Interleukin-1 Targeted Agents

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Introduction

Interleukin-1 (IL-1) was initially discovered in the mid-1980s under various names such as leukocyte endogenous mediator, endogenous pyrogen, and osteoclast-activating factor [1], indicating multiple biological functions attributed to this cytokine. In the past two decades, several other IL-1 members were identified. Currently, 11 family members of IL-1 cytokines and 10 IL-1 receptors (IL-R) have been identified [2]. This review will focus mainly on IL-1α and IL-1β since these represent the best studied cytokines [3].

IL-1α and IL-1β are two cytokines that have similar biological activities [1]. Once they bind to their receptors, they trigger a cascade of inflammatory mediators such as chemokine and cytokine production, neutrophil activation, and the appearance of fever [2]. IL-1α is found in epithelial cells and mucosal membranes throughout the body [4]. IL-1β is predominantly found in innate immune cells such as monocytes and tissue macrophages [1, 5]. IL-1β is secreted systemically, while IL-1α is activated locally in the cell membrane [1]. In the setting of inflammation, IL-1α migrates toward the cell surface activating adjacent cells by binding with IL-1R [6, 7]. During ischemia and cell death, IL-1α and its precursor are released from cells inducing sterile inflammation of neutrophilic predominance [8–10]. This generates tissue destruction at the site of injury [4]. Once IL-1α binds to its receptors on resident macrophages, IL-1β precursor is synthesized by them. The IL-1β precursor is then activated by the pro-inflammatory protease caspase-1 [4, 5]. Activation of IL-1β is stimulated by several additional factors including microbial

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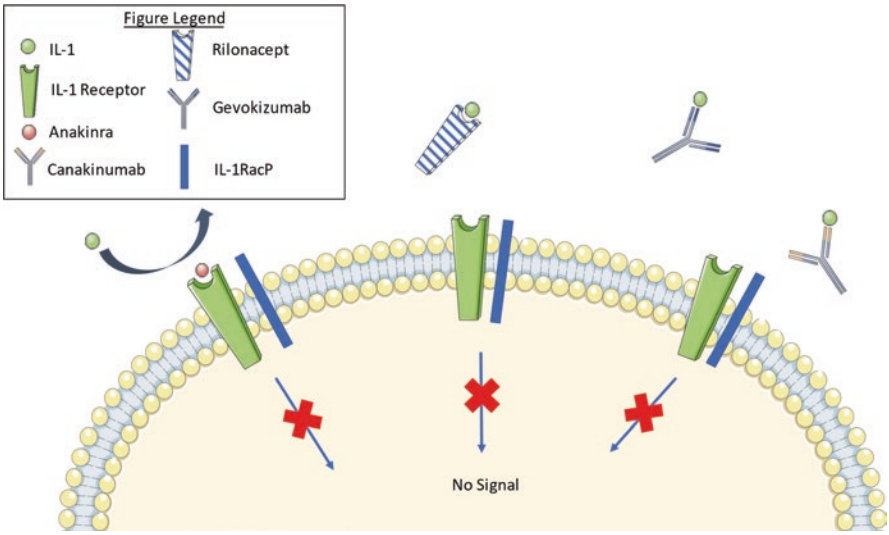

Fig. 9.1 Structure and function of each IL-1-targeted agent and its mechanism of action on IL-1 and IL-1R

products, tumor necrosis factor (TNF), and IL-1β itself [4]. The active IL-1β binds to endothelial receptors, promoting monocyte migration and opening of endothelial intracellular junctions resulting in capillary leak [4]. IL-1Ra is an inhibitory cytokine of the IL-1 family as it binds to IL-1R but does not induce an intracellular proinflammatory response [11].

Inhibition of the IL-1 pathway (Fig. 9.1) has been the target of treatments for several inflammatory conditions such as rheumatoid arthritis (RA) [12], juvenile idiopathic arthritis (JIA) [13, 14], adult-onset Still's disease (AOSD) [13], autoinflammatory syndromes including cryopyrin-associated periodic fever syndrome (CAPS) [15], TNF-associated periodic syndrome (TRAPS) [16], familial Mediterranean fever (FMF) [15], and mevalonate kinase deficiency (hyper-IgD syndrome) [15, 17]. IL-1 agents are also used off label for the treatment of gout [18–21], refractory pericarditis [22], Bechet's disease [23, 24], pyoderma gangrenosum [25], and neutrophilic dermatosis (Sweet's syndrome) [26].

Available IL-1-Targeting Agents

Anakinra is a recombinant IL-1Ra approved by the American Food and Drug administration (FDA) in 2001 [4]. It is similar to the structure of the natural IL-1Ra but differs by an extra methionine residue manufactured from *Escherichia coli* [3]. Anakinra is approved for treatment of RA, JIA, AOSD, and CAPS [2, 3]. Canakinumab is a fully human IL-1β antagonist that blocks IL-1β's interaction with IL-1R. It is approved for treatment of CAPS, TRAPS, mevalonate kinase deficiency,

and AOSD [2]. Rilonacept is a soluble decoy receptor that binds to IL-1 thereby inhibiting the binding of IL-1 to IL-1R. Rilonacept is currently approved for CAPS [2]. Similar to canakinumab, gevokizumab is a potent humanized IL-1β antagonist that has not yet been FDA approved [2, 3].

Infectious Complications of Interleukin-1 (IL-1)-Targeted Agents

Anakinra

Tables 9.1 and 9.2 summarize the risk of infection reported in clinical trials and the described infections for each drug, respectively. A meta-analysis of seven randomized controlled trials (RCTs) and three extension studies demonstrated no increased risk of infections when anakinra was compared to placebo, with a pooled relative

Table 9.1 Summary of risk of infections associated with IL-1-targeted agents

Reference (year)	Study design, No. of patients indication	Agent	Study duration	Risk of infections
Nikfar et al. (2018) [12]	Meta-analysis of 7 RCTs and 3 extension studies (4706 patients); RA	Anakinra	24–52 weeks	No difference of infectious risk between anakinra and placebo (Pooled RR 1.06; CI 0.94–1.20)
Cohen et al. (2002) [27]	Placebo-controlled RCT; 419 patients; RA	Anakinra	24 weeks	Similar risk of infections: 22% in placebo vs. 24% in anakinra. No reported serious infections
Nuki et al. (2002) [28]	Placebo-controlled RCT; 472 patients; RA	Anakinra	76 weeks	No risk of serious infection associated with anakinra, 0.91–1.1 events per 100 patient-years for anakinra vs. 1.4 events per 100 patient-years for placebo
Fleishmann et al. (2003) [29]	Placebo-controlled RCT; 1,414 patients; RA	Anakinra	26 weeks	Serious infections for anakinra 2.1% vs. 0.4% for placebo
Fleishmann et al. (2006) [30]	6 months placebo-controlled RCT followed by an open-label cohort; 1346 patients; RA	Anakinra	3 years	Increased incidence of serious infections with anakinra, EAE 5.37 for anakinra vs. 1.65 for placebo per 100 patient-years; three opportunistic infections in the anakinra group (nontuberculous mycobacteria, histoplasmosis, and esophageal candidiasis)
Schiff et al. (2004) [31]	Placebo-controlled RCT; 1,414 patients; RA	Anakinra	26 weeks	Slight increase in risk of serious infections in high-risk patients (at least one comorbidity) 2.5% for anakinra vs. 1.1% for placebo

(continued)

Table 9.1 (continued)

Reference (year)	Study design, No. of patients indication	Agent	Study duration	Risk of infections
Ridker et al. (2017) [32]	Placebo-controlled RCT; 10,061 patients; acute myocardial infarction	Canakinumab	48 months	Increased incidence of fatal infection or sepsis, 0.31 events per 100 patients-years for canakinumab vs. 0.18 events per 100 patient-years for placebo
Schlesinger et al. (2011) [18]	Double-blind controlled trial comparing canakinumab vs. colchicine; 432 patients; gout	Canakinumab	24 weeks	Increased risk of infection 18% for canakinumab vs. 12% for colchicine. 6 serious infections (pneumonia, sepsis, gangrene, erysipelas, tonsilitis, ear infection)
Schlesinger et al. (2012) [19]	Double-blind controlled trial comparing canakinumab to triamcinolone; 456 patients; gout	Canakinumab	24 weeks	Increased incidence of infection 20% for canakinumab vs. 12% for triamcinolone. Four serious infections (jaw abscess, arm abscess, pneumonia, and gastroenteritis)
Ruperto et al. (2012) [33]	Placebo-controlled RCT followed by an open-label phase; 177 patients; sJIA	Canakinumab	4 weeks (RCT) 2 years (open label)	Similar rates of infection in RCT; one varicella case for canakinumab and one gastroenteritis for placebo. 4% rates of infections in each group in the open-label phase
Ruperto et al. (2018) [34]	5-year long-term extension phase of previous study; 75 patients; sJIA	Canakinumab	5 years	Incidence of serious infection 10.28 per 100 patients-years, four notable infections (toxoplasmosis, CMV infection, *Salmonella* gastroenteritis, and adenovirus infection)
De Benedetti (2018) [15]	Placebo-controlled RCT (16 weeks) followed by secondary randomization (40 weeks); 63 crFMF, 72 MKD, 46 TRAPS patients	Canakinumab	40 weeks	Ten serious infections in the treatment group vs. 2 in placebo group; 7.4 events per 100 patient-years in open-label phase
Sundy et al. (2014) [35]	Placebo-controlled RCT; 1,315 patients; gout	Rilonacept	20 weeks	Similar incidence of serious infections 0.5% for rilonacept vs. 0.9% for placebo
Klein et al. (2020) [22]	Placebo-controlled RCT; 86 patients; recurrent pericarditis	Rilonacept	24 weeks	URTI (23%) for rilonacept vs. 0% for placebo; all infections were reported as mild or moderate; no reported serious infections

Table 9.1 (continued)

Reference (year)	Study design, No. of patients indication	Agent	Study duration	Risk of infections
Hoffman et al. (2008) [36]	Placebo-controlled RCT; 44 patients; CAPS	Rilonacept	24 weeks	Incidence of infection 48% for rilonacept vs. 17% for placebo, mild to moderate URTI being most common (26%) for rilonacept; one case of severe bronchitis reported
Hoffman et al. (2012) [37]	Open-label trial; CAPS	Rilonacept	72 weeks	Two severe infections (pneumococcal meningitis and tooth abscess), one death from pneumococcal meningitis
Ilowite et al. (2014) [38]	Placebo-controlled RCT followed by open-label phase; 71 patients; sJIA	Rilonacept	24 weeks to 2 years	Similar rates of infections between rilonacept and placebo (16% and 20% respectively). Four serious infections for rilonacept (varicella, viral URTI, *Salmonella* gastroenteritis, streptococcal pharyngitis)
Tugal-Tutkun et al. (2018) [39]	Placebo-controlled RCT followed by open-label extension phase; 83 patients; Bechet's uveitis	Gevokizumab	28 to 420 days	Similar risk of infections between gevokizumab and placebo. No opportunistic infections reported

EAE exposure-adjusted event, *CAPS* cryopyrin-associated periodic syndrome, *RA* rheumatoid arthritis, *sJIA* systemic juvenile idiopathic arthritis, *URTI* upper respiratory tract infection

Table 9.2 Summary of described infections associated with IL-1-targeted agents

Agent	Bacterial and viral infections	Fungal and parasitic infections
Anakinra	*Common infections* URTI [40], pneumonia [29, 30], cellulitis [29, 30], UTI [40] *Rare infections* Pulmonary TB [41], TB myositis [42], NTM infection [30], varicella [43], CMV hepatitis [44]	Esophageal candidiasis [30], histoplasmosis [30], visceral leishmaniasis [43]
Canakinumab	*Common infections* Pneumonia [18, 32, 34], cellulitis [32], UTI [32], gastroenteritis [34] *Rare infections* Erysipelas [18], gangrene [18], sepsis [18], tonsilitis [18], subcutaneous abscess [34], streptococcal tonsilitis [34], salmonella gastroenteritis [34], CMV [34], varicella [34], adenovirus [34], TB [32]	Toxoplasmosis [34]

(continued)

Table 9.2 (continued)

Agent	Bacterial and viral infections	Fungal and parasitic infections
Rilonacept	*Common infections* URTI [22, 37] *Rare infections* Severe bronchitis [36], Pneumococcal meningitis [37], tooth abscess [37], Streptococcal pharyngitis [38], Salmonella gastroenteritis [38], Varicella [38]	None reported
Gevokizumab	*Common infections* Nasopharyngitis [39], URTI [39] *Rare infections* None reported	None reported

CMV cytomegalovirus, *NTM* nontuberculous mycobacteria, *TB* tuberculosis, *URTI* upper respiratory tract infection, *UTI* urinary tract infection

risk (RR) of 1.06 (CI 0.94–1.20) [12]. Multiple placebo-controlled RCTs have evaluated long-term safety of anakinra in RA [27–30]. Cohen et al. evaluated the efficacy and safety of anakinra for 24 weeks and demonstrated no serious infections in both groups assigned to methotrexate (MTX) and placebo vs. MTX and anakinra [27]. Similarly, Nuki et al. demonstrated no increased risk of infection with anakinra compared to placebo on evaluation of almost 500 patients with RA for a total period of 76 weeks, with an incidence rate (IR) of 0.91, 1.0, 1.1, and 1.4 events per 100 patient-years for the 30 mg, 75 mg, and 150 mg of anakinra and the placebo groups, respectively [28]. Schiff et al. conducted a post hoc analysis of an RCT, comparing safety of anakinra versus placebo in patients with RA and coexisting comorbidities [31]. Comorbidities were defined as having had at least one cardiovascular, pulmonary, or central nervous system events; infection; renal insufficiency; diabetes; or malignancy [31]. The incidence of serious infections was similar between high-risk patients receiving anakinra (2.5%), compared to all the patients receiving anakinra in the study (2.1%) [31].

Another meta-analysis included 74 RCTs evaluating the safety of multiple interleukin (IL) inhibitors, of which 8 RCTs evaluated anakinra [45]. After stratifying risk for serious infections for each IL inhibitor, an increased odd of serious infection was associated with anakinra compared to placebo (odds ratio 2.67; CI 1.03–6.90). Fleishmann et al. evaluated the safety of anakinra compared to placebo in an RCT, followed by an open-label extension trial for 3 years [29, 30]. A total of 1414 patients were recruited. Serious infections (defined as infections requiring hospitalization and the use of intravenous antibiotics) were observed in 23 patients in the anakinra group (2.1%) vs. only one patient in the placebo group (0.4%); $P = 0.068$ [29]. Pneumonia was the most common serious infection followed by cellulitis, in ten patients and three patients, respectively [29]. Five patients had underlying chronic pulmonary disease and three patients had a history of prior pneumonia [29]. Additionally, out of three patients with cellulitis, two had underlying diabetes and one had a toe ulcer at baseline. Of note, none of these serious infections were fatal.

However, 6 out of 23 patients permanently discontinued anakinra due to infection [29]. Organisms isolated in pneumonia and

cellulitis cases were *Streptococcus pneumoniae* and *Staphylococcus aureus*, respectively. None of the patients developed tuberculosis (TB) or opportunistic infections [29]. The 3-year open-label extension trial that included 1346 patients reported a higher incidence of serious infections with anakinra compared to placebo, with adjusted event rates of 5.37 vs. 1.65 per 100 patient-years, respectively [30]. Pneumonia was again the most common infection (1.50 events per 100 patient-years), followed by cellulitis (1.20 events per 100 patient-years). Rates of infections were significantly lower in patients who did not receive corticosteroids at baseline (2.87 events per 100 patient-years), with an incidence rate of pneumonia of 0.96 events per 100 patient-years and of cellulitis of 0.21 events per 100 patient-years [30]. Overall, the event rate of serious infections was consistently low throughout the entire treatment period [30].

Many of the autoinflammatory conditions for which anti-IL-1 therapy has been studied affect children [3].

In an observational study of 18 patients, the use of anakinra in neonatal-onset multisystem inflammatory disease (NOMID) was assessed. Fifteen patients had upper respiratory tract infections (URTI), and two patients had urinary tract infections (UTI). None of the infections required drug discontinuation [40]. A similar cohort evaluated the use of anakinra for 5 years and found similar results, with URTI being the most common infection [46]. The only two serious infections reported were wound infections, and none of these required drug discontinuation [46].

Although many studies demonstrated no increased risk of infection, some studies did find an increased rate of infection in patients treated with anakinra. Nevertheless, the majority of infections reported were not serious, suggesting an overall good safety profile of anakinra [31].

Canakinumab

Two RCTs assessed the safety and efficacy of canakinumab in gout [18, 19]. Schlesinger et al. evaluated the efficacy and safety of canakinumab vs. daily colchicine in 432 patients [18]. Overall, the incidence of infections was slightly increased with canakinumab use compared to colchicine (18% vs. 12%, respectively) [18]. Additionally, six serious infections (pneumonia, erysipelas, gangrene, sepsis, tonsilitis, and ear infection) were reported in canakinumab vs. none reported in the colchicine group. Similarly, a 12-week RCT followed by a 12-week double blind extension study, β-RELIEVED and β-RELIEVED-II, denoted increased risk of infections in patients receiving canakinumab compared to placebo (20% vs. 12%, respectively), mostly reported as mild infections [19]. Four serious infections occurred in the canakinumab group (1.8%)—jaw abscess, arm abscess, pneumonia, and gastroenteritis—all requiring hospitalization, and three requiring antibiotic therapy [19].

More recently, the CANTOS trial, a placebo-controlled RCT that recruited more than 10,000 patients, evaluated canakinumab use in the treatment of atherosclerosis. In contrast to other trials studying biologic therapies, CANTOS provided the opportunity to observe the risk of infections in patients who have no prior or current history of autoimmune disease and/or receipt of immunosuppression [32]. Infection rates of canakinumab vs. placebo were similar, 3.14 vs. 2.86 events per 100 patient-years, respectively, ($P = 0.14$) [32]. However, fatal infections or sepsis were higher in the canakinumab group vs. placebo, with an IR of 0.31 vs. 0.18 per 100 patient-years, respectively ($P = 0.02$) [32]. Individuals who had fatal infections were more likely to be older and have diabetes [32].

In the pediatric age group, a canakinumab placebo-controlled RCT of sJIA followed by an open-label extension phase [33, 34] demonstrated no differences in the incidence of infections at 29 days [33]. Similarly, serious infections were similar between the two groups in the open-label phase, with 4% in each group [33]. Patients from this study were able to enter an open-label long-term extension phase for 5 years [34]. Serious infections occurred at an incidence rate (IR) of 10.28 per 100 patient-years. The most common infection was gastroenteritis (1.05 per 100 patient-years), followed by pneumonia (0.84 per 100 patient-years) [34]. Other infections included varicella, septic shock, subcutaneous abscess, and streptococcal tonsilitis, all with equivalent rates of 0.42 per 1000 patient-years [34]. In autoinflammatory diseases, a three-part double-blind, placebo-controlled, randomized withdrawal study of patients ($n = 35$) with CAPS demonstrated an increased risk of infection in patients receiving canakinumab compared to placebo (12 vs. 9 patients; $P = 0.03$) [47].

Rilonacept

Rilonacept has been studied for the treatment of gout, pericarditis, and autoinflammatory disorders.

In the RESURGE study, a multicenter placebo-controlled trial that evaluated 1315 patients with gout for a period of 20 weeks, the incidence of serious infections was similar between rilonacept and placebo groups, 0.5% and 0.9%, respectively [35].

Recently, the RHAPSODY trial recruited 86 patients with recurrent pericarditis in a placebo-controlled RCT [22]. Rilonacept demonstrated a significantly lower recurrence of pericarditis. Infections were more frequent in the rilonacept group (23%) compared to placebo (0%). However, all infections were mild to moderate URTI, which did not require drug discontinuation [22].

In autoinflammatory conditions, Hoffman et al. conducted a placebo-controlled RCT on 44 patients with CAPS [36]. Overall, the incidence of infections was more frequent in the rilonacept arm compared to placebo (48% vs. 17%, respectively) with URTI being the most common infection, reported in 26% for rilonacept and 4% for placebo. One case of severe bronchitis was reported with rilonacept, but

there have been no reports of opportunistic infections associated with this agent [36]. In addition to the 44 patients recruited in the Hoffman et al. RCT, an additional 57 patients entered the open-label phase (101 patients total) [37]. Two severe infections (pneumococcal meningitis and tooth abscess) were reported in the open-label phase [37]. Additionally, one death from pneumococcal meningitis was reported in a 71-year-old female patient with a history of recurrent skin infections [37]. The investigator deemed this infection to be unrelated to rilonacept therapy [37]. A placebo-controlled RCT of sJIA patients demonstrated similar rates of infections between rilonacept and placebo (46% and 61%, respectively) [38]. Four serious infections were reported in the rilonacept group (varicella, viral URTI, Salmonella gastroenteritis, streptococcal pharyngitis) [38].

Gevokizumab

Given that this monoclonal antibody is not yet approved, there is limited data of its safety and risk of infections. Cavelti-Weder et al. evaluated the efficacy and safety of gevokizumab in patients with type 2 diabetes in a dose-escalation RCT [48]. Gevokizumab was administered either as a single dose intravenously (0.01–3.0 mg/kg) or as single or multiple subcutaneous doses (0.03–0.3 mg/kg). No serious infectious adverse events were observed at any dose of gevokizumab [48]. More recently, Tugal-Tutkun et al. performed a placebo-controlled RCT followed by an open-label extension phase that evaluated the use of gevokizumab in Bechet's uveitis [39]. This study evaluated 83 patients for a total duration of 420 days. Infections were similar between placebo and gevokizumab (46% vs. 51%, respectively); most common infections were nasopharyngitis and URTI [39]. Positive interferon-gamma released assay (IGRA) was reported in two patients in the gevokizumab group. Both patients received prophylactic TB therapy with either isoniazid or rifampin, with no reported cases of active TB [39].

Tuberculosis

There is scarce and weak evidence regarding the risk of TB with anakinra use. Two cases of pulmonary TB and TB pyomyositis have been reported in association with combined anakinra and corticosteroid use for treatment of RA [41, 42]. Additionally, data from a Canadian RA registry that included over 110,000 patients showed no statistically significant increased risk of TB in patients receiving anakinra, with an adjusted rate ratio (ARR) 1.3 events per 1000 patient-years (CI 0.8–2.1) [49].

Only six cases of TB were confirmed in individuals treated with canakinumab, all reported in the CANTOS trial. The same rate of TB was reported in both arm of the trial (0.06% each), five of those cases occurred in India and one case in Taiwan [32]. It is important to recognize that most RCTs evaluating IL-1-targeted therapies to date have taken place in low TB prevalence areas [3].

Opportunistic Infections

Opportunistic infections have only been reported in four patients with RA receiving anakinra, one case of nontuberculous mycobacteria infection in a patient receiving concomitant prednisone and MTX, one case of esophageal candidiasis in a patient with cirrhosis and on concomitant prednisone, and one case of histoplasmosis [30]. Additionally, one case of CMV hepatitis has been reported in a patient with JIA treated with anakinra [44]. In an observational cohort of 35 patients with systemic juvenile idiopathic arthritis (sJIA) and AOSD, one case of visceral leishmaniasis and two cases of varicella were identified [43]. Visceral leishmaniasis occurred 6 months after anakinra therapy in a child with sJIA. Of note, the child lived in an endemic area, in France, prior to starting therapy [43].

Four cases of opportunistic infections were identified with canakinumab use for sJIA including toxoplasmosis, CMV infection, Salmonella gastroenteritis, and adenovirus infection [34].

Conclusions

IL-1 inhibition has emerged as an important therapy for many patient groups over the last two decades. These biologic agents have been demonstrated to be generally safe, and although there may be an increased risk of infection, when infections do occur, these appear to be mostly mild to moderate in severity with the most common infections being URTIs, pneumonia, and cellulitis. The risk of severe infections associated with anti-IL-1 therapy may be increased in older patients with comorbidities, particularly with canakinumab, but more data is needed. Rare cases of TB and other opportunistic infections have been reported in association with IL-1 therapy, but the exact contribution of the IL-1 therapy to the development of these infections remains unclear.

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