors occur due to impaired self-tolerance due to loss of T cell inhibition. Single-agent ipilimumab therapy has been associated with several distinct neurologic syndromes including Guillain-Barré syndrome (GBS) [14, 15••, 16•], chronic inflammatory demyelinating polyneuropathy (CIDP) [17], meningoradiculoneuritis [18], Bell's palsy [19], Tolosa-Hunt syndrome [20], inflammatory enteric neuropathy [21], myasthenia gravis (MG) [17, 20], inflammatory myopathy [22], transverse myelitis [13], aseptic meningitis [17], temporal arteritis [23], posterior reversible encephalopathy syndrome (PRES) [24], and concurrent myositis and myasthenia gravis-type syndrome [17].

The first GBS patient presented after her third infusion of ipilimumab [15••]. Cerebrospinal fluid (CSF) showed typical albumino-cytologic dissociation. She was given corticosteroids (40 mg methylprednisolone intravenously twice daily) and recovered nearly completely within 4 weeks. The second patient described was enrolled in a clinical trial evaluating ipilimumab. In that patient, the outcome was fatal [11]. Another fatal case of rapidly progressive GBS was preceded by obstructive ileus due to myenteric neuropathy [16•].

Case reports have linked the development of myasthenia gravis to ipilimumab. Anti-acetylcholinesterase receptor antibodies have been described in some patients [20]. Transverse myelitis developed in a patient after two doses of ipilimumab for metastatic melanoma. CSF showed a lymphocytic

Table 1 Monoclonal antibodies discussed in this review

Monoclonal antibody	Brand name	Target	Primary or common uses	Neurological complications
Ipilimumab	Yervoy	CTLA-4 (immune checkpoint inhibitor)	metastatic melanoma	Guillain-Barre syndrome, transverse myelitis, Tolosa-Hunt syndrome, enteric neuropathy, CIDP, Bell's palsy, PRES, myasthenia gravis, temporal arteritis, inflammatory myopathy
Nivolumab	Opdivo	PD-1 (immune checkpoint inhibitor)	non-small cell lung cancer, metastatic melanoma, renal cell carcinoma, Hodgkin's lymphoma	Guillain-Barre syndrome, encephalitis, myasthenia gravis, CIDP, Bell's palsy
Pembrolizumab	Keytruda	PD-1 (immune checkpoint inhibitor)	non-small cell lung cancer, metastatic melanoma, Hodgkin's lymphoma	Guillain-Barre syndrome, myasthenia gravis encephalitis
Brentuximab	Adcetris	CD30 (plus monomethyl auristatin E)	Hodgkin's lymphoma anaplastic large cell lymphoma	axonal polyneuropathy
Bevacizumab	Avastin	VEGF	glioblastoma, radiation necrosis of brain, renal cell carcinoma, colorectal cancers, breast cancer, lung cancer	PRES
Blinatumomab	Blincyto	CD3, CD19	acute lymphoblastic leukemia	encephalopathy, tremor, dizziness
Infliximab	Remicade	TNF-α	Crohn's disease, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, psoriasis	CNS demyelination, CNS infections, Guillain-Barre Syndrome, Headache, demyelinating polyneuropathies, Bell's palsy, CIDP
Adalimumab	Humira	TNF-α	rheumatoid arthritis, ulcerative colitic, Crohn's disease, hidratinitis suppuritiva, psoriasis, uveitis	CNS demyelination, Guillain-Barre syndrome, CIDP, CNS infections

TNF tumor necrosis factor, *CIDP* chronic inflammatory demyelinating polyradiculoneuropathy, *CD* cluster of differentiation, *PRES* posterior reversible encephalopathy syndrome, *CNS* central nervous system, *VEGF* vascular endothelial growth factor

pleocytosis. Other etiologies were excluded and there was gradual improvement after ipilimumab was stopped and high-dose steroid therapy [14].

Patients with neurological adverse events should be evaluated promptly. The immune checkpoint inhibitor should be stopped if the severity of the presentation warrants this. Corticosteroids should be administered without delay, and attention towards possible IVIG or apheresis in select cases that are not improving. Additional considerations include infliximab or rituximab [25]. Due to the long-acting effects of ipilimumab, steroids should likely be administered for at least a month at tapering doses.

Nivolumab

PD-1 is expressed on T cells and binds to its ligands PD-L1 and PD-L2 that are expressed on cancer cells and other immune cells [9]. Nivolumab is a fully human IgG4 immune checkpoint inhibitor antibody which binds PD-1 on activated immune cells to disrupt PD-1 interaction with PD-L1 and PD-L2 ligands, thereby attenuating inhibitory signals and augmenting the host antitumour response [26]. Nivolumab has anti-cancer activity against several tumor types, including melanoma, non-small-cell (squamous cell) lung cancer, renal cell carcinoma, and classic Hodgkin's lymphoma [27–31].

Nivolumab has been associated with a range of mild to severe neurological side effects, such peripheral neuropathies, dysguesia/ hypoguesia, restless legs syndrome, tremor, lethargy, memory disturbance, vertigo, dysarthria, cerebral edema, and abducens and facial nerve paresis [32]. Bilateral optic neuritis has also been observed in association with nivolumab [33, 34]. GBS has occurred with nivolumab alone or in combination with ipilimumab [32, 35]. A case of CIDP thought initially to be GBS has been described in association with nivolumab [36]. Cases of MG have been observed on nivolumab alone or in combination with anti-CTLA-4 mAb [37, 38, 39•]. A case of antibody-positive (acetylcholine receptor) myasthenia gravis with rhabdomyolysis was described in a patient on nivolumab for metastatic melanoma [40]. This patient was found to have acetylcholine receptor antibodies prior to treatment.

Two cases of encephalitis have been described in association with combination of nivolumab and ipilimumab [41••]. The first patient had metastatic melanoma and the second had metastatic small cell lung carcinoma. In both, the encephalitis started within days of the first infusion of immune checkpoint inhibitors. One patient demonstrated antibodies against N-methyl D-aspartate (NMDA) receptors. Both showed significant improvement with steroids and intravenous immune globulin (IVIG), as well as two doses of rituximab in the second patient.

Pembrolizumab

Like ipilimumab and nivolumab, pembrolizumab is an immune checkpoint inhibitor. Like nivolumab, pembrolizumab functions by binding to the PD-1 protein. It is not surprising, therefore, that the clinical applications are similar. A phase 3 trial demonstrated that pembrolizumab could improve survival in melanoma patients as compared to ipilimumab [42, 43]. In the realm of lung cancer, pembrolizumab has been shown to prolong progression-free survival as compared to platinum-based chemotherapy in patients whose tumors express PD-1 receptor [44]. It has also been shown as effective in advanced non-small cell lung cancer when compared to docetaxel [45]. Investigations of pembrolizumab are ongoing in a number of other malignancies.

As is true in other immune checkpoint inhibitors, a number of immune-mediated neurological complications have emerged in the literature. The neuromuscular complications of pembrolizumab appear most striking. MG has been described [46, 47]. One case of acetylcholine receptor antibody-positive MG presented with eyelid ptosis, dysarthria, dyspnea, and fatigable weakness following two infusions of pembrolizumab [48]. Interestingly, multiple cases of exacerbation of pre-existing MG are described in the literature, as well [49•, 50•].

The complications are not limited to the neuromuscular junction, or peripheral nervous system. Cases of GBS as well as a motor-predominant polyradiculopathy have been described in case reports [51•, 52]. A case of bilateral Bell's palsy as a presentation of a GBS variant is reported, as well [53] a patient with bilateral eyelid ptosis and weakness was later found to have a necrotizing myositis involving the diaphragm [54]. Autoimmune limbic encephalitis has been established in numerous case reports [55, 56]. One such patient possessed CASPR2 antibodies [57]. A single report of PRES associated with pembrolizumab has been described [58].

Regarding the treatment of prembolizumab-induced neurological complications, no high-quality evidence exists. It should be noted that two patients described in the literature with MG and the one patient with myositis associated with the drug have died of respiratory complications—early recognition and appropriate supportive care are essential. IVIG or plasma exchange (PLEX) has been used with varying degree of success. Tapering doses of prednisone have also been employed in the myasthenics, including one patient whose manifestations were mild who continued pembrolizumab while on 25 mg of prednisone [46]. In general, discontinuation of the immunotherapy will need to be a central consideration and taken on a patient by patient basis. High-dose corticosteroids should not be delayed in patients with suspected limbic encephalitis. It is the author's opinion that early initiation of corticosteroids should be a strong consideration in any patient with a likely immune-mediated complication of checkpoint inhibitor therapies.

Bevacizumab

Bevacizumab has been on the market for considerably longer than many drugs discussed in this review. It was first approved in 2004. Further, many clinical neurologists may have first-hand experience with the medication, as it has some neurological indications including the treatment of glioblastoma [59–62]. It has also been studied in radiation necrosis of the brain. Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). As such, it is a potent inhibitor of angiogenesis. It has been studied and has use in renal cell carcinoma, colorectal cancers, as well as breast and lung cancer [63–69]. An additional and exciting application of bevacizumab is in neurofibromatosis type 2 (NF2). In one initial case series, four patients with NF2 were administered bevacizumab with stable size of neurofibromas (three patients) or reduction in tumor size (one patient) [70]. In a series of 31 patients with vestibular schwannomas, a majority had an improvement in hearing and a reduction in tumor size [71].

At this point, the neurological complications of bevacizumab have been fairly well described. They can be broadly divided into two categories. One category is hemorrhagic complications. The other category is complications of resultant endothelial dysfunction, namely posterior reversible encephalopathy syndrome (PRES). Regarding hemorrhage or other cerebrovascular events, intratumoral hemorrhage may be most common. A series of cerebrovascular events in patients receiving bevacizumab showed that hemorrhage into a known tumor was the clinical scenario in 7 of 10 cases [72]. Rupture of a cerebral AVM after bevacizumab treatment is described in a single case [73]. A much larger series, meanwhile, reviewed 153 cases of CNS hemorrhage in 99 unique patients. Only 16 patients had a known intracranial tumor. The bleed was a cause of death in nearly half of these patients [74].

The exact risk of hemorrhage or other cerebrovascular complications after bevacizumab treatment is not entirely clear. A case series demonstrated that intracranial hemorrhage is no more common compared to control patients who had not received bevacizumab. The majority of hemorrhages occurred in patients who had intracranial tumor [75•]. More recently, a series described the risk of ischemic stroke and intracranial hemorrhage in patients with recurrent glioblastoma—those who had received bevacizumab were no more likely to have these cerebrovascular complications [76].

Given its effects on the blood vessels, it is logical that PRES is a potential complication and this is well described. In 2006, a single case was published of a patient who developed headache and cortical blindness 11 days following a bevacizumab infusion [77•]. Symptoms resolved within 4 weeks. Also in 2006, dual cases of typical PRES including hypertension following bevacizumab were reported [78••, 79••]. One of these patients had a small amount of intraparenchymal hemorrhage, and subarachnoid blood in the setting of bevacizumab-associated

PRES is described as well [80]. The ideal management of PRES associated with bevacizumab is not evidence-based. Acutely, blood pressure control is key. Long-term discontinuation of the offending drug is likely indicated depending on a patient's unique circumstances.

Brentuximab

Brentuximab vedotin is an antibody directed against CD30. It is useful in the treatment of Hodgkin's lymphoma and anaplastic large cell lymphoma. Isolated anti-CD30 antibodies were minimally beneficial in studies. Therefore, brentuximab vedotin a hybrid drug-antibody conjugate containing an anti-CD30 antibody linked to the antitubulinagent, monomethyl auristatin E. The key neurological side effect to be aware of is polyneuropathy. This is thought secondary to the antitubulin drug rather than any immune-mediated phenomenon. In a phase 1 study, 10 of 45 patients developed symptomatic peripheral polyneuropathy [81]. A phase 2 study showed an objective response in 50 of 58 patients, and complete remission in 33 of them. Polyneuropathy was common, and was noted in 41% of study subjects [82].

The clinical features of 25 patients with brentuximab-associated peripheral neuropathy were recently described [83••]. All of these patients were being treated for a diagnosis of a cutaneous T cell lymphoma (mycosis fungoides or Sezary syndrome). The median time to onset of neuropathic symptoms was 15 weeks. Twelve of 18 patients who were deemed to have a clinically significant neuropathy were shown to clinically worsen after the last dose of brentuximab (a coasting phenomenon). Improvement in neuropathy following cessation of therapy was common; at 24 months, 66% of patients showed improvement. Higher doses of brentuximab were associated with a higher risk of polyneuropathy, as was exposure to additional treatments in the preceding year. Electrodiagnostics have shown this to be an axonal polyneuropathy in the majority of cases. Based on experiences thus far, patients presenting to establish care for a brentuximab-associated polyneuropathy may be counseled about an overall good prognosis for clinical improvement over time.

Blinatumomab

Blinatumomab is a monoclonal antibody developed for use in acute lymphoblastic leukemia patients. It is capable of binding both CD19 and CD3. CD19 is expressed on B-precursor acute lymphoblastic leukemia blasts, while CD3 is present on cytotoxic T cells. Therefore, the bispecific antibody is able to recruit healthy-functioning T cells into the destruction of pathological B cells. Phase 1 and 2 trials showed the drug to have anti-leukemic potential [84, 85]. More recently, a Phase 3 trial

demonstrated that blinatumomab was superior to chemotherapy with regards to overall survival and remission rates [86].

Neurological side effects due to blinatumomab may be especially common. In the phase 2 study published in 2015, 52% of all patients receiving the drug reported neurological side effects to some degree. In general, these tended towards more mild side effects with tremor and dizziness being most common, followed by confusion or encephalopathy. There were no fatal neurological complications, but encephalopathy was the most commonly reported severe neurological side effect. Dexamethasone was reportedly helpful for many neurological side effects, and treatment with the drug was not interrupted. In the phase 3 trial published in 2017, 267 patients were administered blinatumomab and 19 reported a neurological side effect. Encephalopathy and aphasia were observed in four and three patients, respectively. No other neurological side effect was seen in more than a single patient. Seizures may be possible, and were described in a single patient in an earlier smaller study of the drug [87]. A single, additional case is reported of a patient developing seizures following blinatumomab infusions, although this patient was also shown to have cerebral mucormycosis. The seizures abated with dexamethasone [88]. The mechanism of neurotoxicity with regards to this drug is unknown.

Monoclonal Antibodies in Rheumatology

Tumor necrosis factor-alpha (TNF-α) is a cytokine that modulates inflammatory reactions in humans by facilitating migration of leukocytes, augmenting neutrophil activity, inducing pro-inflammatory cytokines and acute phase reactants, and activating production of tissue-degrading enzymes. Patients with rheumatologic conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis have increased concentrations of TNF-α in the lesion or organ involved. Monoclonal antibodies against TNF-α have been shown to reduce pathologic inflammation or induce remission in a significant number of patients with rheumatologic conditions. Therapeutic formulations of monoclonal antibodies against TNF-α include infliximab, adalimumab, omalizumab, certolizumab, and certolizumab; of these, infliximab and adalimumab are widely utilized and will be discussed here.

Infliximab

Infliximab is a chimeric IgG1K monoclonal antibody that neutralizes the biological activity of TNF-α [89]. Although the exact mechanism of action is unknown, in vitro studies have demonstrated that infliximab inhibits the activity of TNF-α in human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Infliximab is considered the prototypic monoclonal antibody TNF-α inhibitor;

initial approval was obtained for Crohn's disease in 1998 and it has since gained additional indications in ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis [90–98].

Extensive safety data are available, including a total of 4779 patients studied in clinical trials, and countless more through post-marketing data [99]. The most common adverse event and neurological side effect is by far headache, occurring in 12–18% of patients studied in the clinical trial setting. Other serious adverse neurological events include central demyelinating events, peripheral demyelination and other neuropathies, and neurologic sequelae of systemic vasculitis. Deepak et al. reviewed a total of 772 neurologic adverse events associated with TNF-α inhibitors from post-marketing data between 2000 and 2009, of which 170 involved use of infliximab for rheumatologic conditions. Of these, peripheral neuropathy was the most common finding (44.1%) followed by CNS demyelinating events (12.9%), facial palsy (12.4%), and optic neuritis (11.8%) [100]. Central demyelinating syndromes encountered included multiple sclerosis, optic neuritis, monophasic demyelinating events, and transverse myelitis [89, 100, 101•, 102••, 103, 104•, 105•]. Treatment involves discontinuation of infliximab with or without intravenous steroids, with some degree of recovery seen in most patients. For this reason, infliximab should be avoided in patients with a personal or family history of MS or other demyelinating diseases.

Infliximab has been linked to development of demyelinating peripheral polyneuropathies. Various clinical patterns are reported, including GBS, CIDP, purely sensory neuropathies, and multifocal motor neuropathy [105•, 106, 107]. Small-fiber neuropathy has recently been described and is potentially underdiagnosed due to normal nerve conduction studies in these patients [108]. The clinical course can be unpredictable and chronic disease may develop either after change of anti-TNF-α agent or after treatment discontinuation without drug reintroduction [107]. For this reason, the discontinuation of therapy should be made on an individualized basis after detailed discussion between patient and physician.

Infliximab can induce a systemic vasculitis, with peripheral neuropathy being the most common neurologic manifestation [109]. Other complications are related to resultant immunosuppression associated with the drug. CNS infections including cryptococcal meningitis, neuroborreliosis, listeria meningitis, herpes zoster encephalitis, and spinal epidural abscess have been reported in case reports and post-marketing data [100, 110–111]. Finally, infliximab has been linked to increased risk of glioblastoma with an odds ratio of 2.8–7.41, although a causal relationship has not been established [112].

Adalimumab

Adalimumab is a recombinant IgG1 monoclonal antibody that binds directly to TNF-α to prevent interaction with p55 and p75 surface receptors. Unlike infliximab, adalimumab is fully

humanized, consisting of human-derived heavy and light chain variable regions and a human IgG1K constant region [113]. It was developed for use in rheumatoid arthritis and robust clinical data have shown it to be well tolerated and effective at slowing progression and improving outcomes [114, 115]. Initial approval was granted in 2002 for the treatment of moderate to severe rheumatoid arthritis in patients with an inadequate response to traditional disease-modifying therapy, and broadened to first-line treatment in 2005 [113]. The United States Food and Drug Administration approval was subsequently granted for psoriatic arthritis, ankylosing spondylitis, Crohn's disease, juvenile idiopathic arthritis, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and most recently, uveitis in 2016 [114, 116–123].

Head-to-head clinical trials comparing the incidence of neurologic and other adverse events between infliximab and adalimumab are lacking, and there is no clear consensus that one is safer than the other [113]. The smaller numbers of adverse events reported in post-marketing surveillance data likely reflects the shorter length of time adalimumab has been in widespread use, rather than a better safety profile [100]. This is supported by a recent Cochrane meta-analysis including over 60,000 participants in 160 randomized controlled trials and 46 open-label extension studies, in which indirect comparison revealed no difference in the rates of adverse events or serious adverse events [124]. It should be noted that this study did not specifically compare the rates of neurologic adverse events.

Like other TNF-α blockers, adalimumab has been linked to exacerbation or new onset of demyelinating disease including monophasic demyelination events, MS, optic neuritis, transverse myelitis, GBS, CIDP, and other peripheral demyelinating neuropathies [101•,106, 107, 125–134, 135•, 136].

This can pose a clinical dilemma in patients with uveitis, which is itself associated with demyelinating disease [125, 137]. Severe or atypical CNS infections have been reported and opportunistic pathogens such as listeria and toxoplasma should be considered in patients on adalimumab who present with new onset seizures, focal neurologic deficits, or meningismus [138–141]. Varicella zoster and herpes simplex encephalitis are rare but may have a fulminant course [138, 141–143]. The incidence of glioblastoma may also be increased [112].

Conclusions

This review has addressed neurological complications of monoclonal antibody-based therapies with applications across different medical specialties. In oncology, immune checkpoint inhibitors such as ipilimumab, nivolumab and pembrolizumab should be recognized by the plethora of immune-mediated complications they may cause. Recognition of these conditions is vital, as steroids and other immunotherapies are warranted and the drug must be discontinued in many cases. PRES is a key complication of bevacizumab to be aware of. Among drugs commonly employed for rheumatologic conditions, infliximab and adaliumab are well associated with central and peripheral demyelinating syndromes. Often, the differential diagnosis might include a complication of the underlying rheumatologic condition being treated.

Clearly, the breadth of applications of therapeutic monoclonal antibodies continues to expand. We may expect many more similar agents to gain use over the coming years. Clinical neurologists must remain abreast of the approval and use of new drugs in this area and continue to report emerging neurological syndromes. Recognizing and managing complications of these and other monoclonal antibodies represents a growing but exciting challenge.

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