Immune Checkpoint Inhibition—Does It Cause Rheumatic Diseases? Mechanisms of Cancer-Associated Loss of Tolerance and Pathogenesis of Autoimmunity

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KEYWORDS

• Immune checkpoint inhibitors • Immune-related adverse events
• Rheumatic diseases • Tolerance • Autoimmunity

KEY POINTS

- Immune checkpoints transmit inhibitory signals, preventing excessive cellular responses and helping to maintain self-tolerance and limit tissue damage during immune responses.
- Immune checkpoint inhibitors (ICIs) are cancer treatment strategies directed at improving the host response to cancer and are associated with the development of immune-related adverse events (irAEs).
- Rheumatic irAEs (Rh-irAEs) arise from ICI therapy and have a broad clinical spectrum that mirrors many classic rheumatic diseases.
- A breakdown in self-tolerance contributes in part to irAEs and Rh-irAEs but cannot account entirely for their emergence.

INTRODUCTION

The treatment paradigm of cancer has been transformed fully with the innovation of various immunotherapeutic modalities, such as tumor-specific monoclonal antibodies (mAbs), recombinant cytokines (interleukin [IL]-2 and interferon α-2b), adoptive

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transfer of ex vivo–activated immune cells, cancer vaccine sipuleucel-T, and more recently mAbs against T-cell regulatory checkpoints molecules.[1] Immune checkpoints have proved attractive and efficacious targets for cancer immunotherapy across multiple malignancies.[2] Immune checkpoint inhibitors (ICIs) target immune checkpoints, which are mechanisms critical for regulating T-cell responses to antigen and subsequent activation and proliferation. By blocking these immune checkpoints, the brakes are taken off the host immune system, and the host antitumor response is augmented. To date, 7 ICIs have been approved by the Food and Drug Administration (FDA), targeting 2 main signaling pathways: cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitory pathways, significantly enhancing overall survival in various cancers, including in the adjuvant setting.[3–11]

Anti–cytotoxic T-Lymphocyte–Associated Protein 4 Blocking Agents

Ipilimumab, a fully human IgG1 mAb, was the first ICI agent to receive FDA approval, in 2011, for metastatic melanoma[12] and in 2015 as an adjuvant therapy for high-risk stage III melanoma after complete resection.[7] No other anti-CTLA-4 inhibitors currently are approved.

Anti–programmed Death 1 Blocking Agents

Pembrolizumab, a humanized IgG4 mAb, was the first anti–PD-1 inhibitor to receive FDA approval, in 2014, for metastatic melanoma.[13,14] Its approval currently is expanded to 13 other cancers, including non–small cell lung cancer (NSCLC), head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma (RCC), and endometrial carcinoma,[4] and also in the adjuvant setting for melanoma.[8] Nivolumab, a fully human IgG4 mAb, was the second anti–PD-1 approved, in 2014, for metastatic melanoma[15] and currently is approved for 6 other cancers, including NSCLC, small cell lung cancer (SCLC), RCC, Hodgkin lymphoma, head and neck squamous cell cancer, urothelial carcinoma, and hepatocellular carcinoma,[3] and as an adjuvant therapy for melanoma.[11] Cemiplimab is the newest human IgG4 mAb against PD-1, approved in 2018 for metastatic and locally advanced cutaneous squamous cell carcinoma.[9]

Anti–programmed Death-Ligand 1 Blocking Agents

Atezolizumab, a humanized IgG1 mAb against PD-L1, was the first anti–PD-L1 inhibitor to receive FDA approval in 2016 for urothelial carcinoma,[10] followed by its approval for SCLC, NSCLC, and triple-negative breast cancer.[5] Durvalumab, a fully human IgG1 mAb against PD-L1, received FDA approval in 2017 for urothelial carcinoma[16] and in 2018 for NSCLC.[6] Avelumab, another fully human IgG1 mAb against PDL-1, was approved in 2017 for metastatic Merkel cell carcinoma[17] and subsequently for locally advanced or metastatic urothelial carcinoma[18] and RCC.[19]

Combination Therapy

Certain ICIs used in combination have elicited high response rates in advanced disease. Ipilimumab plus nivolumab initially was approved in 2016 for metastatic melanoma[20] and then for RCC,[21] and colorectal cancer with high microsatellite instability/mismatch repair deficiency.[22] Another promising combination is nivolumab plus bempegaldesleukin (a PEGylated IL-2) that recently received FDA

breakthrough therapy designation for metastatic and previously untreated unresectable melanoma.[23]

IMMUNE-RELATED ADVERSE EVENTS

The hallmarks of cancer immunotherapy are durable clinical responses that presumably are mediated by persistent activation of the immune system. Such responses could result, however, in off-target inflammatory responses and irAEs that can be severe and occasionally fatal. The phenotype of irAEs varies widely; many patients develop toxicity involving multiple organs, others develop toxicity limited to 1 organ, and some patients may not develop toxicity despite continued ICI therapy. Gastrointestinal, liver, skin, endocrine, and pulmonary irAEs were those reported most frequently across ICI clinical trials. Any-grade irAEs have been reported in up to 90% of patients receiving ICI monotherapy.[24–29] Grade 3/4 toxicity has been reported in 22% of patients receiving anti–PD-1 monotherapy and in up to 59% of those receiving combination ICIs.[20,30–33] A meta-analysis of 21 trials compared 6528 patients who have received ICI with 4926 patients who have not; higher risks of all-grade colitis (RR 7.66' $P<.001$), aspartate aminotransferase elevation (relative risk [RR] 1.80; $P = .020$), skin rash (RR 2.50; $P = .001$), hypothyroiditis (RR 6.81; $P<.001$), and pneumonitis (RR 4.14; $P = .012$) were observed in ICI-treated patients.[27] In regard to high-grade toxicity, higher risks of colitis (RR 5.85; $P<.001$) and aspartate aminotransferase elevation (RR 2.79; $P = .014$) also were observed in ICI-treated patients. Ipilimumab use was associated with a higher risk of all-grade rash ($P = .006$) and high-grade colitis ($P = .021$) compared with anti–PD-1/PD-L1 agents. A total of 613 fatal irAEs have been reported in the World Health Organization pharmacovigilance database between 2009 and 2018; 193 related to anti–CTLA-4 (70% from colitis), 333 to anti–PD-1/PD-L1 (35% from pneumonitis, 22% from hepatitis, and 15% from neurologic irAEs), and 87 to combination ICIs (37% from colitis and 25% from myocarditis). A meta-analysis of 112 trials (19,217 patients) reported death because of irAEs in 0.36% and 0.38% of patients treated with anti–PD-1 and anti–PD-L1, respectively. Fatality rate increased to 1.08% among patients treated with anti–CTLA-4 and 1.23% among those treated with combinations ICIs.[29]

Rheumatic irAEs (Rh-irAEs) increasingly have been reported over the past 3 years.[34] Limited mechanistic understanding of irAEs, including Rh-irAEs, exists to date, and it remains to be fully understood whether or not irAEs arise merely as a consequence of systemic, tumor-agnostic immune activation, a breakdown in self-tolerance induced by checkpoint inhibition, unmasked autoimmunity marked by antigen-specific T-cell responses in susceptible hosts, or an alternative process of autoimmunity altogether.

The spectrum of Rh-irAEs is reviewed. The functions of 2 immune checkpoints targeted most commonly for cancer immunotherapy, CTLA-4 and the PD-1/PD-L1 pathways, are summarized. Subsequently, the role of these immune checkpoints in autoimmunity, the mechanisms and implications of immune checkpoint blockade in the context of cancer therapy, and available mechanistic understanding of irAEs, with a focus on Rh-irAEs are discussed.

RHEUMATIC IMMUNE-RELATED ADVERSE EVENTS

Rh-irAEs have been reported in 5% to 10% of cancer patients treated with ICIs,[35] yet the true incidence rates remain imprecise because most of these adverse events are not typically perceived as severe or life threatening and, therefore, are underreported in oncology trials.[36] A broad spectrum of Rh-irAEs has been reported so far; arthritis, sicca, myositis, and polymyalgia rheumatica are most frequent. Other rheumatic

syndromes also have been reported, however, including de novo onset of sarcoidosis, vasculitis, lupus, antiphospholipid syndrome, scleroderma-like syndromes, hemophagocytic lymphohistiocytosis, bone abnormalities, and flares of preexisting autoimmune diseases after initiation of ICI therapy.[35,37–39] Most of the reported cases occurred after initiation of anti–PD-1/PD-L1 agents or combination ICIs, and median time to onset of rheumatic manifestations was variable (they can develop early on but also several months after ICI initiation). Rh-irAEs may persist despite discontinuation of immunotherapy, as in some patients with arthritis.[40,41] Death attributable to Rh-irAEs has been reported in few patients with complicated myositis or vasculitis.[35] In the following sections, the most common Rh-irAEs are summarized, the most severe ones as critical for early recognition highlighted, and finally the general concepts for management of Rh-irAEs summarized.

COMMON RHEUMATIC IMMUNE-RELATED ADVERSE EVENTS

Arthritis

Two systematic reviews of ICI trials and few additional observational studies have provided data primarily on Rh-irAEs; arthralgia was the most frequent, ranging from 1% to 43%, and arthritis occurred in 1% to 7%.[38,42–46] Most of the reported cases occurred after the administration of anti–PD-1 agents or combination ICIs, and duration between ICI initiation and onset of arthritis was variable (0.1–24 months). Different patterns of inflammatory arthritis have been reported so far. Seronegative polyarthritis was the most frequent (patients had negative rheumatoid factor [RF] and anti-citrullinated peptide (CCP) antibodies, but some had positive antinuclear antibody (ANA)), followed by erosive rheumatoid arthritis (RA)-like (patients had positive RF, anti-CCP, and/or ANA). In addition, some patients presented with features similar to seronegative spondyloarthritis, such as conjunctivitis, urethritis, and skin psoriasis; only a few were tested for HLA-B27 and were found negative. Furthermore, cases of de novo onset of undifferentiated oligoarthritis and monoarthritis have been reported.[47] In a few of these patients, inflammatory arthritis persisted for up to 2 years after ICI discontinuation, requiring immunomodulatory agents and significantly limiting patients' function and quality of life.[48,49] Approximately half of the patients with ICI-induced arthritis reported in literature also had other nonrheumatic irAEs.[47] Arthritis flares have been reported in patients with preexisting inflammatory arthritis when treated with ICIs[39] as well as in a few other patients with degenerative osteoarthritis and gouty arthritis.[46,50]

Moreover, few additional cases of remitting seronegative symmetric synovitis with pitting edema, inflammatory tenosynovitis (hands and/or shoulders), enthesitis, and Jaccoud arthropathy have been reported after initiation of ICIs.[51–56]

Sicca Syndrome

Two systematic reviews of ICI trials have reported sicca symptoms as a treatment-related adverse event, with an estimated prevalence of 1.2% to 24.2%.[43,57] The French registry, Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie (REISAMIC), which included patients who had received anti-PD-1/PD-L1 agents, identified that the prevalence of sicca in patients receiving single agent anti–PD-1 was 0.3% and increased to 2.5% in patients receiving combination ICIs.[44] All patients reported in REISAMIC registry fulfilled the 2002 American-European Consensus Group and the 2017 American College of Rheumatology(ACR)/European League Against Rheumatism (EULAR) diagnostic criteria for true Sjögren syndrome. Few additional small series of patients with de novo onset of

sicca after initiation of ICI have been published.[37,41,58–62] Time to onset of symptoms after ICI initiation ranged from 1 month to 10 months. All reported patients had salivary gland hypofunction, few had dry mouth without keratoconjunctivitis, and 1 patient had bilateral parotid gland enlargement. Few patients had other Rh-irAEs (such as arthritis, polymyalgia rheumatica, cryoglobulinemic vasculitis, and RA flare), and others also had nonrheumatic irAEs. Autoantibodies, including ANA, RF, anti-SSA, or anti-SSB, were found positive in few patients, and 1 patient each was reported to have antisynthetase and anti–Scl-70 antibodies. In a few patients, the diagnosis was confirmed by salivary gland ultrasonography and/or labial salivary gland biopsy.[62]

Polymyalgia Rheumatica

Few observational studies have documented the development of polymyalgia rheumatica as an adverse event in cancer patients receiving ICIs, with an estimated prevalence of 0.2% to 2.1%.[38,44,63] A few other cases reports and small series also have been published.[35,37,44,58,59,64–72] Some of these patients fulfilled the 2012 EULAR/ACR diagnostic criteria for polymyalgia rheumatica. Most of the cases occurred after the administration of anti–PD-1/PD-L1 agents, and duration between ICI initiation and symptoms onset ranged from 0.3 month to 16 months. One of the reported patients had impaired vision,[63] and a few others had associated Rh-irAEs and nonrheumatic irAEs.

LIFE-THREATENING RHEUMATIC IMMUNE-RELATED ADVERSE EVENTS

Myositis

Three systematic reviews of ICI trials have reported myalgia as the second most common Rh-irAEs, with a prevalence ranging from 2% to 21%, whereas myositis was diagnosed less frequently (0.4% to 6%).[43,57,73] Several observational studies[37,44,74–79] as well as case reports and small series[35,58–60,70,75,76,78,80–94] have documented de novo onset of myositis as an adverse event in patients receiving ICIs. Most of the reported cases occurred after the administration of anti–PD-1 agents or combination ICIs, and duration between ICI initiation and symptoms onset was relatively short compared with other Rh-irAEs (0.4–3 months). Different patterns of myositis have been reported, including polymyositis, necrotizing myositis with rhabdomyolysis, nonspecific myopathy, dermatomyositis, and antisynthetase syndrome. In more than one-third of the cases, myositis was associated with myasthenia gravis (MG) or myocarditis; a few patients had the triad of MG/myositis/myocarditis, and others had additional nonrheumatic irAEs. Marked elevation of creatine phosphokinase (up to 19,794 IU/L) has been reported as well as elevation of aldolase, transaminases, and lactate dehydrogenase. Elevation of anti-acetylcholine receptor antibodies and/or troponin also has been reported in patients with the triad of MG/myositis/myocarditis. In a few patients, diagnosis was confirmed by muscle biopsy. Death primarily due to myositis has been reported.

Vasculitis

A few studies and a systematic review of published cases have identified de novo onset of vasculitis induced by ICI therapy, fulfilling the 2012 revised International Chapel Hill Consensus Conference nomenclature for vasculitis.[35,37,63,95–101] Most of the reported cases occurred after the administration of anti–PD-1 agents, apart from temporal arteritis, which was reported more frequently in patients who received anti–CTLA-4. The time between ICI initiation and onset of vasculitis symptoms ranged from 0.25 month to 18 months. Different types of vasculitis have been reported, yet

large vessels vasculitis followed by nervous system vasculitis remain the most predominant types. Antineutrophil cytoplasmic antibodies–associated, necrotizing, granulomatous, uterine lymphocytic, retinal, cryoglobulinemic, autoimmune, cutaneous small vessels, digital, and acral vasculitis also have been reported. The time between ICI initiation and onset of vasculitis symptoms ranged from 0.7 month to 5.5 months. Vision was impaired in 28% of patients with temporal arteritis. Vasculitis-related death has been reported in few patients.[63]

IMMUNE CHECKPOINTS—MECHANISM OF ACTION

CTLA-4 is a coinhibitory molecule expressed on both activated T cells and regulatory T cells (T-reg). CTLA-4 is up-regulated on T cells that have received signal 1 through engagement of the T-cell receptor (TCR) with the cognate antigen–major histocompatabiltiy complex presented by an antigen-presenting cell (APC). CTLA-4 competes with the costimulatory molecule, CD28, for their shared ligands CD80 and CD86, whereas CD28 binding to these ligands results in an activating signal, which amplifies T-cell signaling and proliferation,[102] CTLA-4 dampens T-cell activation and T-cell–mediated immune responses in myriad ways. CTLA-4 signaling decreases CD80/86 expression on APCs,[103] thus decreasing the ability of T cells to engage CD28 and receive the critical signal 2 needed for full activation. CTLA-4 binding decreases IL-2 and IL-2 receptor expression, critical for T-cell proliferation.[104] In addition, CTLA-4 can induce APCs to secrete indoleamine 2,3-dioxygenase (IDO), which catalyzes tryptophan degradation thereby depleting a key molecule necessary for T-cell proliferation.[105] Beyond its coinhibitory effects on early activated T cells, CTLA-4 is constitutively expressed on regulatory T cells (Tregs), promoting their proliferation and immunosuppressive activities through enchanted production of various mediators, such as transforming growth factor-β, IL-10, and IDO.[106] Thus overall, CTLA-4 acts to dampen down T-cell responses by decreasing early T-cell activation and proliferation and enhancing Treg function.

Programmed Death 1

Similarly, PD-1 and its ligands PD-L1 and PD-L2 exert inhibitory functions, although at different stages of immune activation and via different mechanisms compared with CTLA-4. PD-1 and PD-L1 are focused on because they currently are targets of ICI therapy. PD-1 and PD-L1 are expressed more broadly than CTLA-4 and are seen on B cells, Tregs, macrophages, and APCs[107] in addition to T cells. In particular, PD-1 expression is up-regulated on effector/peripheral T cells, and its engagement with its ligand results in disruption of the TCR signaling cascade (via recruitment of tyrosine phosphatases) leading to diminished cytokine production, T-cell cytolytic function, and survival.[108,109] The net impact is that of diminished effector T-cell functionality in the periphery. The PD-1 pathway is thought to have similar immunosuppressive activity on other cell types[110] and its ligation on Tregs also enhances their immunosuppressive function.[109,111]

PD-1 additionally plays a critical role in thymocyte development, regulating thresholds during positive selection, and inhibiting the proliferation of naive autoreactive T cells during negative selection.[107] PD-L1 expression also has been observed in so-called immune-privileged sites, supporting a role for its protecting the site from the immune response.[109] Thus, critical actions of PD-1 and PDL-1 include roles in the establishment of central tolerance and the maintenance of peripheral tolerance.[112] Some tumors have evolved to up-regulate the expression of PD-L1 on their cell

surface, promoting T-cell exhaustion and inhibiting tumor-specific cytolytic T cells, thus harnessing the power of this immune checkpoint to evade detection by the host immune system.[113]

Cytotoxic T-Lymphocyte–Associated Protein 4 and Programmed Death 1: Murine Knockout Phenotype

The critical role of immune checkpoints in maintaining homeostasis of the immune system is illustrated by the phenotypes of their cognate knockouts in mouse models. Germline knockout of CTLA-4 leads to widespread autoimmunity in mice characterized by fulminant infiltration of activated lymphocytes into various organs (eg, spleen, lymph nodes, heart, lung, and liver) and elevated antibody levels and is fatal 3 weeks to 4 weeks after birth.[114] Conditional deletion of CTLA-4 in adult mice similarly results in spontaneous multiorgan lymphoproliferation and organ-specific antibodies but is not fatal, allowing the longer observation of the phenotype, which then was expanded to include the development of histologically evident pneumonitis, gastritis, insulitis, and marked expansion of Tregs.[115] Furthermore, the severity of collagen-induced arthritis is greater in adult mice with CTLA-4 deficiency compared with wild-type mice.[115]

PD-1–deficient mice, in a strain-specific manner, develop complement-mediated glomerulonephritis in a lupus-like pattern,[116] and a subset develops inflammatory arthritis. Compared with CTLA-4 knockouts, the restricted clinical phenotype and the delayed onset of autoimmunity (greater than 1 year) in PD-1–deficient mice likely result from the later stages of immune activation targeted by PD-1.[107]

In both CTLA-4 and PD-1 knockout mouse models, the phenotype varies based on mouse strain, underscoring the significant role of background genes in the development of autoimmunity in the context of ICI.

CYTOTOXIC T-LYMPHOCYTE–ASSOCIATED PROTEIN 4 AND PROGRAMMED DEATH 1 AND AUTOIMMUNITY

CTLA-4 has been implicated in several rheumatic diseases, including RA, systemic lupus erythematosus, and Sjögren syndrome. In RA, CTLA-4-Ig, or abatacept, is a useful treatment strategy attributable to a variety of mechanisms, including decreased Treg cell death, increased T-cell susceptibility to Treg functions, and down-regulation of proinflammatory cytokine production.[117]

The PD-1/PD-L1 pathway has been investigated in autoimmunity, primarily in experimental animal models, with limited study in humans. The putative role of PD-1 in systemic lupus erythematosus is highlighted by the phenotype of the PD-1 knockout mouse (discussed previously). In humans, the PD-1 pathway is down-regulated at various stages of RA disease progression and is reduced further with treatment of early RA,[118] implicating the PD-1 pathway in RA pathogenesis and as a potential treatment target. PD-1 single-nucleotide polymorphisms have been found associated with certain rheumatic diseases, such as RA and ankylosing spondylitis.[107] Although results varied considerably by sex and ethnic group, they are supportive for a strong role of this pathway in autoimmunity. Considering these observations, together with the mechanistic understanding of immune checkpoints, it is not surprising checkpoint inhibition is associated with irAEs that have been observed in almost every organ system.

Mechanisms of Immune Checkpoint Blockade in Cancer

Combination checkpoint blockade (CCB) with CTLA-4 and PD-1 inhibitors results in better antitumor responses but also more prevalent irAEs.[20] The exact mechanisms,

however, underlying the antitumor efficacy of CTLA-4 and PD-1 blockade or the development of irAEs or whether these mechanisms are shared are not fully understood.

CTLA-4 blockade in cancer patients has been shown to overcome cancer-associated tolerance mechanisms and to augment antitumor efficacy by (1) impairing Treg effectiveness and longevity[119] and (2) reducing intratumoral Tregs[120] and possibly expanding and maintaining high-avidity T-cell clones with antitumor responses.[121] Furthermore, antibodies blocking CTLA-4 may lead to antibody-dependent cellular cytotoxicity of Tregs,[120] thus impeding peripheral tolerance and increasing the risk of autoimmunity. PD-1 blockade targets effector T cells in the periphery and thus preexisting antitumor T-cell responses. Clinically, this has translated into a more limited toxicity profile and increased therapeutic efficacy of the PD-1 inhibitors.[32]

It appears that shared and distinct cellular mechanisms underlie the antitumor efficacy related to CTLA-4 and PD-1 checkpoint blockade. Work by Wei and colleagues[122] demonstrated that anti–PDI-1 therapy induces the expansion of tumor-infiltrating CD8 T cells with an exhausted phenotype, whereas anti–CTLA-4 therapy induces the expansion of $ICOS^{+}$TH1-like CD4 effector cells in addition to a subset of exhausted CD8 T cells. Further complicating matters are the observations that alternative inhibitory checkpoints are compensatory up-regulated after immune checkpoint blockade.[123] In the grand scheme of things, it is wise to view immune checkpoints as an intertwined and complex network that continually strives for immune homeostasis. Certainly, irAEs reflect a perturbation of such homeostasis. The putative mechanisms of irAEs are reviewed.

Mechanisms and Immunopathology of Immune-Related Adverse Events

Concurrent with CTLA-4 blockade has been observed the increase in circulating helper T cells type 17, which have been implicated in several autoimmune diseases, including colitis. PD-1 blockade is associated with the increased production of IL-6, IL-17, and enhanced Th1 responses, which could contribute as well to the development of autoimmunity.[124]

Greater diversification of the T-cell repertoire has been demonstrated in cancer patients treated with ICI who developed irAEs compared with those who did not.[15,125] In patients with prostate cancer receiving ipilimumab, an increased number of expanded CD8 T-cell clones in peripheral blood correlated with the presence of severe irAEs.[126,127] This TCR expansion could reflect overall immune activation in the context of ICI, which in turns leads to the mobilization and expansion of a diverse T-cell population, some of which may be autoreactive.

In 1 study, after CCB treatment in the setting of advanced melanoma, increases in the number of plasmablasts and markers of B-cell clonality were observed,[128] which correlated to higher rates of severe, delayed-onset irAEs. These observations support a role for B-cell autoreactivity, specifically in combined CCB, in the development of irAEs.

Despite data for a putative role for B cells in irAEs in general, autoantibody production is not associated strongly with Rh-irAEs in particular. Most patients with Rh-irAEs are seronegative.[34,41] Furthermore, in the limited studies available to date, only a minority of patients develop any positive autoantibodies after ICI therapy,[129] with antithyroid peroxidase antibodies the most common. The latter suggests that humoral immunity may feature more prominently in other, nonrheumatic irAEs.

In Rh-irAEs, the availability of immunopathologic studies supporting the diagnoses, although scant, suggest similar findings to those seen in some, but not all, of the classic rheumatic diseases.[130] For example, synovial fluid analyses from joints of

patients who have developed inflammatory arthritis after ICI show increased cell counts with a neutrophil predominance, similar to findings that can be seen in, but are not specific for, RA. Furthermore, in a report of ICI-induced granulomatosis with polyangiitis, temporal artery biopsies echoed those seen in granulomatosis with polyangiitis and showed an inflammatory infiltrate of the adventitia and muscular layers with narrowing of the arterial lumen.[98]

In contrast, in ICI-induced myositis, the pathologic phenotype is varied and does not necessarily echo that seen in classical dermatomyositis (DM) or polymyositis (PM), with some biopsies showing features of inflammation, whereas others, predominantly muscle fiber atrophy or necrosis—suggesting distinct pathways of immune attack.[34] A series of patients with sicca syndrome had imaging findings of the parotid glands demonstrating hypoechoic lesions and lymphocytic aggregates as seen in Sjögren syndrome. None of these patients, however, was seropositive,[41] and, in other studies, minor salivary gland biopsies from patients with ICI-induced sicca tended to show a predominance of T-cell infiltration compared with the B-cell infiltrates seen in Sjögren syndrome.[62]

Cancer Immunity and Autoimmunity

Overall, there appears to be some shared but also distinct pathologic mechanisms that underlie Rh-irAEs compared with classical rheumatic disease. Furthermore, although CTLA-4 and PD-1 have been associated with autoimmune disease and their inhibition is associated with irAEs, whether their blockade directly causes autoimmunity and rheumatic disease remains unknown. In a landmark study of CTLA-4 function and antitumor immunity by Lute and colleagues,[131] anti-human CTLA-4 antibodies were studied in human *CTLA4* gene knockin mice for their ability to induce tumor rejection and autoimmunity. It was found that the antibody that induced the strongest protection against cancer induced the least autoimmune side effects—effectively uncoupling the autoimmune side effects and cancer therapeutic effects.

Cancer immunity and autoimmunity may overlap but are not one and the same. The effector arms of these immune responses vary, as do the tissues they target and the susceptibilities of those tissues to immune attack; additionally, the influence of host genetics and environmental factors cannot be underestimated. As such, although ICIs and Rh-irAEs provide novel and unique, in vivo opportunities to study autoimmunity, checkpoint inhibition cannot yet be pointed to as a direct causative factor for rheumatic disease. What is clear is that the most successful approaches moving forward, either antitumor or anti-irAEs, will be those that are able to selectively modulate the delicate balance between cancer immunity and autoimmunity.

SUMMARY

Immune checkpoints are critical for the immunomodulation of immune responses, and their absence or blockade has been associated with various manifestations of autoimmunity. ICI has proved an effective, largely tumor-agnostic cancer therapy but is associated with irAEs, including Rh-irAEs, which share variable clinical and pathologic similarities with classic rheumatic diseases. The mechanisms underlying ICI effectiveness and irAE occurrence, however, are far from fully understood. Disruption of self-tolerance and perturbations in T-cell clonality and Treg activity downstream of ICI seem to play prominent roles, but further study is crucial.

Clinics Care Points

ICIs have advanced the treatment of various cancers with remarkable survival benefits; however, their efficacy remains limited by the occurrence of irAEs.

- Rh-irAEs could have long-lasting effects and sequelae and sometimes are life threatening.
- Understanding the potential long-term adverse events of ICIs and how they could have an impact on patients' function and quality of life remains an unmet medical need.
- Identifying the specific immune correlates associated with the occurrence of irAEs could provide information on which targeted agents might be useful for irAEs management without hindering the antitumor immune response of ICI therapy.

DISCLOSURE

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