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Rheumatic manifestations in cancer patients treated with immune checkpoint inhibitors

ABSTRACT

Immune checkpoint inhibitors are a breakthrough therapy for oncological patients. These drugs are considered effective in fighting cancer cells by supporting immune system. Their clinical efficancy is well documented however immune-related adverse events caused by drugs are the subject of interest of many research works. It is estimated that 15% to 90% of patients treated by immune checkpoint inhibitors experienced immune-related adverse events including 0.5–13% that require termination of the oncotherapy and provide immunosuppressive agents. The most common rheumatic manifestations of the immune checkpoint inhibitors therapy was arthralgia, myalgia, inflamatory arthritis, myositis. During the treatment, patients also present symptoms of systemic lupus erythematosus, vasculitis or sicca syndrome.

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KEY WORDS: rheumatic manifestations; oncological diseases; immune checkpoint inhibitors

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are a new group of drugs that have provided hope for limiting cancer progression and increasing survival rate for many cancer patients. The mechanism of action of these drugs is to enhance the function of cytotoxic T-lymphocytes involved in the body's response to the presence of tumour cells. Through inhibition of molecules located on reacting cells (checkpoints), anti-cancer activity involving the immune system is restored. Despite its many beneficial effects, this therapy can induce excessive, uncontrolled activation of the immune system, causing the development of immune-related adverse events (irAEs). This article is to present this new treatment method – immuno-oncotherapy — in oncology and its complications in the form of various symptoms from the spectrum of rheumatic diseases.

ANTIGEN PRESENTATION TO LYMPHOCYTES AS THE FIRST STEP OF THE IMMUNE RESPONSE

T-lymphocytes are an important part of immunosurveillance. A prerequisite for the activation of T-lymphocytes during exposure to an unknown antigen by an antigen presenting cells (APC) is the transmission of excitatory signals, including costimulatory signals. This process occurs through the fusion of multiple molecules, including CD28-CD80/CD86L and CD27-CD70, which are appropriately located on two reacting immune cells. In addition to T-lymphocyte activation signals, inhibitory signals can also be transmitted — by combination of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and CD80/CD86 or programmed death-1 (PD-1) and programmed death ligand-1 (PDL-1). The CTLA-4 molecule has a higher affinity for CD80/CD86 compared

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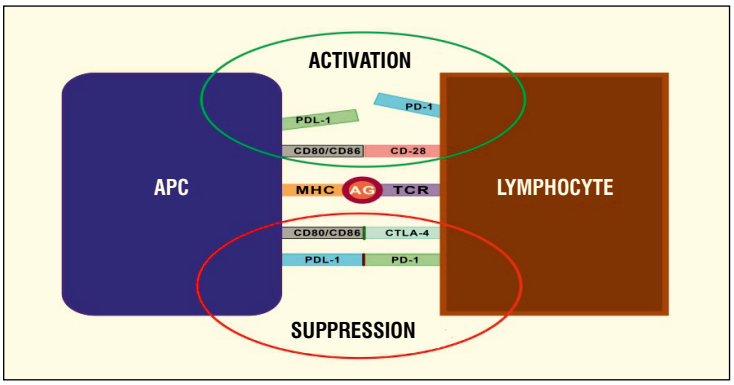

Figure 1. Mechanism of action of PD-1/CTLA-4 checkpoints

to the CD28 receptor and thus, by binding more strongly to CTLA-4 ligands, enables suppression of the immune response. The CTLA-4 molecule suppresses the signal to maintain a constant level of T-cell activation in the face of highly variable concentrations and affinities of ligands for the T-cell receptor (TCR) (Fig. 1). The best explored pathway is CTLA-4, and inhibition of T-cell activation occurs in lymph nodes [1]. Another important mechanism of immune system inhibition is the signal transduction pathway via PD-1/PDL-1 molecules. The primary role of PD-1 is to reduce T-lymphocyte activity in peripheral tissues during the inflammatory response to infection and during autoimmunity. PD-1 present on the T-lymphocyte cell binds to PDL-1, inhibiting the immune system response (Fig. 1). Signals that inhibit T-lymphocyte activation ensure immune tolerance and prevent tissue damage during the immune response [2].

IMMUNE RESPONSE IN TUMOUR DEVELOPMENT

The natural anti-cancer defence in the human body, i.e. immunosurveillance, involves a cytotoxic response directed at tumour cells, resulting in their apoptosis and death. The major cytotoxic cells include TCD8+ lymphocytes, natural killer T (NKT) cells, natural killer (NK) cells and, to a lesser extent, CD4+ lymphocytes. When these mechanisms are inadequately controlled, cancer develops. This process is complex and many molecules and mediators are involved, including the following suppressor molecules: CTLA-4, PD-1, PDL-1. These molecules are overexpressed on lymphocytes in the tumour environment. Their task is to form an inhibitory pathway by binding to the appropriate ligand on the tumour cell. Such a pathway prevents the activation of cytotoxic effector lymphocytes, resulting in their suppression and inactivity. Mechanisms resulting in the predominance of inhibitory pathways, such as PD-1/PD-L1 and CTLA-4, lead — by suppressing the anti-cancer immune response — to a loss of immunosurveillance control [1, 2].

THERAPEUTIC INDICATIONS FOR THE USE OF CHECKPOINT INHIBITORS

The use of immunotherapy aims to stimulate the body's anti-cancer immune response (Fig. 2). Depending on the type of cancer, the use of checkpoint inhibitors modifies existing treatment regimens, providing an opportunity to extend the survival rate of oncology patients. In 2018, the first ICIs were also licensed in Poland. ICIs are used in the treatment of renal cell carcinoma (RCC), non-small cell lung cancer, bladder cancer, Hodgkin's lymphoma, small cell lung cancer (SCLC) and other cancers (Tab. 1) [3, 4].

IMMUNE-RELATED ADVERSE EVENTS

The occurrence of adverse effects during ICI therapy correlates with excessive activation of the immune system. Interference with the signal transduction from APC to T-lymphocyte can lead to a loss of regulatory capacity of the immune system and over-activation towards the body's own tissues (inhibitory signals between APCs and T-lymphocytes are eliminated) [5]. A higher risk of irAEs is associated with the use of combination therapy with PD-1 inhibitors plus CTLA-4. The most common irAEs include rash, fatigue, pneumonia, hypothyroidism (Tab. 1) [3]. The spectrum of

Table 1. Characteristics of checkpoint inhibitors

Drug	Checkpoint inhibition	Application in therapy	Most common adverse effects of this treatment
Nivolumab	PD-1	Head and neck squamous cell carcinoma, melanoma, NSCLC, RCC, Hodgkin's lymphoma, colorectal cancer	Rash, fatigue, hypothyroidism, hepatotoxicity, pneumonia
Pembrolizumab	PD-1	Melanoma, NSCLC, bladder cancer, Hodgkin's lymphoma, head and neck squamous cell carcinoma, gastric adenocarcinoma, breast cancer	Rash, fatigue, hypothyroidism, hepatotoxicity, pneumonia
Avelumab	PDL-1	Merkel cell carcinoma, bladder cancer, RCC	Rash, fatigue, endocolitis
Atezolizumab	PDL-1	NSCLC, bladder cancer, SCLC, breast cancer	Rash, fatigue, hypothyroidism, hepatotoxicity, hypophysitis
Durvalumab	PDL-1	NSCLC, bladder cancer	Rash, fatigue, hypothyroidism, pneumonia, inflammation, endocolitis, recurrent urinary tract infections
Ipilimumab	CTLA-4	Melanoma, RCC, NSCLC	Rash, fatigue, hypothyroidism, hepatotoxicity, endocolitis, hypophysitis

RCC — renal cell carcinoma; NSCLC — non-small cell lung cancer; SCLC — small cell lung cancer

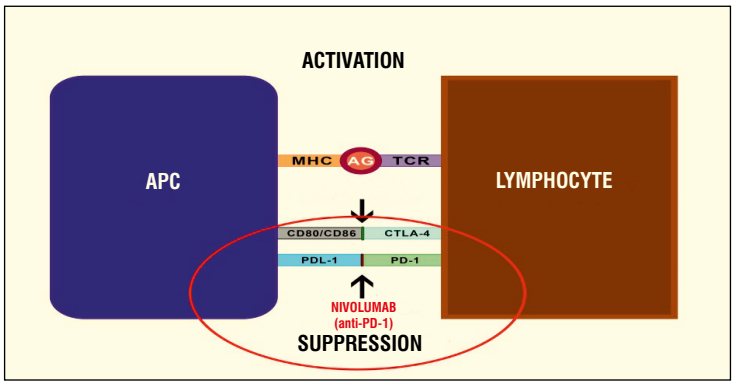

Figure 2. Site of action of selected checkpoint inhibitors

irAEs is not fully understood. It is estimated that 15–90% of patients treated with ICIs develop irAEs, of whom 0.5–13% require discontinuation of therapy and immunosuppression [4, 6].

THE ROLE OF *CTLA-4* AND *PDCD-1* GENE POLYMORPHISMS IN THE DEVELOPMENT OF RHEUMATIC DISEASES

According to current research, the *CTLA-4* gene polymorphisms underlie a variety of autoimmune disorders, including thyroid diseases, type 1 diabetes, myasthenia gravis and some systemic rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc). Single nucleotide polymorphisms (SNPs) within the *CTLA-4* gene are most commonly associated with aetiopathogenesis of these diseases. An emerging variation in the DNA sequence involves the substitution of a single nucleotide for another nucleotide [7]. The *CTLA-4* gene has many variants and polymorphic forms, among which the most commonly examined was +49A/G polymorphism. In a study by Louthrenoo et al. [7], 100 RA patients, 50 SSc patients, 70 SLE patients and 99 healthy controls were analysed for *CTLA-4* SNPs. It was found that out of the four *CTLA-4* loci (+49A/G, –318C/T, –1661A/G and –1722T/C), the A allele polymorphism at the +49A/G locus was significantly more frequent in RA patients. The allele in question occurred more frequently in SLE and SSc patients. In contrast, the frequency of the TC genotype, locus –1722T/C, was significantly higher in anti-Sm positive SLE patients.

The TC genotype was also significantly more frequent in anti-SSA-positive SLE patients.

The PD-1 molecule is encoded by the *PDCD-1* gene located on the long arm of chromosome 2q37. The link with the *PDCD-1* polymorphism was noted among patients with autoimmune diseases such as RA, SLE and multiple sclerosis. Approximately 30 SNPs for *PDCD-1* were identified. In a meta-analysis by Gao et al. [8], SNPs at position PD1.1, PD1.2, PD1.3, PD1.5 and PD1.6 were investigated for SLE. Twenty-eight articles were analysed, involving a total of 4,344 SLE cases and 5,474 healthy controls. SLE patients were found to have a polymorphism in the 4th intron of the gene for the A allele (PD1.3 G/A). Studies by Wang et al. [9] noted that PD-1-deficient mice developed spontaneous autoimmune diseases, such as autoimmune dilated cardiomyopathy and lupus-like disease. In contrast, another study found that interruption of the *PDCD-1* gene in mice caused them to develop lupus-like glomerulonephritis and arthritis [10].

Many complex mechanisms are involved in the development of autoimmune diseases. Interactions between environmental factors, gene susceptibility and their multivariate nature have a significant impact on disease development. It can be hypothesised that as autoimmune symptoms are observed as a result of polymorphisms in *CTLA-4* and *PDCD-1* genes, increased symptoms of autoimmune diseases are noted during treatment of ICIs as a result of the loss of function of the above-mentioned genes.

RHEUMATIC DISORDERS ASSOCIATED WITH CHECKPOINT INHIBITOR THERAPY IN ONCOLOGY PATIENTS

Musculoskeletal symptoms were reported in approximately 5–16% of patients treated with ICIs [11]. The most common findings were joint pain and arthritis [12]. In most cases, the joints involved in the inflammatory process confirmed by ultrasound or magnetic resonance imaging were shoulder joints, metacarpophalangeal joints and proximal interphalangeal joints, knee and wrist joints (Tab. 2) [3]. The available literature describes patients presenting symptoms resembling syndromes such as RA (mainly involving proximal interphalangeal joints, metacarpophalangeal joints and wrist joints), spondyloarthropathies (characterised by inflammatory pain in the spine and large joints, tendinitis), reactive arthritis (manifested by oligoarthritis, conjunctivitis and aseptic urethritis) and polymyalgia rheumatica [4, 13]. The majority of patients showed no evidence of serum RF, anti-CCP or ANA. The study by Kostine et al. [3], based on the cases analysed, found that approximately 20% of patients met the criteria for classification of RA, i.e. 55 out of 271 participants, while polymyalgia rheumatica was found in 11 out of 52 participants (21%). For psoriatic arthritis, the percentage was higher at 55% of patients, i.e. 6 out of 11 participants. The median time to adverse events following drug exposure ranged from 2 to 24 months [4]. A meta-analysis by Benfaremo et al. [14] found that the incidence of joint pain in patients receiving pembrolizumab was approximately 9–12%, nivolumab 6–8%, ipilimumab 5% and 11% for patients receiving combination therapy with nivolumab + ipilimumab. Treatment administered at the time of irAE detection mainly included non-steroidal anti-inflammatory drugs, steroid therapy and disease-modifying drugs [14].

Muscle pain is the second most commonly reported complaint when using ICI therapy. Patients complain of acute/subacute pain and muscle weakness of the shoulder and pelvic girdles, as well as head drop. Rapidly progressive muscle weakness (myasthenia) was present in approximately 7% of patients, and skin lesions typical of dermatomyositis were described in a few cases [4, 14]. A significant increase in creatine kinase (CK) activity was observed in patients with signs of myositis, whereas in those patients who reported only the onset of pain, CK activity was within normal limits. Some

Table 2. Frequency of joint involvement as a symptom of irAEs according to [3]

Joint affected by inflammation	Frequency of symptoms
Upper limb	
Shoulder joint	50%
Proximal interphalangeal joint	50%
Metacarpophalangeal joint	49%
Wrist joint	40%
Elbow joint	13%
Lower limb	
Knee joint	42%
Hip joint	22%
Ankle joint	18%
Proximal interphalangeal joint	8%

analyses imply that CK activity does not fully reflect the severity of disease in patients with ICI-induced myositis [15]. Antibodies associated with the onset of typical myositis were mostly negative, and inflammatory and necrotic lesions were observed in skeletal muscle biopsies [16]. Cases of patients who additionally developed symptoms of myocarditis were described. Primarily, these were patients treated with PD-1 inhibitors [14, 16]. Myocarditis--myasthenia gravis overlap syndromes were also observed. Most of reported cases of myasthenia gravis were associated with the presence of antibodies against the acetylcholine receptor [17]. The co-occurrence of myasthenia gravis and myocarditis was found to increase mortality among patients treated with PD-1 inhibitors [18]. Clinically, a milder form of myopathy accompanied by muscle pain and no or little increase in CK activity responded to treatment with low doses of glucocorticosteroids (GCs). In contrast, severe myositis accompanied by a significant increase in CK activity and/or signs of myasthenia gravis and symptoms of cardiac involvement were grounds for discontinuing ICI therapy. In these cases, patients required more aggressive treatment such as high-dose GCs, plasma exchange or immunosuppressants [19].

Patients who are on ICI therapy may also develop SLE symptoms. According to FDA Adverse Event Reporting System data, SLE was reported as irAE by June 2018 in 18 treated patients, with additional 7 cases of cutaneous lupus, 1 case of lupus nephritis and 1 of CNS inflammation. It should be noted that, compared with idiopathic SLE, the majority of patients were male (male-to-female ratio 1.6:1) and the mean age of onset was 61 years [20]. SLE symptoms were most commonly described during treatment with ipilimumab. The first reported case of ipilimumab-induced lupus nephritis was reported in 2009 in a patient treated for metastatic melanoma. The renal biopsy described deposits of immune complexes and revealed serum dsDNA antibodies [21]. Shao et al. [22] described the case of a patient undergoing therapy with pembrolizumab for melanoma, who was diagnosed with lupus-like cutaneous reaction. In contrast, another patient developed erythematous papules following the use of nivolumab, which was confirmed by histopathology as a lupus-like reaction to the drug [23].

A small group of patients who developed vasculitis were identified. The inflammatory process mainly involved large and medium vessels. Symptoms resembled giant cell arteritis, isolated aortitis, primary vasculitis of the central nervous system, isolated vasculitis of the peripheral nervous system, but also granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis [3, 24]. Vasculitis was mainly manifested by necrosis of the fingers, fever, abdominal pain, skin lesions (purpura), arthritis, muscle pain [3]. In patients with ICI-induced vasculitis, no characteristic autoantibodies were usually observed. Discontinuation of ICI therapy and treatment with aggressive steroid therapy resulted in resolution of clinical symptoms in the majority of cases.

Recently, the spectrum of patients with adverse manifestations of used anticancer therapy has expanded significantly. Cases of patients presenting with symptoms of Sjögren's syndrome and/or dry syndrome were reported in the literature. The ImmunoCancer International Registry [25] published a 2019 report showing that 26 patients (11 women, 15 men, mean age 63 years) presented with symptoms of the above-mentioned syndromes. The patients were treated with PD-1/PD-L1 inhibitors (9 with nivolumab, 7 with pembrolizumab and 4 with durvalumab) and 6 patients received combination therapy. No cases were reported after treatment with CTLA-4 inhibitors. The patients presented with symptoms such as dry mouth (96%) and dry eyes (65%). The criteria for the classification of Sjögren's syndrome were met by 62% of participants, while 11% presented only dry syndrome without associated symptoms. The used therapeutic management focused on relieving dry mouth and dry eye symptoms, 42% of patients received GCs.

Multiple disease entities should be considered in the differentiation of irAEs, including benign bone resorptive lesions and treatment-induced loss of bone mass leading to multiple fractures [26]. The presence of antibodies specific to the disease entities in question is rarely observed among patients. Only a few publications described cases in which positive antibody titres were found (Tab. 3).

Rheumatic disorders associated with checkpoint inhibitor therapy are a new clinical entity. They largely do not meet the criteria for classification of autoimmune diseases. The treatment plan should result from a close collaboration between the rheumatologist and the oncologist to reduce complications and possibly reduce mortality among oncology patients. It should be noted that most of the

Table 3. Differences between typical rheumatic diseases and immune checkpoint inhibitors-induced rheumatic diseases

Most common ICI-induced rheumatic diseases	Disease characteristics
Rheumatoid arthritis	• Mostly polyarthritis, mainly small joints • Arthritis may persist after discontinuation of immune checkpoint inhibitors therapy, up to 3–6 months on average • Most patients without positive autoantibodies • Occasionally detected: RF, anti-CCP
Polymyositis/dermatomyositis	• May be accompanied by myasthenia gravis or myocarditis • Typical skin lesions usually absent • Most patients without positive autoantibodies • Occasionally detected: anti-TIF1-gamma, anti-SRP, anti-Ro52
Sjögren's syndrome/dry syndrome	• The predominant symptom is dry mouth • Frequently inconclusive image in a lip biopsy • Most patients without positive autoantibodies • Occasionally detected: ANA, anti-Ro/SS-A, RF, anti-La/SS-B
Vasculitis	• Therapy is based on withdrawal of ICIs and the use of glucocorticosteroids • Most patients without positive autoantibodies
Systemic lupus erythematosus	• Increased incidence in men • Older age of onset • Most patients without positive autoantibodies • Occasionally detected: ANA, anti-dsDNA

adverse effects of anti-cancer therapy are mild to moderate in nature, so its continuation and the inclusion of immunomodulatory, anti-inflammatory treatment should be considered. Currently, it is not possible to unequivocally distinguish between factors that predispose to the emergence of irAEs, and their occurrence has been observed not only during treatment but also after discontinuation of checkpoint inhibitor therapy.

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