Drugs (2023) 83:1–36
https://doi.org/10.1007/s40265-022-01803-2

CURRENT OPINION

Should We Interfere with the Interleukin-6 Receptor During COVID-19: What Do We Know So Far?

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Accepted: 27 October 2022 / Published online: 12 December 2022

Abstract
Severe manifestations of COVID-19 consist of acute respiratory distress syndrome due to an initially local reaction leading to a systemic inflammatory response that results in hypoxia. Many therapeutic approaches have been attempted to reduce the clinical consequences of an excessive immune response to viral infection. To date, systemic corticosteroid therapy is still the most effective intervention. More recently, new hope has emerged with the use of interleukin (IL)-6 receptor inhibitors (tocilizumab and sarilumab). However, the great heterogeneity of the methodology and results of published studies obfuscate the true value of this treatment, leading to a confusing synthesis in recent meta-analyses, and the persistence of doubts in terms of patient groups and the appropriate time to treat. Moreover, their effects on the anti-infectious or pro-healing response are still poorly studied. This review aims to clarify the potential role of IL-6 receptor inhibitors in the treatment of severe forms of COVID-19.

1 Introduction

Over the past 2 years, several variants of the SARS coronavirus (SARS-CoV2) have been involved in a COVID-19 (Coronavirus Disease 2019) pandemic. COVID-19 is of particular concern due to its high inter-individual transmission [1] and, in certain cases, its association with a significant risk of acute respiratory distress syndrome (ARDS) and ultimately patient death [2–12].

Key Points

The dysregulation of inflammatory response associated with COVID-19 requiring hospitalization has been suggested to be a potential target of monoclonal antibodies. Tocilizumab and sarilumab are monoclonal humanized antibodies directed against the IL-6 receptor.

During severe COVID-19, tocilizumab appears to have demonstrated efficacy by reducing mortality. However, there does not appear to be a class effect as sarilumab failed to demonstrate any similar benefit, although there is a broad discrepancy between studies that is still not explained.

No study has focused on the safety of tocilizumab in acute, infection-associated inflammatory response.

SARS-CoV2 infection can affect many organs but is primarily an infection of the airways, invading the entire respiratory tree [13], from bronchia to alveolar lung parenchyma [14–19]. Transmission of the virus is still a subject of debate. For further information, we recommend that the readers refer to [20–23]. Among the considerable number of inflammatory mediators produced or secreted in the inflammatory response, interleukin-6 (IL-6) has been shown to

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play a significant role [24], which is likely due to its high levels of expression rather than to the singularity of its action, as all mediators produced are somewhat redundant in their actions [25]. Nonetheless, pro-inflammatory mediators, in particular IL-6, are extensively produced by lung epithelial cells during COVID-19 and notably infect type 2 pneumocytes [26]. Such tropism of SARS-CoV2 for type 2 pneumocytes is considered to be a predominant factor in the intense local production of proinflammatory mediators and may significantly contribute to the subsequent alveolar consequences.

The therapeutic management of COVID-19 initially focused on supporting organ failure, essentially oxygen supply in hypoxemic respiratory diseases. The initial lack of specific treatment during this severe viral infection rapidly led to numerous therapeutic attempts to control the virus. Concomitantly, attempts to control the systemic inflammatory response were also undertaken. Among all the tested treatments, corticosteroids were the first to show a potential improvement in survival in more severe situations [27–29]. At the same time, despite their lack of survival benefit in sepsis, the limited information available in ARDS, and the debatable use of single cytokine inhibition during extensive inflammation [30], strategies targeting various cytokine pathways started to be explored in COVID-19 patients. Among them, the most promising results have been achieved with inhibition of the interleukin-6 receptor (IL-6R).

2 Method of Literature Review

For this narrative review, we addressed the question of the place of IL-6 receptor inhibitors in COVID-19. Studies were identified by a double search in PubMed/MEDLINE (National Library of Medicine) databases until April 2022 by two independents authors (AP & FP). Randomized studies and meta-analyses were systematically included. The final selection of papers was made by the authors, as a function of their relevance to the addressed question. Additional articles, cited in those already selected, were included if they were considered of major importance in the field.

3 The Interleukin-6 (IL-6) Pathway and the Inhibition of IL-6 Receptors

Interleukin-6 is a 26 kD cytokine of 184 amino acids. Initially described as a B-cell stimulator, IL-6 is a pleiotropic cytokine that stimulates immune cell differentiation and proliferation, favors expression of IL-17-producing CD_4^+ T helper lymphocytes (Th17), and inhibits of the generation of regulatory T cells (Treg). Aside from having a major quantitative role in chronic and acute inflammation, IL-6 is involved in endothelial activation, favoring vascular leakage, and takes part in the regulation of metabolism and tissue regeneration [31]. Mainly expressed by monocytes and macrophages in response to microbe (and damage)-associated molecular patterns, IL-6 can also be produced by B and T cells during viral infection [32]. Moreover, its expression is upregulated by a positive feedback favored by degradation and reduced expression of Regnase. Such amplification may contribute to the high levels of IL-6 measured in septic patients. Three main interactions of IL-6 with the IL-6R have been described. IL-6 can directly interact with the membrane-bound IL-6R of the receptor allowing interaction with a second ubiquitously expressed transmembrane protein: pg130 (classic signaling). Signal transduction can also be obtained by the binding of IL-6 to the soluble IL-6R (trans-signaling). Finally, gp130 activation has been described, in T cells interacting with specialized dendritic cells (DC). In this situation, DC membrane-bound IL-6R associated with IL-6 activates the gp130 pathway allowing the priming of T_H17 cells [32, 33]. Transduction of the IL-6 signal is then primarily mediated by the gp130-JAK-STAT3 (signal transducer and activator of transcription 3) and gp130-JAK-SHP-2 (SH2-domain containing protein tyrosine phosphatase-2) pathways.

Several inhibitors of the IL-6 pathway have been developed to reduce the consequences of chronic IL-6 stimulation [33], including antibodies directed against the IL-6R, which have a central clinical role in the treatment of chronic inflammation diseases [31, 33]. Among them are tocilizumab, a humanized IgG1, and sarilumab, a human IgG1 antibody, directed against the IL-6R [31]. They bind directly at the IL-6 binding epitope (tryptophan-serine-X-tryptophan-serine domain), allowing inhibition of the three types of signal transduction [32, 33]. Initially developed to treat patients with systemic chronic inflammatory diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis, Castleman disease, and Takayasu arteritis, anti-IL-6R antibodies have been more recently suggested for the treatment of cytokine release syndrome associated with the use of chimeric antigen receptor T (CAR-T) cells [33–37].

During COVID-19, the intensity of the inflammatory response has been shown to correlate with the severity of acute respiratory distress. As a major quantitative mediator expressed in response to cells of innate immunity, IL-6 is strongly associated with hypoxemia [38, 39]. Inhibition of the IL-6R and IL-6 pathway could mitigate the initial inflammatory response, reduce capillary permeability, and thus limit respiratory failure. Moreover, by targeting a specific proinflammatory mediator, these biologic agents may allow the control of inflammation with a less severe immunosuppression than with usual immunosuppressive treatments [33]. Another element that may also take part in the

observed effect of IL-6R blockade by specific antibodies: the redundancy of IL-6 family which may blunt the potential efficiency of IL-6 inhibition by favoring the role of immunomodulatory cytokines from the IL-6 superfamily that transduce their signal through gp130. IL-27 may contribute to reduce Th17 differentiation and promote Tregs production [40, 41]. However these elements need to be confirmed in COVID-19 as IL-27 has also been shown to be involved in the promotion of proinflammatory responses and the Th1 differentiation of T cells [41].

To date, the hypothetical rationale of IL-6R blockade in the specific situation of severe SARS-CoV2 infection is still poorly supported by experimental data. Clinical results are also conflicting. Many uncertainties remain concerning the importance of the intensity of IL-6 production, the correlation with clinical severity, and the timing of the administration of anti-IL-6R inhibitors or local pulmonary bioavailability of these monoclonal antibodies. Finally, the beneficial effect of tocilizumab appears to depend on its concomitant use with corticosteroids [42, 43], as higher doses of dexamethasone are associated with clinical improvement [44, 45] and the doses of corticosteroids used are much lower than those used in bolus therapy for certain immunological diseases [35–37, 46]. Given the cost, the uncertainty of pharmacodynamics during COVID-19 (no pharmacodynamics class effect), and the potential threat of modification of the immune response modification by inhibiting inflammation, the appropriateness of IL-6 pathway inhibitors needs to be closely analyzed.

3.1 Role of IL-6 Receptor Inhibitors: Uncertainty due to Circulating IL-6 Concentration

Clinical studies have broadly confirmed the presence of circulating IL-6 in the blood of moderate and severe COVID-19 patients (see Tables 1 and 2). However, during COVID-19, the initial insult takes place in the lung parenchyma rather than in the blood [13–19, 47]. Therefore, the immunologic response develops mainly in the lungs, especially the alveoli, with cytokine concentrations observed in the circulation being only an approximative marker of the intensity of the proinflammatory response [24]. Numerous studies in patients with disease of varying severity have found consistent values of serum IL-6 levels from 5.0 to approximately 240 pg/mL (see Tables 1 and 2), partially depending on the degree of severity [11, 25, 39, 42, 43, 47–58]. In mild and moderate COVID-19, requiring hospitalization but not intensive care or resuscitation, circulating IL-6 concentrations are particularly low, around 5 pg/mL [42, 59]. In severe COVID-19, requiring mechanical ventilation, IL-6 serum concentrations may reach 125 pg/mL [47, 57, 59–61]. Such IL-6 serum concentration are similar to those measured during influenza, especially H3N2 (30 pg/mL) [62], H1N1 (approximately 150 pg/mL in mechanically ventilated patients) [63], H5N1 [64], and H7N9 (30–200 pg/mL) [62, 64–67], exceptionally reaching 500 pg/mL in the most severe case [66]. In all these situations, serum IL-6 values are much lower than those observed during classical ARDS/sepsis, in which concentrations may reach more than 2500 pg/mL, and cytokine release syndrome (CRS) associated with CAR-T cell activation, with 10-fold higher serum IL-6 concentrations measured [16, 25, 30, 34, 68–77]. Such observations raise questions about the importance of the systemic proinflammatory response during severe COVID-19 [69, 72, 74, 78–80]. These data also raise questions about whether tocilizumab is useful in the early phase of mild to moderate disease. Remarkably, studies demonstrating a potential benefit of tocilizumab in severe COVID-19 (with a PaO_2/FiO_2 around 150) found higher initial circulating IL-6 concentrations (144.1–238.3 pg/mL) [56], confirming the potential link between the systemic component of the response and the potential benefit of the treatment. In conclusion, the systemic magnitude of inflammatory mediator expression thus appears to play a considerable role in the assessment of severity and consequently in the therapeutic management of severe COVID-19 [16, 17].

3.2 Role of IL-6 Receptor Inhibitors: Uncertainty of Clinical Severity and IL-6 Concentration

It is well known that the wide variability in the individual inflammatory response during COVID-19 is responsible for a significant part of the differences in the responses to therapeutic interventions involving specific cytokine inhibitors [16, 81]. Although an early large study [82] found a correlation between the circulating IL-6 levels and mortality, the substantial variability in values, sometimes involving low levels, cast doubt on these conclusions. Initially, blood concentrations of major cytokines such as IL-6 were considered not to correlate with the severity of clinical damage in COVID-19 [24, 25, 83–85] and to be weakly associated with viral proliferation [39, 86]. A better, but still partial correlation (intensive care unit [ICU] vs non-ICU patients) was observed early in IL-6 expression in blood leukocytes (monocytes and CD_4+ lymphocytes) [87]. More recent data have tended to demonstrate a better correlation [88] but a potential publication bias was highlighted in a recent meta-analysis [89]. More than a single measure, the evolution of cytokine expression over time appears to be a potential prognostic predictor [90]. The lack of a strong association between the blood concentration of IL-6 and severity may be partly due to the absence of a correlation noted between the local, alveolar, and systemic inflammatory response, in particular, for IL-6 [91].

Table 1 Serum IL-6 levels during COVID-19 in cohort and retrospective studies

Serum concentration of interleukin-6 (ng/ml)										
Ref.	Prognostic		Severity					Sex		Whole population
	Survival	Death	Asymptomatic	Mild	Moderate	Severe	Critical	M	F	
[130]	–	–	6.44 (2.34–13.94)	15.3 (7.70–22.64)	10.79 (6.93–16.35)	16.09 (8.08–26.47)	21.84 (19.88–32.69)	18.16 (9.16–31.83)	12.67 (6.93–17.09)	-
[49]					13.3 (3.9–41.1)	25.2 (9.5–54.5)				
[11]	6.05 (5.12–6.99)	10.07 (7.36–14.80)	–	–	–	–	Without ARDS: 6.29 (5.36–7.83) with ARDS: 7.39 (5.63–10.89)	–	–	6.98 (5.46–9.02)
[50]	–	–	–	–	–	–	–	–	–	7.9 (6.1–10.6)
[47]	–	–	–	–	–	15.3 (6.2–29.5)	41.5 (24.8–114.2)	–	–	26.6 (7.5–43.4)
[51]	–	–	–	–	about 5	About 12	about. 15	–	–	–
[59]	from 6.41 (2.17) to 159.2 (268.95)	from 10.96 (5.25) to 2291.46 (568.27)	-	-	-	from 5.0 (3.64) to 51.7 (65.6))	from 7.4 (3.64) to 103.9 (43.6)	–	–	–
[39]	-	-	-	-	10.4 (3.8–31.0)	5.8 (3.1–16.9)	64.0 (25.6–111.9)	–	–	–
[60]	-	-	-	-			About 100	–	–	–
[116]	-	-	Non severe: 15·67 +/– 6, 34 Severe: 19.0 +/– 7.74					-	-	-

ARDS acute respiratory distress syndrome

Table 2 Serum IL-6 levels during COVID-19 in clinical trials considering tocilizumab and sarilumab

Article			Serum concentration of interleukin-6 (ng/ml)	
First author or study group	year	Réf.	Placebo / standard of care	Active
Tocilizumab				
Veiga VC	2021	[96]	208 (586)	192 (313)
RECOVERY	2021	[127]	-	-
Stone JH	2020	[43]	25.4 (14.6–40.3)	23.6 (14.0–49.9)
Salvarani C	2020	[42]	34.3 (19.0–59.3)	50.4 (28.3–93.2)
Lescure FX	2021	[52]	13.0 (3.6–23.5)	Two groups : 11.6 (5.1–23.5) 12.7 (5.5–26.5)
Soin AS	2021	[53]	85.2 (232.2)	115.5 (245.6)
Guaraldi G	2020	[56]	144.1 (41.1–385.8)	SC : 90.2 (86.6–401.0) IV : 238.3 -140.2–731.9)
Vazquez Guillamet MC	2021	[57]	48 (26–512.5)	66.8 (55–739.7)
Sarilumab				
SARICOR[a]	2021	[120]	8 (38-80)	S200 mg: 59 (43-88) S400 mg: 70 (43-127)
SARTRE	2021	[58]	13.25 [3.85–43.35]	19.20 [6.00–46.00]
Sivapalasingam S	2022	[61]	"severe patients" (median; min- max) 61.5 (9.10–571.26) "critical patients" 85.6 (9.1-2324.8)	"severe patients" S200: 53.3 (9.1–1713.2) S400: 58.2 (9.10–2771.4) "critical patients" S200: 116.1 (6.82–6531.58) S400: 125.9 (9.1–21545.3)

[a]Patients selected to have IL-6 ≥ 40 ng/ml or elevated

S200 Sarilumab: 200 mg, *S400*: Sarilumab: 400 mg, *IV* intravenous administration, *SC* subcutaneous administration

The lack of a strong association between IL-6 production and clinical outcomes may be partly due to possible immune dysregulation. A major study conducted by Giamarellos-Bourboulis et al. [92] underlined the correlation between intermediate severity, the presence of immune dysregulation, notably defined by HLA-DR expression, and patients with macrophage activation syndrome (highlighted by increased serum ferritin concentration) during COVID-19. These elements, however, show no clear clinical correlation with respiratory severity or the need for mechanical assistance. This observation raises the importance of the inflammatory response kinetics, the clinical consequences of initial proinflammatory mediator release being observed during the compensatory anti-inflammatory response syndrome. On the other hand, the evolution of IL-6 levels during the disease, independently from the use of IL-6 pathway inhibitors, may be of greater prognostic value for survival [57]. A similar variation has been described for ARDS of other origins, leading to the distinction of two groups: hyperinflammatory and hypoinflammatory ARDS patterns [70, 79].

This observation can also be viewed from another perspective in which the increased IL-6 concentration may be, at least in part, due to a compensatory response, in which IL-6 seeks to supplant the failure of other inflammatory pathways [93]. Finally, it would be wrong to assume that the inhibition of IL-6 would be linearly associated with improved survival because the inflammatory reaction does not depend on a single inflammatory mediator [19].

Finally, another important aspect in this field is related to the contrasting functions of IL-6. IL-6 promotes the reduction of type I/III interferon production. Similarly, serum IL-6 concentration correlates with lymphocyte exhaustion (marked by PD-1 or Tim3 expression) [94] and inversely correlates with NK cell count [18].

3.3 Role of IL-6 Receptor Inhibitors: Uncertainty of Administration Timing

Shock (due to endothelial hyperpermeability, resulting in reduced intravascular volume) is essential to the decision to introduce tocilizumab during the CRS [80, 95]. Information on hemodynamic failure is lacking in the vast majority of COVID-19 cases, including its critical forms [27, 42, 43,

52–54, 96–100]. During COVID-19, patients who develop a disproportionate inflammatory response, marked by high blood levels of proinflammatory cytokines, may benefit from a reduction in the intensity of the immune response [15, 71]. Therefore, tocilizumab may have a true therapeutic effect in this context, but the targeted patients, especially in terms of severity, remain very poorly defined [16, 24], and broad use is unquestionably expensive and irrelevant [101].

3.4 Role of IL-6 Receptor Inhibitors: Uncertainty About the Lung Bioavailability of Tocilizumab

The easier accessibility of blood samples has led to the identification of proinflammatory mediators in this compartment [24, 42, 43, 47, 51–54, 59, 71, 77, 79, 83, 84], supporting the perception of an initial systemic response [102, 103]. The bioavailability and duration of efficacy of tocilizumab in the vascular compartment (12 days–3 weeks) [103, 104] appear to be satisfactory in the context of systemic cytokine release. However, as mentioned above, the clinical evolution during COVID-19 is centered on a local and regional bronchopulmonary inflammatory response [14–19, 24, 103, 105–107]. The clinical evolution of COVID-19 is underlined by a major alteration of hematosis during the acute phase, followed by destruction and sustained pathological remodeling of the pulmonary parenchyma. A reduction of parenchymal inflammation appears to be the most crucial parameter to consider for the prevention of severe forms and even reduction of the mortality linked to viral infection. The lack of information on the bioavailability of tocilizumab in the alveolar fluid and the higher pulmonary concentration of IL-8 when patients are treated with tocilizumab rather than with corticosteroids [106] raises doubts about the value of the local use of tocilizumab in the pulmonary parenchyma. Nonetheless, tocilizumab may have a local vascular rather than an alveolar effect. Salvati et al. have demonstrated an improvement in gas exchange, a decrease in alveolo-arterial gradient and a reduction in the radiographic score for patients who received tocilizumab [108]. No definite explanation is currently available, but the improvement in endothelial dysfunction, including permeability and the activation of coagulation, mentioned by the authors [108], may represent a relevant avenue for future investigations [109].

4 Relevance of the Early Administration of Tocilizumab During COVID-19

4.1 Initial Publications on the Administration of Tocilizumab During COVID-19

As early as 2020, the first cohort studies highlighting the potential benefit of tocilizumab included ICU patients [110, 111]. Similarly, there appeared to be a benefit in situations of major systemic inflammatory response, characterized in particular by the severity of pulmonary involvement and the presence of other organ failures, notably the kidney or bone marrow [24, 43, 111]. In a multicenter retrospective Italian cohort of 544 patients, mortality appeared to be reduced by tocilizumab administration, but the difference only occurred for patients with a PaO_2/FiO_2 ratio < 150 [56]. However, the benefit appeared to be mitigated if tocilizumab was administered too late during mechanical ventilation: this drug was able to reduce 28-day mortality by 4-fold (8% vs 36%; $p = 0.001$; HR 0.54, 95% CI 0.29–1.00) when administered during the first 48 hours of mechanical ventilation [110]. Similar results were observed in a multicenter study (23 centers, 118 patients) treated within the first 24 hours of invasive ventilation [112]. Conversely, administration beyond this period was associated with increased mortality (OR: 3.513 [1.15–11.97]; $p = 0.003$) [112].

4.2 Comparative Clinical Trials

4.2.1 Non-Randomized Comparative Studies

Many articles have been published about the potential value of tocilizumab during COVID-19. However, most of these studies were only retrospective non-randomized comparisons [56, 99, 110–117]. In these publications, survival was not systematically improved [57, 110–114, 118], particularly that of ventilated patients [112, 118]. Other studies even reported an increase in mortality [112, 119]. At the time the patients in these retrospective studies were treated, the importance of corticosteroids was just beginning to be recognized [145], and the same is true for clinical improvement and reduction in hospital stay or risk of intensive care admission [143].

There have been rapid changes in the organization of the research plan, allowing the implementation of randomized studies that have provided new information (Table 3). However, the persistence of high heterogeneity in study design has made interpretation difficult.

4.2.2 Randomized Studies: Raw Results

Two IL-6 receptor inhibitors were randomized: tocilizumab and sarilumab. All studies were performed used the intravenous rather than subcutaneous form of these inhibitors. Blinded studies with sarilumab (200 or 400 mg once) found no improvement in survival with this treatment [52, 58, 61, 120]. An open-label randomized trial, including 115 patients mostly requiring oxygen supply, using two different doses of sarilumab (200 or 400 mg once), also found no significant survival benefit or modification in the initial clinical course [120]. Another prospective, randomized, multicentric study

Table 3 Randomized studies of tocilizumab and sarilumab in COVID-19

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[121]	–	68 *vs* 80	100%	–	–	–	Sarilumab	7% (usual care) 15% (sarilumab)	No	On day 14: - mechanical ventialtion or death: 31% (sarilumab) and 22% (usual care) - Mortality (day 14): 9% vs 11% - Mortality (day 28): 12% vs 18% - Mortality (day 90) : 15% vs 21%		On day 4 : worsening of the score for 26% in both groups	* On day 14 : worsening requiring HFNO or mechanical ventilation or death : 37% (sarilumab) and 34%(usual care)
[54]	12.1 +/–6.6 11.4+/–6.9	294 *vs* 144	26.5% vs 30.6%	32.0% *vs* 27.1%		15.3% *vs* 10.4%	Tocilizumab	19.4% *vs* 28.5%	No	At D28 : 19.7% *vs* 19.4%	27.9% *vs* 36.7%		- *Median value for clinical status on 7-category ordinal scale : 1.0 (1.0 to 1.0) *vs* 2.0 (1.0 to 4.0) - *Incidence of ICU admission : 21.3% vs 35.9%
[120]	9 (7-11) 9 (7-12) 9 (8-11)	39 *vs* 37 *vs* 39	100%	–	–	–	Sarilumab	Dexamethasone: 54% vs 46% vs 56% Methylprednisolone: 34% *vs* 43% *vs* 36%	No	D28 : 8% *vs* 11% *vs* 0%	D28: 10% *vs* 16% *vs* 8%	D28: 88% *vs* 84% *vs* 94%	Discharge from hospital: 84% *vs* 84% *vs* 92%

Table 3 (continued)

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[58]	10.0 (8.0, 12.0) *vs* 9.0 (8.0, 11.0)	99 *vs* 102	100% (NB: high oxygen requirement, including face mask, were excluded)	–	–	–	Sarilumab	Methylprednisolone : 100% (standard of care in both group) for at least 3 days	No	D15: 1.96% *vs* 0.0% D28: 1.96% *vs* 2.02%	-	-	*HFNO or NIV or CPAP: - D15: 39.22% *vs* 42.42% - D28: 39.22% *vs* 42.42% *ICU admission: - D15: 9.8% *vs* 7.07% - D28: 9.8% *vs* 7.07% *Median time to hospital discharge: 7 [6–8]
[125]	8.8 +/– 4.8 *vs* 8.9 +/– 4.7	T+R: 430 P+R: 210	T+R: 6.7% P+R: 6.2%	T+R: 78.1% P+R: 83.3%		T+R: 9.1% P+R: 4.3% (ECMO : 6.0 % and 6.2%)	Tocilizumab	T+R: 83.2% P+R: 86.4%	No	D28: 19.5% *vs* 18.1% D60: 22.6% *vs* 25.7%	D28: Mechanical ventilation or death. P+R: 29.0% T+R: 28.6%	Clinical status at day 14 assessed on the 7-category scale: NS	Time to hospital discharge or "ready for discharge": 14 [12–15] *vs* 14 [11–16]

Table 3 (continued)

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[98]	-	T: 353 S; 48 C: 402	T: 1 S: 0 C: 2	T: 101 S: 17 C:110	T: 147 S: 23 C:169	T: 104 S: 8 C:121	Tocilizumab or Sarilumab	T: 50 S: 0 C: 52	**Yes**	- Hospital: **T: 28%** **S: 22%** **C: 36%** **Pooled anti-IL-6R: 27%** **Survival OR: 1.64 (1.14 – 2.35)**	-	-	Organ support-free days (median [IQR]): T: 10 [−1 to 16] S: 11 [0 to 16] C: 0 [−1 to 15]
[43]	T: 9.0 [6.0–13.0] P: 10.0 [7.0–13.0]	T: 161 P: 82	T: 133 P: 61	T: 5 P: 5		T: 0 P: 1	Tocilizumab	–	No	T: 5.6% P: 3.6%	T: 6.8% P: 9.7%	T: 91.3% P: 87.8%	-
[97]	T: 8.0 [0.0 – 31.0] P: 8.0 [0.0 – 36.0]	T: 249 P: 128	T: 161 P: 81	T: 64 P: 36		None	Tocilizumab	T: 55.4% P: 67.2%	**Yes**	T: 10.4% P: 8.6%	mechanical ventilation or death: **T: 12.0%** **P: 19.3%** **(p = 0.04)**	D28: T: 88% P: 84%	-
[42]	T: 7.0 [4.0 -11.0] C: 8.0 [6.0 -11.0]	T: 60 C: 66	T: 100% C: 100%		T: 0% C: 0%	T: 0% C: 0%	Tocilizumab	T: 1.7% C: 6.0%	No	D30: T: 3.3% C: 1.6%	-	-	Admission to the ICU: T: 10.0% C: 7.9%
[127]	T: 9 [7–13] C: 10 [7–14]	T: 2022 C: 2094	T: 46% C: 45%		T: 41% C: 41%	T: 13% C: 14%	Tocilizumab	Systemic corticosteroids: T: 82% C: 82% Dexamethasone: T: 2% C: 2%	**Yes**	**D28: T: 31%** **C: 35%** **(p= 0.0028)**	T: 35% C: 42%	-	-

Table 3 (continued)

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[53]	-	T: 91 P: 88	T: 81 C: 80		T: 28 C: 20	T: 5 C: 4	Tocilizumab	T: 91% C: 91%	No	D28: T: 12% C: 17%	-	-	-Ventilator-free days T: 24.3+/–9.2 C: 23.2 +/–10.6 - ICU admission: T: 78% C: 73%
[96]	T: 10.0 +/–3.1 C: 9.5 +/– 3.0	T: 65 C: 64	T: 39 C: 28	T: 15 C: 26		T: 11 C: 10	Tocilizumab	T: 45 C: 47	No	- D28: T: 21% C: 9% - Hospital: T: 21% C: 9%	T: 7 C: 11	-	Ventilator-free days: T: 19.4 +/–12.0 C: 20.5 +/–10.8
[100]	T: 10 [7 . 13] C: 10 [8–13]	T: 63 C: 67	T: 0% C: 0%	T: 0% C: 0%	T: 0% C: 0%	T: 100% C: 100%	Tocilizumab	Corticosteroids: - Prior randomization: T: 16% C: 18% - After randomization: T: 30% C: 55% Dexamethasone: - Prior randomization: T: 6% C: 7% - After randomization: T: 14% C: 28%	No	D28: T: 11% C: 12%		Median score at D14: T: 2 [2–5] C: 4 [2–7]	-

Table 3 (continued)

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[61]	"median duration of illness" in "critical stratum" : 9.0 days	Phase 2: P: 90 vs S200: 187 Vs S400: 180 Phase 3 (cohort 1) : P : 294 *vs* S200: 489 vs S400: 582; Phase 3 (cohort 2) : P : 6 *vs* S800 : 2	P: 95 S200: 190 S400: 188	"critical patients" (oxygen by nonrebreather mask or HFNO, NIV or IMV): Critical receiving MV: P: 80 S200: 164 S400: 179 Critical not receiving MV: P: 134 S200: 171 S400: 244			Sarilumab	"severe patients": P: 27.4% S200: 27.9% S400: 26.6% "critical patients" Critical receiving MV: P: 27.5% S200: 22.6% S400: 27.9% Critical not receiving MV: P: 35.1% S200: 33.3% S400: 35.7%	No	In patients receiving MV at baseline: D29 mortality: P: 41.9% S400: 36.4% D60: P: 51.6% S400: 39.4% Risk difference: -5.5% [-20.2, 8.7] Critical patient not receiving MV: D29 mortality: P: 15.7% S400: 26.4% D60: P: 25.0% S400: 29.9% Risk difference: +10.7% [.9, 19.3]	-	On day 22: Severe patients: P: 92.0% S200: 92.0% S400: 68.6% Critical patients: P:34.1% S200: 47.9% S400: 60.2% MSOD/IC: P: 47.6% S200: 39.5% S400: 43.9%	

Table 3 (continued)

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[122]	Tocilizumab part: T: 11 (9–15) C: 11 (9–14) Sarilumab part: S: 11 (9–15) C: 11 (8–21)	Tocilizumab part: T: 51 C: 46 Sarilumab part: S: 50 C: 41	WHO-CPS at least 5				Tocilizumab And Sarilumab	- Tocilizumab part: Corticosteroids: Dexamethasone: - Sarilumab part: Corticosteroids: Dexamethasone: 0%	No	Risk of death up to D90: -Tocilizumab part: C: 30% *vs* T: 24%; HR 0.67 [0.30 to 1.49] -Sarilumab: C: 39% *vs* S: 29% ; HR 0.74 ([0.35 to 1.58]	D14 IMV or NIV or ONHD weaning: Tocilizumab part: T: 47% C: 42% Sarilumab part: S: 38% C: 33% ---- D28 VFD: Tocilizumab part: T: 9.8 (9.5) C: 7.2 (9.4) Sarilumab part: S: 7.5 (9.5) C: 4.6 (7.6)	Decrease WHO-CPS at D4: Tocilizumab part: T:28.6% C: 30.2% Sarilumab part: S: 29.2% C: 21.2%	No need NIV or IMV at D14: Tocilizumab part: C: 42% *vs* T: 47% Sarilumab part: C: 338% *vs* S: 33%

Table 3 (continued)

Study			Oxygen therapy				Intervention		Benefit	Criteria			
Ref	Number of days from onset of symptoms	Number of patients	Oxygen	HFNO	NIV	IMV	Anti-IL-6R	Corticosteroids	Yes/No	Mortality	IMV requirement	Improvement of WHO-CPS score	Other
[126]	DX: 9 [7−11] DX+T: 9 [7−11]	DX: 226 DX+T: 224	100%	0%			Tocilizumab	100%	No	- D14: DX: 5% DX+T: 5% - D28: DX: 8% DX+T:7% - D60: DX: 10% DX+T: 8% - D90: DX: 11% DX+T: 8%	D14 IMV or death: DX: 14% DX+T: 12%	Independency from oxygen at: - D14: DX :62% DX+T: 71% - D28: DX: 72% DX+T: 82%	Bayesian analysis: DX+T has a 72.8% chance of being superior to DX alone

C control group / Standard care group / usual care group, *CPAP* continuous positive airway pressure, *DX* Dexamethasone, *DX+T* Dexamethasone and Tocilizumab, *HFNO* High flow oxygen, *IL-6R* Interleukin-6 receptor, *IMV* invasive mechanical ventilation, *MSOD/IC* multi-system organ dysfunction/immunocompromised, *MV* Mechanical ventilation, *NIV* Noninvasive ventilation, *NS* non-significant, *P* Placebo, *P+R* Placebo and Remdesivir, *S* Sarilumab group, *S200* Sarilumab (200 mg) group, *S400* Sarilumab (400 mg) group, *S800* Sarilumab (800 mg) group, *T* Tocilizumab group, T+R: Tocilizumab and Remdesivir, VFD: Ventilator-free days, Positive results are indicated in bold

WHO score: 1, Discharged (or "ready for discharge"). 2, Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen. 3, Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen. 4, ICU or non-ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen. 5, ICU, requiring intubation and mechanical ventilation. 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support. 7, Death

involving 201 patients did not show a significant benefit in sarilumab administration during an 'unfavorable' respiratory course, or against the risk of ICU admission or associated death [58]. Similarly a recent phase II/III randomized trial that included 'critical patients' (defined by low flow oxygen requirement by mask, or high flow nasal oxygen, or mechanical ventilation) did not find any improvement in survival, regardless of the dose of sarilumab (200 mg, 400 mg or 800 mg) [61]. These results are in contrast with those of the REMAP-CAP, which tested sarilumab or tocilizumab and showed a potential benefit [98]. More recently, two French open-label randomized Bayesian studies from the CORIMMUNO-19 research group did not show any survival benefit for moderate [121] or severe patients [122]. Other studies (ClinicalTrials.gov identifiers: NCT044327388, NTC044315298) are still underway and will most likely show a more specific potential benefit in the therapeutic arsenal.

In mild forms of the disease, tocilizumab does not improve weaning from oxygen therapy (either at day 14 [43, 100] or at day 28 [43]) in the overall population of hypoxemic patients. The absence of significant renal, hemodynamic, or respiratory failure (often assessed by the PaO_2/FiO_2 ratio or the need for mechanical ventilation) appears to be associated with the absence of a benefit [42, 43, 99]. However, a post-hoc analysis of the study by Soin et al. suggests the possibility of a survival benefit at day 28 for initially severe patients [53]. Numerous studies have highlighted the probable lack of benefit of tocilizumab in mild forms of COVID-19 [42, 43, 53, 54, 97, 122–124] and its potential value for patients with more severe forms [97].

In more severe disease, the administration of tocilizumab may reduce the risk of mechanical ventilation or transfer to the ICU (both on day 14 [43, 100] and day 28 [43]). However, these results were not confirmed by other studies that included similar patients and assessed the deterioration of their health at the same time points [42, 43, 53, 96, 97, 100, 122, 125]. The absence of a beneficial effect was even observed up to day 60 [97, 125] and day 90 [126] in other studies. The duration of mechanical ventilation could also be reduced, but the low proportion of ventilated patients in the studies makes it difficult to draw any definitive conclusion, mainly because the duration of ventilation has not been reported anywhere else [126].

A recent large, double-blind, placebo-controlled, multicenter study comparing the combination of remdesivir (a selective inhibitor of viral RNA-dependent RNA polymerase) with or without tocilizumab found no difference in mortality, length of hospital stay, or avoidance of invasive mechanical ventilation [125]. Adding remdesivir raises the question of the potential benefit of tocilizumab for patients treated with remdesivir, but tends to demonstrate the absence of the supposed additive or synergistic effect as observed with corticosteroids [125]. The authors also emphasized the imbalance between the groups despite randomization in terms of the requirement for mechanical ventilation or corticosteroid administration at the date of inclusion [125]. However, these parameters probably do not explain the absence of the expected effect.

Two studies (RECOVERY and REMAP-CAP) have reported a reduction in mortality when patients were treated with IL-6 inhibitors.

4.2.2.1 RECOVERY Study In the RECOVERY study [127], mortality at day 28 was 31% (621 patients) in the treated group and 35% (729 patients) in the group without specific treatment (RR: 0.85 [0.76–0.94]; $p = 0.0028$). The risk of developing renal failure requiring dialysis also appears to have been reduced [127]. However, there are many limitations to consider. The difference in all-cause mortality disappeared when focusing on COVID-19-related deaths and only seemed to exist in association with deaths from unknown causes. Another critical element is observed: the survival benefit appeared to only be present for patients receiving concomitant corticosteroid therapy (mortality: 29% vs 35%; RR: 0.79 [0.70–0.89]) [155]. This is particularly important given that 17% of patients did not receive study treatment in the intervention group [127].

The observed difference for the secondary need for invasive mechanical ventilation (265/1754 [15%] vs 343/1800 [19%]; RR: 0.79 [0.69–0.92]; $p = 0.0019$), the observed difference disappeared when focusing on the population not receiving any ventilation at the time of randomization [127]. This suggests a greater benefit for initially more severe patients, in particular those on non-invasive ventilation or high-flow nasal oxygen therapy.

Conversely, no improvement in the duration of mechanical ventilation was observed when tocilizumab was administered to patients already intubated at the time of randomization [127]. Too-high severity of the disease eliminated any benefit, confirming what was previously observed by Rosas et al. [54]. These elements better define a population of interest for the administration of tocilizumab: patients with severe (non-invasive ventilation or high-flow nasal oxygen therapy) but not critical (invasive ventilation).

Interestingly, in their subgroup analysis, the RECOVERY team did not find any benefit of tocilizumab in women, with the full benefit being present in men (an effect also observed for hospital discharge). Such information is of paramount interest given the well-known difference in inflammatory response according to sex [128–131].

Estrogens are known to be capable of modulating inflammatory response without compromising the anti-infectious properties of leukocytes. During COVID-19, androgens are responsible for an increased expression of transmembrane serine protease 2 (TMPRSS2), and may favor the infection

of cells, especially those in the lung [132]. On the other hand, protective interferon-α expression is favored by estrogens and could ease the control of viral infection [128, 132]. Moreover, a decrease in estradiol has been observed in association with IL-6 production [133]. This may partly explain the clinical discrepancy observed in RECOVERY according to sex.

4.2.2.2 REMAP-CAP Study The primary outcome in the REMAP-CAP study was the number of days without the need for respiratory or hemodynamic support for patients initially admitted to the ICU [98]. In-hospital survival was also improved with tocilizumab or sarilumab (72% and 78%, respectively, versus 64%), as was 90-day survival [98].

The frequency of hemodynamic failure (up to 20% need for vasopressor support) and the lack of information related to renal function are two parameters that weaken the importance of the obtained results [98]. Hemodynamic failure during COVID-19 is relatively modest and often delayed whereas renal damage in the most severe forms frequently requires dialysis. In this context, the differences in survival highlight the importance of initial treatment of the actual pathology and confirmation of COVID-19.

Of note, the reduction of hemodynamic and respiratory failure by inhibition of IL-6 receptor antagonists appears to occur to a greater extent for patients with the highest levels of C-reactive protein (CRP) [98]. As CRP is produced in response to IL-6 stimulation (linear correlation), the observed benefit of tocilizumab in this study was the greatest in the population with the most intense inflammatory response [98]. However this correlation remains uncertain as many critical patients have relatively low CRP levels, similar to those with severe disease [134]. Conversely, the presence of invasive mechanical ventilation at the time of treatment is not associated with a benefit in the duration of ventilation but could improve patient survival [98]. The post-hoc nature of these various analyses reduces their impact, but their consistency with the other observations is no less attractive. Finally, the Bayesian model used also raises other questions, in particular about the neutrality of the initial hypothesis, as there is no firmly established data in this specific therapeutic area.

4.2.2.3 Increased Mortality: The TOCIBRAS Study In contrast to the other studies, one study was stopped early (129 of the 150 patients initially planned were included) because of excess mortality (17% vs 3% at day 15 and 21% vs 9% at day 28) in the group of patients receiving the study treatment, even though they were less severe at the time of randomization (more oxygen therapy in the tocilizumab group: 60% vs 44% and less noninvasive ventilation or HFNO (high flow nasal oxygen): 23% vs 41%) [96]. Of note, the results of a post-hoc analysis adjusted for baseline levels of respiratory support were consistent with those of the main analysis and did not show a significant effect on the primary outcome.

No clear explanation is currently available to explain the observed higher mortality. Considering on the one hand the clinical effect of tocilizumab on CRP and on the other hand the attribution of deaths to acute respiratory failure or multiple organ dysfunction secondary to COVID-19, reported by the authors [96], it is possible that the anti-inflammatory effect was associated with an impairment in the control of viral infection. This may have been exacerbated by the use of high amount of corticosteroids (approximately half of the patients received at least 0.5 mg/kg/d of prednisone equivalent).

4.2.3 Randomized Studies: Potential Limitations

The first issue concerning the randomized studies is the broad heterogeneity in patient severity, ranging from room-air breathing to ARDS requiring invasive mechanical ventilation and often neuromuscular blocking drugs [42, 43, 52–54, 61, 85, 96–98, 100, 122, 126, 127]. Similarly, the inclusion [42, 52, 54, 61, 96–98, 122, 127] or not [43, 100, 126] of patients on high-flow nasal oxygen therapy (sometimes at very low flow rates [98]) contributes to confusion in interpreting the results.

The lack of blinding in many studies [42, 53, 96, 98, 100, 122, 126] is also problematic because knowledge of the treatment and the undisputed favorable bias associated with its use may have considerably modified subsequent therapeutic interventions, including the decision to transfer to the ICU or the type of intensification chosen.

The frequency of administration of confounding treatments (antivirals, other cytokine inhibitors, anti-inflammatory drugs, etc.) [42, 43, 52–54, 96–100, 122, 126, 127], which were often distributed heterogeneously during the initial period of the pandemic, has led to more complex analysis even though certain post-hoc analyses do not find any effect of these combined treatments [52].

Positive results obtained with corticosteroids led to their routine administration from June 2020 [27–29]. Their role in tocilizumab [54, 96–98, 100] and sarilumab [52, 98, 121] studies is an additional confounding factor. The potential relationship between the absence of corticosteroids and the poor efficacy of sarilumab has been widely suggested [121]. However, a study investigating the potential benefit of sarilumab and including corticosteroids (methylprednisolone) in the 'standard of care' found no difference between the groups regardless of the intensity of the inflammatory response [58]. Regrettably, the study was designed before the efficacy of dexamethasone was demonstrated, allowing neither the possible confirmation of the potentialization of bitherapy nor the effect of methylprednisolone in COVID-19 [58]. Another study has been recently published

that included severe patients randomized and stratified on corticosteroid use at the time of inclusion [61]. Although no clinical benefit of sarilumab could be demonstrated, a post-hoc analysis tended to demonstrate a potential benefit of the association for the most severe patients (requiring invasive mechanical ventilation) (HR: 0.49; 95% CI 0.25–0.94) [61]. Unfortunately, the class of corticosteroids was not specified. The use of corticosteroids other than dexamethasone further complicates interpretation of the data [97, 98, 127]. The difference in the frequency of corticosteroid use between groups can be considerable [100]. Analysis of these subgroups sometimes showed lower mortality independent of tocilizumab administration [54]. In the most extensive studies, subgroup analysis of the combination with corticosteroids found a disappearance of the initial effect in the absence of the association with corticosteroids, undermining the main conclusions of the studies [127]. The lack of efficacy of tocilizumab in studies that did not include steroid administration tends to confirm the importance of anti-inflammatory treatment in the potential benefit of IL-6 pathway inhibitors [42, 43, 122, 126]. The inability of tocilizumab to control severe inflammatory responses has already been suggested as an explanation for the current conflicting results in randomized studies [85]. Based on all these data, the addition of tocilizumab may enhance the systemic anti-inflammatory effect of steroid therapy, specifically on the IL-6 pathway [100]. However, a recent study from the CORIMMUNO group did not find any reduction in the requirement for mechanical ventilation or mortality with the association of tocilizumab and dexamethasone among patients with moderate to severe disease [126].

An analysis of the influence of tocilizumab on the inflammatory response is also absent from many studies. Inhibition of the IL-6 pathway may be associated with an increase in circulating concentrations of interferon-α, a lack of reduction in IL-2 and TNF levels, and a reduction in IL-10 expression, both of which suggest a more pronounced proinflammatory response in treated patients than in the group of patients who did not receive the anti-inflammatory drug, even though the greater decrease in CRP confirms the effect of tocilizumab [96].

Variations in efficacy as a function of patient severity highlights the importance of the timing of tocilizumab therapy [135]. Intervention that is received too early may promote the failure of viral control [19, 24, 136, 137]. Conversely, treatment that is received too late is clearly associated with a lack of efficacy. This time frame has been generally unclear in clinical studies [53, 54, 96–100], which took into account the length of hospitalization and not the extent of disease progression. Although the importance of the time between symptom onset and treatment is still uncertain, changes in cytokine expression could explain the variation in efficacy of tocilizumab efficacy. In the RECOVERY study, the mean time was 9 days from the onset of symptoms to the start of hospitalization (2 days) [127], reinforcing the results of the non-randomized study of Gupta et al. in which a benefit was observed when the period between symptom onset and ICU admission was < 3 days [99]. In the REMAP-CAP study, the median length of stay from admission to inclusion in the study was 1.2–1.4 days [98]. Subgroup analysis showed that the effect of the treatment disappeared if the patient was hospitalized beyond 7 days after the onset of clinical symptoms [127]. The hypothesis of an early benefit of tocilizumab in severe disease is indirectly reinforced in the multicenter study of Rosas et al. (COVACTA), in which inclusions were made around the 12th day of symptoms, finding no benefit of tocilizumab [54]. Given all available data, the potential benefit of tocilizumab for severely ill patients would be before day 10, probably as soon as they require high flow oxygen or noninvasive ventilation.

Despite the widely used seven-category ordinal scale of clinical status, patient classification in studies remains heterogeneous and contributes to the observed confusion. For example, in different studies, 'severe' included those with pulse oxygen saturation (SpO_2) >90% in room air [53, 96, 100] or respiratory rates >30 cycles per minute [53, 96, 100], even though they are managed outside of the ICU and require neither mechanical ventilation nor high flow nasal oxygen [43, 96, 97, 100]. In other studies, ward and ICU patients were indiscriminately included [52, 53, 96, 97, 127], limiting the ability to distinguish the appropriate population of therapeutic interest.

Similarly, the use of composite outcome criteria is associated with inextricable results [43, 97, 98, 100]. For example, in the study of Salama et al. involving 389 patients admitted to the ward or intensive care unit (14.5% vs 17.2%), the administration of tocilizumab appeared to improve the endpoint of 28-day survival and reduce the need for invasive ventilation or extra-corporeal membrane oxygenation (ECMO), but did not change 28-day mortality, when assessed separately, or mortality at day 60 (11.6% vs 11.8%) [97]. More disturbing is the higher occurrence of death without mechanical ventilation in the placebo group, with no explanation for the absence of therapeutic intensification [97]. Finally, the fact that there was no difference in length of stay or the rate of decrease in clinical severity (assessed by the WHO 7-point scale) argues against the actual effectiveness of the treatment [97].

Finally, the absence of a 'class effect' highlighted by the failure of sarilumab studies to demonstrate a beneficial effect is a significant issue. Sarilumab is an undoubtedly effective IL-6 receptor inhibitor with a 20-fold higher affinity for the IL-6 receptor alpha chain than tocilizumab, and is broadly used [58, 138]. The difference in IL-6R occupancy between sarilumab and tocilizumab [138] may contribute to the observed discrepancy in the clinical results. However, the

higher affinity and the prolonged efficiency of sarilumab can be expected to be associated with a better clinical efficiency. There are many other possible explanations for the failure to demonstrate a clinical effect in this particular pattern of acute viral infection. However, such limitations should be the same for tocilizumab. One hypothesis is that there is a possible specific inhibitor effect of tocilizumab that involves the interaction of other cytokine receptors, such as IL-27.

4.3 Recent Meta-Analysis on IL-6 Receptor Inhibition During COVID-19

The recent original RCT studies have been meta-analyzed, alone or in association with previous cohort studies, providing heterogeneous results (cf. Table 4). Currently, sarilumab does not appear to be a relevant therapeutic option during COVID-19 [139, 140], even if a class effect was used in one meta-analysis [141].

The ability of tocilizumab to reduce short-term mortality during COVID-19 remains unclear in a recent meta-analysis [114, 139–162]. A positive effect on raw mortality values can be observed in many works [114, 139, 140, 143, 146, 148, 151–153, 155–158, 160, 163–165], sometimes only in statistical analysis using a fixed-effect model [142, 154, 160], with a loss of significance in a random-effect model [154, 160], and this improvement in survival does not appear to be confirmed beyond day 60 [140]. In other meta-analyses, no difference in whole population mortality [142, 144, 145, 147, 149, 150, 162, 164] was observed, notably in studies including only RCTs [143, 146, 162, 163], or in sensitivity analyses including only trials with a low risk of bias [114, 140, 142–150, 163], although this point is uncertain [151, 156].

A detailed analysis shows that the potential benefit appears to be possibly stronger for more severe patients. Classified as 'severe' or 'critical', these patients generally corresponded to those requiring high flow oxygen, noninvasive ventilation or invasive ventilation, or to class 6–9 of the WHO classification [154]. However, severe cases include classes 4 and 5 of the WHO classification without distinction. Improvement in patients already invasively ventilated or requiring ECMO is still debatable. Similarly, despite initial hope [98], no survival benefit was observed in patients requiring ICU admission at study inclusion [142, 155], and a benefit for patients already requiring mechanical ventilation is yet to be demonstrated [161, 162]. Delayed administration of tocilizumab is associated with the loss of previous significance despite a large number of available included patients [165].

A reduction in mortality may depend on the concomitant administration of corticosteroids [139, 151, 164]. Similarly, progression to ICU [139], invasive mechanical ventilation [139], or ECMO [139] may be reduced by the combination of tocilizumab and corticosteroids rather than by inhibition of the IL-6 receptor alone. Unfortunately, specific analysis of this combination has not been systematically carried out [114, 140–144, 146, 148, 149, 152, 153, 155, 156, 158, 163, 165]. On the other hand, steroid administration at inclusion does not appear to modify the mortality rate in treated patients relative to the standard of care [147].

Another question to be raised is whether progression to ICU admission can be reduced. Tocilizumab may be effective [142, 147, 148, 155, 156] but has not been so in every meta-analysis [114, 145, 148, 153, 164], and clinical improvement is often absent [114, 140, 143, 146]. More restrictively, tocilizumab may reduce progression to invasive mechanical ventilation [114, 142, 145, 147, 150, 151, 153, 155, 156, 158, 160, 162] but the true effect on this parameter is still unclear [141, 148, 163, 164].

Numerous risks of bias have been highlighted as a major limitation to the interpretation of meta-analyses. They include methodological issues [141, 143, 146, 148, 151, 152, 159, 160, 164, 165], such as open-label design [142, 144, 151, 154, 155, 162], the existence of a second randomization (RECOVERY) [155], using the study drug depending on its local availability [155], modification of outcomes during patient recruitment [155], early termination of studies for futility or safety [155], and heterogeneity in patient recruitment, with a large difference in the incidence of mechanical ventilation [155] and patient severity [149, 160, 162], especially in terms of inflammatory severity [162]. Also lacking is a clear definition of patient severity, the indication for ICU admission, and the need for invasive mechanical ventilation [140, 142, 149, 158, 160, 165]. Considerable variation in the standard of care and the administration of supposed anti-COVID-19 treatments has been extensively documented [140, 143, 146, 151, 155, 156, 159, 162, 164, 165].The potential effect of industry sponsorship has also been reported [142]. Last but not least, the lack of structured reporting of superinfections may constitute an issue in safety analysis [155].

Concerning the meta-analyses themselves, the inclusion of studies before peer review [140, 142, 160, 161, 164], asymmetry of funnel plots for publication or selective reporting [114, 141, 142, 151, 156, 160, 163], and the weight of a small number of trials in the overall analysis [142, 151, 155, 156] were the most noted limitations.

5 Should We Try to Specifically Inhibit the IL-6 Pathway During COVID-19?

5.1 Should Tocilizumab Be Used?

The considerable heterogeneity of the population included in these studies and meta-analysis makes it difficult to

Table 4 Meta analyses of trials of tocilizumab and sarilumab in COVID-19

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[153]	23	6279	1897	Morality: - All types of severity:–**0.062 (- 0.118,–0.005)** - Severe patients:–**0.119 (-0.177,–0.06)**	- All types of severity: 0.003 (-0.135, 0.141) - Severe patients:0.096 (-0.009, 0.200)	- All types of severity:–0.041 (-0.145, 0.063) - Severe patients:–**0.108 (-0.193,–0.024)**	Not evaluated	Not evaluated
[139]	27	10 930	6449	Day 28: OR: **0.86, 95%CI: 0.79-0.95**; P = 0.003 Absolute mortality risk: 22% for IL-6 antagonists and 25% for usual care/placebo - Tocilizumab: **0.83, 95%CI: 0.74-0.92**; P < .001) - Sarilumab: 1.08 (95%CI: 0.86-1.36; P = .52)	Not evaluated	Not evaluated	Progression to IMV, ECMO or death (whole population): - without CS: 0.96, 95% CI: 0.79-1.17 - with CS: **0.71, 95% CI: 0.63-0.80** Progression to IMV, ECMO or death (Tocilizumab): - without CS: 0.95, 95% CI: 0.76-1.20 - with CS: **0.69, 95% CI: 0.61-0. 78** Progression to IMV, ECMO or death (Sarilumab): - without CS: 0.98, 95% CI: 0.67-1.44 - with CS: 1.08, 95% CI: 0.67-1.75 28-days mortality: - without CS: 1.09, 95% CI: 0.91-1.30 - with CS: **0.78, 95% CI: 0.69-0.88**	Not evaluated

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[142]	10	6493	3358	- Mortality: 24.4% vs. 29.0%; OR 0.87, 95% CI: 0.74–1.01; p = 0.07; I^2 = 10%. - Mortality in patients requiring ICU admission at enrollment: 34.7% vs. 39.6%; OR 0.84, 95% CI: 0.65–1.10; p = 0.20; I^2 = 24% - Mortality in trials with low risk of bias: 12.3% vs. 10.7%; OR 1.09, 95% CI: 0.75–1.57; p = 0.65; I^2 = 0%. - Sensitivity analysis using a fixed effect model: **OR 0.85, 95% CI: 0.76–0.96**; p = 0.006; I^2 = 10%; TSA adjusted CI: 0.70–1.04.	34.9% vs. 41.5%; OR 0.73, 95% CI: 0.38–1.39; p = 0.34; I^2 = 60% - Progression to severe disease: 28.9% vs. 36.6% **; OR 0.72, 95% CI: 0.59–0.89**; p = 0.002; I^2 = 26%	8.7% vs. 10.5%; **OR 0.70, 95% CI: 0.54–0.89**; p = 0.004; I^2 = 0%	Not evaluated	Not evaluated
[150]†	36 RCT: 8, Cohorts: 28	6311	3267	- short term mortality: RR: 0.91, 95%CI: 0.72, 1.07, I^2 = 25%).	"Poor outcome": **RR: 0.82 (95% CI: 0.76, 0.90**, I^2 = 3%)	**RR: 0.84, 95% CI: 0.76, 0.93**, I^2 = 0%	Composite factor (mortality or mechanical ventilation): - Receiving CS: 1.02, 95%CI: 0.79, 1.31 - Not receiving CS: 0.98, 95%CI: 0.89, 1.07	- SAE: 0.85, 95% CI: 0.63, 1.16 - Risk of infection: **RR: 0.67, 95% CI: 0.45, 0.99**

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[154]	9	6489	3358	- Fixed-effect model: **OR: 0.87; 95% CI: 0.75, 0.94**; I^2: 24% - Random-effect model: OR: 0.87; 95% CI: 0.71–1.07 - Mortality for moderate disease: * Global: OR: 1.30; 95% CI: 0.64–2.64; I^2: 0% *Fixed-effect model: **OR: 0.84; 95% CI: 0.75–0.94**; I^2: 53% *Random-effect model: OR: 0.89; 95% CI: 0.71–1.18	Not evaluated	Not evaluated	Not evaluated	Not evaluated
[155]	8	6481	3264	- Global population: RR: **0.89, 95% CI: 0.82-0.96** - after exclusion of RECOVERY: RR: 0.89, 95% CI: 0.75-1.06 - ICU patients: RR: 0.94, 95%CI 0.74-1.19 (I^2=60%) - Early mortality (14-15 days): **RR: 2.18, 95% CI: 1.01-4.69**, I^2=31%).	**RR: 0.68, 95% CI 0.50-0.92**, I^2=6%	**RR: 0.79, 95% CI: 0.68-0.91**, I^2=0%	Not evaluated	- AE: RR: 0.97, 95% CI: 0.88-1.07, I^2=28% - SAE: RR: 0.87, 95% CI: 0.72-1.06, I^2=0% - Superinfection: **RR**: **0.64, 95% CI: 0.64-0.97**, I^2=44% - Severe superinfection: **RR: 0.57, 95% CI: 0.35-0.93**, I^2=42% - Neutropenia: **RR: 8.70, 95% CI: 2.34-32.39**

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[156]	52 (9 RCT, 43 observational)	27004 among which RCT patients: 6604	8048 among which RCT patients: 3358	- Considering RCT: **RR: 0.89, 95% CI: 0.82–0.96**, 95%, PI: 0.80–0.97; $I^2 = 0.3\%$ - Considering observational studies: **RR: 0.69, 95% CI: 0.58–0.83**, 95%, PI: 0.28 to 1.73 ; $I^2 = 84.0\%$	- Considering RCT: **RR: 0.81, 95% CI: 0.71 to 0.93**, 95%, PI: 0.60 to 1.09; I^2=0.0% - Considering observational studies: RR: 0.81, 95%, CI: 0.57 to 1.14, 95%, PI: 0.28 to 2.29 ; $I^2 = 70.2\%$	Composite endpoint of ICU admission or IMV: - Considering RCT: **RR: 0.80, 95% CI: 0.70 to 0.92, 95%**, PI: 0.67 to 0.97; I^2=0.0% - Considering observational studies: RR: 1.08, 95% CI: 0.85 to 1.38, 95% PI: 0.67 to 1.73; $I^2 = 18.4\%$	- Considering RCT: RR: 0.99, 95% CI: 0.79, 1.24; $I^2 = 64.6\%$ - Considering observational studies: **RR: 0.67, 95% CI: 0.54, 0.81**; $I^2 = 59.9\%$	Not evaluated
[140]	10 (Sarilumab and Tocilizumab) 20 (Tocilizumab) 11 (Sarilumab) 6 (Klazakisumab) 2 (Olokizumab) 1 (Siltuximab) 1(Levilimab)	6428	-	Tocilizumab: - D28: **RR: 0.89, 95% CI: 0.82 to 0.97**; $I^2 = 0.0\%$ - D≥60: RR: 0.86, 95% CI: 0.53 to 1.40; $I^2 = 0.0\%$ Sarilumab: - D28: RR: 0.77, 95% CI: 0.43 to 1.36 - D≥60: RR: 1.00, 95% CI: 0.50 to 2.0	Progression Score of level of 7 or above: RR: 0.99, 95% CI: 0.56 to 1.74; $I^2 = 64.4\%$ Tocilizumab and clinical improvement : RR: 1.06, 95% CI: 1.00 to 1.13; $I^2 = 40.9\%$	-	Not evaluated	Tocilizumab: - AE: RR: 1.23, 95% CI: 0.87 to 1.72; $I^2 = 86.4\%$ - SAE: RR: 0.89, 95% CI: 0.75 to 1.06; I2 = 0.0% Sarilumab: - AE: RR: 1.05, 95% CI: 0.88 to 1.25 - SAE: RR: 1.17, 95% CI: 0.77 to 1.77

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[114]	45 comparatives studies and 28 single-arm studies	13189 and 1770	3992 and "*not appropriate*"	Risk of mortality: **RR: 0.76, 95%CI: 0.65 to 0.89**, P < 0.01	Clinical improvement (comparative studies): RR: 1.19 (95% CI: 1.00 to 1.42; P = 0.05, I^2 = 81.2%) ICU admission (comparative studies): RR: 0.98 (95% CI: 0.36 to 2.66; P = 0.99; I^2 = 89.4%)	**RR:0.48, 95% CI: 0.24 to 0.97**, p = 0.04	Not evaluated	Secondary infections (comparative studies): RR: 1.24 (95% CI: 0.98 to 1.56; P = 0.07; I^2 = 66.5%)
[163]	13	2120	674	**OR: 0.42, 95% CI: 0.26 to 0.69**, P = 0.0005, I^2 = 55%	Not evaluated	OR = 0.95, 95% CI: 0.53 to 1.72, P= 0.88, I^2 = 61%	Not evaluated	Not evaluated
[143]	38: 3 double-blinded RCT, 4 open-label RCT, 23 prospective cohorts, 5 case-control studies	13 412	4090	Whole population: **OR: 0.54, 95 % CI: 0.42–0.71**, p < 0.00001, I^2 = 79 % Subgroup analysis excluding observational studies: OR: 0.90, 95 % CI: 0.64–1.26, p = 0.54, I^2 = 0 %	Alteration of severity: 0.92–1.20, p = 0.47, I^2 = 84 %	OR: 1.05, 95 % CI:	Not evaluated	- SAE: OR: 0.91, 95 % CI: 0.71–1.15, p = 0.42, I^2 = 46 %
[144]	6	2057	1177	HR: 0.83; 95% CI 0.66–1.05	Not evaluated	Composite endpoint of requirement of mechanical ventilation and all-cause mortality: **OR: 0.62; 95% CI: 0.42-0.91**	Not evaluated	Not evaluated

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[146]	71 (including 6 RCT): - Tocilizumab: 58 - Anakinra: 6 - Tocilizumab and Anakinra: 1 - Sarilumab and Tocilizumab: 1 - Sarilumab: 4 - Siltuximab: 1	22058	7328 (therapy under review) 6563 (Tocilizumab)	Tocilizumab: - Global: **RR: 0.83, 95% CI: 0.72 to 0.96**, I^2=0.0% -Prospective studies: HR: 0.70, 95% CI: 0.44 to 1.10, I^2=0% -Retrospective studies: **HR: 0.52, 95% CI: 0.41 to 0.66**, I^2=76.6% -RCT alone: RR: 0.85, 95% CI: 0.71 to 1.01 I^2=0.0%) Sarilumab: aOR: 2.01, 95% CI: 1.18 to 4.71	Outcomes on the Ordinal scale: * Tocilizumab: - Prospective studies: GenOR: 1.09, 95% CI: 0.99 to 1.19, I^2=84.3% - Retrospective studies: **GenOR: 1.34, 95% CI: 1.10 to 1.64**, I^2=98%. * Sarilumab: GenOR: 1.07, 95% CI: 0.90 to 1.27		Not evaluated	"similar"
[145]	6	1038	-	RR: 1.03; 95% CI: 0.72 to 1.46; p = 0.89, I^2 = 0.0%	- Random-effect: RR: 0.71; 95% CI: 0.37 to 1.38; p = 0.32, I^2 = 36%	- Random-effect: **RR: 0.70; 95% CI: 0.51 to 0.96**; p = 0.02, I^2 =0%	Not evaluated	SAE: - Random-effect: RR: 0.63; 95% CI: 0.35 to 1.14; p = 0.12, I^2 = 57.9% - Fixed-effect: **RR: 0.68; 95% CI: 0.57 to 0.81**; p = 0.00, I^2 = 77.4%
[152]	9	6778	3647	- Meta analysis: * Studies mortality rate: **0.19; 95% CI: 0.18 – 0.2**, I^2: 98.8%	Not evaluated	Not evaluated	Not evaluated	Not evaluated
[157]	26: 23 retrospectives, 1 prospective, 2 randomized controlled	8272	2112	**RR: 1.65, 95% CI: 1.37 – 2.00**, I^2: 70%	Not evaluated	Not evaluated	Not evaluated	Not evaluated

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[147]	8	6314	3267	D28: OR, 0.92; 95% CI, 0.66–1.28; I^2 = 62%	D28: **OR: 0.51; 95% CI: 0.28–0.92**; I^2 = 30%	Incidence of mechanical ventilation à **D28: OR: 0.75; 95% CI: 0.62–0.90**; I^2 = 11%	Steroids at admission: OR: 0.89; 95% CI: 0.56–1.43; I^2 = 81%	- AE: OR: 1.03; 95% CI: 0.71–1.49; I^2 = 43% - SAE: OR: 0.86; 95% CI: 0.67–1.12; I^2 = 0% - Infection: OR: 0.87; 95% CI: 0.63–1.20; I^2 = 0
[148]	29	11 487	2651	**RR: 0.74; 95% CI: 0.59–0.93**; P = 0.008; I^2 = 80%	RR: 1.40, 95% CI : 0.64–3.06 ; P = 0.4; I^2 = 88%	RR: 0.83 95% CI: 0.57–1.22; P = 0.34; I^2 = 65%		Secondary infection: RR: 1.30, 95% CI: 0.97–1.74; P = 0.08; I^2 = 65%
[158]	25	10 201	4056	**OR: 0.70, 95% CI: 0.54–0.90**, P = 0.007; I^2: 74%	Not evaluated	**OR: 0.59, 95% CI: 0.37–0.93**, P = 0.02; I^2: 56%	Not evaluated	Not evaluated
[151]	9	6490	3358	**RR: 0.89, 95% CI: 0.80–0.98**, p = 0.02; I^2: 6%	Not evaluated	**RR: 0.80, 95% CI: 0.71–0.89**, p < 0.0001; I^2: 0%	**RR: 0.87, 95% CI 0.80–0.95**, p = 0.0009; I^2: 0%	Not evaluated
[141]	18 - Tocilizumab: 16 - Sarilumab: 1 - Siltuximab: 1 RCT: 1, Cohort: 14, case control : 3	3303	-	Tocilizumab or Sarilumab: **RR: 0.61, 95% CI: 0.49–0.76**; I^2: 58%	Not evaluated	RR: 0.68, 95% CI: 0.32–1.45; I^2: 75%	Not evaluated	Not evaluated
[159]	17‡	14 054		Not evaluated	"Treatment failure": **RR: 0.62, 95% CI: 0.42 – 0.91**; I^2: 60%		Mortality in SOC vs Tocilizumab and corticosteroid therapy: **RR: 0.62, 95% CI: 0.42 – 0.91**; $I^{2:}$ 60%	RR: 1.11, 95% CI: 0.81 – 1.53, I^2 was 0%, (p = 0.84)

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[164]	39	15 531	3657	OR 0.74, 95% CI: 0.55–1.01, p = 0.057, I^2: 79.5% Studies with adjusted, estimated, Tocilizumab: **HR: 0.50, 95% CI: 0.38–0.64**, p < 0.001	OR: 3.79, 95% CI: 0.38–37.34, p = 0.254 Studies with adjusted, estimated, Tocilizumab: **OR: 0.16, 95% CI: 0.06–0.43**, p < 0.001	OR: 2.21 95% CI: 0.53–9.23, p = 0.277, I^2: 86.57%	**OR: 0.49, 95% CI: 0.36–0.65**, p < 0.05	**OR: 2.36, 95% CI: 1.01–5.54**, p = 0.050, I^2: 87.96%
[165]	64: controlled observational studies: 54, RCT: 10	20 616	7668	- Broad mortality: OR: **0.73, 95% CI: 0.56–0.93**, I^2 = 82%, (p < 0.001) - Patients receiving CS: **OR: 0.67, 95% CI: 0.54–0.84** - In wards: OR: 1.25, 95% CI: 0.74–2.18, I^2: 82.9% - In ICU: **OR: 0.66, 95% CI: 0.59–0.76**, I^2: 0.00% - Tocilizumab before D10: OR: 0.71, 95% CI: 0.35–1.42 - Tocilizumab after D10: OR: 0.83, 95% CI: 0.48–1.45	Not evaluated	Not evaluated	Not evaluated	Secondary infection: OR: 1.04, 95% CI: 0.72–1.52, I^2: 87.8%
[149]	6	5426	2849	RR: 0.90, 95% CI: 0.76 to 1.07, I^2=0%	Not evaluated	Not evaluated separately	Not evaluated	SAE : RR: 0.82, 95% CI: 0.62 to 1.10, I^2=0
[160]#	All experimental treatments: 222 Tocilizumab: 12	All experimental treatments: 102 950 Tocilizumab: 13606	-	- Fixed-effect model: **OR: 0.85, 95% CrI: 0.77–0.95** - Random-effect model: OR of 0.91, 95% CrI: 0.74 -1.16	Not evaluated	**OR: 0.75, 95% CrI: 0.65–0.86**	Not evaluated	Not evaluated

Table 4 (continued)

Study				Benefit				
Ref.	Number of studies included	Total number of patients	Number of patients in Anti-IL6R group	Survival benefit	Progression to ICU admission	Progression to invasive mechanical ventilation	Place of corticosteroids	Serious adverse events
[161]*	15 (including 7 unpublished)	5339	1661	- Oxygen only: median OR: 0.70 (95% CrI, 0.50-0.91). PPBA: 98.9%. PPMCA: 95.5% - NIV: median OR: 0.81 (95%CrI, 0.63-1.03). PPBA: 95.5% PPMCA: 82.2% - IMV: median OR: 0.89 (95%CrI, 0.61-1.22) PPBA: 75.4% PPMCA: 52.9%	Not evaluated	Not evaluated	All included patients have received corticosteroids	Not evaluated
[162]	9	6490	3358	OR: 0.87; 95% CI: 0.73-1.04; I^2: 15% Non severe disease: OR: 0.1.3; 95% CI: 0.77-2.20; I^2: 0% Severe disease: OR: 0.84; 95% CI: 0.63-1.12; I^2: 57%	OR: 0.66; 95% CI : 0.40-1.08; I^2: 29%	**OR : 0.74; 95% CI: 0.64-0.86; I^2: 0%**	Initial use of steroids in more than 50% of participants: OR: 0.87; 95% CI: 0.66-1.13; I^2: 46% Initial use of steroids in more than 50% of participants: OR: 1.07 ; 95% CI : 0.0.70-1.64; I^2: 0%	- One AE: OR: 1.38; 95% CI: 0.87-2.19; I^2: 70% - Serious AE: OR: 0.90; 95% CI: 0.70-1.14; I^2: 0% - Infection: OR: 0.89; 95% CI: 0.65-1.23; I^2: 0% - Serious infection: OR: **0.57; 95% CI: 0.36-0.89 ; I^2: 21%**

AE Adverse event, *CS* corticosteroids, *ECMO* extra-corporeal membrane oxygenation, *IL-6R* Receptor of interleukin-6, *IMV* invasive mechanical ventilation, *NIV* Noninvasive ventilation, *NS* not significant, *PI* prediction interval, *PPBA* Posterior probability of benefit association, *PPMCA* Posterior probability of meaningful clinical association, *RCT* Randomized and controlled trial, *AE* adverse events, *SAE* Severe adverse events, *SOC* standard of care

† Presented results include only the analysis of RCT.

‡ Corticosteroids: Methylprednisolone

Bayesian meta-analysis

* Bayesian reanalysis of previous meta-analysis ([33])

Positive results are indicated in bold

determine the groups of interest [54, 81, 96, 166] and the relevant intervention period [19, 110, 112]. However, the first 2 days following ICU admission or the early period after the introduction of invasive ventilation appear to be the most agreed upon [19, 99, 110, 112]. Conversely, the administration of treatment too early could be useless [1–11] or even deleterious because of the important role of IL-6 in anti-infective control [19, 24, 136, 137].

Despite the limitations discussed above, Stone et al. propose the inclusion of an IL-6 cut-off value in the decision to introduce an IL-6 pathway inhibitor [43]. Furthermore, consistency between the IL-6 level and the amount of tocilizumab administered was partially reinforced in the study by Soin et al., in which high IL-6 levels were probably poorly controlled by too low a dose of tocilizumab [53].

These last elements may explain the importance of the association with corticosteroids. However, the central role that corticosteroids appear to play, recently emphasized by Matthay and Luetkemeyer [101], brings up the relevance of a single cytokine inhibition rather than enhanced inhibition of broad-spectrum proinflammatory mediators by higher doses of steroids. This point is reinforced by the recent results of studies using a high dose of dexamethasone [44, 45].

The current main hypothesis is the association of tocilizumab and dexamethasone to attenuate inflammation. However, preclinical models are urgently needed to decipher these clinical observations.

Finally, a more recent question is the relevance of inhibiting the IL-6 pathway in vaccinated patients. IL-6 (B cell-stimulating factor) plays a central role in B-cell stimulation [32, 93, 137, 167]. Interfering with antibody production in mild to moderate infection may contribute to worsening of the disease rather than preventing deterioration. This aspect is yet to be elucidated.

5.2 Tocilizumab for Whom?

The global magnitude of COVID-19 highlights the urgent need for a better definition of patients eligible for tocilizumab. On the one hand, it is important to not overlook people with a potential survival benefit, but on the other hand, the current waste of product and money is unacceptable [101]. The currently available data strongly discourage early and widespread use of immunotherapies, including IL-6 pathway inhibitors, in low severity COVID-19 [24, 42, 43, 52–54, 56, 58, 81, 97, 127, 168]. At the other end of the severity spectrum, the extent of inflammation and/or duration of disease evolution in the most severe patients requiring invasive mechanical ventilation or ECMO is associated with low efficacy of IL-6 pathway inhibition [85, 101, 110].

Although the heterogeneity of the existing data and the broad spectrum of severity groups [43, 53, 96, 97, 122, 127] makes it difficult to draw conclusions, the available information tends to demonstrate the futility of tocilizumab for mechanically ventilated patients [100]. At the other end of the severity spectrum, no benefit was observed for patients receiving moderate-flow oxygen (stage 5 of the WHO classification) [126]. Conversely, among patients requiring high oxygen flows, tocilizumab may contribute to prevent invasive mechanical ventilation [97]. Similarly, the RECOVERY study suggests that the benefit of the treatment is centered on patients requiring noninvasive ventilation [127]. However, an early study that focused on patients under high-flow oxygen or non-invasive ventilation failed to demonstrate a benefit of tocilizumab in the absence of an association with corticosteroids [42]. Given the pharmacodynamics of tocilizumab, the IL-6 serum concentration may help to define the target population for IL-6R blockade. However, IL-6 measurements are lacking for many randomized studies and the heterogeneity of patients does not make it possible to determine the clinical severity and biological elevation of IL-6. Despite an interesting correlation observed between the potential benefit and CRP levels in the REMAP-CAP study [98], no benefit of tocilizumab was observed for patients with approximately 25 pg/mL [43] or 100 pg/mL IL-6 [53]. Similar observations were noted for higher concentrations of IL-6 (around 200 pg/mL) [54, 96].

In the RECOVERY study, the median time of administration was 9 days from the onset of symptoms [127]. Interestingly, a Spanish observational monocentric study found better 90-day survival (95.0% vs 83.4%) for patients who received tocilizumab later (9 [7–10] vs 6 [5–7] days after symptom onset) [169]. These data suggest a potential benefit of tocilizumab for patients of intermediate severity requiring oxygen therapy but not mechanical ventilation approximately 9 days after the onset of COVID-19 symptoms. As fibrinogen levels appear to be able to predict the pejorative evolution of COVID-19 [170], they could be used (cut-off to be defined) to better define the population of potential interest for tocilizumab treatment. A better definition of severity, probably using biological criteria, such as a cut-off level for inflammatory mediators (CRP, IL-6), would be highly useful in defining the ideal target patients.

6 Safety of Tocilizumab

The major adverse events observed during tocilizumab and sarilumab use in COVID-19 clinical trials are summarized in Table 5.

During the chronic use of IL-6 pathway inhibitors, it is well established that the incidence of serious infection events is approximately 5.5 per 100 patient-years [32, 167, 171, 172].

The potential risks associated with tocilizumab during management of COVID-19 is still unclear. It should be noted that

Table 5 Major adverse events associated with tocilizumab during clinical trials

Article		Adverse events	
First author or study group	Ref.	Placebo	Tocilizumab
REMAP-CAP	[98]	Four bleeding events Seven thromboses	One secondary bacterial infection Five bleeding events two cardiac events One deterioration in vision
Rosas IO	[54]	Patients with at least 1 AE: 116 (81.1%) Infections: 58 (40.6%) Serious: 37 (25.9%) Opportunistic: 1 (0.7%)	Patients with at least 1 AE: 228 (77.3%) Infections: 113 (38.3%) Serious: 62 (21.0%) Opportunistic: 1 (0.3%)
Veiga VC	[96]	Any: 21 (34%) Secondary infection: 14.7 (8.2%) Thrombotic events: 4 (6%) Neutropenia: 0(0%) Severe raised in ALT, AST, or bilirubin level: 3(5%)	Any: 29 (43%) Secondary infection: 11.3 (8.0%) Thrombotic events: 3 (5%) Neutropenia: 1 (1%) Severe raised in ALT, AST, or bilirubin level: 7(10%)
RECOVERY	[127]	-	One pulmonary abscess One external otitis One Staphylococcus aureus bacteremia
Stone JH	[43]	Infection of grade 3 or 4: 14 (17.1%) DVT: 3(3.7%) PE: 2 (2.4%) Stroke: 0 Neutropenia (≥ grade 3): 1 (1.2%)	Infection of grade 3 or 4: 13 (8.1%) DVT: 2 (1.2%) PE: 2 (1.2%) Stroke: 2 (1.2%) Neutropenia (≥ grade 3): 22 (13.7%)
Gupta S	[99]	Secondary infection: 1085 (31.1%) Thrombotic complications: 342 (9.8%) AST or ALT level elevation (> 250U/L): 452 (12.9%)	Secondary infection: 140 (32.3%) Thrombotic complications: 46 (10.6%) AST or ALT level elevation (> 250U/L): 72 (16.6%)
Salvarani C	[42]	Any: 7 (11.1%) Infection: 4 (6.3%) Laboratory abnormalities: 2 (3.2%) Vascular disorders: 0	Any: 14 (23.3%) Infection: 1 (1.7%) Laboratory abnormalities: 8 (13.3%) Vascular disorders: 1 (1.7%)
Hermine O	[100]	At least one: 36 (54%) No. of events: 86 Patients with at least 1 SAE: 29 (43%) Hepatic cytolysis: 4 Neutropenia: 0 ARDS (death): 19 (9%) Bacterial sepsis: 11 Fungal sepsis: 2 PE (death): 3	At least one: 28 (44%) No. of events: 66 Patients with at least 1 SAE: 20 (32%) Hepatic cytolysis: 4 Neutropenia: 4 ARDS (death): 9 (7%) Bacterial sepsis: 2 Fungal sepsis: 0 PE (death): 0
Lescure FX	[52]	Total: 55 (65%) Leading to death: 9 (11%)	Sarilumab (200 mg): - Total: 103 (65%) - Leading to death: 17 (11%) Sarilumab (400 mg): - Total: 121 (70%) - Leading to death: 18 (10%)
Soin AS	[53]	Total: 22 (25%) Serious: 15 (17%) ARDS: 7	Total: 33 (36%) Serious: 18 (20%) ARDS: 7
Guaraldi G	[56]	Secondary infection*: 14 (4%) Neutropenia: 0	Secondary infection*: 24 (13%) Neutropenia: 1 (<1%)
SARTRE	[58]	Overall: 15.7% Infection and infestation: 2.9% Increased Alanine aminotransferase: 2.9% Increased aminotransferase: 2.0% Nervous system disorders: 1.0% Gastrointestinal disorders: 0.0% Blood and lymphatic system disorders: 0.0%	Overall: 18.2% Infection and infestation: 1.0% Increased Alanine aminotransferase: 7.1% Increased aminotransferase: 5.1% Nervous system disorders: 0.0% Gastrointestinal disorders: 1.0% Blood and lymphatic system disorders: 2.0%

Table 5 (continued)

Article		Adverse events	
First author or study group	Ref.	Placebo	Tocilizumab
REMDACTA	[125]	P+R: - Overall: 530 - Of "special interest": 149 . Infection: 33.3% . Serious infection: 24.9% . Opportunistic: 2.3% . Bleeding: 10.3% . Serious bleeding: 3.3% . Stroke: 3.8% . Hepatic events: 1.4% .Gastrointestinal perforation: 0.5%	T+R: - Overall: 1094 - Of "special interest": 268 . Infection: 30.5% . Serious infection: 20.0% . Opportunistic: 0.7% . Bleeding: 12.8% . Serious bleeding: 2.6% . Stroke: 2.3% . Hepatic events: 1.4% .Gastrointestinal perforation: 0.2%
CORIMUNO-SARI-1	[121]	At least one AE :33 (43%) Multiple AE: 11 (14%) Serious AE: 28 (37%) ---ARDS:11 ---Bacteria sepsis:7 ---Hepatic cytolysis: 3 ---Neutropenia: 0 ---Death: 16 (21%)	At least one AE: 37 (54%) Multiple AE: 17 (25%) Serious AE: 27 (40%) ---ARDS: 7 ---Bacteria sepsis: 12 ---Hepatic cytolysis: 6 ---Neutropenia: 5 Death:10 (15%)
SARICOR	[120]	AE: 39 Cytolysis: 1 Nosocomial infection: 3 Bacteremia: 1 Tachyarrhythmia: 2	---S200: AE: 37 Cytolysis: 0 Nosocomial infection: 5 Bacteremia: 1 Tachyarrhythmia: 0 ---S400: AE: 39 Cytolysis: 1 Nosocomial infection: 2 Bacteremia: 1 Tachyarrhythmia: 1
EMPACTA	[97]	Total AE: 187 At least 1 AE: 67 (52.8%) Serious AE: 25 (19.7%) Death: 15 (11.8%) Infection: 16 (12.6%) Serious infection: 9 (7.1%)	Total AE: 250 At least 1 AE: 127 (50.8%) Serious AE: 38 (15.2%) Death: 29 (11.6%) Infection: 25 (10.0%) Serious infection: 13 (5.2%)
Sivapalasingam S	[61]	- Severe patients > TEAE: 7 (28.0%) > SAE: 1 (4.0%) > TEAE LD: 0 - Critical patients > TEAE: 28 (63.6) > SAE: 26 (59.1%) > TEAE LD: 14 (31.8%) - MSOD/IC patients > TEAE: 16 (76.2%) > SAE: 12 (57.1%) > TEAE LD: 9 (42.9%) MSOD/IC patients	- Severe patients * S200: > TEAE: 19 (38.0%) > SAE: 5 (10.0%) > TEAE LD: 2 (4.0%) *S400: > TEAE: 25 (49.0%) > SAE: 16 (31.4%) > TEAE LD: 8 (15.7%) - Critical patients * S200: > TEAE: 69 (73.4%) > SAE: 56 (59.6%) > TEAE LD: 37 (39.4%) *S400: > TEAE: 56 (63.6%) > SAE: 41 (46.6%) > TEAE LD: 22 (25.0%) - MSOD/IC patients * S200: > TEAE: 35 (81.4%) > SAE: 29 (67.4%) > TEAE LD: 20 (46.5%) *S400: > TEAE: 33 (80.5%) > SAE: 27 (65.9%) > TEAE LD: 15 (36.6%)

Table 5 (continued)

Article		Adverse events	
First author or study group	Ref.	Placebo	Tocilizumab
CORIMUNO-19 bis	[122]	Tocilizumab AE: 30 (70%) SAE: 27 (63%) ARDS: 15 Bacterial and fungal sepsis: 13 Hepatic cytotoxicity: 5 Neutropenia: 0 Sarilumab AE: 22 (68%) SAE: 19 (57.6%) ARDS: 9 Bacterial and fungal sepsis: 4 Hepatic cytotoxicity: 5 Neutropenia: 2	Tocilizumab AE: 33 (67%) SAE: 31 (63%) ARDS: 13 Bacterial and fungal sepsis: 27 Hepatic cytotoxicity: 12 Neutropenia:1 Sarilumab AE: 32 (68%) SAE: 31 (64.6%) ARDS: 15 Bacterial and fungal sepsis: 19 Hepatic cytotoxicity: 3 Neutropenia: 0

AE Adverse event, *ARDS* acute respiratory distress syndrome, *DVT* Deep venous thrombosis, *MSOD/IC* multi-system organ dysfunction/Immunocompromised, *PE* Pulmonary embolism, *SAE* severe adverse event, *TEAE* treatment-emergent adverse event, *TEAE LD* treatment-emergent adverse event leading to death

P+R: Placebo and Remdesivir

T+R: Tocilizumab and Remdesivir

*($p < 0.0001$)

patients with suspected active infection were generally excluded from the studies. Numerous studies have investigated the risk of infection, with sometimes conflicting results [114]. Randomized studies show a minor short-term risk [42, 54, 96–100, 120, 127]. The majority of recent meta-analyses that have specifically examined superinfection did not find any increase in risk [114, 146–148, 153, 165]. However, this still a subject of debate [150, 155], particularly due to the issue of adverse events collected in currently available RCTs. Several studies have emphasized the increasing risk of bacteremia [57, 173], pneumonia [57, 119], and any secondary infections [56, 110, 119] following tocilizumab administration. Other studies did not demonstrate any therapeutic or iatrogenic effect of tocilizumab [42]. The most recent meta-analysis provided heterogeneous results, highlighting an increase in the risk of secondary infection [150, 153, 155] or no significant difference in superinfection [114, 146–148, 162, 165], usually not correlated with improved survival. However, in the various RCTs, the risk of infection associated with tocilizumab was only observed when a clinical benefit of the anti-IL-6R was observed. IL-6 pathway inhibition may even be associated with a decrease in infectious risk [43, 99, 113, 118, 162], possibly because of the reduced risk of subsequent immune reprogramming [174, 175]. Regardless of the modification of infectious risk, the benefit obtained allows a reduction in mortality, independently of the occurrence of secondary infections. Conversely, in mild and moderate COVID-19, the risk associated with potential infection appears greater than the expected benefit.

As well described, immune exhaustion is associated with severe COVID-19 [92, 176–178]. Excess IL-6 levels are associated with impaired NK-cell function [179] by the downregulation of activating receptors (NKp30 and NKG2D) [180] and reduction of granzyme B and perforin expression [179, 180]. IL-6 also promotes the reduction of type I/III IFN production and is inversely correlated with NK cell count [18] and lymphocytes depletion (marked by PD-1 or Tim3 expression) [94]. A recent Greek study including COVID-19 patients with macrophage activation-like syndrome and/or complex immune dysregulation demonstrated improved mHLA-DR expression on circulating $CD14^+/CD45^+$ cells ($p = 0.001$) in ICU patients treated with tocilizumab [60]. As a decrease in HLA-DR expression is generally considered to be a marker of immunocompromise, we may expect a potential benefit of inhibiting the IL-6 pathway in the excessive inflammatory state associated with severe COVID-19. However, these observations were not associated with an improvement in proinflammatory cytokine production in vitro by peripheral blood mononuclear cells (PBMCs) in response to endotoxin or heat-killed *Candida albicans* [60]. In summary, tocilizumab may curb immunity exhaustion by limiting the quantity of excess IL-6 and the duration of IL-6 stimulation [181].

Aside from the potential impairment of immunity associated with IL-6 inhibitors, the recommended association with corticosteroids may cause undue concern about an increased risk of nosocomial infections. However, current data on short-term (<10 days) steroid treatment in sepsis [182] or during COVID-19 [27, 28, 183] suggest that it is not a factor that favors secondary infections.

7 Conclusion

IL-6 receptor inhibitors may have a benefit in the management of severe COVID-19 and are now included in guidelines [184]. The timing of administration and intensity of inflammation are the best actors to guide IL-6 pathway blockade. The population most likely to benefit from treatment appears to be high-flow oxygen-dependent patients and, in general, those just admitted to the ICU or shortly thereafter [101]. Conversely, in mild and intermediate COVID-19, requiring only ward-based oxygen therapy, tocilizumab seems unnecessary, and the associated risk has not yet been evaluated. At the other end of the severity spectrum, patients requiring invasive ventilation or even extra-corporeal membrane oxygenation are unlikely to benefit from tocilizumab, the intensity of inflammation rendering the efficacy of interruption of a single pathway unlikely.

A second issue is the place of corticosteroids. The relevance of combining the two treatments or increasing the dose of corticosteroids must be studied. Finally, the risks inherent in using a humanized antibody that disrupts the anti-infectious and scarring response are still very poorly understood, both in the acute phase and later, and need to be carefully studied.

As the guidelines point out, "Further research is needed to identify the optimal patient population for treatment with IL-6 receptor antagonist" [185] to delineate the optimal population who would benefit from IL-6 receptor inhibition in this context [85]. Thus, prospective studies appear to be more appropriate than an iterative meta-analysis of currently existing work.

Acknowledgments The authors warmly thank Nora Touqui for her precious and meticulous proofreading and English improvement of the present article.

Author contributions Conceptualization, FP. Methodology, FP and AP. Validation, FP and AC. Original draft preparation, AP, CM and FP. Writing review and editing: OT, LT and FP.

Declarations

Conflicts of interest AP, CM, CL, OT, LT, and FP have no conflicts of interest to declare.

Funding No external funding source was used in the preparation of this manuscript.

Ethics approval Not applicable.

Informed consent Not applicable.

Data availability Not applicable.

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