Blocking the IL-6 pathway to treat immune checkpoint inhibitor-induced inflammatory arthritis (Review)

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Abstract. The incorporation of immune checkpoint inhibitors (ICIs) into cancer treatment has revolutionized oncology, providing marked advantages in managing various types of cancer. Nevertheless, the increasing use of ICIs has led to the emergence of immune-related side effects, including autoimmune diseases such as inflammatory arthritis. IL-6 signaling is crucial in the development of inflammatory arthritis and is linked to both the benefits and adverse effects of ICIs. The present review summarizes the latest progress in the IL-6 pathway in inflammatory arthritis and discusses the therapeutic potential of IL-6 pathway inhibitors for ICI-induced inflammatory arthritis.

Contents

1. Introduction

Cancer immunotherapy activates the immune system by targeting tumor antigens, enabling recognition and destruction of cancer cells (1). Immune checkpoint inhibitors (ICIs), particularly antibodies against cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1), have markedly improved outcomes in various types of cancer (2-6). CTLA-4 inhibits T cell activation by competing with CD28 for CD80/CD86 binding (7,8). Antibodies such as ipilimumab and tremelimumab block CTLA-4, enhancing anti-tumor immunity (9-12). PD-1, expressed on multiple immune cells, suppresses T cell function through PD-L1/PD-L2 binding (13-16). Blocking this pathway with agents such as nivolumab or pembrolizumab restores T cell activity and shows efficacy in melanoma, lung cancer and other malignancies (17-22).

Although ICIs represent a major breakthrough in cancer therapy (23,24), they are associated with a wide range of immune-related side effects that can affect almost every organ, may lead to treatment discontinuation and compromise overall therapeutic efficacy (25,26). Immune-related adverse events (irAEs) are common, with reports indicating they affect 90% of patients treated with anti-CTLA-4 and 70% of those treated with anti-PD-1/PD-L1 therapies (27). Anti-CTLA-4 therapy has been associated with a higher incidence of side effects compared to anti-PD-1 and PD-L1 treatments. Additionally, combination therapy showed a higher occurrence of adverse effects compared to monotherapy (28). ICI-related irAEs are unique to certain organs, such as skin, liver, colon, thyroid, muscle and lungs (29). According to a previous report, endocrine irAEs were observed in 9.89% of patients, GI toxicities such as diarrhea and colitis occurred to 8.4% of patients and hepatotoxicity occurred to 4.94% (30). Additional irAEs, including those affecting the joints, lungs, kidneys and central nervous system, were observed in 6.5, 5.1, 2.56 and 2.01% of patients, respectively (26,30). Ocular toxicity, cardiotoxicity and inflammation were some of the rare adverse events reported (30). They happened in 0.8, 0.73 and 0.54% of patients, respectively (30). Overall, rheumatologic manifestations, pneumonitis and gastrointestinal symptoms such as diarrhea and colitis were more prevalent than dermatologic adverse events.

Rheumatic irAEs include arthritis, myositis and vasculitis. The most prevalent clinical symptom is arthritis, ICI-induced inflammatory arthritis (ICI-induced IA) among them (31). The incidence of ICI-induced IA ranges from 1-7%. However, ICI-induced IA markedly effects overall quality of life and

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persists longer than other irAEs. It is frequently overlooked due to its lower severity compared to life-threatening events.

Currently, there is no standardized diagnostic and assessment criteria for ICI-induced IA. Moreover, consensus on optimal treatment strategies remains elusive and is the subject of continuing debate (32). For the initial therapy of ICI-induced IA, patients received either non-steroidal anti-inflammatory drugs (NSAIDs) or steroids (such as glucocorticoids) for cases with moderate inflammation (31,33). When patients show no improvement or become resistant to NSAIDs or steroids, TNF inhibitors (TNFi) and IL-6 receptor blockers are employed to manage ICI-induced inflammatory arthritis (34-37). Nevertheless, TNFi may also impair ICI-induced anti-tumor immunity (38). In addition to being beneficial in the treatment of ICI-induced IA, IL-6 inhibitors have also demonstrated anti-tumor effects (39,40). To provide more clinical insights on choosing biological agents, studies examining IL-6 signaling inhibition in patients with ICI-induced IA were reviewed.

2. ICI-induced IA

Certain irAEs, such as colitis and pneumonitis, can be fatal, whereas others, including IA, impair an individual's quality of life. IA frequently goes unnoticed, probably due to its minimal effect on death rates, diagnostic irregularities that might be overlooked by cancer specialists and the extensive range of classification options in the Common Terminology Criteria for Adverse Events grading system used in clinical studies (41). Nevertheless, the importance of early detection of IA is increasingly recognized as a result of the functional loss of patients, reports of the rapid progression of erosions and the continued presence of joint complaints (34,35,42,43). Determining the exact frequency of IA due to irAEs is difficult; nonetheless, up to 43% of patients in immunotherapy trials reported joint pain and it is estimated that 3.0-7.5% of those treated with ICIs develop IA (44-47). Given the number of patients who acquire IA and the increasing use of ICI therapy, it is necessary to conduct further assessment of long-term results. This is especially important in the context of improved survival with ICI treatment and prior findings indicating that symptoms can persist even after ICIs are discontinued (34,35,42,43).

ICI-induced IA may demonstrate resistance to standard therapies and the management of severe and treatment-resistant ICI-induced IA is a topic of debate. The best way to treat ICI-induced IA is to give prednisolone at a dose of 0.5-1.0 mg per kilogram per day. If the use of glucocorticoid alone does not lead to improvement in ICI-induced IA, it is advised to consider the use of a TNFi (32). The problem with this strategy is that it calls for giving high doses of glucocorticoids for a long time, which could lead to problems such as osteoporosis, diabetes, or infections (48). Additionally, TNFi has the potential to reduce the immune response to malignant tumors (38). Given these limitations, more effective methods to treat ICI-induced arthritis in patients with cancer are needed. Reports also indicate IL-6 receptor antagonists have shown efficacy in managing ICI-induced IA, aside from TNFi (36). Additionally, studies indicate that IL-6 promotes cancer development and progression, whereas blocking IL-6 hinders these processes (39,40). Increased concentrations of IL-6 and C-reactive protein (CRP, which has a strong association with IL-6) are linked to decreased survival in patients treated with ICIs (49-51). IL-6 receptor antagonists are considered to work by inhibiting Th17 cells. The reduction of IL-6 does not impede the activity of $CD8^+$ T lymphocytes, which possess anti-tumor properties. Consequently, it is considered that IL-6 inhibition has a lesser impact on malignant tumors than ICIs (52,53). Notably, preclinical studies have demonstrated synergistic effects when combining IL-6 receptor inhibitors with anti-PD-L1 therapies (54). Collectively, these findings suggest that IL-6-targeted therapies represent a viable strategy for the treatment of ICI-induced IA.

3. The effect of IL-6 biologics on ICI-induced IA

IL-6 biological function. IL-6 was first identified as B-cell-stimulating factor 2 (BSF-2), secreted by peripheral blood mononuclear cells activated by mitogens or antigens (55). In 1986, the gene responsible for BSF-2 was successfully cloned (56). BSF-2 was later identified as the same as the hepatocyte-stimulating factor, the hybridoma growth factor and IFN-β2, which was found to have no antiviral properties (55). The molecule was subsequently renamed IL-6 (55). Human IL-6 consists of 184 amino acids, featuring two potential N-glycosylation sites and four cysteine residues (57). The fundamental protein weighs ~20 kDa and glycosylation increases the natural IL-6 size to between 21 and 26 kDa (57).

IL-6 is rapidly produced and triggers an immediate immune response in reaction to infections or tissue damage resulting from burns and traumas (58). IL-6 promotes the conversion of activated B lymphocytes into plasma cells responsible for generating antibodies and stimulates the proliferation of hybridoma and myeloma cells (59). IL-6 not only affects B cells, but also influences T cells by prompting the targeted transformation of immature $CD4^+$ T cells into specialized subsets of effector T cells (60). IL-6, in conjunction with TGF-β, uniquely encourages the differentiation of naïve $CD4^+$ T cells into Th17 cells while inhibiting the TGF-β-driven development of regulatory T cells (Tregs) (61,62). Th17 cells are critical for host defense against extracellular pathogens, but their expansion, driven by IL-6, may also contribute to the breakdown of immune tolerance and the development of autoimmune and inflammatory diseases (58). In fact, in various autoimmune disease models, inhibiting IL-6 during the initial activation phase prevents Th17 and/or Th1 cells from becoming the primary subsets over Tregs within antigen-specific effector T-cell groups (63). This additionally hinders the onset of autoimmune disorders, irrespective of the antigens employed for vaccination. Moreover, IL-6 promotes the formation of T follicular helper cells and the production of IL-21 (64), a key regulator of immunoglobulin synthesis.

IL-6 also exerts multiple pathogenic effects in chronic inflammatory diseases. IL-6 generated by bone marrow stromal cells triggers the receptor activator of NF-κB ligand, a key driver of osteoclast differentiation and activation. Consequently, this process results in bone resorption and osteoporosis (65). IL-6 promotes the production of VEGFs, thereby enhancing angiogenesis and increasing vascular permeability. These pathological features are commonly observed in both cancer and the inflamed synovial tissues of patients with rheumatoid arthritis (58).

Cell signaling pathway mediated by IL-6 and its receptors. Various cell types generate IL-6, which plays a vital role in regulating the acute phase response, inflammation, hematopoiesis, liver regeneration, metabolism, bone remodeling and cancer progression (66). Classic IL-6 signaling is initiated when IL-6 binds to membrane-bound IL-6 receptor (IL-6R), forming a complex that associates with the signal-transducing subunit gp130 (67). The interaction of gp130 with the IL-6/IL-6R complex promotes the formation of gp130 dimers and leads to the assembly of a heterohexameric structure consisting of IL-6, IL-6R and gp130 in a 2:2:2 ratio (58). Traditional IL-6 signaling is largely limited to liver cells, immune cells such as macrophages and neutrophils, as well as inactive lymphocytes, because it requires the presence of membrane-bound IL-6R (68). Nonetheless, IL-6 can also trigger trans-signaling in cells that have gp130 but lack IL-6R. This mechanism includes IL-6 binding to a soluble form of IL-6R, which can be generated through either alternative splicing or proteolytic cleavage (58). The IL-6/soluble IL-6R complex can trigger IL-6 signaling mechanisms in cells that have gp130. Since gp130 is present in all tissues (69), trans-signaling enables a broader array of cells to react to IL-6. Activation of the IL-6 classic or trans-signaling ligand-receptor complexes triggers three intracellular signaling cascades: JAK-STAT, PI3K-Akt and Ras-MAPK pathways (70,71). The Ras-MAPK signaling network also includes the p38 MAPK, JNK MAPK and MEK-ERK5 pathways (see Fig. 1). Then, IL-6/IL-6R signaling regulates downstream gene expression and inflammatory responses by activating these downstream intracellular signaling pathways. IL-6R is primarily found on liver cells and immune cells, restricting the specific targets of IL-6 classic signaling. The IL-6 classic signaling route initiates the acute-phase response and is associated with homeostatic and anti-inflammatory effects (72). In contrast, trans-signaling, due to the widespread expression of gp130, enables IL-6 to exert pro-inflammatory effects in a broad range of tissues (73).

The effect of IL-6 on cancer development. IL-6 is often overexpressed in various types of cancer, both at the local tumor site and systemically (74). Elevated serum IL-6 levels are associated with poor prognosis and decreased survival rates in patients with cancer (75). Mechanistically, IL-6 has been reported to downregulate the expression of CDK2, CDK4 and CDK6, while upregulating the expression of $p27^{Kip1}$ or $p21^{WAF1/CIP1}$, thereby inducing G_1 phase cell cycle arrest and contributing to the carcinogenesis of prostate cancer (76), hepatocellular carcinoma (77,78) and melanoma (79,80). Additionally, IL-6 supports the proliferation of multiple myeloma cells by modulating CDK4 and $p16^{INK4A}$, affecting Rb phosphorylation and cell cycle progression (80). Upon binding to its receptor on malignant cells, IL-6 activates several pathways that promote tumor growth, such as JAK/STAT3, PI3K/AKT and Ras/MAPK, leading to enhanced cell survival, proliferation, invasion, migration and angiogenesis (81). It further promotes tumor invasion through upregulation of matrix metalloproteinases (MMPs), which degrade extracellular matrix components and facilitate metastasis (82,83). Within the tumor microenvironment, IL-6 stimulates stromal and endothelial cells to secrete chemokines and cytokines, which support tumor growth and neovascularization (84). Additionally, it fosters an immunosuppressive milieu, marked by recruiting Tregs, myeloid-derived suppressor cells and immunosuppressive M2 myeloid cells, which hinder robust anti-tumor immune reactions and aid in tumor immune escape (85). Furthermore, the IL-6/JAK2/STAT3 axis has been extensively studied in a wide range of malignancies, including liver, breast, colorectal, gastric and lung cancers, underscoring its role in tumorigenesis and its potential as a therapeutic target (86,87). Several IL-6-targeted strategies have shown efficacy in preclinical and clinical studies, including monoclonal antibodies against anti-IL-6/IL-6R or anti-sIL-6R, along with selective inhibitors targeting IL-6 downstream signaling pathways such as STAT3 or kinase inhibitors (such as JAK inhibitors) (81). Specifically, in medical research, treatments targeting IL-6 such as tocilizumab have proven effective in reducing cancer symptoms and preventing tumor growth (88). Clazakizumab (BMS945429, ALD518), a humanized monoclonal antibody targeting IL-6, has demonstrated good tolerability and alleviates anemia and cachexia associated with non-small cell lung cancer in both preclinical and Phase I/II trials (89). Overall, the strategy of targeting IL-6 signaling represents a promising strategy for cancer therapy.

IL-6 biologics in ICI-induced IA. IA is among the most commonly observed irAEs in patients receiving ICIs therapy. Anti-IL-6 biologic agents have been recommended as a therapeutic option for ICI-induced IA in the current irAEs treatment guidelines. In fact, IL-6 is crucial for the differentiation of naïve $CD4^+$ T cells into Th17 cells, which are implicated in the pathogenesis of multiple autoimmune diseases and may also contribute to irAEs (52). At present, addressing irAEs, including ICI-induced IA, can be effectively managed with anti-IL-6R therapies, which does not compromise antitumor immunity (90). Various therapeutics for ICI-induced IA by blocking IL-6 signaling were discussed below (Fig. 2).

IL-6 direct inhibitors. According to previous reports, five IL-6 inhibitors are used to treat cancer and rheumatoid arthritis (RA) patients. These include Siltuximab (CNTO 328, Sylvant), Sirukumab (CNTO 136), Olokizumab (CP6038), mAb 1339 (OP-R003) and Clazakizumab (BMS945429, ALD518). However, none of them have been evaluated for treatment of ICI-induced IA.

IL-6R direct inhibitors

Tocilizumab (RoActemra or Actemra). Tocilizumab, a humanized monoclonal antibody targeting the IL-6R, blocks both soluble (sIL-6R) and membrane-bound (mIL-6R) forms of the receptor. It has been approved by the US Food and Drug Administration (FDA) for the treatment of RA (91). Tocilizumab's anti-cancer properties have been shown in multiple forms of cancer, such as a colon cancer xenograft model (92), kidney cancer (93), lung carcinoma (88) and breast malignancy (94). Tocilizumab is thus a feasible therapy option for ICI-induced IA. Holmstroem *et al* (95) demonstrated that 84% of patients treated with tocilizumab (8 mg/kg, up to 800 mg) every four weeks for a minimum of two cycles achieved complete remission of ICI-induced IA symptoms. Tocilizumab was shown to have favorable clinical

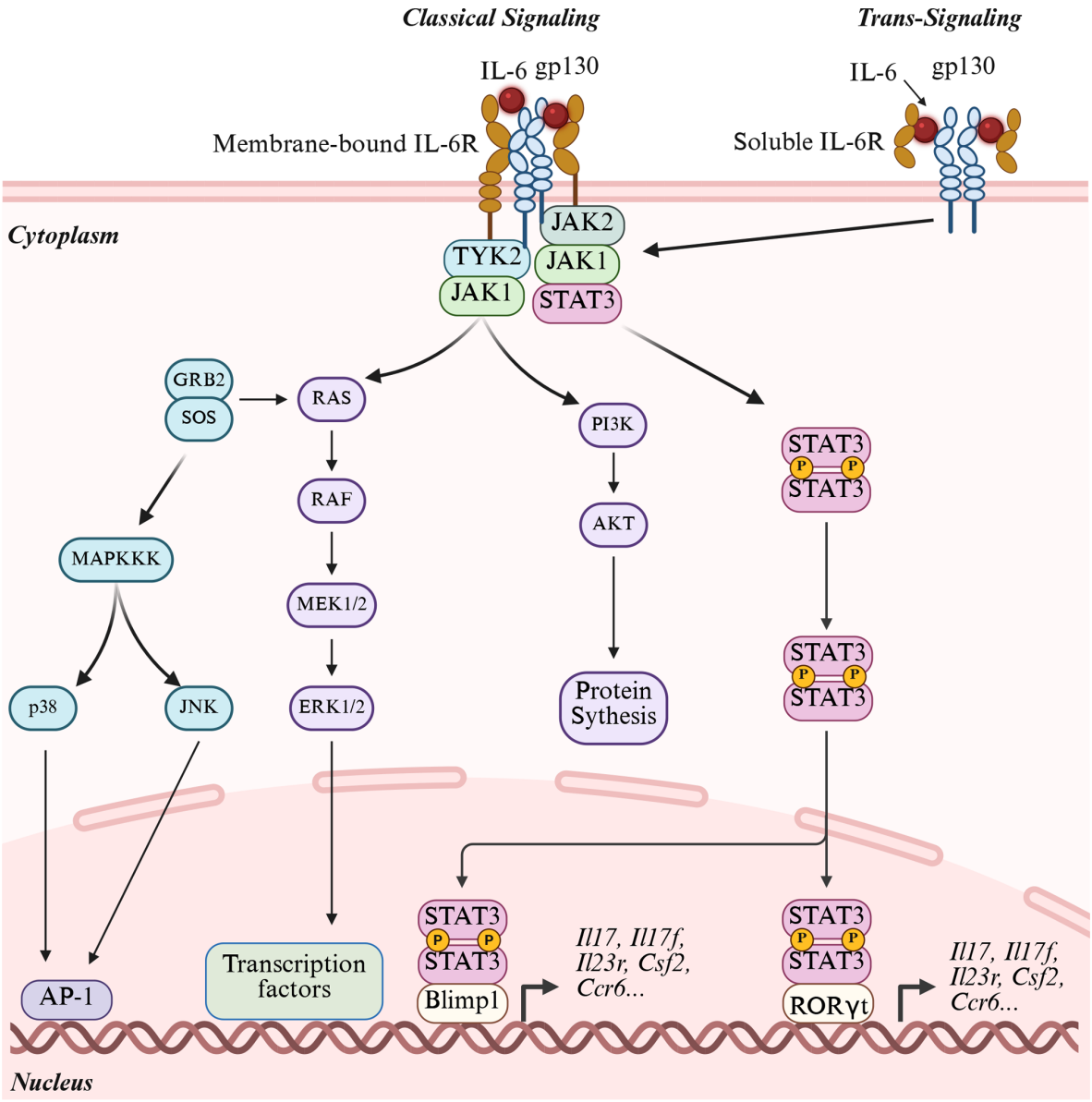

Figure 1. Cell signaling pathway mediated by IL-6 and its receptors. IL-6 and its receptors trigger the activation of three major intracellular signaling pathways, including the JAK-STAT3 pathway, the Ras-MAPK pathway and the PI3K-Akt pathway. The activation of these signaling pathways resulted in the transcription of downstream target genes, subsequently leading to the induction of inflammatory responses. gp 130, glycoprotein 130; IL-6R, interleukin 6 receptor; TYK2, tyrosine kinase 2; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; GRB2, growth factor receptor-bound protein 2; SOS, son of sevenless; MAPKKK, mitogen-activated protein kinase kinase kinase; JNK, c-Jun N-terminal kinase; AP-1, activator protein-1; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK1/2, MAPK kinase 1/2; ERK1/2, extracellular signal-regulated kinase1/2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; Blimp1, B-lymphocyte-induced maturation protein 1; RORγt, retinoic acid receptor-related orphan receptor γt.

effectiveness and a controllable safety profile when used to treat ICI-induced IA (95-102). Kim *et al* (36) noted that three individuals, who experienced severe arthritis during ICI treatment and received tocilizumab, showed marked clinical progress; one individual sustained a lasting anti-tumor response from checkpoint inhibition. Following methotrexate failure, five patients received tocilizumab, resulting in a 100% clinical response rate (103,104). Taken together, tocilizumab efficiently reduced symptoms of ICI-induced IA in patients with cancer (Table I).

Sarilumab (SAR153191 or REGN88). Sarilumab (KEVZARA®), a human anti-IL-6R, was approved by FDA to treat RA on 22 May 2017 (91). Sarilumab has been reported to be effective in the treatment of ICI-induced polyarthritis (37). A 61-year-old renal cell carcinoma patient received biweekly subcutaneous injections of 200 mg sarilumab following failed prednisolone and sulfasalazine treatment (37). As a result, no recurrence of renal cell carcinoma was observed for 2 years following sarilumab beginning, despite no anti-tumor treatment (37). Hence, sarilumab may represent a promising therapeutic option for ICI-induced polyarthritis that is refractory to conventional treatments.

Gp130 direct inhibitors. The soluble gp130-Fc fusion protein (sgp130Fc or FE 999301), anti-gp130 monoclonal antibodies and small molecule inhibitors such as madindoline A, SC144, bazedoxifene, Raloxifene and LMT-28, have demonstrated the ability to inhibit IL-6/JAK/STAT3 signaling. However, most of

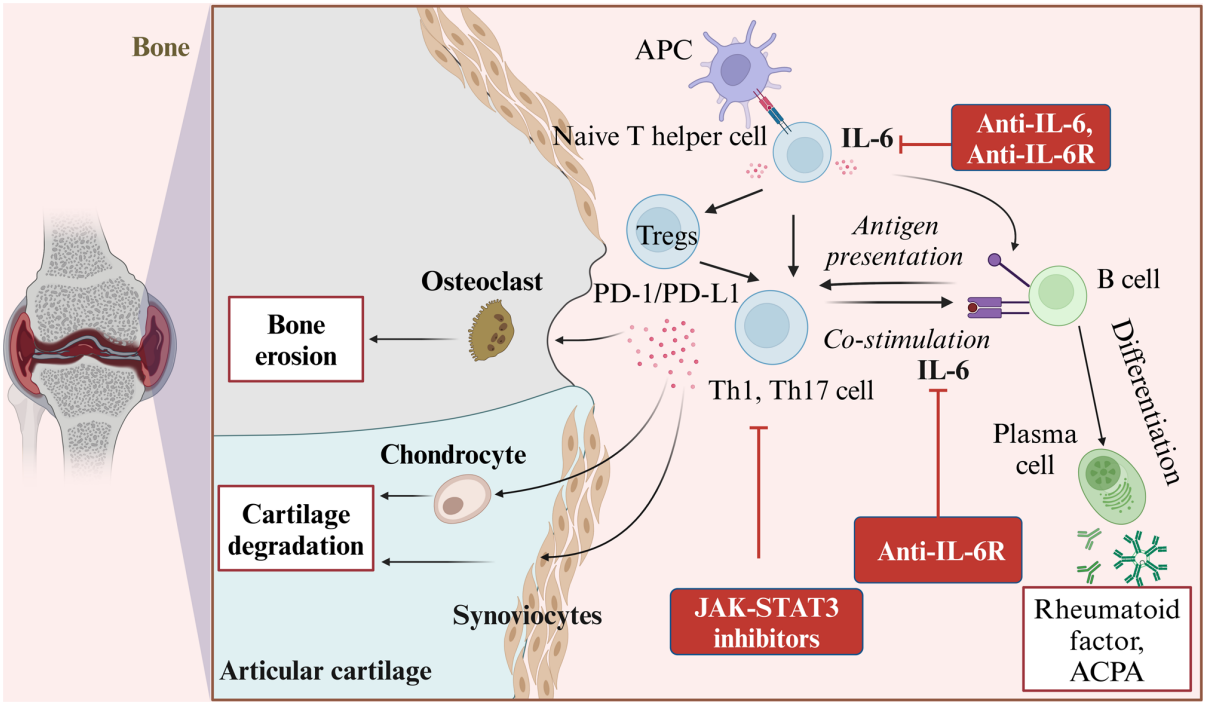

Figure 2. Underlying mechanism for treating ICI-induced IA by targeting IL-6. Tumor cells upregulate PD-L1 and CD80 to evade immune surveillance. Then, ICIs such as anti-CTLA-4 and anti-PD1 reverse this, activating immune response against tumor cells. However, ICIs can also excessively enhance the immune system, resulting in the emergence of irAEs, including autoimmune diseases such as inflammatory arthritis. The IL-6 receptor antagonists were demonstrated to be effectiveness against ICI-induced IA, which was due to their inhibition of the PD-1/PD-L1 mediated T-cell suppression and the differentiation of Th17/B cells. ICI-induced IA, ICI-induced inflammatory arthritis; ICIs, immune checkpoint inhibitors; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; irAEs, immune-related adverse events; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; ACPA, anti-citrullinated peptide antibody; APC, antigen-presenting cell.

these treatments require further evaluation in preclinical and clinical settings, particularly in the context of ICI-induced IA.

JAK inhibitors. Research has shown that JAK inhibitors such as TG101209, CEP 3379, WP1066, sorafenib and AG490 are effective against various types of cancer (105). Nevertheless, none of these agents has been reported to be effective in treating ICI-induced IA. Ruxolitinib, another JAK inhibitor, has shown clinical efficacy in managing ICI-induced myocarditis (106), but its therapeutic potential in ICI-induced IA remains to be determined. Overall, the role of JAK inhibitors in the management of ICI-induced IA is not well established and warrants further investigation.

STAT3 inhibitors. STAT3 inhibitors offer an alternative therapeutic strategy aimed at blocking IL-6/JAK/STAT3 signaling through the prevention of STAT3 phosphorylation. For example, JSI-124 has been shown to suppress tumor growth and progression (107). S3I-201, which is also referred to as NSC74859, binds to the DNA-binding domain of STAT3, thereby inhibiting the proliferation and survival of human breast cancer cells (108). Nonetheless, the efficacy of STAT3 blockers in managing ICI-triggered IA remains largely unclear, necessitating additional studies to clarify this matter.

The underlying mechanism for treating ICI-induced IA by IL-6 signaling inhibitors

Blocking IL-6 signaling reinstates T cell suppression through the PD-1/PD-L1 pathway. Immune checkpoint blockers, including anti-PD-1, anti-PD-L1 and anti-CTLA-4 antibodies, lead to immune-related side effects. This is due to the fact that PD-1, PD-L1 and CTLA-4 are found not only in tumor cells but also in various other tissue cells (109). Dysregulation of these immune checkpoints has been strongly linked to the inflammatory responses. A previous study indicated that PD-1 knockout mice develop more severe arthritis, whereas PD-L1 Fc therapy was shown to prevent collagen-induced arthritis (110). Additionally, PD-1 gene variations have been linked to a higher likelihood of rheumatic arthritis (111). IL-6 counteracts the suppression of T cells mediated by PD-1/PD-L1. The introduction of the anti-IL-6 receptor antibody tocilizumab mitigates IL-6-driven inflammation and restores PD-L1-mediated T cell suppression (112). Therefore, biologic agents targeting IL-6, which effectively treat ICI-induced IA, might work by reinstating T cell suppression via the PD-1/PD-L1 pathway in the synovial tissue (Fig. 2). Conversely, reports indicate that anti-IL-6 biological agents can enhance the anti-cancer efficacy of ICIs by improving the tumor-fighting abilities of cytotoxic T cells (113). Further underlying molecular mechanism is still required to be investigated. Overall, it seems plausible that the fundamental process behind using anti-IL-6 biologic medications to address ICI-induced IA involves restoring T cell suppression in target tissues through the PD-1/PD-L1 pathway.

Targeting IL-6 signaling suppresses Th17/B cell differentiation. The symptoms of irAEs frequently indicated a

Table I. Overviews of Tocilizumab's effectiveness in treating ICIs-induced inflammatory arthritis.

First author/s, year	ICI	Number of ICI induced IA Patients	Tumor	irAE	irAE treatment	ICI continuation	irAE outcome	Tumor outcome	(Refs.)
Kim *et al*, 2017	Ipilimumab, Pembrolizumab	3	Melanoma	Arthritis	Glucocorticoids + Tocilizumab	No	Improvement	Complete response	(36)
Tucker *et al*, 2017	Ipilimumab plus Nivolumab	1	Not available	Arthritis	Glucocorticoids + methotrexate > Infliximab > Tocilizumab	Not available	Improvement	Not available	(26)
Richter *et al*, 2019	Ipilimumab, Nivolumab, Pembrolizumab, Avelumab, Atezolizumab, Ipilimumab plus Nivolumab	34	Melanoma, lymphoma, lung cancer, renal cancer	Arthritis	Glucocorticoids > Methotrexate, hydroxychloroquine > Tocilizumab	Not available	Not available	Not available	(96)
Abdel-Wahab *et al*, 2018	Not available	5	Not available	Arthritis	Glucocorticoids + Tocilizumab	Not available	Not available	Not available	(97)
Mooradian *et al*, 2019	Pembrolizumab, Nivolumab plus Atezolizumab	1	Melanoma and lung cancer	Arthritis	Hydroxychloroquine, Methotrexate, Sulfasalazine > Tocilizumab	Not available	Not available	Not available	(98)
Saygin *et al*, 2019	Not available	1	Melanoma	Arthritis	Glucocorticoids + sulfasalazine > methotrexate > Tocilizumab	Not available	Improvement	Not available	(104)
Pirker *et al*, 2020	Pembrolizumab	1	Melanoma	Arthritis	Glucocorticoids + Tocilizumab	Not available	Improvement	Stable disease	(101)
Verspohl *et al*, 2021	Ipilimumab, Nivolumab, Pembrolizumab	7	Melanoma, lung cancer, head and neck tumor and urothelial carcinoma	Arthritis	Methotrexate, Tocilizumab	Not available	Not available	Not available	(99)

Table I. Continued.

First author/s, year	ICI	Number of ICI induced IA Patients	Tumor	irAE	irAE treatment	ICI continuation	irAE outcome	Tumor outcome	(Refs.)
Holmstroem *et al*, 2022	Pembrolizumab, Nivolumab or Ipilimumab plus Nivolumab	9	Melanoma, Non-Small Cell Lung Cancer, Cutaneous squamous cell carcinoma	Arthritis	Glucocorticoids, Infliximab > Tocilizumab	Not available	Improvement	Not available	(95)
Liapi *et al*, 2022	Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Avelumab, Nivolumab plus Ipilimumab, Nivolumab plus Pembrolizumab	11	Urogenital, melanoma, lung cancer	Arthritis	Glucocorticoids > Prednisolone, methotrexate, hydroxychloroquine > Tocilizumab	Not available	Complete response	Not available	(103)
Ladouceur *et al*, 2023	anti-CTLA-4/ PD-1/ PD-L1 antibodies or combination	1	Melanoma, Lung, Genitourinary and other cancers	Arthritis	Methotrexate > Tocilizumab	Not available	Improvement	Not available	(100)

ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1.

widespread inflammatory reaction, evidenced by a significant increase in CRP levels. CRP, a downstream marker of IL-6 signaling, shows an elevation from baseline levels during the initial occurrence of irAE (114). The rise in circulating IL-6 is considered to result from T-cell activation triggered by ICIs (115,116). High concentrations of IL-6 in the bloodstream cause pro-inflammatory responses via trans-signaling. IL-6 attaches to a sIL-6R, thereby triggering a broader spectrum of cells than traditional signaling (117). Classic IL-6 signaling occurs under low IL-6 concentrations and is restricted to cells expressing IL-6R, such as Th17 cells in specific tissues (118). Increased IL-6 levels have been observed in the tissues of irAEs among two distinct cohorts of 23 patients with solid tumors treated with anti-CTLA-4 and/or anti-PD-1 therapies (119). This increase was associated with a boost in the expression of genes tied to Th17 cells, leading to a greater percentage of Th17 cells within the total T cell population in tissues, thereby contributing to the pathogenesis of irAEs (119). Tocilizumab, an IL-6 inhibitor, has been shown to suppress the differentiation of naïve $CD4^+$ T cells into Th17 cells within synovial tissue (120). Moreover, Th17 cells further promote B cell differentiation into plasma cells that produce anti-citrullinated protein antibodies and rheumatoid factor within the synovial tissue (121,122). Therefore, blockade of IL-6 inhibited the development of ICI-induced IA by inhibiting Th17 and B cell differentiation (Fig. 2).

4. Conclusions

The interplay between IL-6 signaling and immune checkpoint inhibitor therapy highlights the delicate balance between maximizing anti-tumor efficacy and minimizing irAEs. While targeting IL-6 represents a promising strategy to mitigate irAEs, a more comprehensive understanding of its underlying mechanisms and interactions is crucial for developing safe and effective therapeutic approaches. Emerging evidence underscores the complex and context-dependent role of IL-6 in tumor progression and immune modulation, suggesting that IL-6 signaling is not only a contributor to cancer pathogenesis but also a potential therapeutic target. Future research should aim to elucidate the multifaceted roles of IL-6 in oncogenesis and immunotherapy and to design more selective inhibitors that effectively modulate IL-6 pathways or their downstream effects. Such advancements could pave the way for personalized treatment strategies and ultimately improve clinical outcomes for patients with cancer with elevated IL-6 activity.

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Authors' contributions

TH, LZ, YG and CF drafted the manuscript. TH and YG prepared the figures and table. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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