Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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What are the clinical benefits of tocilizumab for COVID-19 patients? Evidence from available case-control studies

Quels sont les avantages cliniques du tocilizumab pour les patients sous COVID-19 ? Données tirées des études cas-témoins disponibles

In December 2019, a novel member of beta-coronaviruses, SARS-CoV-2 emerged in Wuhan, China. However, SARS-CoV-2 is highly contagious and quickly spread throughout the world [1]. Already, the frequency of mortality with the coronavirus disease 2019 (COVID-19) has been accelerated, so that WHO announced the global pandemic with SARS-CoV 2 in 11 March 2020. At the moment, there are more than 20 million individuals infected with the 2019 novel coronavirus (2019-nCoV) worldwide [2]. Most importantly, there is no FDA approved treatment for COVID-19 which in turn has become one of the global health concerns [3].

In general, individuals infected with SARS-CoV-2 experience different clinical presentations from asymptomatic carrier or initial mild acute respiratory disease, to acute respiratory distress syndrome (ARDS) and organ failure [4,5]. According to literature, cytokine release syndrome (CRS) plays a central role in immune pathogenesis of SARS-CoV-2 infection and susceptibility to ARDS [6,7]. Interleukin-6 is responsible for the onset of cytokine storm formation and excessive secretion of inflammatory cytokines [8,9]. Aziz et al. in their studies revealed increased plasma levels of IL-6 in severe cases of COVID-19 [10]. Based on studies, infected persons to more severe SARS-CoV-2 disease have higher plasma IL-6 levels, and therefore it can be considered as a negative prognostic biomarker for surviving [11]. However, tocilizumab, an anti-human IL-6 receptor, is a humanized monoclonal antibody which targets both membrane and soluble IL-6 receptors [12]. Tocilizumab was approved in 2010 by FDA, and since then widely recommended for rheumatoid arthritis, systemic juvenile idiopathic arthritis, and giant cell arteritis [12,13]. It seems that the existing anti-IL-6 drug, tocilizumab, has the clinical benefits in reducing the risk of both syndromes CRS and ARDS during the lack of vaccine and appropriate antiviral therapy against SARS-CoV-2 infection. Ramaswamy et al. found that tocilizumab has short-term survival in patients who had got to severe form of COVID-19 [14]. Herein, we conducted a comprehensive statistical analysis on the all available case-control studies which had investigated the therapeutic effects of tocilizumab against COVID-19.

In the beginning, we performed a systematic search in several online databases such as PubMed, Scopus, Cochrane Library, Embase, medRxiv, and bioRxiv up to August 2020. Using several keywords according to MeSH such as "SARS-CoV 2'', "COVID-19'', "2019-nCoV'', "tocilizumab'', "atlizumab'', "actemra'', "roactemra'', "sarilumab'', "kevzara'', "siltuximab'', and "sylvan'', we selected all relevant case-control studies in relation to the efficacy of this anti-IL-6 drug against SARS-CoV-2 cases without language limitation. In the next stage, we started screening the titles and abstracts of identified records, and irrelevant documents were excluded. Subsequently, the full-text of remained literature were evaluated carefully. The Newcastle-Ottawa Scale was used for assessing the quality of included studies. The required data including first author, country, distribution of SARS-CoV-2 infection between the two groups receiving tocilizumab and placebo, tocilizumab dosage, the abundance of death, discharge, requirement for mechanical ventilation, CRP, plasma IL-6 level, patient condition, and hazard ratio values for mortality were summarized in the *table I*.

The primary outcomes including mortality, discharge and requiring mechanical ventilation were measured using the pooled odds ratio (OR) with 95% confidence intervals (CIs). In addition, laboratory markers such as CRP and IL-6 were analyzed using the mean (SD) difference with 95% CIs between two groups. Based on DerSimonian-Laird method and using random-effect model, all statistical analyses were performed by comprehensive meta-analysis (CMA) software version 2.2 (Biostat, Englewood, NJ, USA). Heterogeneity was assessed by Cochrane Q test P-value ≥ 0.05 and I^2 index > 25%. In addition, publication bias was evaluated by funnel plot, Beggs P-value, and Eggers P-value [15].

Out of 249 primary identified records, we met only 9 case-control studies, and finally, one of those which had conducted by Wadud et al., was excluded due to the mismatch with our main idea, as well as unclear results. Overall, we enrolled a total of 756 participants in the current quantitative study; of all infected patients by SARS-CoV-2, 324 cases had received tocilizumab and 432 cases treated by placebo. These studies were conducted in three countries USA, Italy, and France [14,16–23].

Assessments showed that there is significant reduction in mortality rate of COVID-19 patients which had received tocilizumab. The pooled OR for mortality rate was 0.533 (0.362–0.786) with

Table I

Characteristics of included studies.

Caractéristiques des études inclues.

First author	Location	COVID-19 cases		Dosage	Death		Discharge		Mechanical ventilation		CRP (mg/L)		IL-6 (pg/mL)		Patients condition	Hazard ratio for mortality
		Tocilizumab	Standard care		Tocilizumab	Control	Tocilizumab	Control	Tocilizumab	Control	Tocilizumab	Control	Tocilizumab	Control		
Capra	Italy	62	23	400 mg IV once per day	2	11	23	8	NA	4	NA	NA	NA	NA	Matched for age, gender and disease severity	0.035; 0.004–0.347; *P*-value: 0.004
Roumier	France	30	29	8 mg/kg	3	9	NA	NA	10	16	189.0	167.4	NA	NA	Matched for age, gender and disease severity	0.25; 0.05–0.95; *P*-value: 0.04
Ramaswamy	USA	21	65	400 mg or 8 mg/kg	3	8	NA	NA	13	10	15.9	11.2	371.9	64.4	Comorbidity and oxygen flow were lower in TCZ group	0.25; 0.07–0.90
Rojas-Marte	USA	96	97	NA	43	55	42	NA	NA	NA	17.1	14.6	NA	NA	Patients in the TCZ group were more sever	NA
Klopfenstein	France	20	25	NA	5	12	11	11	0	8	105	158	NA	NA	TCZ patients had a higher Charlson comorbidity index than non-TCZ patients	NA
Colaneri	Italy	21	91	8 mg/kg IV	5	19	NA	NA	3	12	0.63	6.07	NA	NA	Matched for age, gender and disease severity	NA
Quartuccio	Italy	42	69	8 mg/kg IV	4	0	10	69	NA	NA	79.05	24.1	63.5	18.5	TCZ initiated patients were severe cases	0.78; 0.06–0.934; *P*-value: 0.84
Campochiaro	Italy	32	33	400 mg IV once per day	5	11	20	16	2	2	156	169	NA	NA	Matched for age, gender and disease severity	NA

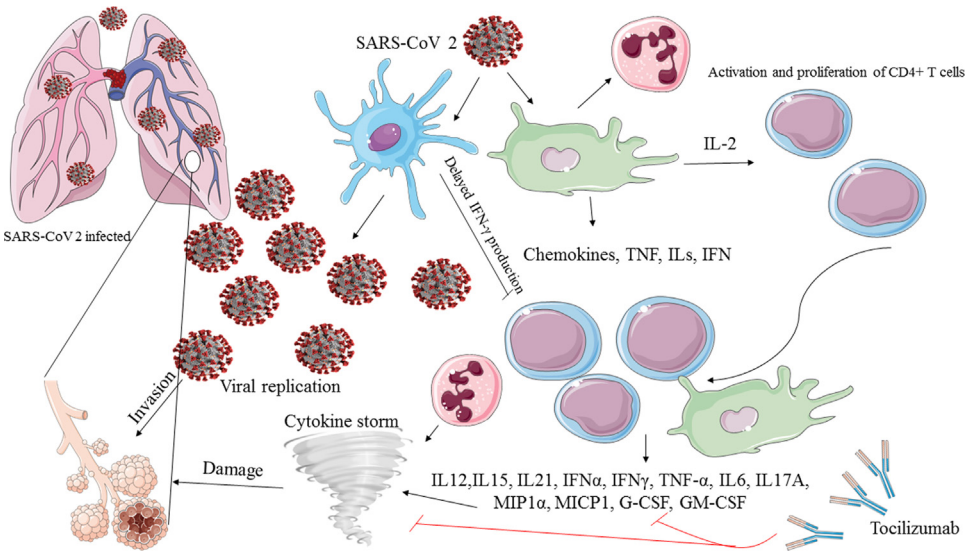

FIGURE 1

Schematic scheme of SARS-CoV-2 pathogenesis and cytokine stormSchéma de la pathogenèse du SRAS-CoV-2 et de la tempête de cytokines

95% CIs and *P*-value: 0.001 (*Q*-value: 20.83; I^2: 66.39; *P*-value: 0.004; Beggs *P*-value: 0.37; Eggers *P*-value: 0.46). In addition, the requiring mechanical ventilation was significantly reduced in tocilizumab initiating group (OR: 0.499; 0.321–0.776 with 95% CIs; *P*-value: 0.002; *Q*-value: 39.26; I^2: 84.72; *P*-value: 0.001; Beggs *P*-value: 0.11; Eggers *P*-value: 0.32). However, there is no significant benefit in discharge rate in patients receiving tocilizumab (OR: 1.096; 0.607–1.981 with 95% CIs; *P*-value: 0.761; *Q*-value: 18.94; I^2: 84.16; *P*-value: 0.001; Beggs *P*-value: 0.15; Eggers *P*-value: 0.02). In relation to CRP and IL-6, we observed a significant increase in the plasma levels of CRP (68.97; 68.85–69.09 with 95% CIs vs. 45.82; 45.72–45.91 with 95% CIs) and IL-6 (166.30; 166.05–166.54 vs. 40.76; 40.59–40.93 with 95% CIs) in tocilizumab-treated patients.

According to previous studies, it has been demonstrated that cytokines play a key role in the regulation of immune-system in response to viral infections [24]. Molecular in vitro diagnostic examinations have revealed the expression of interferons (IFNs), IL-1β, IL-6, tumor necrosis factor alpha (TNFα), and chemokines from macrophages infected with SARS-CoV-2. These pro-inflammatory cytokines can provoke the immune response by constitutive stimulation of immune cells throughout several signaling pathways. Finally, entry of immune cells into the site of infection such as macrophages, neutrophils, and T cells promote apoptosis of pulmonary epithelial/endothelial cells which in turn leads to develop into ARDS [25,26]. Tocilizumab is an IL-6 antagonist which competitively binds to both soluble and membrane IL-6 receptors, and blocks IL-6 signaling pathways [27]. Therefore, tocilizumab can protect human tissues from destructive effects of cytokine storm via interruption of CRS (*figure 1*). Liu et al. suggested the blockade of IL-6 for the treatment of severe cases of COVID-19 [28]. In the present quantitative meta-analysis, we also revealed the efficacy of tocilizumab in treating of COVID-19 patients. We found that tocilizumab can significantly reduce mortality rate and requiring mechanical ventilation in comparison with placebo-treated group. Lan et al. in their meta-analysis about the efficacy of tocilizumab in treating COVID-19 patients concluded a significant decrease in mortality rate of tocilizumab-treated cases compared to control group (16.3% vs. 24.1%) [29]. In accordance with previous studies, we also revealed a significant decrease in mortality rate of COVID-19 cases which received tocilizumab (mortality hazard ratio: 0.212; 0.090–0.501 with 95% CIs; *P*-value: 0.001; *Q*-value: 3.59; I^2: 16.23; *P*-value: 0.30; Beggs *P*-value: 0.50; Eggers *P*-value: 0.43). Khiali et al. in their systematic review study demonstrated long-term safety of tocilizumab in SARS-CoV-2 infected patients [30]. Nevertheless, in rare cases, the usage of tocilizumab can be led to intestinal perforation [31]. Although we observed higher plasma levels of CRP and IL-6 in tocilizumab-treated cases than the control group, but Amoabeng et al. reported a significant decrease of their concentrations following initiation with tocilizumab [32]. The present study has several limitations including:

- low sample size;
- low population of studied individuals;
- different outcomes;

- diversity of patients' condition in both case and control groups;
- the presence of heterogeneity between included studies, and;
- publication bias which reduced the reliability of the proposed results.

There are 24 registered studies for investigation of clinical benefit of tocilizumab against COVID-19. We showed the efficacy of tocilizumab in reducing mortality rate and requiring mechanical ventilation, but we need to further randomized clinical trials for confirming the present findings.

Contribution of authors

Kiarash Ghazvini: first draft.

Mohsen Karbalaei: revision of grammatical errors and response to reviewer.

Masoud Keikha: supervision, data analysis, review and edit manuscript.

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