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Novel treatments for novel side effects: a case report and review of baricitinib use in the treatment of chronic inflammatory demyelinating polyneuropathy caused by immune checkpoint inhibitor use

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have transformed the landscape of solid cancer management. These drugs carry a risk of novel side effects, which have become known as immune-related adverse events (irAEs).

Traditionally, irAEs have been managed empirically with corticosteroids. A subset of these may be steroid refractory and as more evidence emerges about their distinct pathogeneses, a more tailored approach is required. Here, we report the use of a Janus kinase (JAK) inhibitor, baricitinib, in a patient with chronic inflammatory demyelinating polyneuropathy secondary to ICI use. We also review the current literature with regards to the use of these inhibitors in the management of irAEs.

Modulation of the JAK pathway warrants further investigation in the targeted management of irAEs.

STATEMENT OF CLINICAL OR BIOLOGICAL INSIGHT

Immune checkpoint inhibitors (ICIs) are being used increasingly in solid organ malignancies. These drugs carry the risk of immune-related adverse events (irAEs); the management of which is modeled on autoimmune conditions with empirical use of corticosteroids. However, some irAEs may be steroid refractory. In addition, evidence is emerging regarding the clinicopathological disparity in irAEs. In this setting, targeted approaches are becoming important. Modulation of the Janus kinase (JAK) pathway represents one such approach.

PATIENT HISTORY

A patient in their 50s presented with a right axillary mass, which was histologically confirmed on biopsy as metastatic melanoma. Three years prior, they had undergone a wide local excision for a superficial spreading melanoma of the right shoulder. Their only other medical condition was hypertension. The patient underwent axillary and neck nodal dissection.

Unfortunately, they were found to have very advanced disease on histopathology with 40/40 axillary lymph nodes and 12/51 cervical nodes containing melanoma. A subsequent FDG-PET (fluorodeoxyglucose positron emission tomographyscan) revealed progression with disease evident in the left chest wall, D3 duodenal region, right lateral abdominal wall, right groin, and left adductor muscles. The patient was commenced on palliative immunotherapy with the cytotoxic T lymphocyte associated antigen 4 (CTLA-4) inhibitor, ipilimumab, combined with programmed cell death protein 1 (PD-1) inhibitor, nivolumab.

The third cycle was complicated by diffuse myalgia, beginning on day 3. The patient's oncologist checked their creatine kinase and erythrocyte sedimentation rate, both of which were normal. They were commenced on a low dose of prednisolone (10 mg daily) and further immunotherapy was placed on hold. These symptoms progressed and within one week the patient presented to the emergency department with myalgia, back pain and new lower limb weakness, worse on the right. The patient also reported an "electric shock" sensation radiating down both legs. They were admitted and underwent an MRI brain and whole spine revealing abnormal smooth enhancement of the spinal nerve roots suggestive of inflammatory polyneuritis (figure 1). They also had a lumbar puncture showing elevated protein at 2.05 g/L, glucose level of 6.0 mmol/L and white cell count of

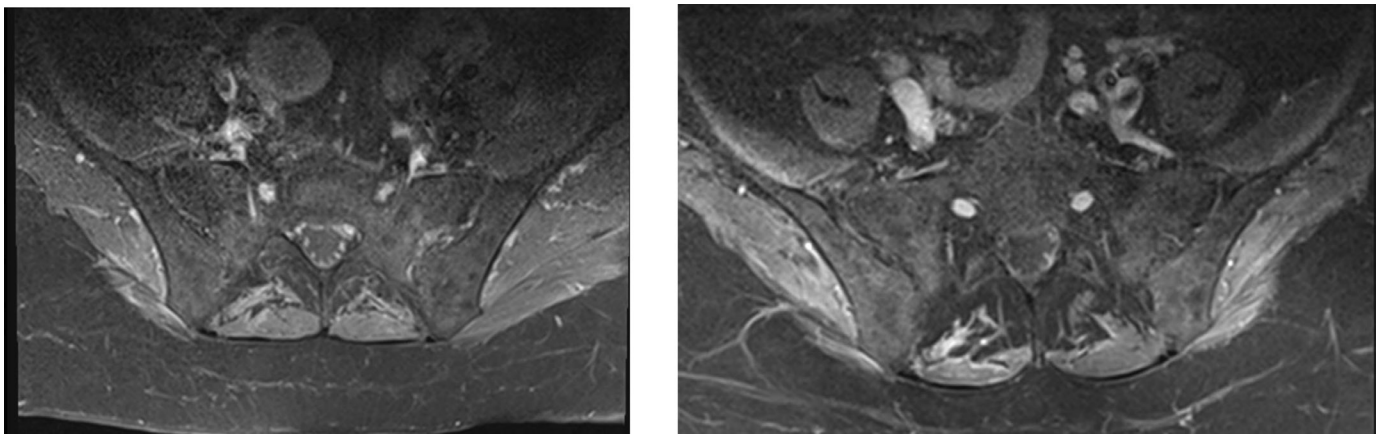

Figure 1 MRI lumbar spine, post gadolinium contrast. On the left is the initial MRI spine, demonstrating abnormal enhancement and uptake in the nerve roots. On the right is the MRI following baricitinib, with resolution of the abnormal uptake in the nerve roots.

40×10^6/L (0.04 x 10^9), respectively. The cytology was negative. GAD65 (glutamic acid decarboxylase antibody 65) was positive, while antiganglioside, cryoglobulins, ENA (extractable nuclear antigen) and serum free light chains were negative.

The initial working diagnosis was an asymmetrical progressive polyradiculopathy, secondary to immunotherapy. The prednisone dose was increased to 100 mg daily and however due to lack of clinical response, the patient was switched to intravenous methylprednisolone. The patient failed to demonstrate improvement. They were then commenced on intravenous immunoglobulin (IVIG) at 2 g/kg. IVIG was discontinued in the setting of non-response, and following consultation with the clinical immunology team, they were commenced on mycophenolate mofetil 500 mg daily and up titrated to 1 g two times a day.

A nerve conduction study demonstrated a mixed, predominantly demyelinating, and axonal neuropathy with both sensory and motor involvement, with motor nerves more affected compared with sensory. The patient was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP).

The patient was completely dependent on full-time carers by this point with bilateral upper and lower limb weakness. They were requiring two assists for any tasks, as well as hoist lifting for transfers. In addition, they described a severe burning pain, "hyperalgesia", requiring input from the acute pain and palliative care services. The patient was managed with gabapentin, oxycodone, and hydromorphone. In the absence of any improvement, mycophenolate mofetil was ceased and prednisolone weaned.

Given there had been no clinical improvement on any of the agents trialed, with worsening pain, special hospital approval was obtained for a 3-month trial of the non-selective JAK inhibitor, baricitinib 4 mg daily. Remarkably, the patient reported improvement within 1 week of this treatment and specifically described this as a feeling of their "legs coming alive". The patient had ongoing improvement on this medication. Eventually, they were discharged from the hospital and were able to regain walking function for short distances, with the aid of a walker. The patient remains wheelchair user for longer distances. There was complete resolution of the neuropathic lower limb pain. In addition, an MRI spine following the 3-month course of baricitinib normalized, with resolution of the abnormal enhancement of the nerve roots and cauda equina. Baricitinib was ceased after 3 months.

On their last follow-up, 10 months since the diagnosis, the impression was of significantly improved CIDP. The patient had also remained in complete metabolic response at this time point and continued to mobilize independently with a walker, for short distances.

DISCUSSION

A case of CIDP following exposure to ICIs is presented, where the patient failed to improve despite immune suppression with several drugs. In the literature, there are a handful of case reports describing the use of the JAK inhibitors in the management of irAEs, however, no large studies have been conducted. Although these agents have shown efficacy in the management of various autoimmune conditions, their role in the management of irAEs remains mostly unexplored. We review the rationale, mechanism of action and existing evidence for the use of these agents in irAEs.

PATHOGENESIS OF IRAES

ICIs are monoclonal antibodies which target the immunosuppressive checkpoint molecules such as CTLA-4, PD-1 and its ligand, programmed death-ligand 1 (PD-L1), aiming to reinvigorate antitumor immune responses by enabling increased immune system recognition of cancer cells. These drugs have significantly altered the management of solid organ malignancies. ICI use in the first-line or second-line setting is approved for more than 50

different cancer indications and it is estimated that there are currently more than 3,000 clinical trials specifically investigating T-cell modulators.[1] In addition, several novel immune checkpoints and their corresponding inhibitors are under investigation.

Immune checkpoints are important regulators of self-tolerance and manipulation of these targets can result in serious toxicity. IrAEs most commonly involve the thyroid, skin, gut, liver, and lung—although any organ system can be affected. These toxicities have been reported to occur in as many as 90% of patients receiving anti-CTLA-4 therapy[2] and 70% of patients receiving anti-PD-1 or PD-L1 therapy.[3] Critically, treatment-related deaths have been reported in 1% of patients in randomized controlled trials.[3]

There is a paucity of high-quality evidence guiding the management of irAEs. Guidelines suggest empirical use of glucocorticoids. The management of irAEs is modeled closely on traditional management of autoimmune conditions. There is emerging evidence, however, regarding distinct immunopathological mechanisms for these events between different irAEs, suggesting that a targeted approach may be beneficial.

While the distinct mechanisms of irAEs are still under investigation, it is becoming apparent that different types of irAEs result from the activation of different arms of the immune system, including both innate and adaptive responses. Immunopathological disparity has been noted in different irAEs, with reactions demonstrating a primarily cellular, humoral or cytokine driven pathogenesis. For example, a higher eosinophilic count has been demonstrated in patients with non-small cell lung cancer receiving ICIs and developing pneumonitis,[4] compared with a predominantly neutrophilic infiltrate in ipilimumab induced colitis.[5] Similarly, antibody mediated inflammation has been proposed to underlie various endocrine irAEs.

Modulation of specific targets in the immune system rather than a "one size fits all" approach has been suggested in the management of irAEs. Modulation of the JAK-signal transducer and activator of transcription (STAT) pathway may represent a new therapeutic strategy.

THE JAK/STAT PATHWAY AND ITS USE IN THE MANAGEMENT OF IRAES

JAKs consist of a family of four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TRYK2). They are cytoplasmic or non-receptor tyrosine kinases which regulate the signal transduction of various cytokines and growth factors. Dysregulated signaling through the JAK-STAT pathway has been recognized in the pathogenesis of various autoimmune conditions and also in cancer. Inflammatory cytokines and interferons (IFNs) implicated in irAEs also signal via the JAK-STAT pathway.

Several studies have demonstrated that inhibition of the JAK-STAT pathway can lead to remission in various autoimmune conditions, such as rheumatoid arthritis and inflammatory bowel disease. A number of JAK-STAT inhibitors have been approved in the management of autoimmune conditions; ruxolitinib and baricitinib (JAK1 and JAK2), tofacitinib (JAK1 and JAK3), and oclacitinib and upadacitinib (JAK1). The benefits of these agents include oral administration and quick onset of action. Their role in the management of irAEs, however, is largely unexplored.

JAKs can phosphorylate tyrosine residues either on themselves or on adjacent molecules. Trans-phosphorylated JAKs lead to the recruitment and phosphorylation of downstream substrates, such as STATs. STATs, in turn, dimerize and translocate to the cell nucleus where they bind to specific gene sequences, regulating transcription.

This pathway confers signaling for many different molecules through type I and type II receptors. Type I receptors bind to interleukins, colony-stimulating factors and hormones such as erythropoietin and growth hormone, while type II receptors are used by IFNs and interleukin (IL)-10-related cytokines (IL-10, IL-19, IL-20, IL-22, IL-22 and IL-26), including those implicated in irAEs.[6]

It is important to note that cell receptors are associated with specific JAKs and given there are only four JAK members, some receptors may be linked to several JAKs. In addition, various cytokines may signal through the same or more than one JAK. Therefore, JAK inhibition can lead to inadvertent inhibition of other signaling pathways and this can result in adverse effects from the use of these drugs. Possible adverse effects related to the use of these agents include serious and opportunistic infections, increased venous thromboembolism and secondary malignant skin cancers.

Specifically, in cancer immunotherapy, the JAK-STAT pathway through the IFN-gamma axis has been demonstrated to be important for the antitumor responses of ICIs, and whether inhibition of this pathway could also reduce efficacy of ICIs remains to be explored. Conversely, signaling through the type 1 IFN axis has been shown to be linked to resistance to ICIs in patients with melanoma and preclinical studies have demonstrated a synergistic effect from dual blockade with JAK-STAT inhibitors and ICIs, demonstrating an ability to overcome resistance.[7]

In the literature, the use of these agents in irAE management is limited to case reports and one case series. Esfahani *et al* present a patient with immune mediated colitis which was refractory to steroids, infliximab and vedolizumab but responded to tofacitinib with clinical remission achieved just 5 days following commencement.[8] Sleiman *et al* also present a similar case of tofacitinib responding immune mediated diarrhea tofacitinib has also been reported to have a role in the management of in immune-related hepatitis[9] and in a larger case series of patients with ICI-related myocarditis, where out of 11 patients with steroid refractory disease, 7 were observed to recover with the use of tofacitinib.[10] One case report has assessed JAK inhibition, with ruxolitinib, in combination with methylprednisolone and abatacept, suggesting a combination approach.[11] To date, there are no case

reports specifically on baricitinib—which we have presented here.

CONCLUSION

In this patient, a severe irAE was effectively managed with the use of a JAK inhibitor, without conferring an impairment in cancer immune surveillance. Given the ease of administration of this medication and fast onset of action, JAK-STAT inhibitors represent a potential new treatment for the management of irAEs and warrant further investigation.

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