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A systematic review on the efficacy and safety of IL-6 modulatory drugs in the treatment of COVID-19 patients

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Abstract. – The pandemic caused by the new SARS-CoV2 coronavirus has led to an effort to find treatments that are effective against this disease that the World Health Organization calls COVID-19. In severe cases of COVID-19, there is an increase in cytokines, among which IL-6 seems to play an important role. A search has been performed for studies using IL-6 blocking drugs (tocilizumab, siltuximab, and sarilumab) in PubMed, Web of Science, and Scopus. Also, a search of ongoing trials registered at clinicaltrials.gov was performed. We found very little published clinical experience with these drugs, consisting mainly of case reports or case series with few patients. The results of clinical trials are necessary to clarify the role of these drugs in patients with COVID-19.

Key Words:
IL-6, Tozilizumab, Siltuximab, Sarilumab, COVID-19.

Introduction

The present COVID-19 (Coronavirus Disease-2019) pandemic was first described during early December 2019 in Wuhan (the Hubei province of China) in a group of patients suffering pneumonia of unknown origin[1]. The agent responsible for the clinical picture was a virus never before identified. This was considered a severe acute respiratory syndrome (SARS)-related coronavirus as it shared 74.5% of its genome identity with the authentic SARS-CoV[2]. It was termed 2019-nCoV or SARS-CoV-2 for its similarity with the coronavirus causing SARS in 2002.

COVID-19 patients exhibit a specific cytokine profile, notably increased in IL-1β, IL-2, IL-6, IL-8, IL-17, TNF, and CCL2[3]. IL-6, a pleiotropic cytokine with proinflammatory activity which affects both the innate and adaptive immune systems[4], predicts low survival in patients with acute respiratory distress syndrome (ARDS)[5]. The rationale for considering involvement of IL-6 in COVID-19-related macrophage activation syndrome (MAS) is based on changes in biochemical parameters such as ferritin, and some preliminary reports showing the efficacy of IL-6 receptor (IL-6R) antagonists[6,7].

The biology of IL-6 action is complex. This cytokine binds to membrane-anchored IL-6R, and the co-receptor gp130 participates in tissue homeostatic and repair responses[8-9]. In concert with other proinflammatory cytokines, IL-6 stimulates endothelial cells to release chemokines which promote T-cell differentiation and B-cell stimulation[10]. Proof of the link between IL-6 and COVID-19 pathophysiology is the result of a recent meta-analysis showing evidence that circulating IL-6 levels are closely linked to the severity of COVID-19 infection[11].

Some attempted therapeutic approaches against SARS-CoV-2 are based on the involvement of IL-6 in the pathophysiology of the disease. This cytokine can be blocked with monoclonal antibodies targeting either its receptor (IL6R) or IL-6 itself. Tocilizumab is a humanized anti-IL-6R monoclonal antibody. Sarilumab is a fully human IgG1 monoclonal antibody that targets both soluble and membrane-bound IL-6R, thus inhibiting both cis- or trans-IL-6-mediated inflammatory pathways[12]. Siltuximab is also a fully human IgG1 monoclonal antibody, in this case against IL-6 itself. At present, tocilizumab, sarilumab, and siltuximab are primarily utilized in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease[13] based on the biology of IL-6. While these IL-6 modulatory drugs have

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been proposed for the management of COVID-19, no study brings together all the knowledge on the results published to date. Therefore, our main goal is to perform a systematic review of the current scientific literature to determine if the treatment of COVID-19 patients with IL-6-based drugs will diminish symptoms or overall disease progression.

Materials and Methods

A systematic review of PubMed, Scopus and the Web of Science was carried out under the search strategy of the following terms: (COVID-19) OR (novel coronavirus 2019) OR (2019-nCoV) OR (SARS-CoV-2) AND (tocilizumab) OR (sarilumab) OR (siltuximab) OR (IL-6 antibodies). The search was performed in and ranged up to April 18, 2020. No filters on language, country of origin or publication date were introduced. The search was expanded to the references of Clinicatrials.gov using the term COVID in an aim to detect ongoing clinical trials. Two authors (JSG and MFG) independently screened the databases, as well as the trial registries, and finally extracted the relevant information. Discrepancies and doubts concerning the relevance of the sources were solved by agreement with two other authors (EN and JJ). All entries which provided information on the evolution of patients treated with anti-IL6 drugs were incorporated, including those publishing clinical trials, non-randomized prospective or retrospective studies, and case reports. The following data were extracted from the entries: first author, type of study, number of patients included in the study, anti-IL-6 therapy administered, as well as other treatments utilized including those compared with anti-IL-6 therapy, and evolution of the patients. For ongoing clinical trials, we selected those which included anti-IL-6 drugs. Registration number, patients features, type of study, country, drug under study, alternative treatment against which anti-IL-6 is compared, and the primary outcome of the study.

Results

Our search strategy initially yielded 30 PubMed entries, 28 Web of Science entries and 12 Scopus entries. After removing duplications, a total of 38 articles were collected. 28 were review articles, letters to the editor or opinion articles and 2 were articles not focused on anti-IL-6 drugs, and therefore excluded. The final 8 articles have data in cases series (2 entries) and case reports (6 entries). We have included one more case series identified during the review from the references of the articles found, for a total of 9 included articles[13].

Luo et al[14] report a case series of 15 patients with COVID-19 treated with tocilizumab between January 27th and March 5th in Wuhan. 46.7% of these patients were in critical conditions. The dosing of tocilizumab ranged within 80 and 600 mg per dose. A single dose was administered in 10 cases, of which 8 cases also added methylprednisolone. 3 of the 4 critically ill patients receiving a single dose died, while the surviving patient worsened its clinical condition. Clinical conditions were stabilized or even improved in 10 patients. The study authors conclude that tocilizumab might be an effective treatment with high IL-6, but more than one daily dose should be administered in critical patients.

Xu et al[13] reported 21 patients diagnosed with severe or critical COVID-19. 20 of those 21 patients recovered and were discharged within 2 weeks after the tocilizumab therapy, with no adverse drug events[13,15]. Other parameters such as the need for supplemental oxygen, C-reactive protein, percentage of lymphocytes in peripheral blood improved after the treatment[13].

Di Giambenedetto et al[16] reported the outcomes of 3 patients hospitalized with COVID-19 diagnosed by real-time PCR and developing rapid respiratory insufficiency. These three patients had favorable outcome with tocilizumab treatment.

The 6 single-case COVID-19 studies published were as follows: (a) patient with an accompanying multiple myeloma: good evolution upon tocilizumab administration[17]; (b) patient with an accompanying metastatic sarcomatoid clear cell renal carcinoma: also responded satisfactorily to tocilizumab treatment[18]; (c) patient with chronic renal failure on hemodialysis with severe COVID-19 disease: tocilizumab treatment was successful[19]; (d) systemic sclerosis patient already on tocilizumab therapy progressing to only mild COVID-19 symptoms[20]; (e) patient with sickle cell disease and severe COVID-19 pneumonia treated successfully with tocilizumab[21]; and (f) patient with COVID-19 pneumonia demonstrating satisfactory changes of CT images after initiating tocilizumab therapy[9].

The ongoing clinical trials with anti-IL-6 antibodies are depicted in Table I. Of these, 8 studies employ tocilizumab, 5 sarilumab and 2 siltux-

Table I. Cilnical trials.

ID trial number	Recruiting status	Number of centers and study design	Country	Population (n patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04332094	Not yet recruiting	Randomized, Pilot, Multicenter, Open-label Clinical Trial	Spain	Patients hospitalized with COVID-19 (n=276)	Early administration of TZM (162 mg SC × 2 doses + TZM 162 mg SC × 2 doses at 12 h (day 1) associated with HCQ (400 mg/12 h PO day 1 followed by 200 mg/12 h PO for 6 days (7 days in total) and azithromycin (500 mg/day PO for 3 days).	Treatment with HCQ (400 mg/12 h PO on day 1 followed by 200 mg/12 h PO for 6 days (7 days in total) and azithromycin (500 mg/day PO for 3 days)	In-hospital mortality Time Frame through hospitalization, an average of 2 weeks Need for IMV at ICU.
NCT04329650	Not yet recruiting	Single Center Randomized Clinical Trial	Spain	Patients hospitalized with COVID-19 need an ICU (n=100)	Single dose of STX 11 mg/kg, IV infusion	Methylprednisone (IV): single dose of 250 mg/24 hours for 3 days followed by 30 mg/24 hours for 3 days.	Proportion of patients requiring ICU admission at any time within the study period (29 days).
NCT04317092	Recruiting	Multicenter, single-arm, open-label, phase 2 study.	Italy	Patients with COVID-19 pneumonia (n=400)	TZM 8 mg/kg (up to a maximum of 800 mg per dose), with an interval of 12 hours.	No comparison group	One-month mortality rate
NCT04315298	Recruiting	Randomized, Adaptive Phase 2/3, Double-Blind, Placebo-Controlled Study	USA	Patients hospitalized with COVID-19 regardless of severity strata (n=400)	Single IV high dose of SLM. Single IV low dose of SLM.	Single IV placebo	Phase 2: Percent change in CRP levels. Phase 3: Time to improvement (2 points) in clinical status assessment using the 7-point ordinal scale in patients with serum IL-6 levels greater than the upper limit of normal (TF: Up to day 29)

(Table Continued)

Table I *(Continued)*. Cilnical trials.

ID trial number	Recruiting status	Number of centers and study design	Country	Population (n patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04330638	Not yet recruiting	Randomized, Interventional Study, Prospective, Factorial Design.	Belgium	Patients with COVID-19 infection (n=342)	Group A: Anakinra (daily SC injection of100 mg for 28 days or until hospital discharge, whichever is first). Group B: STX (*via* single IV infusionat a dose of 11 mg/kg). Group C: Anakinra (daily SC injection of 100 mgfor 28 days or until hospital discharge, whichever is first) + STX (*via* single IV infusion at a dose of 11 mg/kg). Group 4: TZM (*via* single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection). Group 5: Anakinra (a daily SC injection of 100 mg for 28 days or until hospital discharge, whichever is first) + TZM (*via* single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection)	Placebo and standard care.	Time to Clinical Improvement (15 days) defined as the time from randomization to either an provement of imtwo points on a six-category ordinal scale or discharge from the hospital: - Exitus - Hospitalized, on IMV or ECMO; - Hospitalized, on non-IMV or high flow oxygen devices; - Hospitalized, requiring supplemental oxygen - Hospitalized, not requiring supplemental oxygen - Not hospitalized
NCT04321993	Not yet recruiting	Non-Randomized, Parallel Assignment, Interventional	Canada	Patients with moderate to severe COVID-19 disease (n= 1000)	Group A: Lopinavir/ritonavir tablet 200 mg/50 mg 2 tablets PO, every 12 hours for 10 days. Group B: HCQ sulfate tablet 200 mg 2 tablets PO, every 12 hours for 10 day. Group C: Baricitinib 2 mg PO daily for 10 days. Group D: SLM 200 mg SC injection once.	No Intervention: Clinical standard of care	Clinical status of subject at day 15 (on a 7 point ordinal scale): - Not hospitalized, no limitations on activities; - Not hospitalized, limitation on activities; - Hospitalized, not requiring supplemental oxygen; - Hospitalized, requiring supplemental oxygen; - Hospitalized, on non-IMV or high flow oxygen devices; - Hospitalized, on IMV or ECMO; - Exitus.

(Table Continued)

Table I ***(Continued).*** Cilnical trials.

ID trial number	Recruiting status	Number of centers and study design	Country	Population (n patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04331795	Not yet recruiting	Non-Randomized, Single Group Assignment, Interventional	USA	Patients severe to critical COVID-19 (n=50)	Group A: TZM (beginning dose 200 mg). Single dose is provided, patient is eligible to receive up to two doses, with re-evaluation of clinical and biochemical responses performed every 24 hours. Second dose is provided if evidence of clinical worsening or lack of CRP response. Group B: Low dose TZM (beginning dose 80 mg) Single dose is provided, patient is eligible to receive up to two doses, with re-evaluation of clinical and biochemical responses performed every 24 hours. Second dose is provided if evidence of clinical worsening or lack of CRP response.	No comparison group	Clinical response (TF: Assessed for the 24H period after TZM administration). Tmax response: resolution of fever (from Tmax > 38°C in 24H period to Tmax < 38°C in following 24H period measured with commonly accepted clinical methods (forehead, tympanic, oral, axillary, rectal). Tmax within 24-hour (0:00-23:59) on the day prior to TZM, day of TZM, and every 24H after TZM administration. The primary endpoint is absence of Tmax ≥ 38°C in the 24H period following TZM administration. Biochemical response. TF: Assessed every patient's hospitalization, up to 4 weeks after TZM administration. CRP normalization rate: calculated as the ratio of the number of patients who achieve normal CRP value following TZM administration and total number of patients who receive TZM. Time to CRP normalization: calculated as hours between TZM administration and first normal CRP value.

(Table Continued)

Table I *(Continued).* Cilnical trials.

ID trial number	Recruiting status	Number of centers and study design	Country	Population (n patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04320615	Not yet recruiting	Randomized, Parallel Assignment, Multicenter	Switzerland	Patients with severe COVID-19 pneumonia (n=330)	IV infusion of TZM, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose may be given if clinical symptoms worsen or show no improvement.	IV infusion of placebo matched to TZM	Clinical Status Assessed using a 7-Category Ordinal Scale (TF: Day 28)
NCT04310228	Recruiting	Randomized, Parallel Assignment, Multicenter	China	Patients with COVID-19 (n=150)	Favipiravir (on day 1, 1600 mg each time, twice a day; from the day 2 to 7, 600 mg each time, twice a day. PO, no more than 7 days). TZM (IV infusion): first dose 4-8 mg/kg. Recommended dose 400 mg. For fever patients, an additional application (same dose) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours.	No comparison group	Clinical cure: the viral load of the respiratory specimen was negative for two consecutive times (the interval between the two tests was greater than or equal to one day), the lung image improved, and the body temperature returned to normal for more than 3 days, and the clinical manifestation improved.
NCT04306705	Recruiting	Observational, Cohort, Single Center	China	Patients COVID-19 with lung damage	Group A: TZM (8 mg/kg once in 100 ml 0.9% saline solution and administered IV within no less than 60 minutes). Group B: continuous renal replacement therapy (Catheter insertion site is femoral vein).	Standard treatment	Proportion of participants with normalization of fever and oxygen saturation through day 14.

(Table Continued)

Table I *(Continued)*. Cilnical trials.

ID trial number	Recruiting status	Number of centers and study design	Country	Population (n patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04327388	Recruiting	Randomized, Parallel Assignment, Double-blind, Phase 2/3	France	Patients hospitalized with severe COVID-19 (n=300)	SLM dose 1 given IV once on day 1 SLM dose 2 given IV once on day 1.	Placebo once on day 1	Phase 2: time to resolution of fever for at least 48 hours without antipyretics or until discharge, whichever is sooner (TF: Baseline to Day 29) Resolution of fever is defined as body temperature: ≤36.6 C (axilla) or ≤37.2 C (oral), or ≤37.8 C (rectal or tympanic). Phase 3: the percentage of patients reporting each severity rating on the 7-point ordinal scale (TF: Baseline to Day 5) The ordinal scale is an assessment of the clinical status. Score ranges 1-7. Lower score is worse.

(Table Continued)

Table I ***(Continued).*** Cilnical trials.

ID trial number	Recruiting status	Number of centers and study design	Country	Population (n patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04324073	Recruiting	Randomized, Parallel Assignment, Multicenter	France	Patients with moderate, severe pneumonia or critical pneumonia associated with COVID-19 (n=240)	SLM (an IV dose of 400 mg of SLM in a 1 hour-infusion at day 1).	Standard treatment	Survival without needs of IMV utilization at day. Scores ≤5 on WHO progression scale at day four: 0: Uninfected; non-viral RNA detected 1: Asymptomatic; viral RNA detected 2: Symptomatic; Independent 3: Symptomatic; Assistance needed 4: Hospitalized; No oxygen therapy 5: Hospitalized; oxygen by mask or nasal prongs 6: Hospitalized; oxygen by non-IMV or high flow 7: Intubation and IMV, pO2/FIO2≥150 or SpO2/FIO2≥200 8: IMV, pO2/FIO2<150 or SpO2/FIO2<200 or vasopressors (norepinephrine >0.3 µg/kg/min) 9: IMV, pO2/FIO2<150 and vasopressors (norepinephrine >0.3 µg/kg/min) or dialysis or ECMO 10: Exitus
NCT04322773	Not yet recruiting	Randomized, Sequential Assignment, Multicenter	Denmark	Patients infected with SARS-CoV-2 pneumonia (n=200)	Group A: Single dose treatment with 400 mg TZM IV. Group B: Single dose treatment with 2 × 162 mg TZM SC. Group C: Single dose treatment with 1 × 200 mg SLM SC.	Standard treatment	Time to independence from supplementary oxygen therapy (28 days)

Abbreviations: CRP = C-reactive protein; ECMO = Extracorporeal membrane oxygenation; HCQ = hydroxychloroquine; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; PO = peroral; SLM = sarilumab: SC = subcutaneous; STX =Siltuximab: Tmax = Maximum temperature; TF = Time Frame; TZM = tocilizumab.

imab. Two of these trials utilize 2 anti-IL-6 drugs in different treatment arms: one tests tocilizumab and siltuximab and the other tests the responses to tocilizumab and sarilumab.

Expert Opinion

There is pathophysiological background to confer possible benefits to anti-IL-6 drugs in severe COVID-19 patients. However, our study reveals that the available clinical data are scarce, with very few cases, and at times limited to specific scenarios with a narrow clinical scope. This systematic review shows the existence of ongoing clinical trials testing tocilizumab, sarilumab, and siltuximab. In general, these drugs display a good safety profile, and are clinically well-tolerated by patients when treated for original indications[22]. However, adverse effects such as neutropenia, liver enzyme elevation, and lipidic alterations have been reported for tocilizumab. It is clear that none of these drugs should be administered in the setting of severe liver or kidney failure due to the lack of studies evaluating pharmacokinetics and safety. Concomitant infections should be watched, and special attention should be paid to patients with liver enzyme elevation.

The published clinical experience with these drugs in COVID-19, with the few descriptive reports and case series, is very limited. Despite the data from some case series, the lack of a comparison group limits its interpretation until rigorous data are available. For this reason, the results of the ongoing clinical trials to assess the role of IL-6 blockade in COVID-19 are essential.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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