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Jacobs Journal of Vaccines and Vaccination

Review Article

Management of Neurological Adverse Events Associated with Immunotherapy and A Possible Algorithm for Clinical Management

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Received: 02-26-2015

Accepted: 05-29-2015

Published: 08-04-2015

Abstract

Different neurological disorders, including alterations of peripheral nerves, multiple sclerosis (MS), optic neuritis (ON), acute transverse myelitis (ATM) and posterior reversible encephalopathy syndrome (PRES) can be associated with some types of immunotherapy. Likewise, anti-tumor necrosis factor alpha (TNF-*a*) treatments for autoimmune diseases such as rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ankylosing spondylitis (AS), juvenile chronic arthritis, and Crohn's disease have also associated with neurological disorders. This article reviews the most current aspects regarding neurological adverse events associated with immunotherapies and TNF-α inhibitors with emphasis on their management.

Keywords: Immunotherapy; Tumor necrosis factor alpha (TNF-a); Anti-TNF-a; Neurological adverse events; GBS

List of Abbreviations

MS: Multiple Sclerosis;
ON: Optic Neuritis;
ATM: Acute Transverse Myelitis;
RA: Rheumatoid Arthritis;
AS: Ankylosing Spondylitis;
TNF-a: Anti-Tumor Necrosis Factor Alpha;
ONTT: Optic Neuritis Treatment Trial;
GBS: Guillain–Barre' syndrome;
PE: Plasma Exchange;
IFN: Interferon;
CTLA-4: cytotoxic T-lymphocyte antigen-4;
PD-1: Programmed Death-1;
PRES: Posterior reversible encephalopathy syndrome;
iRAE: Immune Related Adverse Events;
MP: Methyl Prednisone

Introduction

Endogenous immune responses against tumor cells can be achieved when monoclonal antibodies act on immune checkpoint proteins, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1). Several lines of evidence give a reason to treat melanoma with immunotherapy [1]. Studies show that immune effector cells in patients with metastatic melanoma have recognized malignant cells and that the patients have established T cells that confer immunologic memory [2]. All the findings support the idea that the immune system is capable of combating melanoma. These antibodies; however, cause a unique set of toxicities called immune-related adverse events (irAEs), which include colitis, hypophysitis, hepatitis, pancreatitis, iridocyclitis, lymphadenopathy, neuropathies, and nephritis which are reported with Ipilimumab [3].

Tumor necrosis factor alpha (TNF-a), a member of the TNF super family of ligands, an important pro-inflammatory cytokine, is involved in the pathogenesis of rheumatic autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel diseases, multiple sclerosis (MS) and various disorders of peripheral nerves [3,4] . Although anti-TNF-a drugs have been successfully used for the treatment of these diseases, they have been associated with different neurological adverse events, systemic lupus erythematosus-like syndromes and vasculitis. The neurological disorders that have been reported include alterations of peripheral nerves [Guillain– Barre' syndrome (GBS), Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies], MS, optic neuritis (ON) and acute transverse myelitis (ATM) [5]. Adalimumab (Humira) and Inflixmab (Remicade) are anti-TNF monoclonal antibodies approved for use in the treatment of rheumatic autoimmune diseases [6]. The most common reported neurological symptoms are paresthesias, visual disturbances, confusion and gait disturbances that developed after a mean of 5 months of therapy. Partial or complete resolution of symptoms are seen in all patients after drug discontinuation [7,8]. Simsek et al. reported 15 cases (one personal and 14 identified in PubMed) of optic neuritis occurring after the treatment with anti-TNF-a [9,10] A recent safety assessment based on clinical trials and postmarketing surveillance of RA patients estimated an annual incidence of demyelination disorders following adalimumab therapy of approximately 1 per 1000 patient-years [11].

Morbidity of irAEs can be limited with patient and physician education as well as good patient– caregiver communication. Early recognition and initiation of treatment of these irAEs are key factors to reduce the risk of complications, since virtually all irAEs are reversible with the use of steroids and other immune suppressants. This review provides detailed description to manage the neurological adverse events associated with immunotherapy.

Patients need to be monitored for motor and sensory neuropathy symptoms, unilateral or bilateral weakness, sensory alterations, and paresthesia. Ipilimumab should be withheld in patients who experience moderate neuropathy (not interfering with daily activities), and should be permanently discontinued in patients with severe neuropathy, such as Guillain-Barré-like syndrome. Medical intervention needs to be instituted for management of severe neuropathy, including prednisone 1–2 mg/kg/day [12, 13]. It is likely not safe to continue use or readminister drug to patients who develop significant CNS adverse reactions. Although there is evidence to suggest that demyelinating diseases occur more commonly in patients with inflammatory bowel disease than among those without IBD, the temporal relationship of these events to initiation of anti-TNF-alpha therapy, and the improvement or resolution of symptoms following cessation of therapy, suggests a causative relationship [11]. Different neurological adverse events and their management:

1. Therapy of multiple sclerosis:

Multiple sclerosis, also known as disseminated sclerosis is a chronic disorder of the nervous system which typically affects young and middle-aged adults. The cause is still uncertain. It seems that there is an inherited susceptibility to the disease. The specific cause may be auto- immune damage triggered by a slow virus or a persistent measles infection or other reasons. Areas of the myelin sheaths surrounding nerves in the brain and spinal cord become damaged, leaving scarring in the form of patches of sclerosed (hardened) fibrous material. The damage is widely scattered through the brain and spinal cord [14].

The course of the disease is notoriously unpredictable, but it often shows a pattern of relapse and remission, with a variety of nervous system symptoms. These include, in the early stages, limb weakness or heaviness, blurred or double vision in one or both eyes, tingling or numbness (but rarely pain) in a limb or in the trunk, and ataxia, where there is vertigo, unsteadiness or poor balance when walking. The bladder can be affected causing frequency, urgency or difficulty in passing water. The first attack commonly clears up completely within 1-3 months, with a recurrence often within 2 years. In a few cases there is no remission, in some others there is no recurrence for more than 10 years. Some patients continue to recover well after relapses, but 50% eventually enter a progressive stage with persistent and increasing disability. In addition to increasing motor disability, there may be urinary retention or incontinence, slurred speech, and mental changes with emotional lability, depression or euphoria. Emotional and mental changes may be a natural reaction to the diagnosis and disability of M.S., but can also be due to the disease process itself creating lesions in the frontal lobes [14].

The diagnosis can be confirmed to some extent by electrical conduction tests on the nerves, by CAT or MRI scans, and by tests on the cerebro-spinal fluid taken by lumbar puncture.

However, it can be difficult to arrive at a totally conclusive diagnosis. During acute flare-ups, short (5-day) courses of corticosteroids are often prescribed. This does help to control the flare ups, but is not thought to alter the long-term prognosis (14).

The commonly used first-line agents as well relatively safe for multiple sclerosis treatment are IFN-b and glatiramer acetate. If treatment with IFN-b or glatiramer acetate is not effective, immunosuppressants such as mitoxantrone can still play a considerable role, especially in rapidly progressing cases. However, mitoxantrone use is limited by its tolerability and potential severe adverse effects. Natalizumab, a monoclonal antibody, is used for treatment of relapsing remitting multiple sclerosis. It can reduce the relapse rate by up to 68% and the disability progression rate by 42%, compared with placebo [15]. Therefore, significant clinical effects can be expected for treatment with natalizumab [15]. But natalizumab carries a risk for the development of progressive multifocal eukoencephalopathy, an often fatal brain disease caused by the John Cunningham virus [15]. Clinical data of the head-to-head Phase III trial of oral fingolimod demonstrated superior efficacy compared with intramuscular IFN-b1a [16,17].

2. Treatment for Guillain–B arre' synd rome (G-BS):

Guillain-Barre´ syndrome is an acute onset, immune-mediated disorder of the peripheral nervous system. The term GBS is often considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the increasing recognition over the past few decades of variants, the number of diseases that fall under the rubric GBS has grown to include axonal variants and more restricted variants such as Miller Fisher syndrome [18,19]. Guillain Barre Syndrome most commonly characterized by some combination of limb paresthesias, generalized weakness, and areflexia.

Pathogenesis of GBS not yet fully understood and current thinking is that GBS may not be a single disease, but a variety of acute neuropathies with a number of related immune-mediated pathogenetic mechanisms. Most common immunopathologic finding: endoneurial inflammation in spinal nerves roots, distal nerve segments, or around potential nerve entrapment sites. Also, target antigens appear to be common to the axon, myelin sheath, or both. The exact antigens, the precipitating event, and the resultant mechanism of injury some what unclear. Prior infection with few agents such as Cytomegalovirus. EBV, campylobacter jejuni etc., is well established as a precipitating event in the development of GBS [20].

Immune therapy includes plasma exchange and IV immunoglobulins. Plasma Exchange (PE) offers significant benefit when applied within the first 4 weeks of onset of GBS, but the largest effect was seen when started within the first 2 weeks [21]. The usual regimen is PE 5 times during 2 weeks, exchanging a total of about 5 plasma volumes [21]. Availability of this invasive procedure requiring a central line and specialfacilities for PE in a hospital setting is sometimes a limiting factor for its initiation. PE is usually well tolerated but hemodynamic instability, dilutional coagulopathy, hypocalcemia and allergic reactions can occur [22]. Relative contraindications for PE include severe cardiac disease or coagulopathy. Intravenous immunoglobulin (IVIG) is another therapeutic modality which is well tolerated; but is associated with certain infusion-related and hematological adverse effects such as chills, headache and myalgias and resolves by stopping the infusion and resuming it 30 min later at a slower rate [23]. Oral corticosteroids or intravenous methyl prednisolone (MP) alone are not beneficial in GBS[24]**.** The explanation for the lack of more obvious benefits from corticosteroids is unclear, but steroids might have harmful effects on recovering peripheral nerves and denervated muscles by inhibiting the possible beneficial function of macrophages in clearing debris [25]. Ventilator care, nutritional support should be provided adequately along with preventive measures to develop deep vein thrombosis and noscomial infections secondary to prolonged hospitalization.

3. Treatment of optic neuritis

In most parts of the world acute demyelinating optic neuritis (ON) is the most common cause of unilateral painful visual loss in a young adult. In those regions where multiple sclerosis (MS) is common, most cases of ON are related to that disorder, although the diagnosis is not made until a second symptomatic episode (relapse) when the disorder can be referred to as MS-associated ON (MSAON). Typical cases can be referred to as demyelinating ON until a diagnosis of MS is made. Since ON can herald a more diffuse demyelinating disease, care should be taken in making an accurate diagnosis, and careful consideration given to treatment options, particularly as other causes of ON not related to MS require quite different management [26].

The pathogenesis of demyelinating ON is thought to involve an inflammatory process that leads to activation of peripheral T-lymphocytes which cross the blood–brain barrier and cause a delayed type hypersensitivity reaction culminating in axonal loss. Clinical recovery reflects the combined effects of demyelination with conduction block and axonal injury on the one hand, remyelination with compensatory neuronal recruitment on the other [26]. However, irreversible axonal damage occurs early in the disease process. A study using ocular coherence tomography (OCT) demonstrated that axonal injury is common in ON and observed retinal nerve fibre layer (RNFL) thinning in 74% of individuals within 3 months of acute ON [27]. The classic triad of inflammatory ON consists of loss of vision, periocular pain and dyschromatopsia, and is unilateral in 70% of adults. Visual loss varies from mild reduction to no perception of light and progresses over 7–10 days before reaching a nadir. Periocular pain occurs in more than 90%

of cases, may precede or coincide with the visual symptoms and usually resolves over days. All patients show reduced contrast sensitivity and dyschromatopsia, which are often out of proportion to the visual acuity deficit. Most persons show mixed red-green and blueyellow colour defects, one type or the other predominating [28].

10-year risk of recurrence of demyelinating ON is about 35% as per Optic Neuritis Treatment Trial (ONTT) [29]. The strongest predictor for the development of MS is the presence of white matter lesions on the initial magnetic resonance image of the brain[26] .A meta-analysis of 12 randomized, controlled trials of corticosteroid treatment in both patients with optic neuritis and multiple sclerosis confirmed that high-dose intravenous corticosteroids were effective in improving short-term visual recovery; and there was no statistically significant benefit in long- term outcome even in those presenting with severe visual loss [30]. Corticosteroids cause side- effects such as insomnia, weight gain and mood alterations, psychotic depression, pancreatitis and osteonecrosis [31]. The ONTT has shown that 28% [32] and 35% [29] of patients developed recurrence of ON within 5 and 10 years, respectively. Not surprisingly, recurrence was more common in patients who were subsequently diagnosed with MS [26].

4. Treatment for posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a clinical-neuroradiological entity [33]. This syndrome is characterized by headache, visual disturbances, seizures, altered mental status and radiological findings of edema in the white matter of the brain areas perfused by the posterior brain circulation [34]. The clinical spectrum of PRES include headache as the most common symptom; however, it may not be present in all cases [35]. Other common signs are consciousness alterations such as lethargy, stupor, and somnolence although coma may develop. Visual disturbances range from blurred vision to cortical blindness, and permanent visual field defects have been reported [38]. Seizures, or status epilepticus (SE), may present as the initial clinical picture in some cases [34, 35]. Although rare, signs of motor dysfunction such as hemiparesis, dystonia and dysmetria may be present [35].

While most cases are due to systemic hypertension (HTN), other conditions and entities have been identified as etiologic or risk factors in the absence of HTN, such as immunosuppressant drugs use, nephrotic state, sepsis, and systemic lupus erythematosus [35, 36, 37].The use of many drugs has been related with PRES pathogenesis; however, the exact mechanisms are yet to be fully explained. Many theories have been suggested for this strong drug-disease relation, including drug-induced HTN, nephrotoxicity, direct neurotoxicity, and endothelial damage [39,40]. Many immunosuppressant drugs have been associated with the development of PRES [41,42]. Bevacizumab, a recombinant humanized monoclonal antibody, produces PRES by both increasing BP and inhibiting vascular endothelial growth factor (VEGF) [43]. Sunitinib is a tyrosine kinase inhibitor which also inhibits VEGF effects, via anti-VEGF receptor [44,45]. Posterior reversible encephalopathy syndrome occurred following infliximab infusion also n few cases [46].

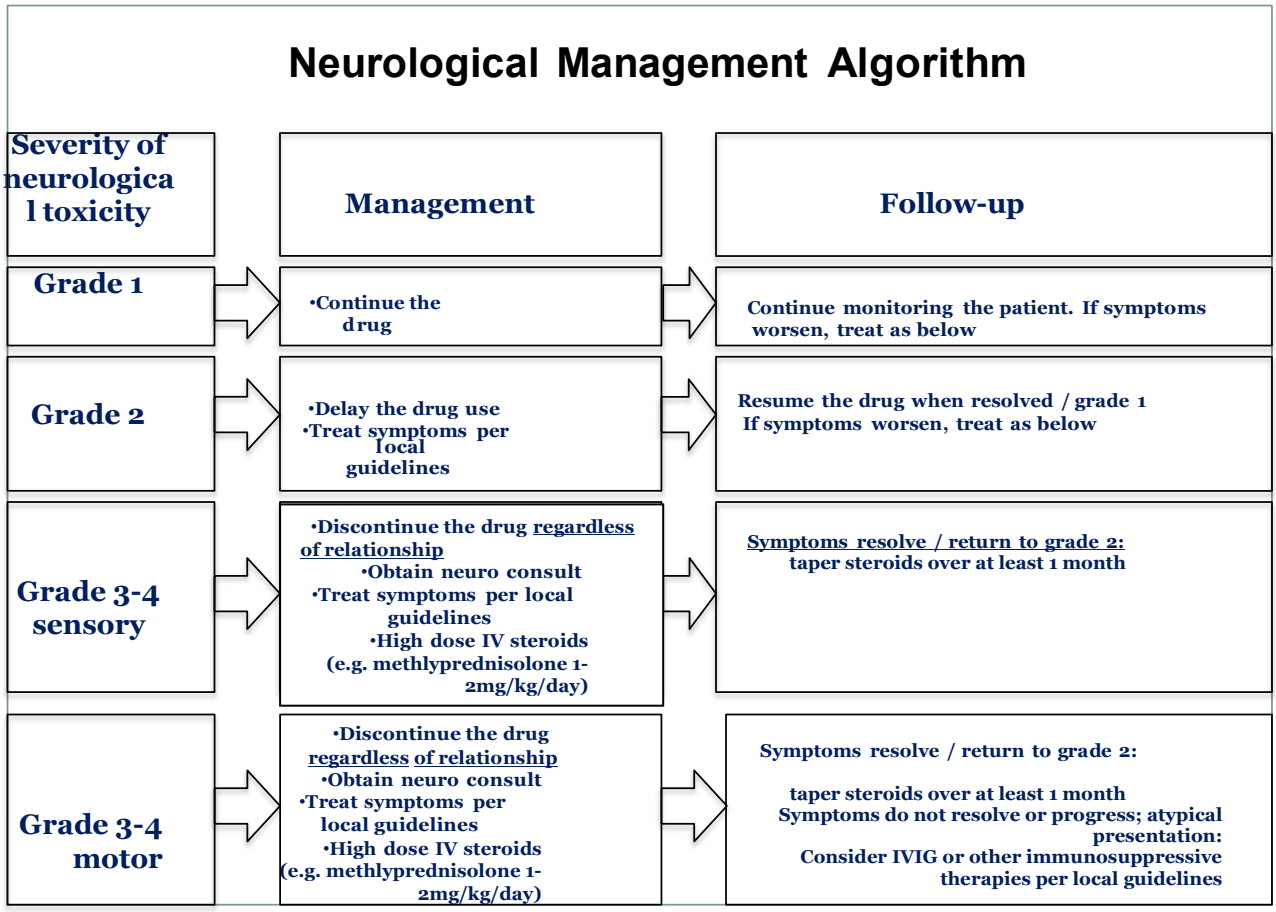
An early etiologic diagnosis allows prompt correction of the cause of PRES. Patients with PRES require the symptomatic measures usually taken in the ICU. The need for upper airway protection should be evaluated continuously in patients with marked consciousness impairment or seizure activity. Hypoglycemia should be looked for routinely and corrected. If glucose is given, 100 mg of thiamine should be administered concomitantly, most notably when there is evidence of vitamin B1 deficiency. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, in particular hypomagnesemia, which require prompt correction [47]. Antiepileptic treatment, appropriate for the electrical and clinical pattern in the patient, should be initiated on an emergency basis and according to current guidelines [47]. Apart from this patients may require blood pressure control, withdrawal of cancer chemotherapy or immunosuppressive agents, Cesarean section, dialysis, or other interventions. Prompt correction of the cause is crucial to decrease the risk of ischemia or bleeding and therefore to avoid permanent disability or death [35].

Proposed algorithm for general management of neurological adverse events

There is a necessity to have a general algorithm, to approach and manage the neurological adverse events due to their diverse symptoms, severity and urgency to treat in order to stop the progression of patients' symptoms and signs. The patients should be educated to notify about any neurological problems such as unilateral or bilateral weakness, sensory alterations, parasthesias or blurred vision. Once the problem notified close monitoring, delay/discontinuation of the concerned drug and corticosteroid treatment are required based on the severity of the event. Based on the events, mild symptoms are considered as grade 1, moderate symptoms are considered as grade 2 and severe and very severe events are considered as grade 3-4.

For grade 1 events, continue the drug with close monitoring of the patient's symtoms and signs. If the symptoms worsen treat the event as grade 2 AE. Grade 2 events should be treated with delaying the drug usage and resume the drug when event resolves to grade 1. If the events in grade 2 persist treat as grade 3-4. Grade 3-4 events should be differentiated whether they are motor or sensory. For sensory grade 3-4 events, discontinue the drug if considered related, Obtain neurologist consultation, treat symptoms per local guidelines, High dose IV steroids (e.g. methlyprednisolone 1-2mg/kg/day) are required. For motor grade 3-4 events, discontinue the drug regardless of relationship, Obtain neurologist consultation, treat symptoms per local guidelines High dose IV steroids (e.g. methlyprednisolone 1-2mg/kg/

day). The algorithm to treat the neurological adverse based on severity is below in figure 1.



Discussion

In recent decades immunologic therapies have become increasingly important in the treatment of different therapies which are particularly immune responsive. Though anti-TNF-a drugs have been successfully used for the treatment of RA, psoriatic arthritis, psoriasis, AS, juvenile chronic arthritis, and crohn's disease, the pitfall is the association of these drugs with some serious adverse events which are significant clinical problems. One of the most important issues is the association between anti-TNF-a therapy and neurological adverse events including alterations of peripheral nerves (GBS, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies), MS, ON and acute transverse myelitis (ATM) [48-52]. Although the current available data supports the efficacy and safety of anti- TNF-a treatment for many autoimmune diseases, this therapeutic option should not be administrated in patients with history of MS or MS-like illness; and possibly patients with history of peripheral nerve illnesses are not good candidates either for TNF-α inhibition. Furthermore, patients receiving anti-TNF-α drugs, who develop new or unusual neurological symptoms, should stop the treatment and be properly evaluated before continuing their therapy [53-57].

An important issue in the development of novel treatments for GBS patients is advanced trial design. As GBS is a rare and heterogeneous disease, a large well-powered clinical trial that can be conducted within reasonable time is hampered. This especially is the case in subgroups of patients with poor prognosis or in otherwise clinical subgroups of patients. Clinical trials should focus especially on patients with a poor prognosis [58-62].

Conclusion

Finally, in the treatment decision making process we should recall that it is the patient who takes the risk – either for her /his potential disease consequences or potential drug induced side- effects/risks. Therefore, benefit–risk evaluations and perceptions are likely to vary among patients and between patients and their physicians.

Conflict of Interest

This paper has been written without external financial funding. There is no conflict of interest.

Acknowledgments

None declared.

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