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Review

Neurological immune-related adverse events with checkpoint inhibitor therapy: challenges for the neurologist

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ABSTRACT

Immune checkpoint inhibitors (ICI) have had a dramatic effect on cancer outcomes with their use increasing as indications expand. Despite impressive efficacy across a range of tumour types, their role in activating the immune system results in frequent immune-related adverse events (irAE). While gastrointestinal, endocrine, respiratory and cutaneous toxicities are common, neurological irAEs (N-irAEs) occur more rarely. N-irAEs have been well reported in the literature, can affect any part of the nervous system and are associated with significant morbidity and mortality. Treating oncologists have a high index of suspicion for irAEs and a low threshold for initiating treatment. The role of the neurologist is to consider the differential diagnosis, direct investigation according to the clinical syndrome and guide management, efficacy monitoring and rehabilitation. Once alternative aetiologies have been excluded, the ICI should be either paused or discontinued depending on clinical severity, and immunosuppressive treatment commenced. There is no high-level evidence for toxicity management in this emerging field, so there is much variation in clinical practice and the medical literature. While describing the range of neurological toxicities related to ICIs and current experience of management and outcome, this review focuses on the potential utility of predictive biomarkers, the risk of re-ignition of pre-existing neurological autoimmune disease and the question of rechallenge after a N-irAE. Given the paucity of data specifically relating to N-irAE, we also discuss cancer outcomes in the context of irAEs and associated immunosuppression and consider some outstanding questions pertinent to ICI-related neurotoxicity and potential future directions for research.

INTRODUCTION

The treatment of cancer has evolved considerably over recent decades—from cytotoxic chemotherapy to molecule-directed therapeutics through to the current utilisation of immunotherapy.[1 2] Immune-based treatments encompass a wide range of different approaches,[1] with adoptive cell therapy with Chimeric Antigen Receptor T cells (CAR-T) and immune checkpoint inhibitors (ICI) the most commonly used in clinical practice. Furthermore, the first cancer tumour-infiltrating lymphocytes (TILs) therapy recently received Food and Drug Administration (FDA) approval for the treatment of advanced melanoma, marking another significant milestone in cancer immunotherapy. While CAR-T therapy is currently limited to haematological malignancies, the use of ICI is expanding, with an estimated 44% of US cancer patients now eligible for this treatment.[3]

The first ICI to be used in clinical practice was ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte associated protein 4 (CTLA-4), which was FDA-approved in 2011, supported by evidence of improved overall survival (OS) in patients with malignant melanoma in the key phase 3 trials.[4 5] This paved the way for the development and approval of other ICIs, beginning with monoclonal antibodies targeting programmed cell death 1 (PD-1), such as pembrolizumab and nivolumab, or PD-1 ligand 1 (PD-L1), such as atezolizumab, durvalumab and avelumab, which have since become some of the most widely used anticancer therapies.[6]

ICIs are also often being used in combination regimens, including those involving other classes of ICI, cytotoxic chemotherapy and biological or targeted therapies.[7] The first ICI combination, nivolumab plus ipilimumab, was granted FDA approval in 2015 for the treatment of metastatic melanoma.[8] In 2022, the combination of nivolumab with another ICI, relatlimab, targeting lymphocyte-activation gene 3 (LAG-3), received approval for unresectable or metastatic melanoma.[9–11] As of the start of 2025, ICIs have been approved for more than 20 indications in a variety of solid organ malignancies, with their use expanding into adjuvant and neo-adjuvant settings (table 1).[12]

ICIs have revolutionised cancer treatment, resulting in sustained survival benefit in a subset of patients, with outcomes varying across different tumour types. For instance, in metastatic melanoma—a disease previously considered inevitably fatal—the combination of nivolumab with or without ipilimumab has demonstrated long-term efficacy, with melanoma-specific survival at 10 years reported as 52% for nivolumab plus ipilimumab and 44% for nivolumab alone.[13] Despite their efficacy against cancer cells, the systemic nature of ICIs can result in a wide spectrum of immune-mediated adverse events (irAEs) across all organ systems. While gastrointestinal, endocrine, respiratory and cutaneous toxicity is most common, neurological immune-related adverse events (N-irAEs) occur in 1%–4% of ICI-monotherapy and up to 14% with

Table 1 Approved immune checkpoint inhibitors

Checkpoint target	Drug
PD-1	Nivolumab
	Pembrolizumab
	Cemiplimab
	Sintilimab
	Camrelizumab
	Dostarlimab
	Tislelizumab
	Penpulimab
	Toripalimab
	Zimberelimab
	Serplulimab
	Pucotenlimab
PD-L1	Durvalumab
	Atezolizumab
	Avelumab
	Envafolimab
	Sugevalimab
CTLA-4	Ipilimumab
	Tremelimumab
LAG-3	Relatlimab*

*Given in combination with nivolumab.
CTLA-4, cytotoxic T lymphocyte associated protein 4; LAG-3, lymphocyte-activation gene 3; PD-L1, programmed cell death 1 (PD-1) ligand 1.

combination therapy.[14 15] This review discusses the current understanding of the N-irAEs and their management with a particular focus on predictive biomarkers, cancer outcomes, risk of pre-existing autoimmune disease (AID) re-ignition and rechallenge. With a growing number of indications for ICI therapy and a wide spectrum of potential neurological toxicities, it is important for clinicians to be aware of this developing area of neurology. Despite progress in clinician awareness and therefore identification and the development of treatment algorithms by oncologists for irAEs over the last decade, many questions and challenges remain.

MECHANISM OF ACTION AND IMMUNE-RELATED ADVERSE EVENTS

Mechanism of action

Immune checkpoints include numerous inhibitory pathways essential for preserving self-tolerance and controlling the strength and duration of immune responses to prevent damage to healthy cells. Tumours exploit these pathways as a key immune evasion strategy.[16] Immune checkpoint blockade, by removing inhibitory signals of T cell activation, allows tumour-reactive T cells to overcome suppressive mechanisms and elicit an effective antitumour response.[17]

Two signals are required for T cell activation, which occurs via interaction of cell surface receptors with peptide antigens on target cells. The first signal is generated via the binding of major histocompatibility complex (MHC)-presented peptide antigen to the T cell receptor (TCR). The second co-stimulatory signal occurs through ligation of the T cell surface receptor CD28 to its ligand CD80 (B7-1) or CD86 (B7-2) on the surface of antigen presenting cells.[18] The activation of CD4+and CD8+ T cells results in T cell proliferation, cytokine and chemokine release, cytokine-mediated T cell maturation and the recruitment of immune effector cells (neutrophils and macrophages) to the site of the inflammatory response.[14] Following T cell activation, the expression of co-inhibitory receptors, including CTLA-4 and PD-1, is upregulated. CTLA-4 is thought to regulate T cell proliferation early in an immune response, primarily in lymph nodes, while PD-1 suppresses T cells later in an immune response, primarily in peripheral tissues.[19] CTLA-4 competitively inhibits the CD28-CD80/86 interaction by binding with higher affinity, thus blocking co-stimulation and switching off activated T cells. PD-1 is a marker of T cell exhaustion and is upregulated on the T cell surface in this context. The binding of PD-1 to its ligand, PD-L1, inhibits downstream signalling of the TCR, thus blocking the TCR-MHC stimulatory signal.[18]

CD80, CD86 and PDL1 are frequently expressed on tumours or in the tumour microenvironment,[18 20] taking advantage of these inhibitory pathways in order to evade immune surveillance. Blockade of the CTLA4–CD80, CTLA4–CD86 and PD-1-PDL1 interaction with ICIs therefore promotes activation of T cells and potentiates exhausted T cells, facilitating destruction of cancer cells[18] (figure 1a). More recently, an additional inhibitory protein has emerged as a target for immunotherapy. LAG-3 exhibits structural similarity to CD4 and is highly expressed on TILs.[21] Primarily via its interaction with the peptide-MHC class II complex, LAG-3 inhibits CD4+T cell function. Its blockage results in T cell activation with multimodal, cytokine and chemokine-mediated immune effect.[9]

Immune-related adverse events

Although inhibition of these T cell pathways is effective for the destruction of cancer cells, irAEs can occur as unintended on-target, off-cancer effects.[15] From a very basic perspective, CD4+T cells are primarily regarded as T helper cells which facilitate immune responses through cytokine production and activation of other immune cells with effector mechanisms. CD8+T cells primarily exert cytotoxic, direct effector function.[22] Both these cell types undergo enhanced activation and expansion in the context of ICI therapy, with a variety of pathological mechanisms proposed in irAEs. These include (i) diversification and expansion of autoreactive CD4+T cells; (ii) activation of cytotoxic CD8+T cells; (iii) epitope spreading, the development of an immune response to epitopes distinct from and non-cross-reactive with the primary epitope;[23] (iv) antigenic cross-reactivity to target tissues following the release of self-antigens from attacked tumour cells; (v) proliferation and activation of autoreactive B cells, resulting in antibody-mediated cytotoxicity; (vi) release of pro-inflammatory cytokines, decreasing the function and survival of regulatory T cells and triggering pro-inflammatory intracellular signalling; (vii) direct off-target effect of ICIs on cells expressing the target ligand[15] (figure 1b).

NEUROLOGICAL IMMUNE-RELATED ADVERSE EVENTS

Typically, irAEs occur within 6 months following ICI treatment initiation. However, they can manifest at any stage during treatment, with cases of late onset reported, even after treatment discontinuation.[24] The overall incidence of any irAEs reported across clinical trials is 74% for PD-1/PDL1 inhibitors, 89% for CTLA4 inhibitors and 90% when used in combination. However, the incidence of higher grades of toxicity (Common Terminology Criteria for Adverse Events (CTCAE) grades 3–4, table 2) is lower—occurring in 14%, 34% and 55% patients, respectively.[25] Compared with other organ systems, N-irAEs are rare, with the overall incidence in clinical trials of 6.1% for anti-PD-1 antibodies, 3.8% for CTLA-4 inhibitors and 12% when used in combination.[26] Across these studies, higher grade toxicity occurred in <1% of patients,[26] although the frequency

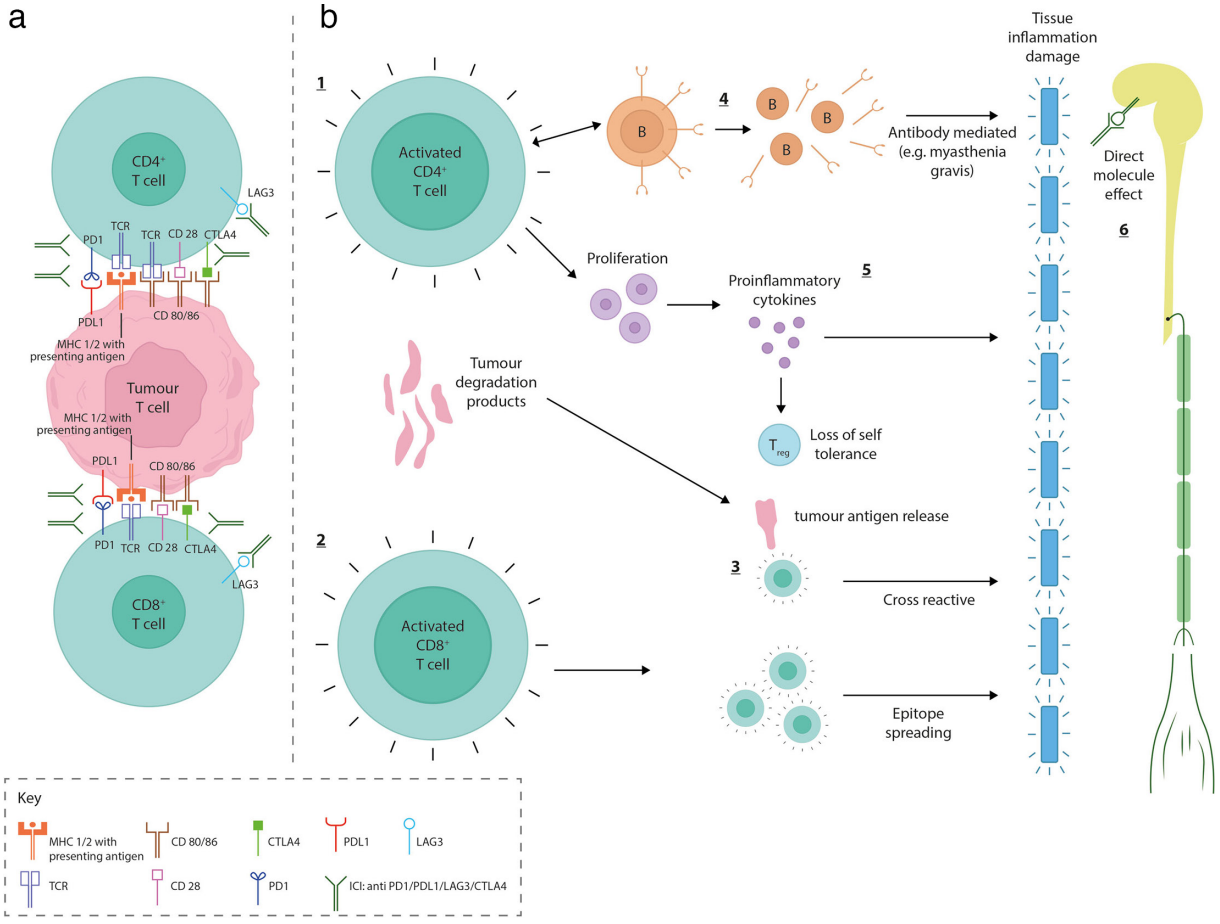

Figure 1 (a) Mechanism of action of immune checkpoint inhibitors. Here, we show the relationship between programmed cell death 1 (PD-1), cytotoxic T lymphocyte associated protein 4 (CTLA4) and lymphocyte-activation gene 3 (LAG-3) on T cells with their antigen-presenting cell (APC) ligands (including PD-1 ligand 1 (PDL-1)) as relevant targets for the immune checkpoint inhibitor drug class. b Proposed pathophysiological mechanisms of immune checkpoint inhibitor (ICI) neurotoxicity. (1) Diversification and expansion of autoreactive CD4+ T cells. (2) Activation of cytotoxic CD8+ T cells. (3) Epitope spreading and antigenic cross-reactivity. (4) Proliferation and activation of autoreactive B cells. (5) Release of pro-inflammatory cytokines, decreasing the function and survival of regulatory T cells and triggering pro-inflammatory intracellular signalling. (6) Direct off-target effect of ICIs on cells expressing the target ligand. Text in this figure has been adapted from Casagrande *et al*.[15] The authors of this paper created the illustration.

is marginally higher (2.2%) in real-world data.[27] Given that the LAG-3/PD-1 inhibitor relatlimab has only relatively recently been approved, there is limited data with regard to N-irAEs for this. However, no N-irAEs were observed in the pivotal phase II/III trial,[11] and only two cases each of myositis and myasthenia have been reported in the FDA Adverse Event Reporting System (FAERS) (from a total of 43 reported adverse events).[28] Further data are therefore required in this regard.

N-irAEs affecting the peripheral nervous system are seen more commonly than in the central nervous system (CNS).[29] However, the spectrum of neurological syndromes spans the whole neuroaxis. In descending order of observed frequency, these include myositis (32%), neuropathies/neuritis (22%), myasthenic syndromes (14%), encephalitis (13%), cranial neuropathies/neuritis (7%), other CNS inflammatory syndromes (6%), meningitis (3%), myelitis (2%) and CNS demyelination (2%).[2 29] Overlap with other neurological toxicities or with other organ systems can also occur. Although rare, N-irAEs can result in long-term disability, and significant mortality rates are associated with particular presentations.[30]

Table 2 Common terminology criteria for adverse events

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
ADL, activities of daily living.

Peripheral nervous system immune-related adverse events

Myositis and neuromuscular junction disorders

Myositis is among the most commonly observed N-irAE, comprising approximately a third of all cases. The clinical features of ICI-associated myositis range from myalgia and elevated creatine kinase (CK) to severe myopathies, most commonly in a limb-girdle pattern. Ocular and bulbar weakness are observed in approximately 50% patients, with neck and facial weakness seen

in a third. Myositis-specific antibodies are positive in a third of patients, with a myopathic EMG and muscle oedema on MRI seen in the majority.[2]

Compared with myasthenia gravis (MG) seen outside of the immunotherapy setting, ICI-related myasthenia tends to occur more frequently in male patients, at an older age,[31] and is associated with a higher overall mortality.[32] Acetylcholine receptor antibodies are positive in approximately 60% of cases[2 31] with neurophysiological evidence of neuromuscular junction dysfunction on repetitive nerve stimulation or single fibre EMG in 50%.[33] While isolated myasthenic syndromes occur in a significant minority of patients with N-irAEs, treatment with ICI has provoked the onset of a newly-recognised clinical entity—myasthenia, myositis and myocarditis—or the so-called triple M (MMM) syndrome, which can also be associated with transaminitis (MMMH).[34] While myasthenia, myositis and myocarditis can all occur in isolation, identification of one of these conditions should prompt investigation for the others co-existing (either in pairs, or as the complete MMM syndrome), as early intensive therapy has been shown to have a positive survival outcome[35] in a syndrome with an in-hospital mortality rate of 38%.[36] In patients with myocarditis and myositis and/or MG, cardiac arrythmias are reported in 67% patients and impaired ejection fraction in 18%.[37] Cardiac function should therefore be closely monitored in this scenario. Both myasthenia alone and the MMM syndrome are most commonly associated with PD-1 inhibitors.[2 35]

Neuritis

After myositis, neuropathic N-irAEs are commonly reported. Acute/subacute inflammatory polyradicular presentations, often described as Guillain-Barré-like, are most common. Small case series or well-described case reports also document painful mononeuritis multiplex and ICI-related sensory neuronopathy with and without anti-Hu (paraneoplastic) antibodies. Albuminocytologic dissociation is observed in the CSF of 50% patients, but elevated CSF white cell count (with predominant lymphocytosis) is also described.[2 38] Neurophysiology and histology suggest pathophysiological heterogeneity, with patchy vasculitis, anti-ganglioside antibody-associated demyelination and T cell predominant axonal polyradiculoneuritis all reported in this context.[14] Of note, it is important to exclude infiltrative neoplastic cells as a differential diagnosis in certain cancer types.

Central nervous system immune-related adverse events

Encephalitis

Encephalitis is the most frequent CNS toxicity associated with ICIs, seen in 13% of patients with N-irAEs.[29] Common clinical features include encephalopathy, fever, seizures and meningism, with three main phenotypes having been identified: (i) meningoencephalitis with inflammatory changes on MRI and/or CSF studies; (ii) limbic encephalitis, associated with high-risk paraneoplastic antibodies and neuroendocrine cancers; and (iii) cerebellar ataxia/cerebellitis.[39] A further phenotype has also been described—a diffuse encephalopathy without inflammatory changes seen on paraclinical tests—but associated with a worse clinical outcome, with careful consideration and thorough investigation of the differential diagnosis recommended in this scenario.[33] Isolated aseptic meningitis, presenting as headache with or without fever and a systemic inflammatory response, is less commonly observed but carries a favourable prognosis.[29 40]

In ICI-related meningoencephalitis, CSF studies demonstrate a lymphocytic pleocytosis and elevated protein. Magnetic brain imaging is generally normal but can demonstrate leptomeningeal or pachymeningeal contrast enhancement and/or patchy parenchymal T2/FLAIR hyperintensities.[39] Limbic encephalitis presents similarly to that seen in the non-ICI setting with subacute anterograde amnesia, temporal lobe seizures and behavioural change[39] with focal changes on MRI and CSF pleocytosis.[41 42] Cases of limbic encephalitis commonly occur in association with anti-Hu and anti-Ma2 antibodies, but with other paraneoplastic or non-paraneoplastic antibodies also having been observed in this context.[39 42] Cerebellar ataxia/cerebellitis is rare, occurring in 3.6% patients with N-irAE,[29] with approximately 62% cases associated with anti-neuronal antibodies.[43] Elevated serum or CSF neurofilament light chain (NfL) levels have been reported in ICI-related encephalitis reflecting neuronal damage, but this is not a specific diagnostic biomarker.[41]

Transverse myelitis

Transverse myelitis is rare following ICI therapy, estimated to occur in <0.01% of treated patients.[44] Typical presenting clinical features include paraparesis, sphincter dysfunction and sensory impairment, with approximately 40% experiencing proprioceptive ataxia. MR spinal imaging typically demonstrates longitudinally extensive lesions, with patchy contrast enhancement, and as with other inflammatory disorders of the CNS, CSF demonstrates a pleocytosis and elevated protein.[45] While cases in the literature are sparse, a poor response to initial corticosteroids has been observed, and therefore prompt treatment with second-line treatments including IVIg and plasmapheresis is recommended.[45 46] It should also be noted that previous spinal radiotherapy had been administered in approximately half of reported cases and therefore might represent a predisposing risk factor.[46]

Demyelinating and vasculitic disorders

Other inflammatory disorders of the CNS such as demyelination/multiple sclerosis (MS),[47] myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) or neuromyelitis optica spectrum disorder (NMOSD) and CNS vasculitis[48] have also been reported, as have cases of precipitous, extensive ADEM-like presentations.[47] Within the MS groups, two patterns have been observed—those with existing MS who relapsed after ICI use and those with a diagnosis of radiologically isolated syndrome who then developed symptoms after ICI and thus fulfilled MS diagnostic criteria.[47]

Rare presentations of N-irAEs

N-irAEs rarely affecting other areas of the nervous system have also been described in case reports or small case series. Cranial neuropathies represent 7% of N-irAEs, with the facial nerve the most commonly affected, followed by the optic, vestibulocochlear and trigeminal nerves. Oculomotor nerve palsy has also been reported.[2] Vestibulocochlear toxicity can be particularly disabling with vertigo and in some cases irreversible deafness occurring. Although in places referred to as vestibulocochlear neuritis,[2] there is a suggestion that it may be more related to direct toxicity of the vestibulocochlear apparatus itself.[49] A growing awareness of ICI-related dysautonomia syndromes is reflected in recent publication of numerous individual case reports with intestinal dysmotility as the most common manifestation (66.7%), orthostatic hypotension and abnormalities of sudomotor control in others, sometimes in association with neuritis or encephalitis. Outcome is poor with 27.8% direct

mortality, but some recovery can be achieved with early recognition and assertive immunosuppression.[50 51]

INVESTIGATIONS AND TREATMENT

For patients with cancer, in whom some will have been exposed to prior treatments, careful consideration needs to be given to the differential diagnosis of any neurological presentation before a diagnosis of ICI-related N-irAE is made. This is especially true given the low relative frequency of N-irAEs compared with other tissue-specific toxicities and the broad spectrum of clinical presentations. Attention should be given to the direct effects of the cancer (compression, metastases), indirect effects (hypercoagulability, coagulopathy, metabolic disturbances), toxicity of previous treatments and non-neurological irAEs causing neurological side effects.[39] Given the range of potential neurological clinical phenotypes and differential diagnoses, the role of a neurologist is key in navigating these decisions within the framework of an immuno-oncology multidisciplinary team. It is particularly important to ensure a correct diagnosis in order to avoid potential iatrogenic harm from immunosuppressive treatments and allow re-introduction of ICI therapy if this is not deemed to be causative.

The European Society for Medical Oncology[52] and American Society of Clinical Oncology[53] have published well-established guidelines for oncologists to aid investigations and treatment, which have also been incorporated into local protocols.[54] Investigations are tailored according to the clinical presentation, but the potential for overlap syndromes and their high associated mortality rates mean it is worth investigating for concurrent myasthenia, myositis and myocarditis with ECG, echocardiogram, BNP, CK and troponin when any of these three conditions are seen. The general approach to treatment is to pause ICI treatment and give immunosuppressive therapies, depending on the grade of toxicity—as determined by the Common Terminology Criteria for Adverse Events (CTCAE) (table 2, figure 2).[55] With lesser toxicity grades, clinical monitoring only may be warranted, whereas with higher grades, prompt treatment with corticosteroids is indicated and may require further immunosuppressive or symptomatic treatment dependent on the clinical condition. It is important to note that ICI-related toxicities are often monophasic but may require additional immunosuppression if relapses occur.

Additional immunosuppressive/modulatory treatments typically include intravenous immunoglobulin (IVIg), plasma exchange (PLEX) and rituximab when the presentation is likely to be (or proven to be) antibody-mediated as we take guidance from analogous autoimmune disorders. But others have also been used, including mycophenolate mofetil, anti-IL1R (anakinra), anti-IL6 (tocilizumab), Janus Kinase Inhibitors, anti-integrinα4, cyclophosphamide and infliximab.[56] The hierarchy of treatments to be used in second-line immunosuppression is not well understood and requires further research. It is possible that separate treatment algorithms will be required for different N-irAEs, especially as individual disease pathogenesis becomes better understood.

In relatively large case series of neurotoxicity, ICI discontinuation is almost universal.[29 33] Across all clinical phenotypes (myositis/NMJ disorders, polyradiculoneuropathy, sensory neuronopathy, cranial neuritis, meningoencephalitis), the majority of patients were treated with corticosteroids, which were the only immunosuppressive treatment in 39%–52% patients. Other subsequently administered treatments included IVIg; 33%–37%, PLEX; 8%–15%; and others (including rituximab, cyclophosphamide, tocilizumab) in 16%–25% patients.[29 33] With regard to corticosteroid treatment, dosing, formulation and duration varies widely, but the general advice is to aim for the lowest dose and shortest duration of treatment with appropriate safety measures included to avoid steroid-associated complications.

There are some indicators that certain clinical characteristics may help predict prognosis.[29] For example, compared with lung cancer, patients with melanoma have a higher rate of change from severe to minor disability, as do patients with myositis or neuromuscular junction disorders. Older patients and those with paraneoplastic-like syndromes are less likely to improve. Importantly, the type of ICI is not related to the responsiveness of the ICI-related toxicity to treatment.[29]

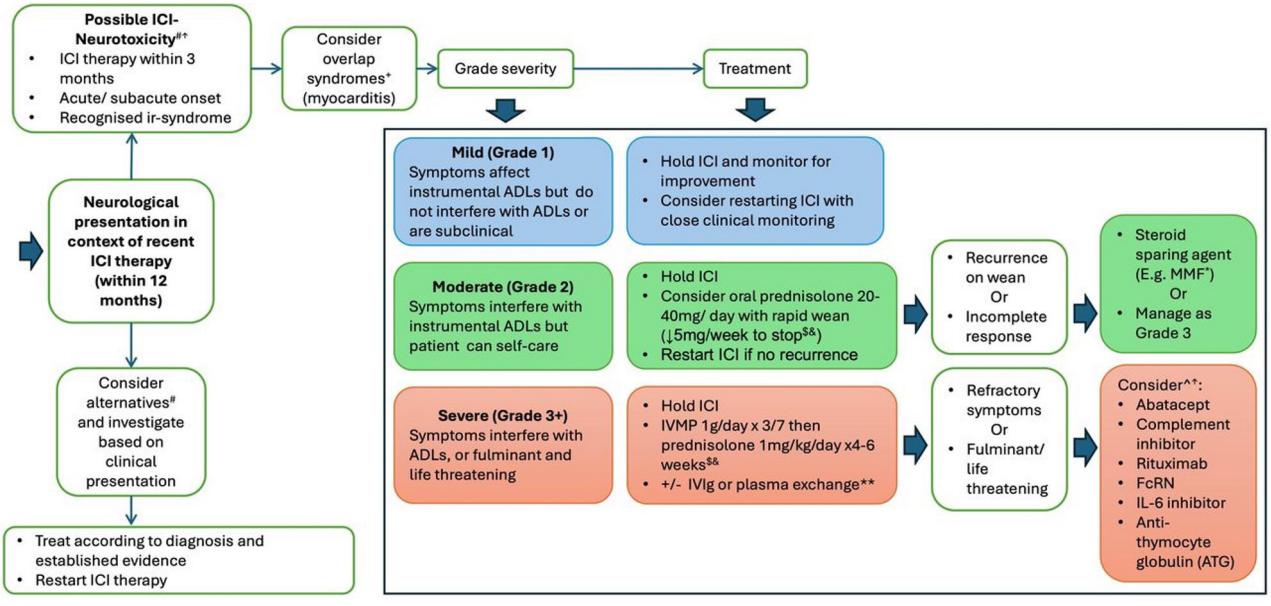

Figure 2 Proposed workup for investigation and management of ICI-related n-irAE. Carr *et al*. Pract Neurol. 2024 Nov 26:pn-2024-004327. doi: 10.1136/pn-2024-004327. ADL, activities of daily living; ICI, immune checkpoint inhibitor; IVIg, intravenous immunoglobulin; n-irAE, neurological immune-related adverse event.

MULTIDISCIPLINARY APPROACH AND ROLE OF MULTIDISCIPLINARY TUMOUR BOARDS

While it is evident that managing irAEs often requires a collaborative approach, there is a lack of practical guidance on how to implement this effectively in everyday clinical practice.[57]

In the case of N-irAEs, referral to outpatient general neurology or neuro-oncology services is often inappropriate due to long waiting times and the urgency typically associated with N-irAEs.[14] In recent years, some initiatives have been undertaken to implement multidisciplinary teams aimed at improving the management of irAEs. The Dana-Farber Cancer Institute/Brigham Women's Hospital launched one of the first inpatient programmes focused on managing irAEs, showing the feasibility of using the electronic medical records to accurately triage patients to a dedicated immune-toxicity service.[58] In 2017, Massachusetts General Hospital established the Severe Immunotherapy Complications (SIC) service, a multidisciplinary care team for patients admitted with irAEs. After SIC service initiation, reductions were observed in the irAE readmission rate (14.8% post-SIC vs 25.9% pre-SIC).[59]

Multidisciplinary tumour boards serve as a platform where oncologists and subspecialists collaborate to address clinical cases, particularly those of greater complexity, to improve the quality of patient care.[57] A pilot programme for patients treated with ICI at the Sidney Kimmel Comprehensive Cancer Centre at Johns Hopkins Hospital showed that a virtual multidisciplinary immune-related toxicity (IR-tox) team of oncology and medicine subspecialists was a feasible and used service, aiding in toxicity identification and management. For all referrals (n=117), the IR-tox team responded with recommendations within 24 hours. All the providers who contacted the team used all or some of the recommendations, and most (74%) changed their management based on team advice. Interestingly, only three out of 10 referrals for suspected N-irAEs were confirmed to be actual irAEs. Similar diagnostic revision rates have been reported in a UK cohort, highlighting the diagnostic challenge associated with this rare type of toxicity.[57] A 2-year update from the IR-tox programme confirmed its utility.[60] However, the generalisability of the above-mentioned experiences, originating from academic centres or referral general hospitals, remains to be assessed. Additional initiatives are currently ongoing, including novel strategies balancing hyper-specialisation and network integration.[61]

In the UK, a national ICI neurotoxicity multidisciplinary advice service has recently been established. Coordinated through the National Hospital for Neurology and Neurosurgery and University College London Hospitals (UCLH-NHNN), the service is delivered by a team of consultants with expertise in neurology, oncology, neuroradiology, cardio-oncology and rheumatology, supported by clinical nurse specialists. It provides expert guidance in cases of uncertain diagnosis or symptoms refractory to first- and second-line therapies that require treatment escalation. Referrals are submitted via email using a standardised proforma, with cases reviewed biweekly through virtual meetings. In cases requiring urgent input, advice is available via telephone or email.[14] All conditions are supported by two clinical nurse specialists: an oncology ICI-toxicity clinical nurse specialist and a neurology clinical nurse specialist with expertise in immunosuppression and its safety monitoring. This underscores the critical role of clinical nurse specialists within MDTs, who play a key part in care coordination and provide patients with essential information, education and emotional support.[62]

What do oncologists want from a neurologist?

The diagnosis and management of irAEs are currently handled primarily by oncologists and acute oncology services. While this approach has led to growing familiarity with N-irAEs among oncologists, it remains outside their core area of expertise.[14] In a collaborative London neurology-oncology model, face-to-face review by a consultant neurologist within a median of 13.9 days from oncology referral resulted in good functional outcome at 6 months (median mRS=2.1) and low N-irAE mortality rate of 6.2%.[62] In urgent cases, rapid neurological assessment is necessary, potentially involving patient transfer to specialised centres capable of providing advanced care, such as mechanical ventilation for respiratory muscle involvement.[54]

Neurologists play an essential role in:

- Directing the selection of appropriate investigations and treatment of N-irAEs. This is critically important, especially with the need to consider other potential differential diagnoses, including those not related to immunotherapy.
- Guiding initial dosing and tapering of corticosteroid therapy and adapting immunosuppressant treatment based on symptomatology guided by the experience in the analogous autoimmune neurological disease.
- Follow-up of N-irAEs to monitor for recurrences, worsening symptoms or new manifestations.
- Care of long-term survivors to optimise quality of life of patients who have experienced N-irAEs and have associated disability.
- Risk assessment, counselling and support of cancer patients with pre-existing neurological AIDs or consider immunotherapy rechallenge in patients with prior N-irAEs.
- Educating patients and oncologists, general practitioners and other specialists, particularly emergency medicine physicians, about recognising and managing N-irAEs.

From an academic standpoint, collaboration between oncologists and neurologists is indispensable for advancing clinical and translational research aimed at improving patient outcomes and elucidating the mechanisms underlying N-irAEs. While the establishment of a translational research programme has proven feasible,[59] these initiatives face significant challenges that demand a multidisciplinary approach, with neurologists playing a pivotal role.

PREDICTIVE BIOMARKERS OF IMMUNE-MEDIATED ADVERSE EVENT (IRAE)

Understanding which patients are at higher risk of developing irAEs would be advantageous for clinical monitoring, allowing closer surveillance for those at risk and prompt treatment when indicated. Given the relative rarity of neurological toxicity, data are lacking with regard to specific risk factors and predictive biomarkers, but information can be cautiously extrapolated from studies of other irAEs. However, the majority of studies exploring this topic have been retrospective and in populations of patients with different cancers and treatments, and many in which N-irAEs were not reported. Therefore, it is difficult to generalise and be definitive about the conclusions drawn.

Risk factors associated with baseline clinical characteristics

Immune system functioning is recognised to be influenced by an individual's age, including in T cell proliferation rates and cytokine production.[63] It follows that differences in age may have an effect—both on the efficacy of ICI treatment but also on rates of irAEs. This is reflected in a large study of the FDA database where a higher incidence of irAEs was observed in

those aged >65 years old,[64] although the evidence is conflicting and this may vary by the organ-specific irAE.[65] While AID in general is known to be more common in females, a meta-analysis of 13 studies (n=2982) found no statistically significant difference in irAEs according to patient sex.[66] However, these results contrast with other findings suggesting that women experience an increased risk of severe symptomatic irAEs.[67]

Obesity has been associated with general autoimmunity[68] as well as T cell exhaustion and increased PD-1 expression.[69] In relation to this, higher body mass index has been suggested to be associated with an increased risk of irAEs for patients treated with PD-1/PD-L1 inhibitors.[70–72] Patients with pre-existing AID may be at increased risk for irAE or flares of their underlying disease (see later section *Risk of relapse in patients with pre-existing autoimmune disease*).[73 74] Nevertheless, previous series have demonstrated the feasibility of administering immunotherapy to patients with AID, though this requires careful patient monitoring and case-by-case multidisciplinary discussion as highlighted above.[73 75 76] Other baseline characteristics, such as a history of allergy,[77] vitamin D deficiency[78] and vaccination status,[79] have been suggested as potential risk factors. However, much of the available evidence is derived from retrospective series, which are inherently prone to bias, thereby highlighting the need for further rigorous and methodologically robust research.

Different ICIs also vary in their reported irAE frequencies and target-organ predilection. With respect to N-irAEs, myositis, myasthenic syndromes, GBS/neuropathies, encephalitis and cranial neuropathies occur more frequently in patients treated with anti-PD-1/PD-L1 agents, and meningitis in those who receive CTLA4.[2 39] The incidence of myelitis is similar across all ICI classes.[2]

Biomarkers from routinely available clinical data

In addition to patient-specific risk factors, information from routinely collected clinical data has also been investigated as a potential tool to help in determining the risk of irAE. Several factors have been evaluated, including elevated baseline absolute counts of lymphocytes, monocytes and platelets[80] and eosinophils,[81 82] neutrophil-lymphocyte ratio,[80] platelet-lymphocyte ratio[80 83] and monocyte-lymphocyte ratio[80]—albumin[77] and Lactate Dehydrogenase (LDH).[84] However, while some associations have been suggested, these findings remain unvalidated and cannot be reliably applied to clinical practice.

Experimental biomarkers

Similarly, although not available through routine clinical practice, many other biomarkers have been investigated for their association with irAEs. Pre-existing autoantibodies, proinflammatory cytokines, autoreactive tissue-resident T cells and T cells targeting viral antigens as a result of chronic viral infections have all been associated with the development of irAEs.[85–89] An analysis of peripheral blood samples from patients with melanoma treated with anti-PD-1 monotherapy or anti-PD-1 and anti-CTLA-4 combination identified two pretreatment factors in circulation—activated CD4+memory T cell abundance and TCR diversity—associated with severe irAEs, regardless of the organ system affected.[90] A recent study analysing peripheral blood T cell repertoire of patients with metastatic non-small cell lung cancer (NSCLC) treated with ipilimumab and nivolumab suggested that patients who experienced irAEs had lower T cell richness at the time of toxicity compared with the non-toxicity group.[91]

Higher levels of CD8+ effector memory type 1T cell frequencies had an accuracy for predicting neurological irAE of 82.1%.[92] The same study also found an association between the chemokine CXCL10 and N-irAE (OR 1.10) along with other baseline cytokines. Human leucocyte antigen (HLA) type,[93] lipid profiles[94] and the makeup of the gut microbiome[95 96] may also help predict irAEs.

Specific factors related to the underlying tumour have been proposed to confer risk for the development of irAEs. For example, cancers with a higher tumour mutational burden (TMB), such as melanoma and NSCLC, have been suggested to be associated with higher risk.[97] However, no association between TMB and toxicity was found in a meta-analysis and meta-regression including 117 clinical trials and a total of 12 450 patients treated with ICI.[98]

Prospective translational studies, such as EXACT (NCT05331066), which is ongoing, are needed to elucidate the mechanisms underlying irAEs with the aim of identifying biomarkers and developing strategies to predict irAEs. A recently established UK-wide programme, MANIFEST, aims to examine potential biomarkers at scale.[99]

IMPACT OF IMMUNE-MEDIATED ADVERSE EVENTS (IRAES) ON CANCER OUTCOMES

Based on the hypothesis that patients capable of mounting, a stronger immune response to ICIs may experience both the anticancer therapeutic benefits and adverse effects associated with immune function restoration; the relationship between the onset of irAEs and improved clinical efficacy is an area of active investigation, with findings to date yielding contrasting results.[100–106]

Multiple studies have suggested associations between irAEs and improved efficacy across various tumour types. Several studies suggest that discontinuing ICIs due to high-grade irAEs does not correlate with poorer clinical outcomes.[107–109] Conversely, it has been proposed that patients who experience severe irAEs may also exhibit greater responsiveness to ICIs.[110] However, many of these studies have not accounted for baseline factors associated with clinical outcomes or addressed immortal-time bias, potentially leading to an overestimation of this association.[111]

A recent analysis examined the relationship between OS and the occurrence of irAEs in patients with five cancer types (non-small cell lung cancer, small cell lung cancer, renal cell carcinoma, urothelial carcinoma and triple-negative breast cancer). Individual patient-level data from 14 clinical trials were analysed, comparing atezolizumab (as monotherapy or combined with chemotherapy±bevacizumab) to standard-of-care treatments. Specific methodology was employed to address key limitations of toxicity analyses, including immortal-time bias, study heterogeneity and baseline covariates associated with safety and efficacy. The results showed that patients who experienced low-grade (G1-2) irAEs had considerably improved OS (HR=0.65, p<0.01) versus those without irAEs.[101] The lack of association between high-grade irAEs and improved outcomes may be explained by several factors: the reduced therapy duration due to treatment discontinuation for severe toxicities; the administration of steroids and other immunosuppressive agents that could counteract ICI effects; and the potential for severe, and possibly life-threatening irAEs, to directly worsen outcomes[101]

Overall, the literature suggests either low-strength or no correlation between irAEs and OS, suggesting that irAE rates should not be regarded as a reliable surrogate for OS when assessing the efficacy of ICI therapy.[24 100]

Impact of immune-suppressive treatment for immune-mediated adverse events (irAEs) on cancer outcomes

Steroids represent the cornerstone of irAEs treatment, serving as the first-line option to suppress immune activation in most cases. Some refractory cases may require other immunosuppressive drugs, and several steroid-sparing agents have been adopted, with their efficacy extrapolated from the management of idiopathic autoimmune disorders.[112] Given that the mechanism of action of ICI relies on stimulating a robust and durable immune response, concerns have been raised that the immunosuppressive properties of steroids might interfere with ICI efficacy. However, the impact of systemic steroids on immunotherapy efficacy remains unclear, representing a complex issue still under investigation.[113]

Two key considerations regarding steroid use with ICIs are timing and dosing.[113] Retrospective studies suggest baseline corticosteroid use at ICI initiation is associated with worse survival outcomes.[114 115] This may often reflect the need for steroids for cancer-related symptoms, which act as an independent adverse prognostic factor. However, higher doses of baseline steroids (>/= 50 mg prednisone-equivalent) have also been suggested to be independently associated with poor OS of advanced melanoma on anti-PD-1 therapy when compared with lower baseline prednisone doses after controlling for confounding factors. On the contrary, low-dose steroids (eg, approximately 10 mg/day of prednisone or equivalent) at baseline may not compromise anti-tumour efficacy.[113 114 116] Similarly, early steroid use, especially high doses, after therapy initiation may increase the risk of adverse clinical outcomes, potentially by disrupting the development of an anti-tumour immune response.[117 118]

However, some analyses indicate that steroids may not negatively impact efficacy outcomes.[119 120] Nonetheless, persistent immortal time bias and the diverse indications for corticosteroid use must be carefully considered, as they may constrain the interpretation of these analyses.

A recent post hoc analysis by Verheijden *et al* on individual patient data from the anti-PD-1 plus anti-CTLA-4 treatment arms of six international phase II/III registrational trials across different tumour types (melanoma, MSI-H/dMMR colorectal cancer, renal cancer, oesophageal squamous cell carcinoma, mesothelioma, NSCLC) showed that corticosteroid peak dose to treat irAEs was associated with impaired progression-free survival (PFS) and OS, while cumulative dose was not.[121] These findings align with a previous analysis indicating that a high peak dose of corticosteroids was similarly linked to reduced survival.[117 122 123] This may be particularly relevant for N-irAEs, given the frequent requirement for high-dose steroids in their management. While previous experiences suggested that TNF inhibition and other second-line immunosuppressants may be associated with impaired survival,[121 124] a significant association between the use of second-line immunosuppressants and survival could not be established in the analysis by Verheijden *et al*.[125]

Finally, corticosteroids are linked to a range of well-known adverse effects, including a higher risk of infection and side effects affecting bone, muscle, metabolism, cardiovascular health, and neuropsychiatric function.[126] Careful screening, consent and appropriate safety monitoring are essential prior to initiating immunosuppressive therapy.[127]

RISK OF RELAPSE IN PATIENTS WITH PRE-EXISTING AUTOIMMUNE DISEASE

As well as triggering de novo AID, ICI therapy may also exacerbate pre-existing autoimmune conditions. Pre-existing AID of any type is relatively common—seen in a quarter of cancer patients in a large US registry.[128] Therefore, a not uncommon scenario in clinical practice is the patient with cancer and pre-existing AID with relevant questions arising about the risk of a flare following ICI administration.

Patients with pre-existing AID have tended to be excluded from clinical trials, and therefore data regarding this have been gained from observational studies. In a large meta-analysis of patients with pre-existing AID in any organ system and receiving ICI (n=23 897), flares occurred in 36% patients although the majority were mild. Flares mostly occurred in patients with psoriasis/psoriatic arthritis, inflammatory bowel disease and rheumatoid arthritis. Additional de novo AID in this cohort was observed in 23%, where patients with AID were 30% more likely to report an irAE compared with patients without (RR 1.3). However, if patients were receiving treatment for the pre-existing AID, the risk of irAE was lower (RR 1.1).[129] In one study, 19% of patients with pre-existing neurological disease had a de novo irAE in a different organ system, with gastrointestinal and respiratory irAEs being the most common.[130]

There is limited detailed data regarding the exacerbation of pre-existing neurological AID following ICI treatment—summarised in table 3. Aoun *et al* reported outcomes of 24 patients with MG undergoing ICI treatment. Fourteen of these patients were 'stable' at baseline, with no recent exacerbations, one had 'active' MG and no data on clinical disease state were available for nine patients.[131] Exacerbation was observed in 71% cases with moderate to severe weakness reported in 88%. The majority of patients were treated with steroids, and 65% also receiving IVIg or PLEX. Complete resolution of MG relapse after treatment was seen in 29% patients—47% had an incomplete resolution and 24% died. Of note, acetylcholine receptor antibody titres did not predict relapse or relapse severity.[131] A further case has also been reported recently whereby a patient with pre-existing MG developed MMM syndrome and died after a single dose of nivolumab.[132]

Cases of other pre-existing neuromuscular conditions are even more scarce in the literature. In six cases of pre-existing myositis, 4/5 cases of dermatomyositis and 1 case of inclusion body myositis experienced exacerbations after ICI initiation, with some cases requiring additional treatment with IVIg, PLEX or alternative immunosuppressive agents.[131] In five patients with a history of GBS in the past, worsening was reported in one patient only.[131] However, this patient was treated with ICI while still in the acute phase of vaccine-induced GBS, after being concomitantly diagnosed with metastatic melanoma, reflecting a scenario often experienced in clinical practice where anti-cancer treatment is prioritised over other active medical issues.[133] One case of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) did not worsen following ICI treatment.[131]

Cases of pre-existing demyelinating disease of the CNS in the context of ICI have been reported more frequently, although data are still limited. Rates of disease flares (either clinical or radiological disease activity) range widely, from 0% to 60% patients.[129 131 134–137] Older patients with more inactive disease are less at risk,[136 138] as are those who continue on a disease-modifying therapy (DMT) through ICI treatment.[131] Flares of demyelinating disease mostly occur in the first 6–7 months[135 136] following ICI but have also been reported up to 12 months later.[131 134] It should be noted that the majority of patients in these studies who were on treatment with DMTs had these discontinued before initiation of ICI. In addition, patients tended to be earlier in their disease, including patients with RIS and not on treatment, and therefore new inflammatory activity

Table 3 Outcomes of pre-existing neurological autoimmune diseases following treatment with immune checkpoint inhibitors

Autoimmune disease	ICI	n =	Flare of existing AID; n (%)	New irAE; n (%)	References
Multiple sclerosis	**NR**	**291**	**52 (18)**	**NR**	**Lopez-Olivo *et al* 2024**
	All	**11**	**1 (9)***	**4 (36)**	**Chavaz *et al* 2023**
	PD-1	8	NR	NR	
	PD-L1	1	NR	NR	
	PD-1/CTLA-4	2	NR	NR	
	All†	**66**	**2 (3)‡**	**24 (36)§**	**Quinn *et al* 2024**
	PD-1	67	1	NR	
	PD-L1	9	1	NR	
	CTLA-4	9	0	NR	
	All	**18**	**3 (17)¶**	**NR**	**Androdias *et al* 2024**
	PD-1	12	2	NR	
	PD-L1	3	0	NR	
	PD-1/CTLA-4	3	1	NR	
	All	**16**	**0**	**8 (50)**	**Conway *et al* 2023**
	PD-1	13	0	NR	
	PD-1/CTLA4	2	0	NR	
	CTLA4	1	0	NR	
	All	**10**	**6 (60)**	**NR**	**Aoun *et al* 2023**
	PD-1	3	2	NR	
	PD-L1	2	2	NR	
	PD-1/CTLA4	1	0	NR	
	CTLA4	4	2	NR	
Demyelinating disease (MS/RIS)	**All**	**24**	**3 (12.5)****	**9 (38)**	**Hasan *et al* 2023**
	PD-1	20	NR	NR	
	PD-L1	1	NR	NR	
	PD-1/CTLA4	4	NR	NR	
NMOSD	**CTLA4**	**1**	**1**	**NR**	**Aoun *et al* 2023**
Autoimmune encephalitis	**NR**	**1**	**1 (100)**	**NR**	**Aoun *et al* 2023**
Paraneoplastic syndromes††	**PD-1**	**3**	**3 (100)**	**NR**	**Aoun *et al* 2023**
CIDP	**NR**	**1**	**0**	**NR**	**Aoun *et al* 2023**
GBS	**NR**	**5**	**1 (20)**	**NR**	**Aoun *et al* 2023**
Myositis	**NR**	**6**	**5 (83)**	**NR**	**Aoun *et al* 2023**
Myasthenia gravis	**All**	**24**	**17 (71)**	**NR**	**Aoun *et al* 2023**
	PD-1	20	15	NR	
	PD-L1	3	2	NR	
	CTLA-4	1	0	NR	
	PD-1	**1**	**1‡‡**	**NR**	**Emile *et al* 2024**

*Clinical relapse.
†*Some patients received >1 ICI*.
‡1× radiological disease activity only, 1× clinical relapse.
§Including 3 with new N-irAE (encephalopathy, AIDP, neuronopathy).
¶2 x radiological disease activity only, 1× clinical relapse.
**2 x radiological disease activity only, 1× clinical relapse (all in patients with RIS).
††cerebellar ataxia, cerebellar ataxia with peripheral neuropathy and limbic encephalitis.
‡‡Patient developed MMM syndrome.
AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CTLA-4, cytotoxic T-lymphocyte associated protein 4; GBS, Guillan-Barre syndrome; MG, myasthenia gravis; MMM, myasthenia, myositis and myocarditis syndrome; MS, multiple sclerosis; N-irAE, neurological immune-related adverse event; NMOSD, neuromyelitis optica spectrum disorder; NR, not reported; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RIS, radiological isolated syndrome.

may just be representative of the natural history of the disease, rather than due to ICI therapy itself.

TREATMENT RECHALLENGE

Whether to rechallenge a patient with a history of ICI-related toxicity is important, particularly if there are no other alternative oncological treatments available. This decision is highly nuanced and requires careful discussion between the oncologist and patient and associated specialists. The most common cause of death in patients with neurological irAE is still cancer progression,[27 139] but the decision to restart ICI must be balanced against the potential morbidity and mortality associated with further irAE. Data for rechallenge in N-irAE are relatively sparse, with international guidelines generally cautioning against this.[52 53]

In general, studies of irAE have reported relapses in the range of 29%–60%.[140] With regard to N-irAE, the literature is limited to case reports and small case series—comprehensively compiled by Villagran-Garcia *et al* (table 4).[140] Given the small numbers,

Table 4 Outcomes of immune checkpoint inhibitor rechallenge

Initial N-irAE	ICI	n =	IS at rechallenge n (%)	Flare of n-irAE n (%)	References
Aseptic meningitis	**All**	**7**	**0**	**0**	**Villagran-Garcia *et al***
	PD-1/CTLA-4	6	0	0	
	PD-1	1	0	0	
	All	**3**	**2 (67)**	**1 (33)**	**Eldani *et al***
	PD-1/CTLA-4	2	1 (50)	0	
	PD-1	1	1 (100)	1 (100)	
	NR	**7**	**1 (14)**	**0**	**Cuzzubbo *et al***
Meningo-encephalitis	**All**	**8**	**2 (25)**	**2 (25)**	**Villagran-Garcia *et al***
	CTLA-4 &/or PD-1	5	1 (20)	2 (40)	
	PD-L1	3	1 (33)	0	
Encephalitis	**PD-1**	**1**	**0**	**1 (100)**	**Villagran-Garcia *et al***
Brainstem encephalitis	**PD-1**	**1**	**0**	**1 (100)**	**Villagran-Garcia *et al***
Cerebellitis	**PD-1**	**1**	**0**	**0**	**Villagran-Garcia *et al***
Inflammatory myositis	**PD-1 &/or CTLA-4**	**8**	**4 (50)**	**0**	**Villagran-Garcia *et al***
Myasthenia Gravis	**PD-1**	**3***	**2 (67)**	**1 (33)**	**Villagran-Garcia *et al***
	PD-1	**1**	**1 (100)**	**0**	**Eldani *et al***
Myelitis	**All**	**2**	**0**	**0**	**Villagran-Garcia *et al***
	PD-1	1	0	0	
	PD-L1	1	0	0	
Bilateral ON/polyradiculopathy	**CTLA-4**	**1**	**1 (100)**	**0**	**Villagran-Garcia *et al***
Myelitis & trigeminal neuropathy	**PD-1/CTLA-4**	**1**	**0**	**0**	**Villagran-Garcia *et al***
Cranial neuropathies	**Various**	**5**	**0**	**0**	**Villagran-Garcia *et al***
(VI – 1, VII – 2, VIII - 2)					
AIDP	**All**	**2**	**2 (100)**	**0**	**Villagran-Garcia *et al* 2022**
	PD-1	1	1 (100)	0	
	CTLA-4	1	1 (100)	0	
	PD-1	**1**	**1 (100)**	**0**	**Eldani *et al* 2024**
CIDP	**PD-1/CTLA-4**	**1**	**0**	**1 (100)**	**Villagran-Garcia *et al***
LEMS	**PD-1**	**1**	**0**	**1 (100)**	**Villagran-Garcia *et al***
Axonal neuropathy	**PD-1**	**1**	**0**	**0**	**Villagran-Garcia *et al***
Lumbosacral radiculoplexopathy	**PD-1**	**1**	**1 (100)**	**0**	**Villagran-Garcia *et al* 2022**
Cervical radiculopathy	**PD-1**	**1**	**0%**	**0**	**Villagran-Garcia *et al* 2022**
Atypical myopathy phenotype	**PD-1**	**1**	**1 (100)**	**0**	**Villagran-Garcia *et al* 2022**
Various†	**NR**	**10**	**5 (50)**	**6 (60)**	**Dubey *et al* 2020**
Various†	**PD-1 &/or CTLA-4**	**14**	**NR**	**4 (29)‡**	**Pepys *et al* 2023**
Cranial neuropathies	**Various / NR**	**28**	**NR**	**2 (7)**	**Pichon *et al* 2024**

Individual references available from Villagran-Garcia *et al*.
*Includes one patient with myasthenia gravis flare post-ICI.
†Not individually defined.
‡Not clear if recurrence or new N-irAE.
AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; IS, immunosuppression; LEMS, Lambert-Eaton myasthenic syndrome; N-irAE, neurological immune-related adverse event; NR, not reported; ON, optic neuritis; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

it is difficult to draw definitive conclusions regarding relapse of N-irAEs after retreatment, although the relapse rate has been shown to be higher than in those who did not receive additional ICI treatment.[27] In those studies with relatively higher patient numbers, the overall relapse rate appears to be in the range 0%–29%,[139–141] but as high as 60% in one study.[27] Of particular note, the risk of recurrence in aseptic meningitis appears to be low, with only one case reported among a total of 17 retreated patients.[140 142 143]

SUMMARY AND FUTURE CONSIDERATIONS

There are a number of important points of difference regarding neurotoxicity of ICI therapies compared with other irAEs: first the relative rarity and second the marked clinical heterogeneity of neurological presentations mean that cohort building, biobank establishment and subsequent clinical research progress has been limited. Although ICI therapy has been in use for over a decade, the medical literature is limited to case reports and small case series. Neurological clinical expertise is evolving, but with ever-expanding indications,[90 91] these rare events will increase in frequency.[3] While progress has been made, many questions and challenges to improve patient outcomes remain (box 1).

The first step in improving recognition of these adverse events should focus on education—both for patients and healthcare professionals, and the basis of this will be careful and accurate phenotyping of the neurological syndromes. Proposed checklists for patients[144] and referral guidelines to neurology[145] have been suggested, but further work needs to be done to ensure symptoms are recognised and reported early so that treatment can be initiated in an expedient manner. These should be practical and

Box 1 Outstanding questions in neurological immune-related adverse events

1. What is the mechanism of neurotoxicity?
2. Which patients are most at risk? Need to identify clinical predictors and biomarkers specific to neurological disease.
3. Which treatment, at what dose and for what duration should immunosuppressive therapy be given?
4. Which third-line treatments are most efficacious (after steroids, IVIg, PLEX)?
5. How do N-irAEs and their treatment affect cancer outcomes?
6. What are the risks to patients with pre-existing autoimmune neurological disease?
7. What are the risks of ICI retreatment following N-irAE?
8. What are the economic costs of N-irAEs and its treatment?

useful to oncologists, oncology clinical nurse specialists but also emergency and acute physicians who are often the first point of contact for these patients. International guidelines encourage early involvement of neurologists, which is imperative for both accurate anatomical localisation and diagnosis and for guidance on therapeutic management. But how to provide neurological expertise in a timely manner, within current neurology service infrastructure, is a challenge to be addressed. While not a primary concern for treating physicians, the economic costs of ir-AEs are significant and should be factored into service development plans. For example, a typical course of treatment can cost $40–$100 k with immune-related adverse events adding an estimated 8%–25% more to the total spend.[146]

Basic laboratory work based on clinically well-defined neurological syndromes will be essential in further delineating the mechanisms of N-irAEs and to develop sensitive and specific risk stratification and diagnostic biomarkers, appropriate disease activity monitoring approaches and guide the development of more effective, potentially syndrome-specific, management algorithms.

Neurologists will be required to contribute to the important issue of ICI re-challenge, with the potential for toxicity relapse or development of higher-grade toxicity needing to be carefully balanced with prospective cancer outcomes. In addition, the risk of treating patients with pre-existing AID will need to be carefully navigated. Ultimately, in order to identify and treat patients efficiently, to minimise long-term effects of toxicity and maximise cancer outcomes, effective communication across medical specialities is key. Oncologists, neurologists, radiologists, general physicians and general practitioners need to be aware of the risks of treatment and have established pathways so that patients can be managed effectively.

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