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Cytokine 143 (2021) 155544

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

# Perspectives on anti-IL-1 inhibitors as potential therapeutic interventions for severe COVID-19

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ARTICLE INFO

*Keywords:*
COVID-19
SARS-CoV-2
Cytokine release syndrome
Interleukin-1 blockade
Anakinra

ABSTRACT

The overproduction of proinflammatory cytokines, resulting in what has been described as a cytokine storm or cytokine release syndrome (CRS), may be the key factor in the pathology of severe coronavirus disease 2019 (COVID-19) and is also a crucial cause of death from COVID-19. With the purpose of finding effective and low-toxicity drugs to mitigate CRS, IL-1 blockade agents, which are one of the safest ways to stop this overwhelming innate immune response, are already available in several preliminary reports or are under observational trials and may offer an important treatment option in hyperinflammatory COVID-19. In this review, we described the key information in both case reports and clinical studies on the potential beneficial features of IL-1 inhibitors in COVID-19 patients.

## 1. Introduction

Coronavirus disease 2019 (COVID-19), a global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been confirmed to infect ~91.8 million people on all continents, leading to ~1.99 million deaths worldwide (updated on January16, 2021), with the number of new cases continuing to increase [1,2]. The clinical symptoms are wide-ranging and include mild fever, cough, rhinorrhea, sneezing, sore throat, fatigue, anorexia, diarrhea, myalgia and pneumonia. COVID-19 deaths are primarily caused by acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS), a state of unregulated systemic hyperinflammation leading to rapidly progressive multisystem organ failure [3]. Immunomodulators or selective cytokine blockade agents have been suggested to abrogate the dysfunctional immune response in hyperinflammatory COVID-19 and are currently being investigated in clinical trials [4,5]. These molecules target an important immunecheckpoint or an upstream cytokine. Monoclonal antibodies or inhibitors targeting the IL-1 receptor, as a master cytokine of local and systemic inflammation, can inhibit proinflammatory molecules and influence the activation of the innate immune response [6]. The three drugs currently available either block IL-1 binding to the IL-1 receptor (anakinra) or bind directly to IL-1 (rilonacept and canakinumab) in US Food and Drug Administration (FDA)-approved biologic therapies [7]. Current case reports and registered trials of IL-1-targeting agents using either anakinra or canakinumab at various doses come with a recommendation for the clinical improvement of hyperinflammatory COVID-19. This review aims to summarize the available and latest research perspectives that support the use of anti-IL-1 drugs as potential therapeutic interventions for severe COVID-19.

## 2. Anakinra – Targeting bothIL-1 alpha (α) and IL-1 beta (β) in COVID-19

As an immunosuppressive drug, anakinra is a 17-kDa recombinant nonglycosylated homolog of the human IL-1 receptor antagonist with a short half-life of approximately 3–4 h and a good safety profile and has been approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndrome by the US FDA and the European Medicines Agency (EMEA) [8,9]. Anakinra, unlike rilonacept and canakinumab, competitively inhibits the binding of IL-1 alpha (α) and IL-1 beta (β) to the IL-1 receptor [10]. Anakinra has been used in several preliminary reports in patients with severe COVID-19 and has shown a significant survival benefit in patients with hyperinflammation without

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https://doi.org/10.1016/j.cyto.2021.155544
Received 2 December 2020; Received in revised form 16 January 2021; Accepted 12 April 2021
Available online 17 April 2021
1043-4666/© 2021 Published by Elsevier Ltd.

increased adverse events.

### 2.1. Case reports

Several case reports of COVID-19 patients treated with anakinra have been published; their main characteristics are summarized in Table1.

The first report about COVID-19 treated with anakinra dated back to February 28, 2020 [11] and described a critical case of a 50-year-old man with COVID-19 who was effectively treated with anakinra. The use of anakinra was started with the following dosage schedule: 200 mg intravenously followed by 100 mg every 6 h subcutaneously. This first report suggested that in the cytokine storm occurring during severe COVID-19, anakinra may represent a safe and promising strategy to reduce inflammation, preventing multiorgan dysfunction, and an appropriate tailored treatment strategy is crucial. Franzetti et al. [12] reported the first successful treatment case with anakinra and remdesivir in a 57-year-old man with severe COVID-19 on March 10, 2020. The dosage was 100 mg every 6 h subcutaneously for seven days.This case highlighted the high tolerability and interesting immunomodulatory profile of anakinra in the setting of severe COVID-19 associated with remdesivir therapy. González-García et al. [13] reported a case of severe COVID-19-associated pneumonia in a nonsmoking 47-year-old man who was successfully treated with subcutaneous anakinra alone, with no safety problems. Anakinra was initiated at 100 mg every 6 h subcutaneously. On day 11, anakinra was reduced to 100 mg every 8 h until completing a total duration of treatment of 14 days. Finally, on day 19, the patient was discharged with no need for oxygen supplementation.

Recently, Nemchand et al. [14] presented a case of a 50-year-old man with cytokine storm and acute respiratory distress syndrome (ARDS) as a result of COVID-19 who commenced a 7-day course of intravenous anakinra (150 mg two times per day). After administration of anakinra, there was a significant reduction in the cytokine storm evidenced by reductions in ferritin, fever and white cell count and his oxygen requirement. This report suggested that anakinra may have a positive effect on the proinflammatory state that is associated with cytokine storms in COVID-19 infection.

The first documented case of COVID-19-related fulminant myocarditis successfully treated with anakinra and dexamethasone wasrecently reported by Trpkov et al. [15]. In this case, a 62-year-old female with COVID-19 developed acute respiratory failure, and cardiogenic shock received treatment with recombinant anakinra intravenously at a dose of 100 mg twice daily for 12 days and dexamethasone, resulting in a rapid reduction in serum inflammatory markers and a marked recovery in CMR-based markers of inflammation and contractile dysfunction. The patient was subsequently discharged home. The significant clinical improvement observed in this patient provided support for the recent anakinra treatment of COVID-19-related respiratory failure.

In the first report of a hematology case, Day et al. [16] provided further evidence of the utility of this agent in the clinical context described and demonstrated that anakinra was safe in hematology patients and resulted in a clinical improvement in three patients with acute leukemia and confirmed or suspected COVID-19 pneumonia with a life-threatening hyperinflammatory syndrome. One acute myeloid leukemia (AML) case was started on subcutaneous anakinra at a dose of 100 mg three times a day (TDS), dexamethasone and IV immunoglobulin (IVIg), and the patient was discharged 35 days after commencing chemotherapy. The second AML case was started on subcutaneous anakinra 100 mg TDS, dexamethasone and IVIg. After seven days in the ICU, he was discharged back to the ward, where anakinra and steroids were progressively reduced. In the third case, anakinra was started at 200 mg intravenously twice a day. Ten days after starting anakinra, the patient defervesced, and his oxygen requirements were sustainably reduced. Anakinra was weaned, and the clinical picture continued to improve on the ward before discharge 31 days after admission.

Clark et al. [17] presented the beneficial effects of intravenous anakinra from an analysis of four immunosuppressed patients with severe COVID-19 and evidence of cytokine storm. The four patients were treated with an anakinra dose of 200 mg once a day intravenously, with subsequent clinical improvement in the patients, including reductions in ventilatory and inotropic support and improved biochemical findings, with rapid improvements in inflammatory markers. This case series showed the expected tendency for safety in using intravenous anakinra, which played a beneficial role both clinically and biochemically in patients with concomitant bacterial infections and late-stage COVID-19.

In view of the short half-life of anakinra (3 h), intravenous drugs were typically administered every 6 h. Pontali et al. [18] reported experience with the early use of high intravenous (IV) doses of anakinra in 5 patients with severe/moderate COVID-19 with pulmonary involvement. All 5 patients experienced rapid resolution of systemic inflammation and remarkable improvement in respiratory parameters, with reduction in the oxygen support requirement and early amelioration of chest computed tomography scan abnormalities before discharge in 3 patients. All patients were discharged 6 to 13 days after the start of anakinra. No secondary infections or other adverse events were observed.

In another case series, Aouba et al. [19] reported using anakinra in 9 patients with moderate to severe COVID-19. Anakinra was subcutaneously administered at designated doses (100 mg/12 h from day 1 to day 3, 100 mg/24 h from day 4 to day10). Among the nine patients, a 47-year-old woman developed acute respiratory failure following the first administration of anakinra, resulting in a premature stop. The rest of the patients all showed good clinical and biological outcomes. C-reactive protein (CRP) levels were restored to within the normal range in 5/8 patients, and a controlled chest CT scan showed that the extension of lesions had stopped in all patients. In this study, it was concluded that the use of anakinra was safe and feasible.

Dimopoulos et al. [20] reported the treatment of eight severe COVID-19 patients who were diagnosed with secondary hemophagocytic lymphohistiocytosis (sHLH) with anakinra. Seven of the eight patients received anakinra at 200 mg TDS IV for 7 days. The last one was treated with an anakinra dose of 300 mg once daily intravenously for 4 days, followed by 100 mg once daily. After anakinra administration termination, a reduction in the need for vasopressors and significantly improved respiratory function were observed in all patients. This study supported the concept that anakinra treatment may improve the respiratory function of severe COVID-19 patients who have sHLH.

A brief case series that focused on the use of anakinra to prevent mechanical ventilation in eleven severe COVID-19 patients featuring cytokine storms and acute hypoxic respiratory failure (AHRF) was reported by Navarro-Millán et al. [21]. Subcutaneous anakinra was initiated at 100 mg every 6 h and was gradually tapered off completely after a maximum of 19 days. Seven of these patients who initiated anakinra36 hours after the onset of AHRF did not require mechanical ventilation, and all were discharged from the hospital. Four patients who started anakinra more than 4 days after the onset of AHRF required mechanical ventilation. Of those, 3 patients were extubated, and 1 died. These dataindicated that anakinra played a crucial role in the beneficial outcomes in COVID-19 patients with evidence of cytokine storms when initiated early after AHRF onset.

### 2.2. Clinical trials

A retrospective cohort study (ClinicalTrials.gov NCT04318366) in Italy was the first to describe high-dose intravenous (IV) anakinra in patients with COVID-19, acute respiratory distress syndrome (ARDS), and hyperinflammation. In the study, 29 patients received IV infusions of high-dose anakinra (5 mg/kg twice a day), with a median treatment time of 9 days [22]. The outcomes of the patients in the high-dose anakinra group were compared with those of the 16 patients in the comparison group who received standard therapy only. At 21 days, the survival rates were 90% in the high-dose anakinra group and 56% in the

**Table 1**
Main details of 11 cases reporting the use of anakinra intreatment-COVID.

| Country | Numbers of patients | Age | Gender | Past history | Co-administered Drugs | S.C./I.V. doses and duration of anakinra treatment | Treatment Result (after starting anakinra) | References |
|---|---|---|---|---|---|---|---|---|
| Italy | 1 | 50 | Male | None | None | 200 mg I.V. followed by 100 mg every 6 h S.C. | Inflammatory markers reduced (day 3)<br>Respiratory parameters improved (day 13)<br>Discharged from the ICU (day 18) | [11] |
| Italy | 1 | 57 | Male | Tobacco smoke | Remdesivir<br>Ceftriaxone<br>Azithromycin | 100 mg every 6 h S.C. for 7 days | Consolidativelesionsreducted (day 16)<br>Supplemental Oxygen discontinued (day 32) | [12] |
| Spain | 1 | 47 | Male | Asthma | Azithromycin<br>Hydroxychloroquine<br>Enoxaparin | 100 mg every 6 h S.C. On day 11, reduced to 100 mg TDS until<br>completing a total duration of treatment of 14 days | Respiratory improvement (day 10)<br>Discharged (day 19) | [13] |
| UK | 1 | 50 | Male | Renal stones<br>Holecystitis<br>Body mass index of 30 kg/m2 | Intravenous Co-amoxiclav | 150 mg TDS I.V. for 7 days | Oxygen requirements were minimal with oxygen saturations of 93% (day 7)<br>Planned for extubation (day 21)<br>Death (sagittal sinus thrombosis, day 21) | [14] |
| Canada | 1 | 62 | Female | primary progressive multiple sclerosis | Dexamethasone | 100 mg BD I.V. for 12 days | CMR demonstrated marked improvement (12 days)<br>Discharged several days later | [15] |
| UK | 3 | 40 | Male | Acute myeloid leukaemia | Corticosteroids | 100 mg TDS S.C. for 1 day | Defervesced (day 2)<br>Discharged (day 35) | [16] |
| | | 31 | Male | Acute myeloid leukaemia | Dexamethasone<br>IVIg | 100 mg TDS S.C. for 7 days and progressively reduced | Ferritin reduced to 35760 μg/L (day 4)<br>Oxygen requirements began decreasing (day 5)<br>Discharged from ICU (day 7) | |
| | | 36 | Male | Acute lymphoblastic leukaemia | None | 200 mg BD I.V. for 10 days | Defervesced and Oxygen requirements reduced (day 10)<br>Discharged day 21 | |
| UK | 4 | 30 | Male | Renal failure<br>Renal transplant | Tacrolimus<br>Eftriaxone | 200 mg OD I.V. for 10 days | Weaned off positive airway pressure (day 3)<br>Ferritin 4969 mg/L (day 10)<br>Discharged day 12 | [17] |
| | | 48 | Male | Renal failure<br>Renal transplant<br>Transfusion dependent beta-thalassaemia intermedia<br>Splenectomy | Ceftriaxone<br>Teicoplanin | 200 mg OD I.V. for 21 days | Weaned off inotropes (day 1)<br>Anakinrareducedandstopped (day21)<br>Discharged (day45) | |
| | | 68 | Female | Non– Hodgkin's lymphoma | Ceftriaxone<br>Meropenem<br>Ambisome | 200 mg OD I.V. | Ferritin 20479 μg/L (day 1)<br>Ferritin 5118 μg/L (day 3)<br>SARS-CoV-2 viraemia disappeared (day 24) | |
| | | 49 | Female | End-stage renal failure secondary to lupus nephritis<br>Antiphospholipid syndrome with thromboses<br>Ischaemic heart disease | Ceftriaxone<br>Gentamicin<br>Temocillin<br>Teicoplanin<br>Meropenem<br>Caspofungin | 200 mg OD I.V. and increased sequentially to 300 mg BD | Ferritin 30086 μg/L(day 17) Ferritin and CRP notable improvement,<br>Transaminases started to normalize (Increased Anakinra to 300 mg BD,2 days later) | |
| Italy | 5 | 62 | Male | Cardiovascular disease<br>Hyperlipidemia | Hydroxychloroquine<br>Enoxaparin<br>Antiviral<br>Azythromycin | 100 mg TDS I.V. for 24 to 48 h | Discharged 6 to 13 days after start of anakinra<br>No secondary infections or other adverse events were observed | [18] |
| | | 59 | Male | None | Same as above | Same as above | | |
| | | 40 | Female | None | Same as above | Same as above | | |
| | | 55 | Female | Cardiovascular disease<br>Hyperlipidemia | Methylprednisolone<br>Enoxaparin<br>Azythromycin | Same as above | | |
| | | 56 | Male | None | Hydroxychloroquine<br>Enoxaparin<br>Antiviral<br>Azythromycin | Same as above | | |

(*continued on next page*)

**Table 1** (*continued*)

| Country | Numbers of patients | Age | Gender | Past history | Co-administered Drugs | S.C./I.V. doses and duration of anakinra treatment | Treatment Result (after starting anakinra) | References |
|---|---|---|---|---|---|---|---|---|
| France | 9 | 55 | Male | High blood pressure | Non-available | 100 mg BD S.C. from day 1 to day 3, then at 100 mg OD from day 4 to day 10 | Non-feverish and showed good clinical (day 3) Chest CT scan showed the extension of lesions stopped (day 5 to day 8) CRP levels normalised in 5/8 patients (day 11) | [19] |
| | | 54 | Male | Obesity | Non-available | Same as above | | |
| | | 56 | Male | Obesity | Non-available | Same as above | | |
| | | 55 | Male | None | Non-available | Same as above | | |
| | | 54 | Male | None | Non-available | Same as above | | |
| | | 84 | Male | High blood pressure Diabetes | Non-available | Same as above | | |
| | | 62 | Male | None | Non-available | Same as above | | |
| | | 60 | Male | High blood pressure Obesity | Non-available | Same as above | | |
| | | 46 | Female | Obesity | Non-available. | Same as above | Treatment stop (showed an acute respiratory failure 6 h after the first and only dose of anakinra) | |
| Greece | 8 | 51 | Male | Arterial hypertension | Hydrocortisone Hydroxychloroquine Meropenem Teicoplanin Azithromycin | 200 mg TDS I.V. for 7 days | Death (day 12) | [20] |
| | | 74 | Male | DM2 Arterial hypertension Benign prostate hypertrophy | Hydrocortisone Hydroxychloroquine Meropenem Teicoplanin Azithromycin | Same as above | Death (day 9) | |
| | | 67 | Male | CHD Dyslipidemia Arterial hypertension | Hydrocortisone Hydroxychloroquine Meropenem Teicoplanin Azithromycin | Same as above | Alive, weaning from MV (day 22) | |
| | | 84 | Male | CHD COPD Benign prostate hypertrophy Dyslipidemia | Hydroxychloroquine Meropenem Teicoplanin Azithromycin | Same as above | Death (day 19) | |
| | | 56 | Male | Arterial hypertension | Hydroxychloroquine Piperacillin/ tazobactam Colistin Azithromycin | Same as above | Alive, weaning from MV day 31 | |
| | | 68 | Male | DM2 CHD Dyslipidemia Arterial hypertension Stroke | Hydroxychloroquine Ceftaroline Azithromycin | Same as above | Alive, on MV (day 28) | |
| | | 67 | Male | DM2 CHD Dyslipidemia Arterial hypertension Stroke | Hydroxychloroquine Ceftaroline Azithromycin | Same as above | Alive, on MV (day 28) | |
| Netherlands | | 71 | Female | Arterial hypertension Metastatic colon cancer Dyslipidemia | Ceftaroline | 300 mg OD I.V. from day 1 to day 4, then at 100 mg OD from day 5 to day 9 | Alive, discharged day 9 | |
| US | 11 | 61 | Male | DM2 Asthma Obesity CHD | None | Below 100 mg every 6 h S.C. for 7 days, to 100 mg OD S.C. on day 8, then discontinued | Discharged | [21] |
| | | 48 | Male | Obesity | None | Below 100 mg every 6 h S.C. on day 1, to 100 mg every 6 h S.C. on day 2, to 100 mg S.C. TDS on day 6, to 100 mg BD S.C. on day 10, to 100 mg OD S. C. on day 13, then discontinued | Discharged; Received anakinra 100 mg daily for 5 days as outpatient | |
| | | 60 | Female | COPD | Methylprednisolone | 100 mg every 6 h S.C. for 2 days, to 100 mg S.C. TDS on day 3, to 100 mg BD S.C. on day 5, to 100 | Discharged | |

(*continued on next page*)

**Table 1** (*continued*)

| Country | Numbers of patients | Age | Gender | Past history | Co-administered Drugs | S.C./I.V. doses and duration of anakinra treatment | Treatment Result (after starting anakinra) | References |
|---|---|---|---|---|---|---|---|---|
| | | | | | | mg OD on day 8, then discontinued | | |
| | | 74 | Male | Hypertension<br>Gastroesophageal reflux disease<br>DM2<br>Hyperlipidemia | Methylprednisolone | 100 mg every 6 h S.C. for 3 days, to 100 mg S.C. TDS on day 4, to 100 mg BD S.C. on day 10, then discontinued on day 12 | Hospitalized without oxygen support;<br>Required MV for 19 days. | |
| | | 63 | Male | Hypothyroidism | Methylprednisolone | 100 mg every 6 h S.C. for 2 days | Death.<br>Anakinra discontinued after 8 doses due to bacterial infection | |
| | | 81 | Female | Gastroesophageal reflux disease<br>B-thalassemia | Methylprednisolone | 100 mg every 6 h S.C. for 3 days, to 100 mg S.C. TDS on day 4, to 100 mg BD S.C. on day 9, to 100 mg OD on day 11, then discontinued | Discharged | |
| | | 62 | Male | Hypertension<br>Obesity<br>Pre-DM2<br>Hyperlipidemia<br>Benign prostatic hyperplasia | Methylprednisolone | 100 mg every 6 h S.C. for 4 days, to 100 mg S.C. TDS on day 5, to 100 mg BD S.C. on day 7, to 100 mg OD on day 8, then discontinued | Discharged | |
| | | 66 | Male | None | Methylprednisolone | 100 mg every 6 h S.C. for 2 days, to 100 mg S.C. TDS on day 3, to 100 mg BD S.C. on day 15, to 100 mg OD on day 16, then discontinued | Discharged | |
| | | 65 | Male | Hypertension<br>DM2<br>Benign prostatic hyperplasia<br>Cerebrovascular accident | Methylprednisolone | 100 mg every 6 h S.C. for 3 days, to 100 mg S.C. TDS on day 4, to 100 mg BD S.C. on day 9, to 100 mg OD on day 12, then discontinued on day 17 | Discharged<br>Required MV for 5 days. Met criteria for CSS before and after extubation but consulted for anakinra treatment only after extubation. | |
| | | 43 | Male | None | Methylprednisolone | 100 mg every 6 h S.C. for 5 days, to 100 mg S.C. TDS on day 6, then discontinued | Discharged<br>Required MV for 7 days. Patient was intubated on day 1 of anakinra | |
| | | 42 | Male | Hypertension<br>Benign prostatic hyperplasia | None | 100 mg every 6 h S.C. for 1 days, to 100 mg S.C. TDS on day 2 then discontinued on day 4 | Discharged | |

*Abbreviations:* BD = twice a day; comorbidity index; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; DM2: type 2 diabetes mellitus; I.V. = intravenous; OD = once a day; TDS = three times a day; S.C. = subcutaneous; CRP = C reactive protein; CSS = Cytokine storm syndrome; MV = mechanical ventilation.

standard treatment group [18]. The mechanical ventilation-free survival rates were 72% in the anakinra group versus 50% in the standard treatment group. Discontinuation of anakinra was not followed by inflammatory relapses. The study suggested that treatment with high-dose anakinra was safe and had comparable benefits for survival and clinical outcomes.

Moreover, Huet et al. [23] reported the Ana-COVID study in France, a cohort study including a prospective cohort group and a historical control group. Fifty-two consecutive patients were included in the anakinra group, and 44 historical patients were identified in the cohort study. Compared with the historical group, subcutaneous (SC) fixed-dose anakinra (100 mg twice daily for 72 h, then 100 mg daily for 7 days) significantly reduced both the need for invasive mechanical ventilation and mortality among patients with severe COVID-19.

All these studies suggested that anakinra could represent a safe and efficient treatment for severe forms of COVID-19. Several different phases of prospective clinical trials, as of December 2020, are now enrolling and should provide meaningful data on the potential merit of anakinra for COVID-19; most are in phase *II* or *III,* indicating a growing interest in this class of anti-IL-1 agents. Table 2 lists these clinical trials, which have currently been registered around the world (ClinicalTrials.gov) [24-35].

## 3. Canakinumab –Targeting IL-1-beta (β) in COVID-19

Canakinumab, a fully human monoclonal antibody neutralizingIL-1β in the inflammatory cascade with linear dose-dependent pharmacokinetics and a long elimination half-life of 26 days, is currently approved to treat uncommon autoinflammatory diseases such as systemic juvenile idiopathic arthritis (sJIA), CAPS, familial mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) [36-39]. IL-1β is regarded as the "summit" cytokine of the innate immune response and promotes the production of cytokines and chemokines and the activation of macrophages. Moreover, IL-1β induces its self-generation as well as the synthesis of IL-6[40] which has been considered the leading role in cytokine storms. This cascade process may cause exaggerated inflammation, endothelial dysfunction, and even myocardial injury. In addition, canakinumab significantly reduced the incidence of atherothrombotic events and heart failure exacerbations, which are particularly high risks for COVID-19-related mortality[41]. Given these characteristics of IL-1β, canakinumab, an IL-1β antagonist, may be a promising therapeutic option to attenuate the dysregulated immune response for severe COVID-19.

Ucciferri et al. [42] reported the first retrospective analysis to describe the use of canakinumab to treat patients with COVID-19. In ten patients with confirmed SARS-CoV-2 infection, bilateral pneumonia,

**Table 2**
12 registered clinical trials of anakinra for COVID-19 by December 2020.

| Status | Clinicaltrials.gov Identifier | Study | Clinial Phase | Enrollment | Location | References |
|---|---|---|---|---|---|---|
| Not yet recruiting | NCT04366232 | Efficacy of Intravenous Anakinra and Ruxolitinib During COVID-19 Inflammation (JAKINCOV) | Phase II | 54 | France | [24] |
| Not yet recruiting | NCT04341584 | CORIMUNO-ANA: Trial Evaluating Efficacy of Anakinra In Patients With Covid-19 Infection | Phase II | 240 | France | [25] |
| Not yet recruiting | NCT04603742 | Anakinra in Adults with Severe COVID-19 and Features of Cytokine Storm Syndrome: A Randomized, Double-blind, Placebo-controlled Trial | Phase II | 100 | US | [26] |
| Active,not recruiting | NCT04462757 | SCIL-1Ra in COVID-19 Feasibility & PK/PD (SCIL_COV19) | Phase II | 5 | UK | [27] |
| Recruiting | NCT04412291 | A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation, toCompare Standard-of care With Anakinra and Tocilizumab Treatment the Immunomodulation-CoV Assessment (ImmCoVA) Study | Phase II | 120 | Sweden | [28] |
| Recruiting | NCT04357366 | suPAR-guided Anakinra Treatment for Validation of the Risk and Management of Respiratory Failure by COVID-19 (SAVE) | Phase II | 400 | Greece | [29] |
| Recruiting | NCT04443881 | Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to Covid-19 (ANA-COVID-GEAS) | Phase II/ III | 180 | Spain | [30] |
| Recruiting | NCT04324021 | Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection. | Phase II/ III | 54 | US and Italy | [31] |
| Recruiting | NCT04643678 | Efficacy of Anakinra in the Management of Patients With COVID-19 Infection in Qatar: A Randomized Clinical Trial | Phase II/ III | 80 | Qatar | [32] |
| Recruiting | NCT04362111 | Early Treatment of Cytokine StormSyndrome in Covid-19 | Phase III | 30 | US | [33] |
| Recruiting | NCT04364009 | Anakinra for COVID-19 Respiratory Symptoms | Phase III | 240 | France | [34] |
| Recruiting | NCT04680949 | suPAR-Guided Anakinra Treatment for Validation of the Risk and Early Management of Severe Respiratory Failure by COVID-19(SAVE-MORE) | Phase III | 600 | Greece | [35] |

hyperinflammation, and respiratory failure, a dose of 300 mg of canakinumab (subcutaneously) was safe, well tolerated, and associated with a significant decrease in the level of systemic inflammatory response and an improvement in oxygenation. The rapid improvement of serum inflammatory biomarkers after canakinumab administration suggests that the IL-1β pathway plays an important role in the pathophysiology of COVID-19.

Caracciolo et al. [43] presented a case of an 85-year-old male presenting with COVID-19 complicated by ARDS and cardiac and renal failure rescued by canakinumab administered as compassionate use. After administering canakinumab at a single 300 mg dose on days 25 and 31, the patient's renal function was ameliorated, and his inflammatory symptoms were relieved; his high IL-6 levels and NK cells expressing $CD56^{bright}$ (associated with cytokine release) were significantly reduced. Nevertheless, the patient succumbed to severe pulmonary bacterial infection and sustained SARS-CoV-2 positivity on day 58. In summary, canakinumab rescued a high-risk patient from multiorgan failure complicated with COVID-19. This may indicate that canakinumab could be a useful treatment for severe COVID-19 cases. Of note, IL-1β is physiologically conducive to host defense against infection by enhancing the antimicrobial action of phagocytes and inducing Th1 and Th17 adaptive immune responses [44]. Therefore, canakinumab treatment for severe COVID-19 may be associated with an increased incidence of serious infections.

A blinded randomized controlled trial, termed the Three C study (NCT04365153), is being carried out, which exclusively assesses whether canakinumab prevents progressive respiratory failure and cardiac dysfunction in COVID-19 patients with myocardial injury and increased inflammation [45]. More randomized controlled trials are needed to prove the safety and efficacy of canakinumab injection in severe COVID-19 patients to provide more "life-saving" treatment for clinicians.

## 4. Rilonacept – A potentially valuable therapeutic drug in severe COVID-19

Rilonacept is a recombinant protein consisting of the extracellular portion of the human IL-1 receptor type I and the IL-1 receptor accessory protein fused with the Fc portion of human IgG1 [46]. The extracellular domains of the IL-1R components have strong affinities for both IL-1α and IL-1β, thereby neutralizing their activities and functioning as an "IL-1 trap". Rilonacept has been approved for the treatment of CAPS by the FDA. Another unique feature of rilonacept is that it can also potentially bind to IL-1Ra. Furthermore, rilonacept has a longer half-life of 6–8 days; therefore, the interval of injections can be extended to a week [47].

Rilonacept has shown effective inflammatory inhibitory effects in a variety of inflammatory diseases. In a phase III trial of rilonacept in sJIA, patientswere randomly allocated in a 1:1 ratio to receive either 4 weeks of placebo followed by 20 weeks of rilonacept or 24 weeks of rilonacept, and rilonacept was generally well tolerated [48]. Efficacy of the drug was confirmed in active sJIA. Rilonacept was found to maintain inflammatory remission in IL-1 receptor antagonist (DIRA)-deficient patients [49]. The once weekly injection was well tolerated and correlated with increased quality of life. In a randomized, double-blind, placebo-controlled clinical trial, 47 patients with familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) were enrolled and injected weekly with 160 mg rilonacept for 6 weeks. Ninety-six percent of the patients receiving rilonacept experienced at least a 30% reduction in the mean key symptom score, in contrast to 29% of patients receiving placebo (ClinicalTrials.gov Identifier: NCT00288704) [50]. Previously, rilonacept was also shown to be a possible treatment option for colchicine-resistant or colchicine-intolerant FMF patients: in a small, randomized, double-blind, alternating treatment study, rilonacept given at 2.2 mg/kg weekly reduced the attack frequency to 0.77 per month in comparison to 2 per month in the placebo-treatment group. (ClinicalTrials.gov Identifier: NCT00582907) [51]. Currently, a number of clinical trials are being carried out for chronic inflammatory diseases, including type I diabetes (NCT00962026) [52] atherosclerosis (NCT00417417) [53] hepatitis (NCT01903798) [54] and chronic kidney disease (NCT01663103) [55]. In view of its improving effect on inflammation, rilonacept may be used as a potentially valuable therapeutic drug in severe COVID-19 patients with increased inflammation.

## 5. Conclusions

Emerging evidence has shown that CRS might be one of the most important and deadly complications in severe patients with COVID-19.

Anti-IL-1 inhibitor therapies may offer an important treatment option in COVID-19 patients with CRS, which may induce rapid and sustained blockade of inflammation and significantly change the disease course and its long-term outcome. Interestingly, Haralampos presented a 70-year-old woman who was diagnosed with CAPS 5 years ago and was initially treated with anakinra daily and subsequently canakinumab 150 mg every 8 weeks [56]. She had her last canakinumab injection 10 days before she was diagnosed with COVID-19. It is worth noting that her white cell count was $4.28x10^9$/L, and her CRP level was 9 mg/dL at that time. After a few days, her symptoms disappeared, and her SARS-COV-2 test was negative 12 days later. No definite conclusion can be drawn from this case. However, the presentation of this case aims to fuel a fruitful discussion on this issue, which is that cytokine blockade may protect patients from a cytokine storm and thus ameliorate the gravity of the clinical picture of their COVID-19 infection. The numbers of new cases and prospective randomized trials evaluating a number of different anti-IL-1 therapies in patients with COVID-19 are continuing to increase; further information regarding the effectiveness and potential clinical benefits and risks of these therapies is needed. New evidence will continue to inform clinicians and scientists worldwide about the role of anti-IL-1 therapy in critically ill COVID-19 patients.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81470982), and Tianjin Health Industry High-level Talent Selection and Training Project - Jinmen Medical Talents.

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