“My cancer treatment is a pain in the neck”

Immunotherapy with checkpoint inhibitors: A rheumatologist’s perspective

Bonnie L Bermas, MD

Rheumatic Diseases Division

Dr. Morris Ziff Distinguished Professorship in Rheumatology

This is to acknowledge that Bonnie L. Bermas, MD has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Bermas will not be discussing off-label uses in her presentation.

Bonnie L. Bermas , MD
Professor of Internal Medicine
Dr. Morris Ziff Distinguished Professorship in Rheumatology

Personal Statement

I was drawn to rheumatology as a subspecialty because I was intrigued with how our immune system, designed to protect us from foreign antigens, could also cause autoimmune disease. As I started rheumatology training, I became fascinated by the intersection of rheumatologic disorders with other medical circumstances in which the immune system was altered. Along those lines, I have spent much of my career trying to understand the impact of pregnancy on rheumatic conditions and the special considerations for disease management during gestation. As cancer patients treated with immune checkpoint inhibitors started to present with rheumatologic immune related adverse events (irAEs), I realized that here was another opportunity to try to understand how a changing immune system, in this case the direct result of immune checkpoint inhibitors, could create and impact rheumatologic disorders. Similar to my experience in treating pregnant patients with rheumatic disease, relying on a multi-disciplinary team and a flexible approach is essential in managing patients who develop rheumatologic immune related adverse events with immune checkpoint therapy.

Purpose:

Review and update current knowledge on the rheumatologic immune related adverse events that occur with immune checkpoint cancer therapy.

Objectives:

At the end of this lecture the attendee should be able to:

1. Understand why rheumatologic immune related adverse events can occur.
2. Describe the common rheumatologic immune related adverse events that occur with immune checkpoint cancer therapy.
3. Understand the management concerns with patients with pre-existing and de novo rheumatologic disorders while undergoing immune checkpoint therapy.

Introduction

Over the past two decades, the role of tumor cells in "down-regulating" usual immune surveillance has been increasingly appreciated (1,2). Tumor cells can evade the immune system in several ways. For example, tumor cells can lose MHC class I expression. They can also promote an immune tolerant micro-environment through changing the cytokine milieu. Tumor cells can also upregulate the expression of immune checkpoint molecules such as PD-1 and PD-ligand 1(PD-L1) to put a brake on the immune system. For the purposes of this presentation, we are doing to focus on immune checkpoint inhibitors used to treat cancer and how they cause immune related adverse events (irAEs) in particular rheumatologic irAEs.

Regulation of T cell activation

Immune checkpoint inhibitors have revolutionized the management of cancer (3). In 2011, Ipilumab, an anti-CTLA4 therapy, was the first FDA approved immune checkpoint inhibitor for use in the treatment of unresectable or metastatic melanoma. Since then, several other therapies have been approved and more are in development. These therapies work through the immune system to increase the activity of T-cells and enhance anti-tumor activity. There are two general arms of the immune system that these drugs address (4). Centrally, anti-CTLA4 prevents the engagement of the second signal of T cell activation, CD28 on the T cell with CD80/86 (B7) on the antigen presenting cell, causing a brake in immune activation. Peripherally, PD-1 expressed by the T cell, can engage with its ligand PD-L1/L2, and cause T cell exhaustion.

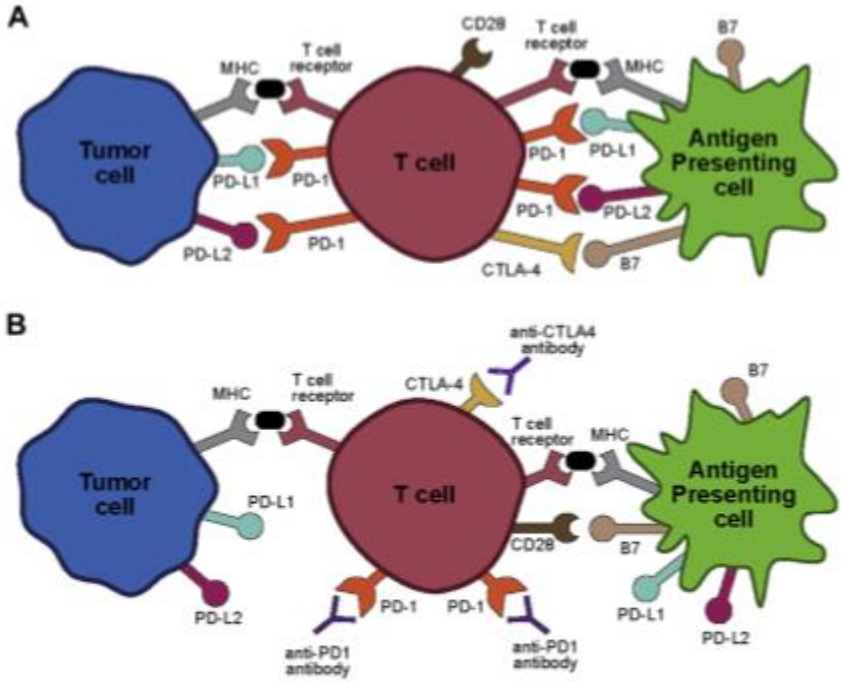


Fig. 1. Mechanism of action for immune checkpoint inhibition targeting CTLA-4 and PD-1. (*A*) Inhibition of T-cell activation by interactions with tumor cells and APCs. PD-L1 and PD-L2 on tumor cells and APCs bind to PD-1 on the T cell and B7 on APCs binds to CTLA-4 on the T cell. (*B*) Antibodies to PD-1 or CTLA-4 block inhibitory interactions, allowing for positive co-stimulation (B7 binds CD28).

Immune checkpoint inhibition

As mentioned above, the first approved immune checkpoint inhibitor was ipilimumab that works by blocking CTLA-4 from binding to its ligand CD80/86 (B7). This then promotes the second signal- CD28 engaging with CD80/86 (B7) enabling T cell activation. In a clinical trial published in 2010, treatment with ipilimumab alone or in combination with glcyporotein 100 (gp100) vaccine improved survival from 6 .4 months to 10 months. Grade 3 or grade 4 immune related adverse events occurred in 10-15% of patients (4).

In 2011, Ipilimumab was approved by the FDA for the treatment of melanoma. Other immune checkpoint inhibitors such as Nivolumab and Pembrolizumab that target PD-1 and atezolizumab, avelumab, and durvalumab- that target PD-L1 have been approved for the treatment of lung cancer and renal cell cancer amongst other cancers. Checkpoint inhibitor therapy has a different pattern of anti-tumor response when compared to traditional chemotherapy. Some patients will show an initial growth in metastases prior to regression. This has led to the development of different tumor response criteria called immune-related response criteria (irRC).

Immune related adverse events

Early on, immune related adverse events were reported in patients treated with immune checkpoint inhibitors. Horvat reported on the Memorial Sloan Kettering Cancer Center experience with ipilimumab (5). Of 298 patients, 254 (85%) experienced an irAE of any grade. 103 (35%) of patients were given systemic corticosteroids and 29 (10%) also received anti-TNFalfa therapy. Overall survival and time to failure were not impacted by either irAEs or the need for systemic corticosteroids.

Other groups have likewise reported on various immune related adverse events (6).These events occur across many different organ systems. Colitis and pneumonitis have caused the most morbidity and mortality

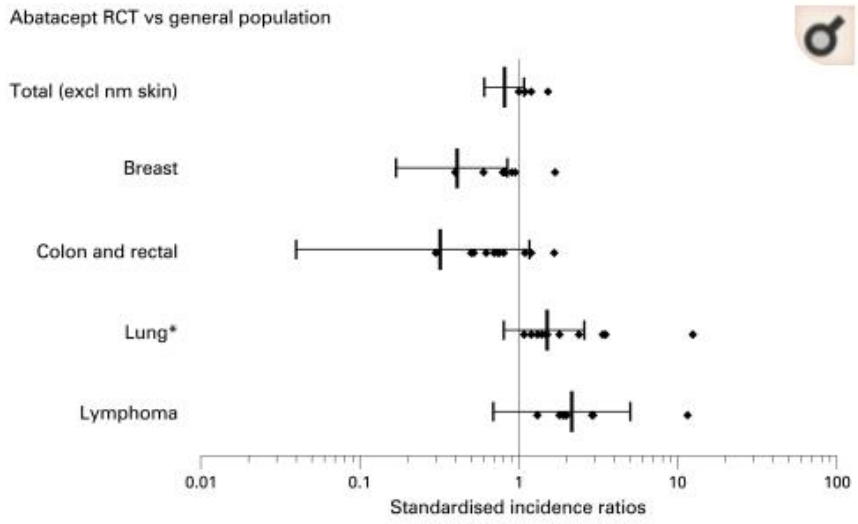
Immune Related Adverse Events with Immune Checkpoint Inhibition

Dermatologic Maculopapular rash Pruritis DRESS
Gastrointestinal Colitis Hepatitis
Endocrine Hypophysitis Hypothyroidism/Hyperthyroidism Type I Diabetes
Pulmonary

Pneumonitis Sarcoidosis
Other Uveitis Myocarditis Myositis Guillain-Barre Nephritis
Rheumatologic

Why rheumatologic symptoms?

It makes sense that immune checkpoint inhibition may be associated with rheumatologic disorders. Abatacept, a biologic that used to treat rheumatoid arthritis and less commonly systemic lupus erythematosus, is a fusion molecule of the surface portion of CTLA-4 and IgG1. As such, it binds to CD 80/86 (B7) preventing the second signal in T cell activation that occurs when CD80/86 (B7) binds with its ligand CD28 (7). One can think of abatacept as the "anti-ipilimumab". In 2005, this biologic was shown to be effective in the management of rheumatoid arthritis (8). This does beg the question; however as to whether patients on abatacept are more likely to develop cancers (9). Fortunately, this does not appear to be the case.



In terms of the PD-1/PD-L1 pathway, T cells from patients with rheumatoid arthritis and psoriatic arthritis show increased resistance to PD-1 mediated suppression. This is thought to be due to the presence of soluble PD-1 in the inflammatory environment of the synovium (10-13).

Spectrum of rheumatologic disorders described after therapy with immune checkpoint inhibitors.

Shortly after the growth of immune checkpoint inhibitor use for cancer therapy, case reports of rheumatic immune related adverse events started to appear in the literature. In 2014, Goldstein et. al, reported on two cases of giant cell arteritis after ipilimumab treatment (14). These cases occurred after four and five treatment cycles respectively. In both cases the patients had symptoms suggestive of GCA such as occipital headache, scalp tenderness, jaw claudication, facial swelling and polymyalgia rheumatica. Both patients had positive temporal artery biopsies. The patients both responded well to high dose glucocorticoid therapy.

Polymyalgia rheumatica, a disorder that predominately occurs in those older than 50, presents as pelvic girdle stiffness without obvious synovitis and in the setting of elevated inflammatory markers such as an ESR or c-reactive protein. This disorder is associated with giant cell arteritis in about 15% of patients. Kuswanto et al, reported on four cases of PMR-like presentation after patients were treated with either a PD-1 or a PD-L1 inhibitor. Immunotherapy was discontinued but symptoms persisted. All patients were started on glucocorticoid therapy and one patient required methotrexate as well to control symptoms (15).

We are indebted to our colleagues at Johns Hopkins for putting together one of the first and largest case series of rheumatologic immune related AEs. Cappelli et. al, described 13 patients who were referred to Johns Hopkins rheumatology after developing rheumatologic symptoms after checkpoint inhibition (16). These patients were treated for a variety of cancers including melanoma, small cell lung cancer and renal cell carcinoma. Eight patients were treated with combination therapy of nivolumab and ipilimumab, and five patients were treated with mono therapy. Nine patients had inflammatory arthritis- they were able to confirm synovitis through imaging and were able to demonstrate inflammatory synovial fluid in four. Four patients presented with SICCA syndrome. The authors were able to describe three patterns of arthritis: polyarthritis similar to rheumatoid arthritis; reactive arthritis with urethritis, conjunctivitis and oligoarthritis; seronegative spondyloarthritis with inflammatory back pain and large joint involvement. Other irAEs were identified including pneumonitis, colitis, interstitial nephritis and thyroiditis. Anti-nuclear antibodies were present in 5/13 patients, 3 of those with sicca syndrome. Belkhir and others also reported their experience from the Gustave Roussy Cancer Center in France (17). This center had established both a national pharmacovigilance registry and also 2400 internists and rheumatologists were canvasses across France. Patients were included if they had received immune checkpoint therapy and had either a diagnosis of rheumatoid arthritis or PMR. They reported on ten cases of rheumatic inflammatory diseases. All of the patients received nivolumab or pembrolizumab, one patient received ipilimumab in addition to nivolumab. Six patients developed sero-positive RA and four patients presented with PMR. In three patients where sera was available before treatment, two out of three had a positive ccp. Median time after exposure was one month (range 19) months. Three of the patients with RA were successfully treated with corticosteroids alone; three required the addition of hydroxychloroquine or methotrexates. All of the patients with PMR responded to corticosteroids. One patient required the discontinuation of nivolumab.

While the vast majority of reports of rheumatic immune related AEs have been generally in the areas of 1) Inflammatory arthritis 2) polymyalgia rheumatica type presentations (PMR) and 3) Sicca syndrome, (18,19), cases of dermatomyositis (20), lupus nephritis (21), and Jacoud's arthropathy (22) have also been reported. Given the spectrum of rheumatic presentations, it is tempting to attribute all joint symptoms to the drugs, but bony metastasis should be considered and ruled out in these patients (23).

What is the incidence of rheumatic immune related AEs?

It has been difficult to establish how common these irAEs are mainly because often we do not have a denominator that reports exposed persons. While patients may be referred to a rheumatology clinic, the number of at risk patients is unknown. Moreover, it is possible that patients with milder joint pain may not be considered as having severe enough symptoms to count as having an adverse event. Kostine reported on 524 patients that received, immune checkpoint inhibition. In their cohort, 35 (6.6%) were referred to the department of rheumatology for rheumatoid arthritis like symptoms (n=7), polymyalgia rheumatic symptoms (n=11), psoriatic arthritis (n=2) and non-inflammatory musculoskeletal conditions (n=15) (18). This is similar to the pattern of involvement others have seen. (19).

Rheumatologic immune related AEs are not limited to these entities. There have been case reports of dermatomyositis (20), lupus nephritis (21) and Jacoud's arthropathy (22). Nonetheless, one ought to use caution and not assume that all joint pain or rheumatologic symptoms are due to an adverse event, as there have been case reports of bony metastasis presenting with joint pain (23).

Does treatment regimen determine phenotype of rheumatic irAEs ?

CTLA-4 +(PD-1 or PD-L1) n=14	PD-1 or PD-L1 monotherapy n=16
Knee arthritis Reactive arthritis phenotype Higher c-reactive protein Other irAEs (79.6%)	Small joint involvement Other irAEs (56%)

This group felt that the CTLA-4 regimens were more likely to present with knee arthritis and a reactive arthritis regimen (24). When I took the data from Kostine's group one can appreciate that the while the anti-CTLA -4 containing regimens appear to have more non-rheumatic irAEs, (other studies have shown that overall irAEs are more common with anti-CTLA-4), rheumatic irAEs are more common in protocols targeting the PD-1/PD-L1 pathway (18)

	CTLA-4 (n=5)	PD-1/PD-L1 (n=407)	Combo (n=112)
Rheumatic irAEs	0	30 (7.4%)	5 (4.5%)
Non-rheumatic irAEs	3 (60%)	82 (20%)	52 (46%)

Are rheumatologic irAEs more common in those with pre-existing rheumatic conditions?

Sixteen patients with pre-existing rheumatologic condition were evaluated (RA-5, PMR-5 Sjogren's -2, SLE -2, GCA -2. Receiving ipilimumab (5) or nivolumab (7) or pembrolizumab (5) or combination (number not delineated) Six had an irAEs, only one (GCA) flare of underlying rheumatologic condition- patient on nivolumab. In a systematic review of 123 patients with pre-existing autoimmune diseases, 75% had exacerbation of pre-existing autoimmune disease, irAEs or both (26).

Does the development of an immune related adverse event portend better cancer outcome?

If we go back to the Mayo clinic experience, of their 6 patients that had an irAE, five were still alive. In contrast, amongst the 10 patients who did not have irAEs, only one was alive (25). Similarly, in Kostine's study, patients who had irAEs had a higher response rate to immune checkpoint inhibitor therapy than those who did not (85.7% versus 35.3% $p<0.0001$) (18). And, in a study of 148 patients with melanoma who were treated with nivolumab +/- peptide vaccine, 68% of patients developed an irAEs. Grade III/IV events were infrequent. There was a statistically significant overall survival amongst those who had any irAE ($p<0.001$) (27).

How can we treat these patients?

If the symptoms are mild, then NSAIDs, low dose glucocorticoids and intra-articular steroids can be used. In those refractory to therapy, one can consider adding hydroxychloroquine or methotrexate. The group from Hopkins suggest that for arthritis that does not respond to steroids, tnf-alfa blockade is helpful (16). Others suggest that this approach may be problematic as it may ultimately render the cancer non-responsive to therapy. IL-6 has been advocated by some (28), but monitoring for colitis in patients receiving this therapy is essential, as IL-6 has been associated with colonic perforation in those with diverticular disease. It is likely that blockade of IL-17 while it may ameliorate both psoriatic skin lesion and colitis, it may be associated with a worse response to cancer therapy (29).

What does the future hold?

As we gather more information on the irAEs in patients being treated with ICI therapy, we will learn a lot not only about cancer therapy but also about autoimmune diseases. We may also eventually be able to predict which patients will be at risk for specific types of irAEs. It turns out that unctional CTLA-4 single nucleotide variants (SNVs) are associated with autoimmune endocrinopathies. Recently, Queirolo et. al, evaluated 173 metastatic melanoma patients treated with ipilimumab for endocrine irAEs. They explored the association of CTLA-44 -16661 A>G single nuclear variants.

Homozygous G/G genotype 33% endocrine irAEs

Heterozygous A/G genotype 6.5% endocrine irAEs

Homozygous A/A genotype 2.9% endocrine irAEs

So one can imagine in the future that we will not only be able to tailor cancer therapy to individual malignancies but also we will be able to personalize treatment to minimize toxicities.

Conclusions:

- Immunotherapy such as immune checkpoint inhibitors have revolutionized cancer therapy
- ICI are associated with immune related adverse events
- Rheumatologic IRAEs occur in about 5% of patients.
- Most common rheumatologic IRAEs are
  - PMR like symptoms
  - Inflammatory arthritis (oligo, reactive, symmetric)
  - SICCA symptoms
- Most patients can be treated through their rheumatologic symptoms and continue their immunotherapy
- Patients can receive NSAIDs and glucocorticoids as first line therapy: Often higher doses of glucocorticoids are necessary
- DMARDs such as methotrexate and some biologics can be used
- Patients who have a past history of rheumatologic disorder need to be monitored carefully
- Great opportunity for multi-disciplinary collaboration and to deepen our understanding of the immunology of both cancer and autoimmune disorders.

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