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Review Article

# Tocilizumab: From Bench to Bedside-A Comprehensive Review

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**Abstract**

Interleukin-6 (IL-6) is a multifunctional cytokine central to inflammation, infection, and tumor microenvironment regulation. Dysregulated IL-6 signaling contributes to tumor growth, immune evasion, and resistance to therapy. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor (IL-6R), was initially approved for rheumatoid arthritis and other autoimmune disorders due to its potent anti-inflammatory effects. Recent preclinical and clinical studies have revealed that IL-6 plays a crucial role in cancer biology, and blocking its pathway may have therapeutic potential in oncology. This review summarizes the current understanding of IL-6 mechanisms in cancer progression and evaluates tocilizumab's mechanism of action, pharmacologic profile, and safety in both inflammatory and oncologic contexts. Data from emerging studies suggest that tocilizumab not only mitigates cytokine release syndrome (CRS) associated with immunotherapies such as CAR-T cell treatment but also exerts direct inhibitory effects on the tumor microenvironment by reducing pro-tumorigenic cytokine signaling and enhancing the efficacy of concurrent anticancer therapies. Despite these promising findings, several challenges remain, including determining optimal dosing strategies, identifying responsive tumor types, and assessing the long-term impact of IL-6 inhibition on immune surveillance and tumor recurrence. Tocilizumab's expanding role in cancer therapy underscores the growing importance of targeting immune-modulatory pathways in oncology. Future investigations should focus on refining its integration into multimodal cancer treatment strategies and elucidating its synergistic potential with emerging immunotherapeutic and targeted agents.

## Introduction

### Overview of IL-6 / IL-6R biology in human physiology

Interleukin 6 (IL-6) is a 26-kDa pro-inflammatory glycoprotein produced by immune and non-immune cells in response to various stressors, including inflammatory, infectious and other injurious stimuli. It plays a pivotal role in orchestrating the immune response by regulating the recruitment, activation and differentiation of inflammatory cells, and is a key mediator in the pathogenesis of fever [1,2]. Beyond its immunomodulatory functions, IL-6 significantly influences systemic iron and zinc homeostasis, contributing to hypoferremia and anemia commonly observed in chronic inflammatory conditions [3]. In the context of cancer, IL-6 emerges as a central cytokine within the tumor microenvironment. It plays different roles and contributes to cancer cells' protection, development and even death [4]. From promoting tumorigenesis, to regulating cells' signaling pathways, it is a key determinant of the cancer cells' survival, proliferation, dissemination, defense, repair and apoptosis [2]. Hence, IL-6 serves as a critical determinant in the dynamic interplay between inflammation and cancer biology.

### Brief history of tocilizumab

Tocilizumab, a monoclonal antibody targeting the interleukin-6 (IL-6) receptor, was first discovered and developed in 1997 by the

Japanese pharmaceutical company Chugai as a therapeutic agent for rheumatoid arthritis (RA) [5]. Marketed under the trade name Actemra, this humanized immunoglobulin (IgG1 kappa) functions by inhibiting IL-6 from binding to its receptor, which is expressed on various cell types, predominantly hepatocytes and leukocytes [5,6]. Tocilizumab received its initial regulatory approval in 2005 for the treatment of multicentric Castleman disease [7]. Subsequently, the U.S. Food and Drug Administration (FDA) approved its use for RA in 2010, followed by active systemic juvenile idiopathic arthritis (JIA) in 2011 and polyarticular JIA in 2013. In 2017, its indications expanded to include giant cell arteritis and severe or life-threatening cytokine release syndrome associated with CAR T-cell therapy. Most recently, in 2021, tocilizumab was approved for the treatment of systemic sclerosis-associated interstitial lung disease, further underscoring its therapeutic versatility across a spectrum of inflammatory and autoimmune conditions [8-13].

Tocilizumab has demonstrated therapeutic potential beyond its approved indications, with multiple off-label applications emerging in recent years. Notably, it received emergency use authorization for the treatment of SARS-CoV-2, where its IL-6 receptor blockade helped mitigate the hyperinflammatory response associated with severe COVID-19 cases. Additionally, tocilizumab has been employed in managing severe or life-threatening cytokine release syndrome (CRS) induced by bispecific T-cell engager (BiTE) therapy, highlighting its role in immunomodulation [14]. Beyond infectious and oncologic contexts, emerging evidence suggests cardiovascular implications of IL-6 inhibition. A study by Swerdlow et al. demonstrated that blocking the IL-6 receptor may reduce the risk of coronary heart disease (CHD), highlighting a potential role for tocilizumab in patients predisposed to cardiovascular events. These findings expand the therapeutic horizon of IL-6-targeted interventions, positioning tocilizumab as a promising candidate in the prevention and management of inflammation-driven pathologies [15].

## Mechanism of IL-6 / IL-6R Signaling in Cancer

### IL-6 classic *vs* trans-signaling

The IL-6 signal transduction pathway is initiated when interleukin-6 binds to either a membrane-bound IL-6 receptor (IL-6R), known as the classical or cis-signaling pathway, or to a soluble IL-6R found in body fluids, referred to as the trans-signaling pathway. Both signaling modalities converge on the same intracellular cascade, mediated by the ubiquitously expressed glycoprotein 130 (GP130). The IL-6R, an 80-kDa protein, upon binding IL-6, associates with a 130-kDa GP130 molecule to form a ternary IL-6–IL-6R–GP130 complex. This complex dimerizes with an identical unit, resulting in a hexameric structure. The intracellular domains of the two GP130 molecules then align to form a homodimer, which serves as the platform for downstream signaling activation [5].

### Downstream signaling pathways: JAK/STAT3, MAP kinase, PI3K/AKT, NF-κB

Signal transmission proceeds via activation of tyrosine kinases-JAK1, JAK2, and TYK2-which phosphorylate the signal transducers and activators of transcription (STAT) proteins, specifically STAT1 and STAT3 [16]. These phosphorylated STATs translocate into the nucleus, where they initiate transcription of target genes. This pathway is tightly regulated by negative feedback mechanisms involving the suppressor of cytokine signaling (SOCS) proteins and the protein inhibitor of activated STAT (PIAS), both of which inhibit excessive signaling [17].

In addition to the JAK/STAT pathway, IL-6 signaling activates two other major cascades. The second involves Ras translocation to the plasma membrane, leading to activation of Raf, mitogen-activated protein kinase (MEK), and extracellular signal-regulated kinases (Erk1/2). The third pathway stems from JAK-mediated phosphorylation of phosphoinositide 3-kinase (PI3K), triggering the PI3K–protein kinase B (PKB/Akt) axis [16].

### Effects on tumor cells (proliferation, apoptosis, differentiation, metastasis)

STAT3-mediated transcription regulates a broad array of genes involved in critical cellular functions [16]:

- **Cell survival**: Survivin, XIAP, Mcl-1, Bcl-2, Bcl-xL
- **Proliferation**: Cyclin D1/D2, Cyclin B1, p53, p21
- **Differentiation**: COX-2/PGE2
- **Angiogenesis**: VEGF, HIF-1α, bFGF, MMP-2
- **Immunomodulation**: IL-10, MHC class II, CD80, CD86

### Effects on tumor microenvironment: immune cells

Within the tumor microenvironment, IL-6 is abundantly produced not only by tumor cells and stromal cells but also by tumor-associated macrophages, granulocytes, and fibroblasts. It acts as a central mediator of inflammation and tumor progression, promoting cancer cell proliferation, survival, and invasiveness. This is facilitated by the induction of angiogenesis-promoting factors such as IL-1β, IL-8, CCL2, CCL3, CCL5, GM-CSF, and VEGF. The transcriptional upregulation of IL-6 is primarily driven by nuclear factor kappa B (NF-κB) and hyperactivated STAT3. Additionally, adipocytes, T lymphocytes, and myeloid-derived suppressor cells (MDSCs) contribute to elevated IL-6 levels in the tumor milieu. IL-6 also enhances protein synthesis in metabolically active cancer cells via activation of the mTORC1 sensor [18-20].

### Systemic effects

Beyond its oncogenic roles, IL-6 has been implicated in cancer-

associated cachexia, a syndrome characterized by muscle and adipose tissue wasting. Muscle contraction itself is a known source of IL-6 production, linking its expression to physical activity. In cachectic cancers, elevated systemic IL-6 levels are associated with reduced protein synthesis rather than increased muscle degradation. IL-6 induces inflammatory and proteolytic pathways, and tumor-derived proteolysis-inducing factor (PIF) has been shown to activate caspase-mediated apoptosis, accelerating proteolysis and further suppressing skeletal muscle protein synthesis [21-22].

## Cytokine release syndrome

### Mechanism and pathophysiology

Cytokine release syndrome (CRS) is a systemic inflammatory response characterized by the rapid release of cytokines into the bloodstream by activated immune cells, which can escalate to multi-organ failure (MOF) and potentially death. The pathophysiological mechanism is initiated when damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) bind to pattern recognition receptors (PRRs) on the membranes of antigen-presenting cells (APCs). This interaction triggers the secretion of pro-inflammatory cytokines—primarily interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-gamma (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cytokines activate surrounding immune cells, creating a self-amplifying positive feedback loop that intensifies systemic immune activation [23,24]. Clinically, CRS manifests with fever, hypotension, and hypoxia, often necessitating high-dose vasopressors and mechanical ventilation. Laboratory abnormalities may include leukopenia, prolonged prothrombin time (PT), and partial thromboplastin time (PTT), elevated liver enzymes, and signs of acute kidney injury [25].

### Role of IL-6

CRS is a well-recognized complication of cancer immunotherapies, particularly chimeric antigen receptor (CAR) T-cell therapy and bispecific T-cell engager (BiTE) therapy, and to a lesser extent, immune checkpoint inhibitors (ICIs). The engagement of CAR T-cells, BiTEs, or ICIs with target cells leads to excessive cytokine secretion-primarily IL-6 and IFN-γ-by B cells, T cells, and natural killer (NK) cells. These cytokines further activate macrophages, endothelial cells, dendritic cells, and other immune components, amplifying the inflammatory cascade [25].

### Tocilizumab action and brief background introduction

Tocilizumab, an IL-6 receptor antagonist, was approved by the U.S. Food and Drug Administration (FDA) in 2017 as the first-line treatment for CRS. By blocking both classical and trans-signaling pathways of IL-6, tocilizumab effectively reduces systemic cytokine levels. It is typically administered at a dose of 8 mg/kg, up to a maximum of 800 mg, and may be repeated every 8 hours if clinically indicated. The drug is generally well tolerated. Corticosteroids serve as second-line therapy due to their potent immunosuppressive and anti-inflammatory effects [25].

A study by Lakomy et al. demonstrated that early administration of corticosteroids in combination with tocilizumab may prevent the progression of low-grade CRS to more severe forms, offering a promising strategy for early intervention [26].

Beyond immunotherapy-induced CRS, certain malignancies can trigger CRS as a paraneoplastic inflammatory syndrome. Hematologic cancers such as lymphomas and multiple myeloma (MM), as well as solid tumors including renal cell carcinoma, lung cancer, and sarcomas, have been implicated. In a study conducted by Blay et al., tocilizumab successfully resolved paraneoplastic fever in 34 patients, highlighting its potential utility in managing inflammation-driven symptoms in cancer patients [27].

## Tocilizumab

### Pharmacology and safety

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody that targets both membrane-bound and soluble interleukin-6 receptors (IL-6R), effectively inhibiting IL-6–mediated inflammatory signaling-a central driver of autoimmune pathology in diseases such as rheumatoid arthritis (RA) and giant cell arteritis (GCA) [28,29]. TCZ is available in intravenous (IV) and subcutaneous (SC) formulations, with flexible dosing validated through pivotal phase III trials such as SUMMACTA and BREVACTA. These studies demonstrated comparable pharmacodynamic suppression of IL-6, soluble IL-6R, CRP, and ESR across dosing regimens. The absolute bioavailability of SC tocilizumab was approximately 80%. Steady-state trough concentrations at week 24 were highest with SC weekly dosing (~40 μg/mL), intermediate with IV every 4 weeks (~18 μg/mL), and lowest with SC every 2 weeks (~7.4 μg/mL) with SC weekly dosing achieving the highest steady-state trough concentrations (~40 μg/mL), particularly necessary for patients over 100 kg [30]. Long-term data from RA cohorts show that TCZ is well tolerated over periods up to five years, with adverse events such as upper respiratory tract infections, neutropenia, elevated liver enzymes, and hyperlipidemia occurring at rates comparable to other biologic DMARDs, and no significant increase in cardiovascular risk [28]. In GCA, the safety profile is similar, though infection rates-particularly serious infections-are higher, likely due to the older age and comorbidities of the patient population. In the pivotal WA28119 trial, serious infection rates ranged from 4.4 to 9.7 events per 100 patient-years [31], and observational studies confirm that TCZ remains well tolerated for up to three years, with

low discontinuation rates and manageable adverse events such as cytopenias, elevated transaminases, and hypercholesterolemia [32,33].

Beyond IL-6 inhibition, TCZ may exert broader immunological effects by modulating other inflammatory mediators and immune cell populations, including T cells, B cells, and neutrophils-mechanisms increasingly relevant in both autoimmune and oncologic contexts [34]. Its role in managing cytokine release syndrome and severe COVID-19 has been well documented, with meta-analyses showing significant reductions in mortality and progression to mechanical ventilation, leading to its inclusion in WHO treatment guidelines and regulatory approvals across the EU, US, and Japan [35]. Real-world evidence (RWE) complements randomized controlled trials (RCTs), especially in underrepresented populations such as the elderly, patients with comorbidities, and those with rare conditions like myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), where TCZ has shown promise in relapse prevention and clinical stabilization [36]. Despite its broad therapeutic potential, limitations remain, including insufficient data on long-term malignancy risk, optimal use in pediatric oncology, and standardized protocols for neuroinflammatory diseases. Future research should focus on personalized dosing strategies based on body weight and pharmacogenomic profiles, biomarker-guided therapy to optimize patient selection, and long-term safety surveillance for rare adverse events such as gastrointestinal perforations and malignancy risk. Comparative effectiveness studies in elderly, obese, and comorbid populations, formulation of innovations to improve adherence, and health economics analyses to guide global access are also warranted. Mechanistic studies exploring TCZ's role in oncologic pathways and its integration with immunotherapies such as checkpoint inhibitors and CAR-T cell therapy could further expand its clinical utility.

### Biosimilars

Tocilizumab biosimilars have gained regulatory approval in several high-income countries, including the United States and the European Union, where they are increasingly integrated into clinical practice. In the U.S., the FDA has approved multiple biosimilars such as Tofidence (tocilizumab-bavi), Tyenne (tocilizumab-aazg), and Avtozma (tocilizumab-anoh), with both intravenous (IV) and subcutaneous (SC) formulations available [37-39]. The European Medicines Agency (EMA) has similarly approved these agents, facilitating broader access across the EU [40]. However, in low- and middle-income countries (LMICs), access remains limited due to regulatory fragmentation, high development costs, and lack of local manufacturing infrastructure [41,42]. For example, while India and China have biosimilar frameworks, inconsistent enforcement and regional disparities hinder widespread adoption [43].

The cost differential between biosimilars and the originator biologic, Actemra®, is a key driver of their adoption. In the U.S., biosimilars launched with wholesale acquisition cost (WAC) discounts of 16% (Tofidence) and 26% (Tyenne), with average sales price (ASP) discounts reaching 35% for Tyenne by Q1 2025 [44]. In Europe, biosimilars are often priced 20-30% lower than the originator, with some countries achieving up to 40% savings through tendering systems [45]. A cost-effectiveness analysis in Spain found that biosimilar tocilizumab offered the lowest lifetime treatment cost (€183,741) among biologic comparators, while maintaining equivalent quality-adjusted life years (QALYs) to the originator [46]. These savings could translate into expanded access, with modeling suggesting that a 30% discount could increase treatment coverage by up to 43% in some European countries [45].

Despite these advantages, biosimilar uptake in low-income countries (LICs) remains minimal. WHO prequalification of tocilizumab for COVID-19 treatment has not yet translated into widespread biosimilar availability, largely due to high prices (up to $600 per dose) and limited supply chains [47]. Although the expiration of key patents has removed intellectual property barriers, the lack of WHO-prequalified biosimilars continues to restrict access in LICs [42].

From a clinical standpoint, biosimilars have demonstrated comparable safety and efficacy to the reference product. A 52-week randomized controlled trial of BAT1806 (BIIB800) showed nearly identical ACR20 response rates (90.4% *vs*. 90.3%) and similar treatment-emergent adverse event (TEAE) rates (55.9% *vs*. 62.1%) compared to Actemra [48]. Another phase 3 trial of CT-P47 (Avtozma) confirmed equivalent efficacy and immunogenicity, even among patients who switched from the originator [49]. Additionally, a head-to-head study of Complarate® and Actemra® found no significant differences in adverse events or anti-drug antibody formation [50]. These findings support the European League Against Rheumatism (EULAR) position that biosimilars are appropriate substitutes when supported by robust evidence.

## Challenges, Risks, and Limitations

### Immunologic Consequences of IL-6 Blockade

Clinical experience with tocilizumab in the treatment of rheumatoid arthritis has provided valuable insights into its safety profile. Among its most notable adverse effects is an increased susceptibility to infections, primarily due to drug-induced neutropenia and cytopenia. Reported infections include upper respiratory tract infections, colitis, and reactivation of latent pathogens such as tuberculosis, endemic fungal infections, hepatitis B and C viruses, and herpes zoster. Tocilizumab may also impair wound healing, increasing the risk of open wound infections, and has been associated with rare but serious complications such as

pancreatitis, gastrointestinal perforation secondary to colitis, and central nervous system demyelination (e.g., multiple sclerosis, Guillain-Barré syndrome). Importantly, these side effects are predominantly observed with long-term use, in contrast to the limited dosing (typically one or two administrations) required for managing CAR T-cell therapy–related CRS [51-54]. Nonetheless, the immunosuppressive effects of IL-6 inhibition may pose challenges to anti-tumor immune defense mechanisms.

**Biomarker gaps (IL-6, CRP, downstream markers)**

Laboratory abnormalities have also been documented in patients receiving tocilizumab, particularly in the context of COVID-19 treatment. A study by Avyat et al. reported elevated liver enzymes and potassium levels, thrombocytopenia, and reduced PT and PTT. Other studies have identified hyperlipidemia, subcutaneous injection site reactions, and infusion-related reactions as common side effects [14,54,55]. Notably, elevations in liver enzymes were not associated with permanent or clinically significant hepatic injury in clinical trials [54].

**Potential resistance mechanisms of IL-6 pathway blockade**

An additional safety concern is the development of anti-drug antibodies against tocilizumab, which may occur whether the drug is used as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs). This immunogenicity could potentially compromise therapeutic efficacy and warrants monitoring [54]. The cumulative experience with tocilizumab across diverse clinical settings underscores the importance of individualized treatment strategies, particularly regarding timing and dosage, to optimize therapeutic outcomes [56]. Targeting the IL-6/JAK/STAT3 axis presents further complexity due to the extensive crosstalk within intracellular signaling networks. Tumor cells may circumvent IL-6 blockade by activating alternative pathways such as PI3K/AKT and MAPK, thereby sustaining their survival, proliferation, invasiveness, and angiogenic potential [57].

**Experimental and Translational Evidence for IL-6 Pathway Inhibition in Oncology**

Interleukin-6 (IL-6), which is highly expressed in the tumor microenvironment, has been shown to promote tumorigenesis. Consequently, targeting the downstream components of the IL-6 signaling pathway may help disrupt tumor-promoting mechanisms. This hypothesis is supported by several preclinical studies. The IL-6 pathway, along with its key downstream effectors JAK and STAT3, is implicated in tumor progression, immune evasion, and resistance to immunotherapy. Cancer patients exhibiting hyperactivation of this pathway, particularly through sustained JAK and STAT3 signaling, often have a poor prognosis [58,59]. Targeting the IL-6/JAK/STAT3 pathway has been shown to inhibit tumor cell growth and reduce the immunosuppressive environment created by tumor-promoting factors.

A 2016 preclinical study using a KRAS-mutant mouse model of lung cancer demonstrated that IL-6 inhibition significantly suppressed tumor cell proliferation, reduced STAT3 activation, and led to a decrease in pro-tumor marker expression, while simultaneously increasing anti-tumor marker expression. These findings indicate that blocking the IL-6 pathway not only disrupts the tumor-supportive microenvironment but also promotes a shift toward an anti-tumor immune state [60]. Similarly, another preclinical study in a mouse model of colorectal cancer showed that inhibition of the IL-6/JAK/STAT3 pathway resulted in PD-L1 upregulation, thereby reversing resistance to anti-PD-L1 therapy [61]. Another preclinical study in a mouse model of glioblastoma multiforme demonstrated that IL-6 knockout disrupted downstream signaling pathways and led to increased PD-L1 expression. These findings suggest that combining anti-IL-6 and anti-PD-L1 therapies could offer a promising strategy for cancer treatment [62]. Tocilizumab, a recombinant monoclonal antibody targeting the IL-6 receptor (IL-6R), has shown encouraging results in various preclinical tumor models. In one study using a mouse model of triple-negative breast cancer, tocilizumab enhanced the cytotoxic effects of cisplatin on both breast cancer cells and cancer stem cells. This suggests that tocilizumab may exert its therapeutic effects early in tumor development and interfere with pro-metastatic signaling pathways [63]. Chen et al. explored the use of tocilizumab in preclinical models, addressing a gap in the current literature. They investigated the effects of tocilizumab in combination with PD-1 inhibitors in a mouse model of immune checkpoint inhibitor-induced myocarditis within the context of lung cancer. The study demonstrated that co-administration of tocilizumab not only enhanced antitumor activity but also mitigated immune-related cardiac inflammation. Elevated levels of IL-6 were associated with poorer clinical outcomes and were significantly increased during myocarditis induced by immune checkpoint therapy. Tocilizumab exerted its therapeutic effects by inhibiting the IL-6/JAK2/STAT3 signaling pathway, thereby reducing inflammation mediated by proinflammatory M1 macrophages and limiting tumor cell proliferation [22].

**Tocilizumab Clinical use and trials**

Tocilizumab has recently emerged as a leading targeted monoclonal antibody with diverse therapeutic applications. In oncology, it has received FDA approval for the management of immune-related adverse events, specifically severe or life-threatening cytokine release syndrome (CRS) in patients undergoing CAR-T cell therapy [11]. Moreover, tocilizumab is frequently used off-label to manage immune-mediated toxicities such as CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) in patients treated with bispecific T-cell engagers (BiTEs) and other bispecific antibodies. For example, bispecific agents like teclistamab have

demonstrated significant efficacy in patients with relapsed or refractory multiple myeloma. However, their clinical use is often limited by high rates of immune-related adverse events, including CRS and ICANS [64,65]. In a real-world study, tocilizumab was administered as a single prophylactic dose prior to treatment with BCMA (B cell maturation antigen) and GPRC5D (G protein-coupled receptor family C group 5 member D)-targeted bispecific antibodies. The results demonstrated low rates of cytokine release syndrome (CRS) at 10.1% and immune effector cell-associated neurotoxicity syndrome (ICANS) at 5.9%, without compromising treatment efficacy [66]. Another critical consideration in CRS management is the timing of tocilizumab administration. Optimal timing remains undefined and varies across different CAR T-cell constructs, leading to inconsistencies in clinical practice and uncertainty regarding best practices [67].

In the Phase 1/2 MonumenTAL-1 study, eligible patients with triple-class exposed relapsed/refractory multiple myeloma (RRMM) received talquetamab-the first and only FDA-approved bispecific antibody targeting GPRC5D. CRS occurred in 73-79% of patients across all cohorts, with 35.0-47.4% receiving tocilizumab with or without other interventions. Tocilizumab (8 mg/kg IV) was given as a single prophylactic dose prior to talquetamab step-up dosing. When combined with increased dexamethasone use following talquetamab administration, this approach led to a reduction in both the incidence and severity of CRS compared to the overall MonumenTAL-1 population [68].

In a retrospective review assessing the use of tocilizumab for managing cytokine release syndrome (CRS) associated with blinatumomab, a bispecific T-cell engager used in acute lymphoblastic leukemia, tocilizumab was shown to reduce the risk of CRS effectively. Among 16 post-marketing cases, CRS was reported as resolved in 15 patients, and no instances of fatal CRS were documented following tocilizumab treatment [69].

Similarly, in the DeLLphi-301 trial, which evaluated the bispecific T-cell engager tarlatamab in patients with relapsed/refractory small cell lung cancer, tocilizumab was employed therapeutically rather than prophylactically. It was administered to patients receiving either 10 mg or 100 mg doses of tarlatamab and was successful in managing CRS [67]. These clinical trials support the potential for tocilizumab to be incorporated into outpatient treatment protocols, which may help reduce hospital stays in cases where it is not administered prophylactically before BiTE or bispecific antibody therapy. A 2024 clinical trial investigating the safety and feasibility of administering CAR-T therapy in the outpatient setting demonstrated that early use of tocilizumab, even in cases of grade 1 CRS, enabled 15 out of 35 patients to avoid hospitalization. These findings suggest that future strategies incorporating early intervention with tocilizumab may decrease hospitalization rates, enhance patient care, and minimize treatment-related complications [70]. In the ZUMA-1 Cohort 3 study, the use of prophylactic tocilizumab and levetiracetam was investigated for their impact on the incidence of CRS and ICANS following treatment with axicabtagene ciloleucel (axi-cel). Tocilizumab was administered 48 hours after axi-cel infusion. The results demonstrated a reduction in overall CRS rates in the prophylactic group compared to historical controls, with a significantly lower incidence of grade ≥2 CRS. Importantly, there was no significant increase in ICANS, suggesting that tocilizumab does not exacerbate neurotoxicity, contrary to earlier concerns. Additionally, patients who received prophylactic tocilizumab experienced shorter hospital stays, and some were eligible for early discharge, supporting the feasibility of outpatient management [71].

Another potential use of tocilizumab in cancer care is its role in mitigating cachexia, a severe and often life-threatening complication characterized by significant weight loss, muscle wasting, and systemic inflammation. Since IL-6 is a key driver of cancer-associated cachexia, IL-6 blockade with tocilizumab may offer therapeutic benefits. In an observational study involving patients with non-small cell lung cancer (NSCLC) and elevated IL-6 levels, treatment with tocilizumab was associated with improved survival outcomes and favorable changes in clinical parameters, including body weight, serum albumin, C-reactive protein (CRP), the modified Glasgow Prognostic Score (mGPS), and symptom burden. Given the current lack of effective treatments for cancer cachexia, tocilizumab may represent a promising therapeutic option in this setting [72]. In a small-scale retrospective observational study, one group of patients received a combination of tocilizumab and corticosteroids, while the other group was treated with corticosteroids alone, with the aim of managing cancer cachexia and reducing systemic hyperinflammation. Despite the limited sample size, the results suggest that tocilizumab combined with corticosteroids may be effective in alleviating cancer cachexia associated with systemic hyperinflammation. Therefore, this combination therapy shows promise as a novel approach for treating cancer cachexia in patients experiencing systemic inflammatory responses [73].

**Future Directions**

While tocilizumab (TCZ) has demonstrated promising potential in combination cancer therapies, several critical gaps remain that must be addressed to optimize its clinical application. One of the most pressing unmet needs is the lack of large, randomized controlled trials evaluating TCZ in combination with immune checkpoint inhibitors (ICIs), chemotherapy, and targeted therapies. Most current evidence is derived from preclinical models or small cohort studies, which limits generalizability and long-term outcome assessment [74,75]. Long-term follow-up is essential to

determine the impact of TCZ on overall survival, progression-free survival, and patient-reported outcomes such as quality of life [76]. Another promising avenue is the development of new formulations or modified IL-6R blockade strategies. Advances in antibody engineering have led to the creation of bispecific antibodies and long-acting IL-6 inhibitors, which may offer improved pharmacokinetics, reduced dosing frequency, and enhanced tumor penetration [3]. These innovations could expand the therapeutic window and reduce the risk of immune suppression. Precision medicine approaches, including biomarker-driven therapy, are also critical for identifying patients most likely to benefit from TCZ. However, the use of biomarkers in this context presents several challenges. IL-6 levels, while elevated in many cancers, are not always predictive of treatment response due to their dynamic nature and variability across tumor types and disease stages [77]. Moreover, the lack of standardized assays and cutoff values complicates clinical decision-making. STAT3 activation and tumor microenvironment profiling may offer additional insights, but these require invasive sampling and complex interpretation [78]. Integrating TCZ into biomarker-guided treatment algorithms will require robust validation and harmonization of diagnostic tools.

Optimizing combination regimens and treatment sequencing is another area of active investigation. The timing of TCZ administration-whether concurrent with ICIs or as a preemptive strategy-may influence outcomes. For example, prophylactic TCZ has shown promise in reducing immune-related adverse events without compromising antitumor efficacy [79]. Further studies are needed to determine the ideal scheduling and dosing strategies across different cancer types. Finally, safety monitoring remains paramount. While TCZ can mitigate inflammation and toxicity, excessive immune modulation may dampen antitumor responses. Balancing immunosuppression with therapeutic efficacy requires robust pharmacovigilance and real-time immune profiling. Future trials should incorporate immune monitoring protocols and adaptive dosing strategies to ensure patient safety [76,78].

In summary, the future of TCZ in oncology lies in rigorous clinical validation, innovative drug design, personalized treatment approaches, and careful safety oversight. Addressing these areas will be essential to fully realize the potential of IL-6 blockade in cancer therapy.

## Conflict of Interest

The authors declare that they have no conflicts of interest and received no financial support for the research, authorship, or publication of this article.

## References

1. Luheshi G, Rothwell N (1996) Cytokines and Fever. Int Arch Allergy Immunol 109: 301-307.
2. Kumari N, Dwarakanath BS, Das A, Bhatt AN (2016) Role of interleukin-6 in cancer progression and therapeutic resistance. Tumor Biol 37: 11553-11572.
3. Tanaka T, Narazaki M, Kishimoto T (2014) IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 6: a016295.
4. Lacina L, Brábek J, Král V, Kodet O, Smetana K (2018) Interleukin-6: a molecule with complex biological impact in cancer. Histol Histopathol 34: 125-136.
5. Ohsugi Y (2019) The immunobiology of humanized Anti-IL6 receptor antibody: From basic research to breakthrough medicine. J Transl Autoimmun 3: 100030.
6. Wolf J, Rose-John S, Garbers C (2014) Interleukin-6 and its receptors: A highly regulated and dynamic system. Cytokine 70: 11-20.
7. Venkiteshwaran A (2009) Tocilizumab. mAbs 1: 432-438.
8. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B (2017) Tocilizumab (Actemra). Hum Vaccines Immunother 13: 1972-1988.
9. Antonio AA, Santos RN, Abariga SA (2022) Tocilizumab for giant cell arteritis. Cochrane Database Syst Rev 5: CD013484.
10. Khanna D, Lescoat A, Roofeh D, Bernstein EJ, Kazerooni EA, et al. (2022) Systemic Sclerosis-Associated Interstitial Lung Disease: How to Incorporate Two Food and Drug Administration-Approved Therapies in Clinical Practice. Arthritis Rheumatol 74:13-27.
11. Le RQ, Li L, Yuan W, Shord SS, Nie L, et al. (2018) FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. Oncologist 23: 943-947.
12. Santomasso BD, Nastoupil LJ, Adkins S, Lacchetti C, Schneider BJ, et al. (2021) Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol 39: 3978-3992.
13. Rejeski K, Subklewe M, Locke FL (2023) Recognizing, defining, and managing CAR-T hematologic toxicities. Hematology Am Soc Hematol Educ Program 2023: 198-208.
14. Preuss CV, Anjum F (2025) Tocilizumab. In: StatPearls.
15. Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JEL, Shah T, et al. (2012) The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. The Lancet 379: 1214-1224.
16. Ara T, Declerck YA (1990) Interleukin-6 in bone metastasis and cancer progression. Eur J Cancer 46: 1223-1231.
17. Yao X, Huang J, Zhong H, Shen N, Faggioni R, et al. (2014) Targeting interleukin-6 in inflammatory autoimmune diseases and cancers. Pharmacol Ther 141: 125-139.
18. Johnson DE, O'Keefe RA, Grandis JR (2018) Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 15: 234-248.
19. Fisher DT, Appenheimer MM, Evans SS (2014) The two faces of IL-6 in the tumor microenvironment. Semin Immunol 26: 38-47.
20. Wu S, Cao Z, Lu R, Zhang Z, Sethi G, et al. (2025) Interleukin-6 (IL-6)-associated tumor microenvironment remodelling and cancer immunotherapy. Cytokine Growth Factor Rev 85: 93-102.
21. Carson JA, Baltgalvis KA (2010) Interleukin 6 as a Key Regulator of

Muscle Mass during Cachexia. Exerc Sport Sci Rev 38: 168-176.

22. Chen G, Chen B, Wu Y, Nie H, Zhong Z, et al. (2025) Bridging the tumor microenvironment: the pivotal role of cancer-associated fibroblasts in tumor cachexia development. Mol Cancer 24: 194.
23. Shah D, Soper B, Shopland L (2023) Cytokine release syndrome and cancer immunotherapies – historical challenges and promising futures. Front Immunol 14: 1190379.
24. Xiao X, Huang S, Chen S, Wang Y, Sun Q, et al. (2021) Mechanisms of cytokine release syndrome and neurotoxicity of CAR T-cell therapy and associated prevention and management strategies. J Exp Clin Cancer Res 40: 367.
25. Synnott D, O'Reilly D, De Freitas D, Naidoo J (2025) Cytokine release syndrome in solid tumors. Cancer 131: e70069.
26. Lakomy T, Akhoundova D, Nilius H, Kronig MN, Novak U, et al. (2023) Early Use of Corticosteroids following CAR T-Cell Therapy Correlates with Reduced Risk of High-Grade CRS without Negative Impact on Neurotoxicity or Treatment Outcome. Biomolecules 13: 382.
27. Blay JY, Brahmi M, Dufresne A, Swalduz A, Avrillon V, et al. (2025) Anti-IL-6R Ab tocilizumab to treat paraneoplastic inflammatory syndrome of solid cancers. ESMO Open 10: 104088.
28. Parisi S, Ditto MC, Ghellere F, Panaro S, Piccione F, et al. (2025) Update on tocilizumab in rheumatoid arthritis: a narrative review. Front Immunol 16: 1470488.
29. Singh JA, Beg S, Lopez-Olivo MA (2011) Tocilizumab for Rheumatoid Arthritis: A Cochrane Systematic Review. J Rheumatol 38: 10-20.
30. Abdallah H, Hsu JC, Lu P, Fettner S, Zhang X, et al. (2017) Pharmacokinetic and Pharmacodynamic Analysis of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis From 2 Randomized, Controlled Trials: SUMMACTA and BREVACTA. J Clin Pharmacol 57: 459-468.
31. Stone JH, Spotswood H, Unizony SH, Aringer M, et al. (2022) New-onset versus relapsing giant cell arteritis treated with tocilizumab: 3-year results from a randomized controlled trial and extension. Rheumatology 61: 2915-2922.
32. De Boysson H, Le Besnerais M, Blaison F, Daumas A, Jarrot PA, et al. (2021) Assessment of the efficacy and safety of tocilizumab in patients over 80 years old with giant cell arteritis. Arthritis Res Ther 23: 143.
33. Calderón-Goercke M, Loricera J, Aldasoro V, Castañeda S, Villa I, Humbría A, et al. (2019) Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. Semin Arthritis Rheum 49: 126-135.
34. Ghasemi K, Ghasemi K (2022) Evaluation of the Tocilizumab therapy in human cancers: Latest evidence and clinical potential. J Clin Pharm Ther 47: 2360-2368.
35. Tleyjeh IM, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, et al. (2021) Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect 27: 215-227.
36. Schirò G, Iacono S, Andolina M, Bianchi A, Ragonese P, et al. (2024) Tocilizumab treatment in MOGAD: a case report and literature review. Neurol Sci 45: 1429-1436.
37. FDA approves first biosimilar to Actemra to treat adult and pediatric arthritis.
38. Fresenius Kabi□s Biosimilar Tyenne® (tocilizumab-aazg) Becomes the First IV and Subcutaneous Tocilizumab Biosimilar Approved by the FDA.
39. U.S. FDA approves Celltrion□s AVTOZMA® (tocilizumab-anoh), a biosimilar to ACTEMRA®.
40. Tyenne (2024) Eur Med Agency.
41. Biosimilars access toolkit.
42. COVID-19 drug recommended by WHO remains unaffordable and inaccessible for most people.
43. Global Tocilizumab Biosimilars Market Research Report 2024.
44. SAMSUNG BIOEPIS (2025) Biosimilar Market Dynamics.
45. Clarke K, Ainslie-Garcia M, Ferko N, Shastri K (2024) Modelling the opportunity for cost-savings or patient access with biosimilar adalimumab and tocilizumab: a European perspective. J Med Econ 27: 952-962.
46. Pérez-Ruiz F, Crespo-Diz C, Schoenenberger-Arnaiz JA, Cerezales M, Crespo C, et al. (2025) Cost-effectiveness analysis of subcutaneous biosimilar tocilizumab in patients with rheumatoid arthritis in Spain. Farm Hosp 49: 278-285.
47. Rahimi F, Bezmin Abadi AT (2022) WHO prequalified tocilizumab and vaccine boosters against COVID-19. Int J Surg 99: 106593.
48. Joszt L (2022) Tocilizumab Biosimilars Show Similar Safety, Tolerability, Immunogenicity to Reference: ACR Abstracts.
49. Gerd Burmester, Jakub Trefler, Artur Racewicz, Janusz Jaworski, Agnieszka Zielińska, et al. (2025) Efficacy and Safety of Biosimilar CT-P47 Versus Reference Tocilizumab: 1-Year Results of a Randomised, Active-Controlled, Double-Blind, Phase III Study in Patients with Rheumatoid Arthritis. Clin Drug Investig 45: 551-563.
50. Comparison of Complarate® (Tocilizumab Biosimilar) and Actemra® in Patients With Rheumatoid Arthritis.
51. Fishman JA, Hogan JI, Maus MV (2019) Inflammatory and Infectious Syndromes Associated With Cancer Immunotherapies. Clin Infect Dis 69: 909-920.
52. Schoels MM, van der Heijde D, Breedveld FC, Burmester GR, Dougados M, et al. (2013) Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement. Ann Rheum Dis 72: 583-589.
53. Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, et al. (2013) Longterm Safety and Efficacy of Tocilizumab in Patients with Rheumatoid Arthritis: A Cumulative Analysis of Up to 4.6 Years of Exposure. J Rheumatol 40: 768-780.
54. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, et al. (2020) Translating IL-6 biology into effective treatments. Nat Rev Rheumatol 16: 335-345.
55. Ayvat P, Kayhan Omeroglu S (2024) Tocilizumab treatment in COVID-19 patients: therapy's side effects and effect on mortality. Eur Rev Med Pharmacol Sci 28: 2107-2116.
56. Elahi R, Karami P, Heidary AH, Esmaeilzadeh A (2022) An updated overview of recent advances, challenges, and clinical considerations of IL-6 signaling blockade in severe coronavirus disease 2019 (COVID-19). Int Immunopharmacol 105: 108536.

57. Liang Y, Shao Y, Gu W (2025) Role of interleukin-6 in resistance to tumor therapy. Discov Oncol 16: 1791.

58. Ludwig H, Nachbaur DM, Fritz E, Krainer M, Huber H (1991) Interleukin-6 is a prognostic factor in multiple myeloma. Blood 77: 2794-2795.

59. Gai X, Zhou P, Xu M, Liu Z, Zheng X, et al. (2020) Hyperactivation of IL-6/STAT3 pathway leaded to the poor prognosis of post-TACE HCCs by HIF-1α/SNAI1 axis-induced epithelial to mesenchymal transition. J Cancer 11: 570-582.

60. Caetano MS, Zhang H, Cumpian AM, Gong L, Unver N, et al. (2016) IL6 Blockade Reprograms the Lung Tumor Microenvironment to Limit the Development and Progression of K-ras–Mutant Lung Cancer. Cancer Res 76: 3189-3199.

61. Li J, Xu J, Yan X, Jin K, Li W, et al. (2018) Targeting Interleukin-6 (IL-6) Sensitizes Anti-PD-L1 Treatment in a Colorectal Cancer Preclinical Model. Med Sci Monit 24: 5501-5508.

62. Lamano JB, Lamano JB, Li YD, DiDomenico JD, Choy W, et al. (2019) Glioblastoma-Derived IL6 Induces Immunosuppressive Peripheral Myeloid Cell PD-L1 and Promotes Tumor Growth. Clin Cancer Res 25: 3643-3657.

63. Alraouji NN, Al□Mohanna FH, Ghebeh H, Arafah M, Almeer R, et al. (2020) Tocilizumab potentiates cisplatin cytotoxicity and targets cancer stem cells in triple□negative breast cancer. Mol Carcinog 59: 1041-1051.

64. Moreau P, Garfall AL, Van De Donk NWCJ, Nahi H, San-Miguel JF, et al. (2022) Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med 387: 495-505.

65. Devasia AJ, Chari A, Lancman G (2024) Bispecific antibodies in the treatment of multiple myeloma. Blood Cancer J 14: 158.

66. Kowalski A, Lykon J, Diamond B, Coffey D, Kaddoura M, et al. (2025) Tocilizumab prophylaxis for patients with multiple myeloma treated with bispecific antibodies. Blood Adv 9: 4979-4986.

67. Ahn MJ, Cho BC, Felip E, Korantzis I, Ohashi K, et al. (2023) Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med 389: 2063-2075.

68. Schinke C, Vij R, Jagannath S, Sanchez L, Pianko M, et al. (2025) MM-216: Prophylactic Tocilizumab to Mitigate Cytokine Release Syndrome and Outpatient Dosing of Talquetamab in Relapsed/Refractory Multiple Myeloma: Updated Phase 1/2 Monumental-1 Results. Clin Lymphoma Myeloma Leuk 25: S908.

69. Choudhry J, Parson M, Wright J (2018) A Retrospective Review of Tocilizumab for the Management of Blinatumomab (a Bispecific T Cell Engager)-Induced Cytokine Release Syndrome (CRS). Blood 132: 5211-5211.

70. Furqan F, Bhatlapenumarthi V, Dhakal B, Fenske TS, Farrukh F, et al. (2014) Outpatient administration of CAR T-cell therapies using a strategy of no remote monitoring and early CRS intervention. Blood Adv 8: 4320-4329.

71. Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Jacobson CA, et al. (2024) Tocilizumab Prophylaxis Following Axicabtagene Ciloleucel in Relapsed or Refractory Large B-Cell Lymphoma. Transplant Cell Ther 30: 1065-1079.

72. Du Y, Liu X, Pan R, Zhang X, Si X, et al. (2024) Tocilizumab for Advanced Non□Small□Cell Lung Cancer With Concomitant Cachexia: An Observational Study. J Cachexia Sarcopenia Muscle 15: 2815-2825.

73. Chen P, Wang D, Zhan Z, Chen L, Chen Y (2024) Tocilizumab in combination with corticosteroids: potential for managing cancer cachexia with systemic hyperinflammation. Front Immunol 15: 1477310.

74. Chen Y, Luo Y, Liu Y, Luo D, Liu A (2025) Dual efficacy of tocilizumab in managing PD-1 inhibitors-induced myocardial inflammatory injury and suppressing tumor growth with PD-1 inhibitors: a preclinical study. Cancer Immunol Immunother 74: 52.

75. Chung AW, Kozielski AJ, Qian W, Zhou J, Anselme AC, et al. (2022) Tocilizumab overcomes chemotherapy resistance in mesenchymal stem-like breast cancer by negating autocrine IL-1A induction of IL-6. Npj Breast Cancer 8: 30.

76. Athale J, Busch LM, O'Grady NP (2022) Cytokine Release Syndrome and Sepsis: Analogous Clinical Syndromes with Distinct Causes and Challenges in Management. Infect Dis Clin North Am 36: 735-748.

77. Li B, Jin J, Guo D, Tao Z, Hu X (2023) Immune Checkpoint Inhibitors Combined with Targeted Therapy: The Recent Advances and Future Potentials. Cancers 15: 2858.

78. Mc Neil V, Lee SW (2025) Advancing Cancer Treatment: A Review of Immune Checkpoint Inhibitors and Combination Strategies. Cancers 17: 1408.

79. Doherty K (2024) Prophylactic Tocilizumab Reduces Toxicity, Boosts Efficacy in Immune Checkpoint Inhibitor–Treated Melanoma.