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Can Janus kinase inhibitors be used to treat immune checkpoint inhibitor associated adverse events?

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Abstract

Immune checkpoint inhibitors (ICI) such as cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), programmed death ligand-1 (PD-L1), and lymphocyte activation gene-3 (LAG-3) are increasingly used to treat cancer patients since they were shown to reduce tumor progression and increase survival of patients with different types of cancer. However, ICI may also affect self-tolerance and lead to immune-related adverse events (irAEs) which are not very frequent but can present in almost all organ systems including joints, tendons, and muscles. Indeed, arthritis and myositis are among the most frequent irAEs. Glucocorticoids, immunosuppressants, and biologics are used to treat affected patients. This commentary deals with the question of whether Janus kinase inhibitors could be an option in this clinical situation.

Keywords

Immune checkpoint inhibitors, immune-related adverse events, Janus kinase inhibitors, cancer, arthritis, myositis

Introduction

In individuals with a normal immune system, immune checkpoints are responsible for the maintenance of self-tolerance and the prevention of autoimmune diseases. In patients with cancer, tumor cells have the ability to enhance these inhibitory pathways in order to avoid anti-tumor activities of the immune system. The targets of immune checkpoint inhibitors (ICI) are cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), programmed death ligand-1 (PD-L1), and lymphocyte activation gene-3 (LAG-3). By inhibition of these checkpoint pathways, immune responses of patients can be augmented [1]. Thus, ICI were shown to slow tumor progression and increase the survival of patients suffering from different types of cancer [1, 2]. However, these agents may also cause inflammatory and immune-related adverse events (irAEs) by inhibiting the mechanisms responsible for self-tolerance. Such irAEs can virtually affect all organ systems, and some may even be life-threatening [3, 4].

Rheumatologists are increasingly being engaged in consulting patients treated with ICI for cancer [5], since several rheumatologic irAEs have been reported, including inflammatory arthritis, polymyalgia rheumatica, and myositis [3–5]. The differential diagnosis includes several musculoskeletal syndromes, such as crystal-induced arthropathy, and more mechanical problems such as osteoarthritis. Once a rheumatic irAE is diagnosed, the cooperation of rheumatologists and oncologists, together with the patients, is critical to agree on a treatment strategy. Oncologists may want to continue ICI even in the setting of an ongoing symptomatic ICI-induced inflammatory arthritis (ICI-IA). The main argument here is that ICI-IA, in contrast to cancer, is not a life-threatening irAE. This is why many patients choose to rather continue ICI as long as possible in order not to stop this life-extending therapy.

In one of the earliest studies on patients who received ICI (n = 1,293), irAEs with symptoms suggestive of inflammatory rheumatic musculoskeletal diseases (RMD) were clinically diagnosed in 3.3% [4]. This included inflammatory arthritis (n = 34), myopathy (n = 10), and other rheumatic syndromes (n = 17). Inflammatory arthritis was mostly polyarticular, and glucocorticoids were required in 76% of patients [4].

In another study, ICI-IA occurred in 6% of ICI-treated patients who had a mean age of 74 years with 48% being female. The incidence of ICI-IA was 7.2 per 100 patient-years [5]. The time from starting ICI to a diagnosis of ICI-IA was about 4 months (median). Of interest, only 16% received care from rheumatologists, and 16% were prescribed disease-modifying antirheumatic drugs (DMARDs) (46% by rheumatologists). Patients with ICI-IA had no increased hazard ratios (HR) for mortality: 0.86 [5].

In the first systematic review and meta-analysis to report on moderate to severe chronic non-endocrine irAEs after treatment with ICI, 229 studies with 323 patients were selected out of almost 7,000 articles [3]. The median age of the patients was 65 years with 58% being male. The majority had metastatic disease (75%), and the primary cancer site was melanoma in 43% and non-small cell lung cancer in 31%. The most commonly used ICI were pembrolizumab (24%) and nivolumab (37%). The response rates to treatment with ICI were: complete in 13%, partial in 23%, stable disease in 16%, and progression in 12% of patients. The most common chronic irAEs were rheumatological (20%) and neurological (19%), while gastrointestinal (16%) and dermatological (14%) irAEs were a bit less frequent. The irAE persisted for a median of 180 days with a broad range (84–2,370). Almost a third of patients had ongoing symptoms or were still being treated. About half of the patients had chronic irAEs (52%) that persisted for > 6 months. Treatment with ICI was permanently discontinued in 60%, and 76% of patients received glucocorticoids. Toxicities persisted for months to years, and the majority of patients required discontinuation of ICI and initiation of immunosuppression.

The need for classification criteria to better define ICI-IA has been recently expressed to be able to better study this condition [6]. There is a consensus definition by the Society for Immunotherapy of Cancer (SITC) [7] which proposes to guide treatment decisions by the severity (Table 1) of the irAEs [8]. However, even though broad knowledge has already been accumulated, evidence for the pharmaceutical management of these patients is still limited to observational studies [9–11]. There are almost no studies on Janus kinase inhibitors (JAKi) to treat ICI-IA.

Table 1. Grading of joint and muscle related adverse events*

irAE	Grade 1	Grade 2	Grade 3	Grades 4–5
Arthralgia[1]	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	n.a.
Arthritis[2]	Mild pain with inflammation erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage	n.a.
Joint effusion[3]	Asymptomatic, clinical or diagnostic observation only; no intervention needed	Symptomatic; limiting ADL	Severe symptoms; limiting self-care ADL; invasive intervention indicated	n.a.

Table 1. Grading of joint and muscle related adverse events* (*continued*)

irAE	Grade 1	Grade 2	Grade 3	Grades 4–5
Myalgia[4]	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	n.a.
Myositis[5]	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

*: Extracted from National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0; 2017. Available from (page 95–98): https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. 1: a disorder characterized by a sensation of marked discomfort in a joint. 2: a disorder characterized by inflammation involving a joint. 3: a disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation. 4: a disorder characterized by marked discomfort sensation originating from a muscle or group of muscles. 5: a disorder characterized by inflammation involving the skeletal muscles. CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/). MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). irAE: immune-related adverse event; ADL: activity of daily living; n.a.: not applicable

Management of immune checkpoint inhibitor associated inflammatory arthritis

In the initial management of ICI-IA, it is important to identify whether the signs and symptoms point to inflammatory arthritis or symptoms exacerbation of a pre-existing traumatic injury or activated osteoarthritis [11]. This is clinically relevant since the latter recently described clinical situation can be managed without reducing the efficacy of the ICI [12]. Furthermore, the number of joints involved is critical, and the pattern of involvement such as of the hands and symmetry [rheumatoid arthritis (RA) like pattern]. According to consensus definitions [7, 13], irAEs can be chronic and active (requiring immunosuppression) or chronic and inactive (for example, endocrine irAEs where only hormone replacement is required). Much like other irAEs, ICI-IA can persist after cessation of ICI for months to years.

Importantly, patients may experience more than one irAE over the course of therapy with ICI, and also after their cessation. Indeed, almost half of the patients treated with ICI experienced at least one other manifestation [3–6]. Thus, common irAEs may present prior to, concurrently with, or after ICI-IA including colitis, skin rashes (psoriasis and others), pneumonitis, and endocrine irAEs [3–6].

Similar to many other inflammatory RMD and most irAEs, corticosteroids in different doses are the treatment for ICI-IA graded 2 or higher (Table 1) as outlined in SITC guidelines [13]. For example, the recommended initial dose for grade 2 ICI-IA is 10–20 mg of prednisone or equivalent per day [11, 14]. For the above mentioned irAEs corticosteroid doses may differ substantially [15]. However, for patients with chronic active irAEs such as ICI-IA, it is rather important to find effective steroid-sparing immunesuppression given the side effects of long-term steroid use [9, 10]. Thus, therapeutic steroid-sparing agents should be used for patients with ICI-IA if they are unable to taper steroids and/or don't have a sufficient clinical response. Another relevant aspect of sparing glucocorticoids in the treatment of ICI-IA is that there is evidence of corticosteroids reducing the effectiveness of ICI's anti-tumor efficacy. It has been shown that doses of 10 mg of prednisone given in parallel with ICI have impacted antitumor responses [11, 14].

Steroid-sparing agents such as methotrexate (MTX), and biologic DMARDs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi) or anti-interleukin-6 receptor (anti-IL-6R) antagonists have been successfully used in cancer patients treated with ICI.

In a recently published multicentre, retrospective, observational study of 20 cancer patients with ICI-IA [16], 13 were treated with an agent targeting IL-6R (65%), mostly tocilizumab s.c. (n = 12) and 5 (25%) with a TNFi (adalimumab n = 2, etanercept n = 2, and infliximab n = 1), while one patient each was treated with the IL-1R antagonist anakinra, the JAKi baricitinib and the anti-IL-12/23 monoclonal antibody ustekinumab, all for 17 weeks (median). Overall, the use of bDMARDs or JAKi led to complete (35%) or partial (50%) resolution of the rheumatological irAE, with discontinuation (30%) or reduction (35%) of glucocorticoids following bDMARD initiation. Four patients (20%) with an RA-like phenotype did not improve on tocilizumab (n = 2), etanercept (n = 1), or anakinra (n = 1), and one patient received a JAKi

(baricitinib after tocilizumab failure). At the last follow-up, 8/20 patients (40%) were still receiving the bDMARD or JAKi with an ongoing anti-tumor response. In 7 patients, the bDMARD was even discontinued after improvement or resolution of the irAE, only 1 patient experienced a flare. The patient who had discontinued the ICI was treated with etanercept one year later over 4 months with the resolution of irAE [16]. Overall, complete (n = 5) or partial (n = 1) anti-tumor responses were seen in 6 patients (30%), while 4 had stable disease (20%). On the other hand, cancer progression occurred in 50% of the patients: prior to bDMARD initiation in 6 patients and leading to death in 4 patients treated with tocilizumab (n = 3) or etanercept (n = 1). While 3 patients continued ICI in combination with a bDMARD, one received the combination of anti-PD-1/anti-CTLA-4 which was later reduced to anti-PD-1 monotherapy. ICI was permanently discontinued in 12 patients (60%) due to rheumatological irAE (n = 10) or another toxicity (n = 2), and temporarily in 5 patients (25%). Among these patients rechallenged with ICI, in combination with bDMARD, only one had to permanently discontinue ICI due to irAE relapse despite ongoing adalimumab treatment [16]. Taken together, all kinds of outcomes could potentially occur, and in the absence of clear guidance, different therapies were chosen by the treating physicians.

In another French multicentre observational study [17], 23 cancer patients with ICI-IA started a second course of ICI > 3 months after discontinuation of ICI [17]. At the time of ICI rechallenge, 18 patients had no symptoms of ICI-IA (78%) and 5 had grade 1 (22%), and 11 patients (48%) received no treatment for ICI-IA, while another 11 were still on prednisone (48%), 2 on conventional synthetic (cs) DMARDs (9%) and one on anti-IL-6 (4%). Flares of ICI-IA occurred in 12 patients (52%) within 4 weeks (median) after the rechallenge. Of interest, the phenotype of ICI-IA, disease activity, and the treatment at the time of ICI rechallenge were similar irrespective of ICI-IA recurrence [17].

JAKi for immune checkpoint inhibitor associated inflammatory arthritis

The system of JAK inhibition and signal transducers and activators of transcription (STAT) has an established role in cancer, inflammation, and immunity which is under the influence of cytokines and growth factors. There are different JAKi: JAK1, JAK2, JAK3, and tyrosinkinase (TYK) 2. They associate with cytokine receptors, mediate receptor tyrosine phosphorylation, and recruit STAT proteins [2]. Tyrosine-phosphorylated STATs dimerize before they are transported into the nucleus to function as transcription factors. A negative feedback loop is created by specific suppression of cytokine signaling. Germline mutations and polymorphisms of JAK family members both correlate with specific diseases such as severe combined immunodeficiency (JAK3 mutation). Somatic JAK mutations mainly occur in hematologic malignancies. JAK family somatic alterations also play a role in T-cell malignancies and acute B-cell lymphoblastic leukemia. Loss of JAK2 copy numbers is associated with ICI resistance [2]. Many JAKi developed in the last years are approved for the treatment of myeloproliferative disorders, rheumatoid and psoriatic arthritis, atopic dermatitis, ulcerative colitis, graft-versus-host disease, alopecia areata, ankylosing spondylitis, and even in patients hospitalized for coronavirus disease 2019 (COVID-19) [2].

Taken together, JAK and STAT protein families play complex and essential roles in cellular processes by influencing downstream signaling of cytokines with different physiologic effects. Therefore, certain JAKs and STATs favor tumorigenesis while others are associated with productive anti-tumor responses.

Signs of an inappropriately activated IL-6-JAK-STAT3 pathway are found in many cancers, and this is often associated with a worse prognosis since IL-6 and JAK-STAT3 signaling drives tumor proliferation, survival, invasiveness, metastasis, and angiogenesis while creating an immunosuppressive microenvironment of the tumor [18]. Cytokines predictive of irAEs such as IL-6, IL-12, IL-23, and IL-17 are induced by JAK-STAT signaling, and this is critical to the immunopathogenesis of primary autoimmune disorders and cancer progression. Therefore, targeted modulation of the JAK-STAT axis promotes tumor suppression while preserving anti-cancer immune activity. Indeed, persistent inflammation driven by cytokines has been shown to cause immunosuppression [18, 19].

However, the JAK-STAT axis also plays a critical role in inflammatory signals leading to anti-tumor immune activity and therapeutic responses to ICI. Inflammatory cytokines other than IL-6 that signal via

JAK-STAT may also contribute to inflammation and predict irAEs, including interferons and granulocyte colony-stimulating factor (G-CSF). Furthermore, JAK inhibition also impairs the production of IL-10, CXCL9, 10, and 11. This may help to clear irAEs and modulate positive effects on the tumors and their microenvironment. In addition, JAKi may suppress the activation and differentiation of B cells, and inhibit plasmablast development and antibody production [20].

For intact IFN-γ signaling, JAK1 and JAK2 are critical to the generation of effective antitumor responses to ICI. Indeed, tumor cell resistance to IFN-γ is an established mechanism of resistance to PD-1/PD-L1 blockade which works through loss of direct antiproliferative and proapoptotic effects on cancer cells, reduced major histocompatibility complex (MHC) expression and antigen presentation, as well as diminished recruitment of T cells to tumors [21]. STAT1 also mediates the expression of the Th1 cytokines IFN-γ and IL-12 which are critical to the performance of innate and adaptive antitumor responses [21]. Thus, if Th1 immunity via JAK1, JAK2, or STAT1 inhibition is blocked, less robust tumor responses may occur. However, inhibition of the JAK-STAT axis may also lead to anti-cancer effects that act in synergy with ICI [18, 19].

If the JAK1 inhibitor itacitinib is administered after anti-PD-immunotherapy, immune functions and antitumor responses in mice were shown to improve [22]. In a phase 2 clinical trial patients with metastatic non-small cell lung cancer had good response rates (67%) when treated with itacitinib after anti-PD-immunotherapy [22]. Of interest, even patients who did not respond to anti-PD-1 immunotherapy and had multiple features of poor immune function to anti-PD-1 alone did improve after JAK inhibition and showed a clinical response after the addition of itacitinib. The authors also found that treatment with itacitinib induced the revival of exhausted and effector memory T cells. In contrast, other patients with persistent inflammation had progressive disease. The authors concluded that JAK inhibition may improve the performance of anti-PD-1 therapy by positively influencing the dynamics of T cell differentiation [22]. Another recent paper confirmed this in patients with Hodgkin's lymphoma [23]. The observed effect seems to be due to an inhibitory effect on the function of interferons.

Finally, there are several recent case reports on the management of patients with irAEs receiving JAK-STAT inhibitors, but no large studies have been published to date [24, 25]. However, direct JAK1/3 inhibition by tofacitinib has been applied in five cases of refractory immune-related colitis. Recently, more case series and reports on the efficacy of JAKi in gastroenterological irAEs have been published—mainly showing positive effects [26–28].

Conclusions

Treatment with ICI causes inflammation and irAEs in about 5% of the cancer patients they could be treated. Next to corticosteroids therapies, targeting TNF-α and IL-6 works in some but not in all patients with irAEs due to ICI. Even though there are only a few reports on the efficacy of JAKi in rheumatologic irAEs, it seems likely that there are options in this often complicated clinical situation. It is unknown at present whether the different properties of JAKi [29] have to be taken into account. The recent meta-analysis on malignancies associated with JAKi has shown that JAKi was associated with a higher incidence of malignancy compared with TNFi but not compared to placebo or MTX. Importantly, cancers were rare events in all comparisons [30]. In our recent report on a patient with concomitant psoriatic arthritis (PsA) and chronic lymphatic leukemia who was treated with Bruton's tyrosine kinase inhibitor zanubrutinib, we argued against the treatment of PsA with a JAKi for different reasons [31]. This is clearly different in the case of rheumatologic irAEs in ICI-IA patients. However, we are looking forward to seeing more (controlled) data in this regard. In general, treatment strategies need to be tailored based on the patient's medical history and the severity of their symptoms.

Abbreviations

bDMARDs: biologic disease-modifying antirheumatic drugs

DMARDs: disease-modifying antirheumatic drugs

ICI: immune checkpoint inhibitors

ICI-I: immune checkpoint inhibitors-induced inflammatory arthritis

irAEs: immune-related adverse events

JAKi: Janus kinase inhibitors

PD-1: programmed cell death-1

STAT: signal transducers and activators of transcription

TNFi: tumor necrosis factor inhibitors

Declarations

Author contributions

JB: Investigation, Writing—original draft, Writing—review & editing. KK: Writing—review & editing.

Conflicts of interest

Jürgen Braun who is the Associate Editor and Guest Editor of Exploration of Musculoskeletal Diseases had no involvement in the decision-making or the review process of this manuscript. The other author declares no conflicts of interest.

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