Full Title:

Immune-related Adverse Events Associated with Cancer Immunotherapy: A Review for the Practicing Rheumatologist

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Short running head: Rheumatic irAE with cancer immunotherapy

Key Indexing Terms: Immune checkpoint inhibitors, rheumatic irAE, inflammatory arthritis, myositis, vasculitis, immunotherapy

Sources of Support: None

Conflict of Interest: None

Word count: 3907

Abstract:

Immune checkpoint inhibitors have revolutionized cancer therapy by blocking inhibitory pathways of the immune system to fight cancer cells.   Their use is often limited by the development of autoimmune toxicities, which can affect multiple organ systems and are referred to as immune-related adverse events (irAE). Amongst these are rheumatologic irAE, including inflammatory arthritis, myositis, vasculitis, and others.   Rheumatologic irAE seem to be different from irAE in other organs and from traditional autoimmune diseases in that they can occur early or have delayed onset, and can persist chronically, even after cancer therapy is terminated.   As immune checkpoint inhibitors are increasingly used for many types of cancer, it is important for oncologists and rheumatologists to recognize and manage toxicities early.   In this review, we discuss currently approved immune checkpoint inhibitors, their mechanisms of action and systemic toxicities, with focus on rheumatic immune related adverse events, their management and impact on further cancer therapy.

Immune checkpoint inhibitors

Immunotherapy has emerged as a new pillar in the treatment of cancer and has transformed outcomes of patients with previously untreatable malignancies (1,2). Unlike traditional chemotherapy, which commonly has the secondary effect of immunosuppression, modern immunotherapy aims at up-regulating the immune system to augment antitumor responses.   Immune checkpoint inhibitors (ICI) have emerged as one of the most promising forms of immunotherapy(3).

Immune checkpoint inhibitors increase antitumor activity by blocking intrinsic down-regulators of the immune system, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) (4).   Normally, these regulatory receptors, or checkpoints, maintain the balance between T cell activation and inhibition.   The primary aim of immune checkpoint inhibitors is to reduce the suppression of effector T cells, particularly CD8+ T cells, improving their ability to mount tumor-specific immune responses (5).   CTLA-4 is upregulated early after T-cell activation in central tissues including lymphoid and thymic tissues (Figure 1).   It transmits an inhibitory signal to activated T-cells at a proximal step in the immune response, by preferentially binding to CD80/86 expressed by antigen presenting cells (APCs), thereby blocking the second signal required for T cell activation. Antibodies targeting CTLA-4 neutralize this central checkpoint, allowing ongoing T cell activation and thereby enhancing their anti-tumor activity.

In contrast, PD-1 is believed to play a role in T cell inhibition in the peripheral tissues, at a later stage of the immune response (Figure 1). When effector T cells encounter continuous antigen (as in chronic infection or cancer), they lose the ability to respond to the antigen - a condition known as *T cell exhaustion*. This is partly mediated by the enhanced expression of immune checkpoints such as PD-1. The binding of PD-1 to its ligands, PD-L1 and PD-L2 (which are expressed by many tumor cells) interferes with downstream signalling and can lead to T cell exhaustion. Antibodies that block the interaction of PD-1 with PD-L1/PD-L2 serve to neutralize this checkpoint, restoring T cell effector function (5,6).

The widespread use of immune checkpoint inhibitors has led to remarkable clinical outcomes, with complete remissions and sustained clinical responses seen in some patients with previously refractory cancers such as melanoma, lung cancer, renal cell carcinoma, and Hodgkin lymphoma. To date, the FDA and Health Canada have approved 7 immune checkpoint inhibitors (and one combination), which target either CTLA4 or PD-1/PD-L1 pathways for a variety of different cancers (Table 1) (7). Indications for these (either alone or in combination) continue to grow rapidly as more data is available. Other immune checkpoint pathways have also been identified and are currently being investigated for clinical use in an increasing number of cancer types and stages.

Immune related adverse events associated with immune checkpoint inhibitors

Unfortunately, activating the immune system to fight cancer can also lead to serious, undesirable off-target immune and inflammatory events known as

immune related adverse events (irAE). These have been reported in up to 80% of patients receiving monotherapy and up to 95% with combination therapy (PD-1 and CLTA-4) (8–12). There have been higher rates reported with CTLA-4 blockade than with PD-1 blockade (13). The clinical spectrum of irAE is broad and can affect multiple organ systems (Figure 2). Furthermore, many patients can develop more than one irAE involving multiple organ systems (14). The most common irAE include rash, colitis, thyroiditis, hypophysitis, hepatitis, pneumonitis and arthritis, with clinical severity ranging from mild to severe and occasionally fatal. Most events occur within the first 3-4 months of therapy but can occur anytime during treatment and even possibly years after cessation of immunotherapy. Although some irAE can be transient, others require chronic immunosuppression. In addition to the morbidity of irAE, a recent meta-analysis reported a fatality rate of 1.3% and as many as a third of patients are forced to stop these potentially life-saving therapies due to toxicity (15). Early symptoms are often non-specific, including fatigue and malaise; furthermore, many cancer patients assume these side effects are expected and often under-report symptoms, leading to delay in diagnosis. Therefore, awareness and early recognition is essential to optimize long term outcomes.

Rheumatic immune related adverse events

Rheumatic irAE (Rh-irAE) secondary to immunotherapy are likely under-reported in clinical trials with the majority of our learnings coming from case reports and case series (16). As such, our understanding of the prevalence, incidence, clinical features, optimal management and prognosis of Rh-irAE continues to evolve with ongoing clinical experience. In early clinical trials, arthralgias and myalgias were

the most commonly reported Rh-irAE, with a prevalence of 1-43% and 2-20% respectively (17).   With the increased use of ICIs in clinical practice, a wide range of Rh-irAE have been described, most commonly inflammatory arthritis, but also myositis, vasculitis, new onset fractures, resorptive bone lesions, sicca syndrome and sarcoidosis(18–20).

Inflammatory Arthritis:

Inflammatory arthritis secondary to ICI (ir-IA) has been described in several case series, and retrospective cohort studies (6,18,19,21–25).   The prevalence was reported as 3.8% in one study (19). The most common patterns include (1) PMR-like (shoulder and pelvic girdle stiffness), (2) small joint symmetric inflammatory arthritis (predominantly hand) with diffuse tenosynovitis, and (3) large joint, asymmetric oligoarthritis, predominantly involving the knees. In addition, there have been reported cases of a reactive arthritis-like triad (urethritis, conjunctivitis, and arthritis) (18) and psoriatic arthritis.

Ir-IA may be different from the classic inflammatory rheumatic diseases that they mimic and may have differing long term outcomes.   There has been no gender predilection reported, with generally equal cases in men and women.   The majority of cases have been seronegative (although RF and CCP positive cases have been reported), with high prevalence of enthesitis/tenosynovitis and often require higher doses of corticosteroids than traditionally used. Although they have been reported after one dose, they can occur up to two years after receiving immunotherapy and can often become chronic, despite stopping immunotherapy,

unlike other irAE, such as colitis and pneumonitis. Joint involvement pattern at baseline, severity of symptom onset and requirement of long term immunosuppression may differ by underlying immunotherapy regimen (26).

In one case series of 26 patients of European descent with ir-IA, researchers found that there was a higher prevalence of shared epitope (SE) alleles and DRB1*04: 05 compared to population controls, and similar prevalence of at least one SE allele compared to RA patients of European descent. Interestingly, despite being SE positive, these patients were negative for RF and CCP antibody, which raises questions regarding potential underlying mechanisms. Furthermore, they found certain clinical features (enthesitis, trigger fingers, inflammatory low back pain, reactive arthritis) only in patients lacking SE alleles. Further research is needed to determine if distinct HLA alleles are associated with unique ir-IA phenotypes and their risk of development (27).

In addition to inflammatory arthritis (presenting with synovitis), there is emerging literature on a subset of patients with inflammatory-type joint pain without synovitis (6,23). In our experience (25), similar to that reported in the literature, these patients can present with debilitating pain and progressive osteophytosis, which responds to low dose corticosteroid and anti-malarial therapy.

Myositis:

Myositis is an increasingly recognized irAE (ir-Myositis), although it remains relatively uncommon, affecting $\leq$ 1% of patients exposed to ICI (28,29). Ir-

Myositis offers some unique insights into traditional autoimmune myositides (AIM). First, if immune checkpoint inhibitors are considered as a class, this "single" exposure can recapitulate a broad spectrum of AIM, including dermatomyositis (30–32), necrotizing myositis (28,33) and granulomatous myositis (34). This supports the fact that the same exposure could be responsible for more than one traditional AIM. On the other hand, ir-Myositis has been reported to overlap with myocarditis and myasthenia gravis (35,36) much more frequently than when observed in the setting of traditional AIM (37). Similarly, although myositis has been reported to occur in 5% of patients with thymomas, in one series of 8 patients with thymoma treated with Avelumab, 4 (50%) developed myositis (38). Finally, most (though not all)(28,32) cases of ir-Myositis from ICI reported to date have been seronegative (38–40). Thus, myositis from irAE probably have important differences with traditional AIM and a subset of ir-Myositis may represent a new entity.

In one of the most detailed series to date (N=10), Touat et al. described a unique constellation of features that characterize ir-Myositis as follows: (1) early (within 2 months of ICI initiation) and severe onset of symptoms; (2) limb-girdle weakness associated with myalgias, as well as axial and oculomotor weakness; (3) striking creatinine kinase elevations with myopathic changes on electromyography; (4) absence of myositis-specific and anti-acetylcholine receptor antibodies; (5) necrosis and inflammation on histopathology; and (6) good response to ICI discontinuation with or without corticosteroids (40).

Ir-Myositis tends to occur early, often after the first or second dose of immune checkpoint inhibitors. Ir-Myositis ranges from mild, with some cases resolving spontaneously upon discontinuation of the offending drug (40), to severe peripheral and respiratory weakness requiring mechanical ventilation (41). Although myositis represents one of the less common irAE, it is associated with a high case fatality rate (17%), second only to myocarditis (39.7%) (15). Mortality in cases of ir-Myositis overlapping with myocarditis or other neuromuscular symptoms is even higher (over 50% in one study) (42), and results from cardiac or respiratory failure (31,40).

Recognizing myositis from immune checkpoint inhibitors is, in most cases, straight-forward, with patients generally presenting with rapidly progressing proximal muscle weakness and elevated muscle enzymes. Other symptoms include distal, axial and oculo-bulbar weakness, dysphagia, diaphragmatic weakness, and rash(28,40,43). However, diagnosis may be delayed, with some patients attributing their symptoms to their cancer and related problems. Furthermore, ir-Myositis may be difficult to distinguish from cancer-associated myositis, myocarditis and myasthenia gravis. Finally, elevated liver enzymes have been mistakenly attributed to hepatitis, which is a more common irAE than myositis(44). In general, a high level of clinical suspicion is essential given the high risk of mortality and muscle biopsy may be required.

Vasculitis:

Vasculitic irAE (ir-Vasculitis) affecting the large, medium or small size vessels have been reported. A large pharmacovigilance study and a systematic review published in 2018 identified numerous cases of vasculitis (45,46). Large vessel vasculitis, including giant cell arteritis (GCA) and isolated aortitis, and nervous system vasculitis, including primary angiitis of the central nervous and peripheral nerve involvement, were most frequent. The median duration of ICI therapy preceding symptom onset was 3 months, ranging from 1 week to 18 months after initial ICI exposure. Several other cases of vasculitis have been described, including two cases of acral vasculitis causing digital necrosis with amputation of the distal digits despite aggressive immunosuppression (47). PR3-ANCA granulomatosis with polyangiitis was described in a patient following sequential treatment with ipilimumab then pembrolizumab (48). Single organ vasculitis of the uterus (49), eye (50,51) and skin (52) have also been reported. Interestingly, a patient with eosinophilic granulomatosis with polyangiitis was successfully treated with ipilimumab then pembrolizumab for metastatic melanoma without a flare of his vasculitis (53).

There seems to be little difference between the clinical, biological or histopathological presentation of ir-Vasculitis and idiopathic forms of these diseases. The predominance of large vessel vasculitis also fits with the PD-1/PD-L1 pathway dysfunction in GCA highlighted by the work of Zhang et al (54). They showed that the tissue microenvironment of GCA lacks the inhibitory ligand PD-L1 and enriches for PD-1 expressing T cells. Inhibiting the PD-1/PD-L1 interaction intensified T cell accumulation in the vessel wall and profoundly enhanced tissue inflammation and remodelling of the vessel wall, affecting the process of

neoangiogenesis and intimal hyperplasia. Immune checkpoint inhibitors iatrogenically produce a similar effect and could therefore accelerate the autoimmune process in the GCA microenvironment.

General principles for management of irAE

The Common Terminology Criteria for Adverse Events (CTCAE) can be used to grade the severity of adverse events and help guide management decisions (Table 2) (55). Grades 1 and 2 are considered mild, grades 3 and 4 are severe, and grade 5 indicates that the patient died due to an adverse event. In the past few years, multiple groups including the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group, European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have released clinical guidelines on management of irAE secondary to immunotherapy, based on expert consensus (10,56–59). The goal of treatment is to carefully balance immune function, by administering enough immunosuppression to treat adverse events and prevent organ damage, without mitigating the anti-tumor effects of immunotherapy.

Successful management of patients with irAEs requires a multidisciplinary, patient centered approach. Champiat et al. proposed a practical approach to management of patients receiving immunotherapy including prevention, anticipation, detection, treatment and ongoing monitoring (10).

Referral to Rheumatology

As delay in diagnosis and treatment of rh-irAE can lead to long term disability and disease chronicity, it is important to identify those at risk and refer early to rheumatology. SITC guidelines have recommended rheumatology referral for any patient with (1) joint swelling, (2) CTCAE grade 2 and above symptoms, (3) symptoms persisting for more than 6 weeks or requiring prednisone 20mg daily or equivalent that cannot be tapered to < 10mg/day within 4 weeks and (4) suspected myositis, presenting with muscle weakness and elevated creatinine.

The decision regarding earlier rheumatology referral depends on geographic variation, oncologist comfort and experience with rheumatic disease, and availability of local rheumatologists. Ideally, we recommend referral to rheumatology for patients with any rheumatic symptoms (Grade 1 or higher), prior to starting prednisone. We encourage oncologists to develop referral relationships with one or two local rheumatologists. This will hopefully facilitate urgent evaluation of patients and allow the rheumatologist to accrue clinical experience with immunotherapy related toxicity, leading to improved patient care.

Management of patients with Rh-irAE

The role of the rheumatologist is to diagnose and optimize management of rh-irAE in order to facilitate ongoing immunotherapy, if indicated, for the underlying cancer.

It is important for rheumatologists to remember that generalized musculoskeletal symptoms (myalgia, arthralgia, weakness) can be associated with underlying cancer, pre-existing arthritis, metastatic disease, infection or side effects of other medications.   They can also occur with other ir-AEs including endocrine, gastro-intestinal and neurological.   Therefore, evaluation of patients requires a careful history and physical examination and familiarity with possible AEs involving various systems and organs.   Inflammatory markers including C-reactive protein are often helpful biomarkers for diagnosis and monitoring response to therapy, but can be elevated due to underlying malignancy or other non-rheumatic irAE. Xrays can be helpful to evaluate for erosive disease and exclude metastases. Laboratory tests, biopsies, and autoimmune serologies are recommended as directed by the clinical phenotype.   In those with ir-Myositis, careful evaluation for myocarditis and myasthenia gravis should be undertaken.

Current management guidelines released by ASCO, ESMO and SITC recommend treatment based on severity of clinical presentation.   There are currently no clinical trials on optimal management and majority of recommendations are based on expert consensus.   For those with mild symptoms (Grade 1), conservative management with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) is recommended without interruption of immunotherapy.   For large joint involvement, intra-articular corticosteroid injection may be beneficial (60).

For Grade 2 reactions, oral corticosteroids are recommended (0.5-1.0 mg/kg/d), tapering over 4-6 weeks, while holding ICI therapy. If prednisone taper is not tolerated, disease modifying anti-rheumatic drugs (DMARDs) should be started, depending on clinical presentation. In our experience, some patients with ir-IA have a good response to low dose (10-20mg) prednisone and can tolerate ongoing ICI therapy, particularly with concurrent DMARD therapy.

For Grade 3 or above reactions, high dose oral or intravenous corticosteroids are recommended with permanent discontinuation of ICI. Patients should be monitored closely, either in hospital, or with close out-patient follow up, until resolution of symptoms. Early use of concomitant steroid sparing agents may be needed, depending on clinical presentation and response to corticosteroids. The choice of agent usually depends on the type or irAE.

As ir-IA tends to be chronic, we recommend earlier initiation of DMARDs. Hydroxychloroquine, sulfasalazine, methotrexate, anti-tumor necrosis factor alpha inhibitors (TNFi) and interleukin-6 inhibitors have all been used successfully for inflammatory arthritis (20,61,62). The choice of DMARD for ir-IA depends on severity of symptoms, patient preference, and access to medication. Mycophenalate mofetil (MMF) has been used preferentially for hepatitis, while TNFi are commonly used for colitis. IVIG, plasmapheresis, methotrexate, azathioprine and MMF have been used for myositis (40,63) and cyclophosphamide and plasmapheresis have been used for vasculitis (45).

The decision to restart immunotherapy depends on type and severity of irAE, stage and response of underlying malignancy, and alternate treatment options and should be done on a case by case basis with the patient and oncologist. In general, further immunotherapy is not recommended for those with Grade 3 or higher adverse events but may be necessary if there are no other options for underlying malignancy. One patient who developed dermatomyositis after ipilimumab was re-challenged with the same drug 14 months after discontinuation because of tumour recurrence. She had a flare of the dermatomyositis (32). In contrast, two patients who developed ir-Myositis were re-challenged because of tumor progression, one with the same drug (Avelumab) and the other with an alternative drug (Ipilimumab/Nivolumab replaced by Pembrolizumab). Neither had a recurrence of their myositis (64).

Impact of irAE treatment on cancer outcomes

There are no prospective, randomized controlled trials evaluating whether concomitant immunosuppressive therapy negates the anti-tumor response of immunotherapy. Although most data suggest that the use of corticosteroid treatment is not associated with adverse tumor response (65–67), recent reports have suggested that there may be an association with negative tumour response, particularly at higher doses (63,68). No undesirable tumor effects have been reported with use of MMF, infliximab or methotrexate (17,66,67). This data comes from small, retrospective studies, with potential for significant bias. Long term data, in larger populations, across various cancer types and manifesting with different adverse events is needed.

Most guidelines recommend cessation of immunotherapy in patients with grade 2 or higher adverse events. This can lead to anxiety regarding progression of the underlying malignancy. Nevertheless, Schadendorf et al. found that despite discontinuing immunotherapy (nivolumab plus ipilimumab) due to adverse events, patients had similar long term tumor responses than those who remained on therapy (69). Furthermore, in a follow up study, they found that patients whose cancer progressed after discontinuing immunotherapy were able to re-capture a favorable response with restarting treatment, with a similar toxicity profile (70).

All currently published guidelines recommend cessation of immunotherapy with active adverse events requiring systemic immunosuppression. There is little experience with combination of long-term immunosuppression with ongoing immunotherapy. That said, our preference (similar to others in the literature (23)) is to continue immunotherapy in patients with inflammatory arthritis, as these respond to corticosteroids and disease modifying drugs. More research is needed to understand the complex interactions and clinical implications involved in the long-term care of these patients.

Impact of irAEs on cancer outcomes

A common clinical question is whether the development of irAE predicts a favorable tumor response. This would certainly make sense as it implies that immunotherapy has done its job in "turning on" the immune system to fight

cancer, thus leading to an autoimmune reaction. The answer to this remains controversial (9). Many clinical studies have found a correlation between the development of irAE and favorable cancer outcomes. (67,71–77). This seems to be independent of tumor type (reported in melanoma, renal cell carcinoma, lung cancer), type of immunotherapy (observed for both PD-1 and CTLA-4 inhibitors), or type of adverse event (seen with endocrinopathies, vitiligo, colitis, arthritis, etc).   However, this finding has not been universal.   A retrospective study of ipilimumab in 298 melanoma patients found no difference in tumor response between those who developed irAEs and those who did not (78). Further research is needed to conclusively answer this question.

Pre-existing rheumatic disease

Patients with auto-immune disease (AID) were largely excluded from clinical trials, making cancer treatment decisions in these patients challenging (79). A large systematic review of 123 patients with pre-existing (AID) treated with ICI has been published(80). Of these, 72 (59%) had rheumatologic conditions including inflammatory arthritis, sarcoidosis, vasculitis, spondyloarthritis, Behcet's, myositis, PMR, systemic lupus erythematosus, rheumatic fever and Sjogren syndrome. Overall, about 50% had exacerbation of the pre-existing AID and 34% had *de novo* irAE. The occurrence of adverse events was not different between patients with active versus inactive pre-existing AID, but fewer adverse events were seen in patients on therapy for their AID at the time of immune checkpoint inhibitor initiation. Overall, 17.1% discontinued ICIs permanently because of adverse events.

Additionally, Menzies and colleagues reported a retrospective review of 52 patients with pre-existing AID, of which 27 (52%) were classified as rheumatologic, who were treated with anti-PD-1 therapy for advanced melanoma (81). The overall tumour response rate was 33%. Thirty-eight percent had a flare of their underlying AID requiring immunosuppression and only 4% discontinued ICI due to their AID flare. More recently, 16 patients with pre-existing rheumatic disease from the Mayo clinic were treated with ICIs. Of these, 6 (38%) experienced an irAE, with only 1 (6%) being a flare of the underlying rheumatologic disease (82).

These reports show that immune checkpoint inhibitors can be used successfully in patients with AID. The response rate and incidence of adverse events is still unclear and prospective studies are needed in patients with pre-existing AID. Nevertheless, experts agree that having a pre-existing AID is not an absolute contra-indication for treatment with immune checkpoint inhibitors. This challenging treatment decision should be made on a case by case basis with collaborative consultation between patient, oncologist, rheumatologist and other specialists. Rheumatologists have an important role in the initial assessment of disease activity, treatment and close monitoring of the underlying autoimmune disease. Further studies are needed to answer important questions such as effect of concomitant immunosuppressive therapy on tumour response, potential biomarkers to predict irAE and optimal preventive and treatment strategies for patients with underlying autoimmune disease.

Conclusion

In the last decade, immune checkpoint inhibitors have changed the paradigm of cancer care. They now have an established role in all phases of cancer treatment, from (neo)adjuvant settings all the way to refractory metastatic disease, in an every-growing number of indications.   The enhancement of immune responses with immune checkpoint inhibitors has led to the emergence of irAE. Much of the initial focus of irAE identification and management was on rash, colitis and endocrinopathies, in part because these are more common and in part, because they can be associated with significant morbidity.

Until now, the importance and recognition of Rh-irAE has lagged.   There are several reasons for this, including (1) many symptoms of Rh-irAE, including arthralgias and myalgias, can be mistakenly attributed to the underlying malignancy, (2) treating physicians may have difficulty recognizing synovitis or may under-estimate the severity of the symptoms, (3) symptoms are often delayed, and (4) symptoms are unlikely to require hospitalization or be life-threatening.   As awareness increases and experience accumulates, we are learning more about rheumatic irAE and their management.   As experts in systemic auto-immune disease, rheumatologists are well suited to be important members of the team in identifying and treating patients with irAE and assisting with systemic immunosuppression.

There are also many outstanding questions and significant opportunities for education and research in the field of Rh-irAE.   Thus, the Canadian Research Group of Rheumatology in Immuno-Oncology (CanRIO) was created to share knowledge, develop rheumatology-specific management guidelines and undertake studies to define the natural history and optimal treatment of Rh-irAE. The potential to compare and contrast Rh-irAE with traditional AID and to gain further insight into the latter, is also an exciting prospect and bodes well for future collaborations with other established Canadian and international rheumatology cohorts.

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Mechanism of action of immune checkpoint inhibitors

CTLA-4 mediates inhibition in the central lymphoid compartment.
CTLA-4 modulates the immune response by:
* Preferentially binding CD80/86 proteins on APCs,
* Preventing the binding of CD28 (2nd signal needed for T cell activation), and
* Inhibiting T cell activation.

Antibodies that block CTLA-4 can lead to ongoing T cell activation. These T cells can then migrate to the peripheral tissues and attack tumor cells.
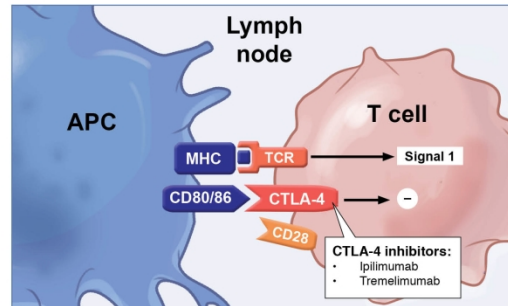

Abbreviations: APC, antigen-presenting cell; CD28, cluster of differentiation 28; CD80/86, cluster of differentiation 80 or 86; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; MHC, major histocompatibility complex; TCR, T cell receptor.

PD-1 mainly exerts its inhibitory effect on T cells in peripheral tissues.
The binding of PD-1 on T cells to PD-L1/PD-L2 on tumor cells can lead to:
* Inhibition of downstream signalling,
* Suppression of T cell function, and
* T cell exhaustion.

Antibodies that block PD-1, PD-L1, and PD-L2 can restore T cell effector function for reactivated anti-tumor response.
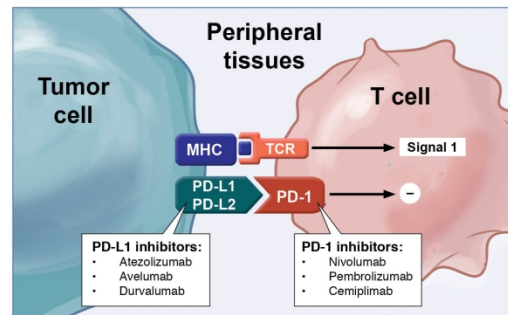
Abbreviations: MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1/2, programmed death-ligand 1 or 2; TCR, T cell receptor.

Figure 1. Mechanism of action of immune checkpoint inhibitors

215x279mm (300 x 300 DPI)

Figure 2.   Systemic irAEs Associated with Immune Checkpoint Inhibitors

215x279mm (300 x 300 DPI)

Table 1. List of FDA and Health Canada Approved Immune Checkpoint Inhibitors and Their Indications

NAME	MOLECULAR TARGET	INDICATIONS
Ipilimumab (Yervoy®)	CTLA-4	Metastatic melanoma
Nivolumab (Opdivo®)	PD-1	Metastatic melanoma, NSCLC (squamous and non-squamous), Renal cell carcinoma, Hodgkin lymphoma, SCCHN, Urothelial carcinoma, HCC, dMMR and MSI-H colorectal cancer
Pembrolizumab (Keytruda®)	PD-1	Metastatic melanoma, Hodgkin lymphoma, NSCLC, Urothelial carcinoma, HNSCC, dMMR of MSI-H solid tumor, PD-L1 gastric and gastroesophageal junction adenocarcinoma
Atezolizumab (Tecentriq®)	PD-L1	Metastatic urothelial carcinoma, metastatic NSCLC
Avelumab (Bavencio®)	PD-L1	Metastatic Merkel cell carcinoma, Urothelial carcinoma
Durvalumab (Imfinzi®)	PD-L1	Urothelial carcinoma, NSCLC
Cemiplimab (Libtayo®)	PD-1	Squamous cell skin carcinoma
Combination Ipilimumab + Nivolumab	CTLA-4 + PD-1	Metastatic melanoma, RCC, HNSCC, Metastatic NSCLC with high PD-L1 expression

NSCLC = non small cell lung carcinoma, RCC = renal cell carcinoma, SCCHN = squamous cell carcinoma of the head and neck, HCC = hepatocellular carcinoma, dMMR = mismatch repair deficient, MSI-H = microsatellite instability-high

Table 2. Common Terminology Criteria for Adverse Events (CTCAE) Grades (v.5)

GRADE	SEVERITY OF ADVERSE EVENT
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL **
Grade 4	Life threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping, managing money etc.

**Self care ADL refers to bathing, dressing, feeding, toileting, etc.