Interleukin-6 Targeted Agents

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Introduction

Interleukin-6 (IL-6) is best known for its pro-inflammatory effects. However, this pleomorphic cytokine also has anti-inflammatory, pro-resolution, and regenerative properties; it is important for pathogen clearance and triggers the release of acute-phase proteins via the liver. Anti-inflammatory and antibacterial activities of IL-6 are mediated by classical signaling, whereas pro-inflammatory effects are mediated by trans-signaling. Monoclonal antibodies against IL-6R, such as tocilizumab, do not discriminate between classical signaling and trans-signaling, blocking both pathways. An increased incidence of bacterial infections has been observed in patients treated with monoclonal antibodies against IL-6R, particularly in those who are receiving concomitant corticosteroids. In this chapter, the mechanism of action and the incidence and types of infections reported in patients receiving IL-6 blocking agents are reviewed.

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Mechanism of Action and Expected Impact on Infection Risk

Interleukine-6 (IL-6) is a pleomorphic pro-inflammatory cytokine linked to immune regulation, acute phase response, and hematopoiesis [1, 2]. Its activity is expressed throughout the membrane-bound and the soluble IL-6 receptor (IL6-R). The membrane-bound form or "*classical*-signaling" pathway is mainly expressed in hepatocytes and hematopoietic cells, and it interacts with a second protein, gp130, resulting in a functional receptor complex that may trigger the downstream signaling cascade. The soluble form of IL-6R is involved in the "*trans*-signaling" pathway, and it is able to potentially activate all nucleated cells, as gp130 is present ubiquitously (see Fig. 10.1). Notably, the membrane-bound pathway is related to tissue regeneration and protects from bacterial infection, whereas the soluble receptor is linked to pro-inflammatory activity [3]. IL-6 dysregulation has been linked to several autoimmune disorders, such as rheumatoid arthritis (RA), vasculitis, and inflammatory bowel disease [2, 4].

To date, two agents targeting IL-6 and/or its receptor have been approved for different immune disorders: tocilizumab (TCZ) and siltuximab.

TCZ is a humanized IgG1 monoclonal antibody that inactivates both the membrane-bound and soluble forms of IL6-R. It is approved for RA, polyarticular or systemic juvenile idiopathic arthritis and, recently, for giant cell arteritis [1, 5]. Recently, the role of TCZ in both prevention and treatment of graft vs. host disease (GVHD) has been investigated [6, 7]. The drug can be administered through intravenous infusion or subcutaneous injection, and the duration of treatment depends on

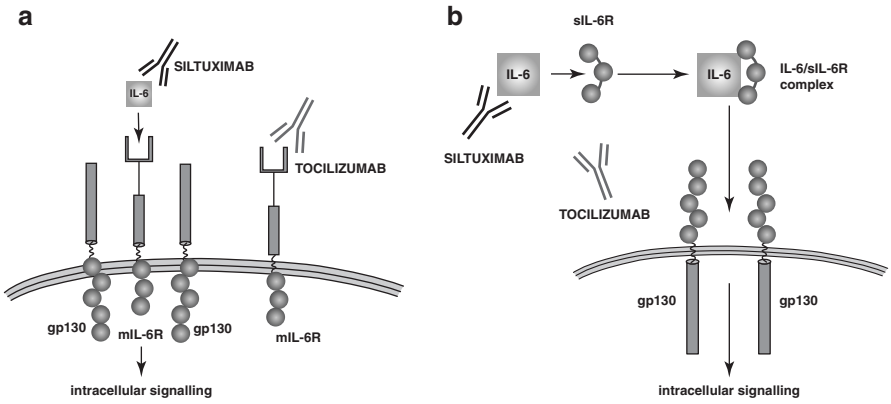

Fig. 10.1 Signaling pathways of IL-6 and activity of IL6-targeted agents. (**a**) *cis*-signaling expressed through the membrane-bound IL6-receptor (mIL-6R). Once IL-6 binds to mIL-6R it interacts with gp130, forming a receptor complex and triggering the intracellular signaling. (**b**) *trans*-signaling, IL6 interacts with the soluble form of the receptor (sIL-6R), produced by the cleavage of mIL-6R, resulting in a functional complex (IL-6/sIL-6R). This complex interacts with gp130, preceding the intracellular cascade. Tocilizumab interacts with both mIL-6R and sIL-6R, while siltuximab binds directly IL-6. The final effect of both drugs is the prevention of the downstream intracellular signaling

the patient's response. Of concern, the effects of TCZ cannot be reversed after administration, and at high serum concentrations, it has a terminal half-life of approximately 16 days. Although its half-life does not necessarily preclude its use, the impossibility of eliminating the drug may be problematic in patients more prone to sudden fluctuation of their disease.

Siltuximab consists of a human-murine IgG1 monoclonal antibody able to bind and inactivate circulating IL-6. It has been approved for the treatment of multicentric Castleman's disease [8]. In addition, different agents targeting IL-6 or its receptor are under clinical development, such as sirukumab and olokizumab for the treatment of RA. Recently, a novel agent called sarilumab has been approved from FDA for moderate to severe RA. Clazakizumab reached promising results in a double-blind, phase 2, randomized clinical trial in psoriatic arthritis patients [9]. In addition, a novel gp130 fusion protein called olamkicept that only binds the complex IL-6/soluble IL6R is under evaluation in a phase 2 trial in patients with active inflammatory bowel disease (ClinicalTrials.gov Identifier: NCT03235752).

Because of their activity, these agents show a prompt action in decreasing inflammatory markers, such as C-reactive protein. Indeed, their immunomodulatory effect may result in severe and potentially life-threatening bacterial infections characterized by significant discrepancy in both clinic and laboratory markers [10, 11]. Previous researchers have shown that IL-6 has a key role in supporting immunocompetent responses to all types of infections, especially bacterial [12].

Available Clinical Data

Most data about the infection risk associated with IL-6 inhibitors come from studies on patients treated with TCZ for rheumatoid arthritis (RA). In several randomized controlled trials (RCT), the occurrence of severe infections was generally assessed as a secondary outcome among safety issues (see Table 10.1). Severe infections were generally defined as events resulting in hospitalization or death. To note, in most studies, there was no predefined protocol for systematic search or surveillance for infectious complications. In addition, it is worth mentioning that the infection risk in RA is complex and likely multifactorial. High disease activity, multimorbidity, treatment/disease-related immunosuppression, and polypharmacy all likely contribute.

Data from RCTs including patients with moderate to severe RA show different infection incidence rates, varying from 1.53 (0.57–4.08) serious infections per 100 patient-years in naive patients up to 9.98 (4.99–19.96) in patients already treated with TNF inhibitors [19, 23]. The hypothesis is that cumulative and longer immunosuppression could lead to an increased risk of severe infection. Notably, the median age and the comorbidities of patients enrolled in RCT are usually lower than that of real-life cohorts.

Real-life studies exhibit even higher percentages. Indeed, an open-label real-life study conducted in Germany including 850 patients treated with TCZ for active rheumatoid arthritis found a rate of serious infection of 5.3%, with a rate of 4.4

Table 10.1 Principal studies evaluating the incidence rate of severe infections in patients treated with TCZ for autoimmune disorders

Author, study, year, reference	Study design	Indication for TCZ	Study duration	Patients (Total)	TCZ dose	Control group (N, type)	Prior treatment	N of SI/ arm	Incidence rate (95%CI)
Kremer (LITHE), 2011 [13]	Phase III RCT	RA	1 year	1196	4 mg/kg 8 mg/kg	393, placebo	MTX	12/399 14/398	3.7 (2.1–6.52) 4 (2.37–6.75)
Gabay (ADACTA), 2013 [14]	Phase IV RCT	RA	24 weeks	326	8 mg/kg	163, Adalimumab	MTX	6/163	6.52 (2.93–14.51)
Genovese (TOWARD), 2008 [15]	Phase III RCT	RA	24 weeks	1220	8 mg/kg	415, placebo	DMARD	22/805	5.9 (3.88–8.96)
Maini (CHARISMA), 2006 [16]	Phase II RCT	RA	20 weeks	359	2 mg/kg 8 mg/kg	49, MTX	MTX	4/53 3/50	19.87 (7.46–52.94) 15.79 (5.09–48.96)
Fleischmann LITHE, 2013 [17]	Phase III RCT	RA	2 years	1196	4 mg/kg 8 mg/kg	392, placebo-MTX	MTX	16/597 40/983	3.1 (1.9–5.06) 3 (2.2–4.09)
Smolen (OPTION), 2008 [18]	Phase III RCT	RA	24 weeks	623	4 mg/kg 8 mg/kg	204, placebo	MTX	3/214 6/205	3.05 (0.98–9.46) 6.05 (2.72–13.47)
Jones (AMBITION), 2010 [19]	Phase III RCT	RA	24 weeks	673	8 mg/kg	284, MTX 101, placebo	MTX-naive	4/288	1.53 (0.57–4.08)
Yazici (ROSE), 2012 [20]	Phase III RCT	RA	24 weeks	619	8 mg/kg	207, placebo	DMARD	10/412	7.87 (4.23–14.63)
Nishimoto (SAMURAI), 2007 [21]	Phase III RCT	RA	1 year	306	8 mg/kg	148, DMARDs	DMARD	12/158	7.64 (4.34–13.45)
Nishimoto (SATORI), 2009 [22]	Phase III RCT	RA	24 weeks	127	8 mg/kg	66, MTX	MTX	2/61	7.17 (1.79–28.68)
Emery (RADIATE), 2008 [23]	Phase III RCT	RA	24 weeks	499	4 mg/kg 8 mg/kg	160, placebo	TNFi	3/163 8/175	5.72 (1.84–17.74) 9.98 (4.99–19.96)
Burmester (TAMARA), 2011 [24]	Phase III OL study	RA	24 weeks	286	8 mg/kg	/	DMARD	9/286	6.74 (3.51–12.95)
Nishimoto (STREAM), 2009 [25]	OL	RA	5 years	143	8 mg/kg	/	DMARD	25/143	5.7 (3.85–8.44)

TCZ tocilizumab, *SI* severe infections, *CI* confidence interval, *DMARD* disease-modifying antirheumatic drug, *MTX* methotrexate, *OL* open label, *RCT* randomized controlled trial, *TNFi* tumor necrosis factor inhibitor

events per 100 patient-years over 52 weeks of follow-up [26]. An extremely large Japanese post-marketing surveillance cohort of patients treated with TCZ for the same indication reached nine events per 100 patient-years [27]. Finally, in a US cohort, the rate of severe infections requiring hospitalization attested up to 14.9 events per 100 patient-years [28]. As already stated, the higher median age and the higher rate of previous treatments with anti-TNF agents could account for the difference in infection incidence rates reported in RCTs and in observational studies.

Even the dose of TCZ administered seems to play a role in increasing the risk of infection. A phase III randomized controlled trial evaluating the clinical response of TCZ administered at different doses showed a risk of severe infections of 5.72 (1.84–17.74) with TCZ 4 mg/kg, but this risk was nearly doubled (9.98, 4.99–19.96) for the dosage of 8 mg/kg [23]. A meta-analysis conducted by Shiff et al. including eight different studies (of them, five phase III trials) exhibited a similar rate of serious infection in control group and TCZ 4 mg/Kg group, attesting both at 3.5 per 100 patient-years. In addition, serious infections increased at 4.9/100 patient-years if TCZ was administered at 8 mg/kg [29]. However, the authors found that older age, high body mass index, and previous administration of a TNF inhibitor were associated with infection development, regardless of the treatment group. This latter aspect has been confirmed in other larger studies evaluating patients previously exposed to anti-TNF agents [23, 30].

A systematic review published in 2015 compared the clinical impact of disease-modifying antirheumatic drugs (DMARDs) on infections development [31]. TCZ was associated with an incidence rate of serious infections of 5.45 per 100 patient-years, a risk even higher if compared to other immunomodulant agents such as rituximab (see Table 10.2).

A randomized, double-blind, phase III trial comparing sarilumab vs. adalimumab showed similar rates of infections (28.8% in sarilumab group vs. 27.7% in adalimumab group) and serious infections (1.1% in both groups) [32]. Recently, a large cohort study of 16074 patients receiving TCZ was propensity score-matched to a cohort of 33,109 patients treated with TNF inhibitors, focusing on the risk of serious infections [33]. The authors found that the risk of severe infections was similar between the two groups; however, TCZ was found to be associated with an increased risk of skin and soft tissue infections (HR 2.38, 95% CI 1.47–3.86) and serious infections including bacterial, viral, and opportunistic agents (HR 1.19, 95% CI 1.03–1.33) if compared to TNF-α inhibitors.

Although specific sites of infection were rarely reported in previous studies, severe infections consisted mainly in lower respiratory tract infections, followed by

Table 10.2 Rates of severe infections per 100 patient-years observed in different studies

Drug	Number of patients enrolled	Rates of severe infections (95%CI)
Abatacept	5953	3.04 (2.49–3.72)
Rituximab	2926	3.72 (2.99–4.62)
Tocilizumab	5547	5.45 (4.26–6.96)
Infliximab	4592	6.11 (5.24–7.12)
Etanercept	7141	4.06 (3.26–5.08)
Adalimumab	6570	5.04 (3.80–6.69)

urinary tract infections, cellulitis, and primary bloodstream infections that required hospital admission and systemic antibiotic therapy [23, 29].

Even though patients exposed to IL6-targeting agents may be at increased risk of opportunistic infections, few studies evaluated this aspect. The previously mentioned meta-analysis showed an absolute number of 22 opportunistic infections, with a rate of 0.23 events per 100 patient-years [29]. Fourteen of these infections were considered serious events. Of interest, eight cases were *Mycobacterium tuberculosis* reactivation, followed by *P. jirovecii* infection, cryptococcosis, and *Mycobacterium avium* infection. Similarly, a post-marketing study in Japan found a rate of pulmonary tuberculosis reactivation of 0.05%, similar to other anti-TNF-α agents [27]. However, the authors reported an increased risk of nontuberculous mycobacteria and *P. jirovecii* infections, accounting for 0.22% and 0.16%, respectively. Even varicella-zoster virus (VZV) reactivation during TCZ administration has been observed, but its incidence is comparable to other biological agents. A retrospective study from the USA showed an incidence of VZV reactivation of 4.3% during TCZ treatment, a rate consistently lower if compared with the occurrence of VZV reactivation during rituximab, reaching up to 19.4% [34]. However, absolute incidence rate per 100 patient-years was similar in both groups (2.15 TCZ vs. 2.27 rituximab). Little is known about hepatitis B virus (HBV) reactivation in patients treated with TCZ. Although data are restricted to case reports, mainly because HBc-positive patients were excluded from randomized trials, HBV reactivation is a possible event, usually with self-limited viremia and without clinical implications [35, 36]. A retrospective study of 152 patients treated with DMARDs (25 of them receiving TCZ) recorded an overall HBV reactivation of 4.6%, and the absence of anti-HBs was found to be a risk factor for reactivation [37]. These findings suggest to perform a microbiological work-up before starting a IL6 or a IL6-R-targeted agent, including screening for latent tuberculosis infection and serological status for HBV, in order to prevent reactivations [38, 39].

More recently, IL-6 inhibitors have been employed in mild to critically ill patients with COVID-19 diagnosis with controversial results in terms of overall mortality. To date, seven randomized controlled trials have been published including a total of 3204 patients treated with IL-6 inhibitors vs. 2982 receiving placebo and/or best available treatment [40, 41] (see Table 10.3). The overall rate of infection among the two groups was of 4.7% and 3.7% with a median follow-up duration of 28 days. No study had a predefined protocol for the active search of infection complications. It is worth mentioning that the RECOVERY study accounts for more than half of patients treated with TCZ in published RCTs. Patients enrolled in this study presented with a mild to moderate COVID-19; thus, they were generally at low risk of superinfection; indeed the infection rate was very low in both treatment and control arms [46]. Differently, in RCT studies focusing on patients with critical disease, the infection rates were higher in both treatment and control arms [44].

Real-life experiences drew a very different picture [47–50] (see Table 10.3). Reviewing four observational studies including a total of 257 patients treated with IL-6 inhibitors and 471 controls, the rates of infections were 42% vs. 19.3% with a

Table 10.3 Reported cases of infectious complications in patients treated with tocilizumab for COVID-19

Reference	Study type	Numbers of patients included in treatment and in control group	Setting (i.e., moderate severe or critical COVID-19)	Numbers of infections in treatment arm and in control group or risk estimation (i.e., RR, RD, etc.)	Type of infections reported in treatment arm (i.e., bacterial, fungal, viral, opportunistic etc.)	Follow-up duration (days)	Systematic search for superinfection
Stone, 2020 [42]	RCT, multicenter USA	161 vs. 82	Moderate disease	13 (8.1%) vs. 14 (17.1%) RR 0.47 [0.23–0.95]	Not reported	28 days	No
Salvarani, 2021 [43]	RCT, multicenter Italy	60 vs. 66	Mild disease	1 (0.6%) vs. 4 (6.1%) RR 0.26 [0.03–2.28]	Bacterial	30 days	No
Hermine, 2021 [40]	RCT, multicenter France	64 vs. 67	Mild to moderate disease	2 (1.2%) vs. 13 (19.4%) RR 0.16 [0.04–0.70]	Bacterial	28 days	No
Rosas, 2021 [44]	RCT, international	295 vs. 143	Critical disease	113 (38.3%) vs. 58 (40.5%) RR 0.95 [0.75–1.22]	112 bacterial, 1 fungal	28 days	No
Salama, 2020 [41]	RCT, international	249 vs. 128	Mild to moderate disease	19 (7.6) vs. 21 (16.4%) RR 0.91 [0.51–1.64]	Not reported	28 days	No
Gordon, 2021 [45]	RCT, international	353 vs. 402	Critical disease	1 vs. not reported	Bacterial	21 days	No
Recovery Collaborative Group, 2021 [46]	RCT, UK	2022 vs. 2094	Mild to moderate	3 vs. not reported	Bacterial	28 days	No
Somers, 2020 [47]	Observational controlled study, USA	78 vs. 76	Critical disease	42 (54%) vs. 20 (26%) p-value <0.001	Bacterial and fungal	28 days	No
Kimmig, 2021 [48]	Observational study, USA	54 vs. 57	Critical disease	29 (53.7%) vs. 16 (28.1%) p-value 0.029	26 bacterial, 3 fungal	Not reported	No
Falcone et al., 2021 [49]	Observational study, Italy	51 vs. 264	Mild to severe disease	20 (29%) vs. 49 (18.5%) OR 5.09 [2.2–11.8]	Bacterial and fungal	30 days	No
Pettit, 2020 [50]	Observational study, USA	74 vs. 74	Moderate to severe disease	17 (23%) vs. 6 (8%) p-value 0.013	1 bacterial, 2 fungal	58 days	No

statistically significant association with the exposure to IL-6 inhibitors in all studies, even after adjustment for confounding factors [49].

Most infections consisted of bloodstream infections due to bacterial agents, with few cases of candidemia, only one opportunistic infection was reported in a patient with CMV syndrome and high levels of CMV DNA on blood sample.

Conclusions and Suggested Prevention Strategies

Current evidence on the infection risk associated with the use of IL-6- or IL-6R-targeted agents consists mostly of studies including patients treated with tocilizumab for a chronic autoimmune condition such as RA. On the other hand, during the COVID-19 pandemic, a huge amount of data on these agents has been obtained from its use in hospitalized patients for COVID-19. The incidence of severe (secondary) infections in observational studies was higher than that observed in randomized controlled trials for both conditions. For patients with RA, such incidence seems to be similar or slightly higher than that associated with the use of other DMARDs, in particular anti-TNF-α agents. However, a systematic active search or surveillance screening for infectious disease during or after tocilizumab treatment has not yet been performed. The concomitant or prior use of immunosuppressive drugs and the severity of the underlying condition are other confounding factors hampering a real estimation of the infection risk in patients treated with IL-6 inhibitors.

In general, it seems advisable to implement the prevention strategies suggested for patients receiving anti-TNF-α therapy, including screening for latent tuberculosis and chronic HBV infection (followed by appropriate prophylaxis or therapy if needed). However, the performance of these assays was challenging during COVID-19 surges. Age-appropriate inactivated vaccination (i.e., trivalent inactivated influenza, pneumococcal or Hib vaccines) has been also suggested in patients with chronic diseases treated with IL-6 inhibitors.

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