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REVIEW

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Tocilizumab in COVID-19 pneumonia: Practical proposals based on a narrative review of randomised trials

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Abstract

In this article, we express our opinion about tocilizumab as an effective treatment in coronavirus disease 2019, based on a narrative review and a deep analysis of tocilizumab randomised trial results. Eight trials were included. No one was in favour for controlled arm about main endpoint of death or mechanical ventilation incidence at day 28–30. Five trials on heterogenous populations seem to not demonstrate tocilizumab efficacy, but showed encouraging results in subgroup analysis on severe/critical patients (in favour for tocilizumab). Trials on severe/critical COVID-19 pneumonia as REMAP-CAP and RECOVERY showed mortality benefit of tocilizumab administration; CORIMUNO, REMAP-CAP and RECOVERY showed that tocilizumab decreased the incidence of mechanical ventilation. No safety signal about tocilizumab used was noticed in all trials. We concluded that tocilizumab reduces mortality and mechanical ventilation requirement if administered with the right timing in COVID-19 pneumonia. The challenge now is to define the optimal group and timing for tocilizumab benefit and we suggest that: (i) tocilizumab has a place in treatment of severe/critical COVID-19 pneumonia, with a high level of O_2 flow or noninvasive ventilation or high flow nasal cannula; (ii) possibly early after intubation in patients on mechanical ventilation. Initiating tocilizumab in critically ill patients early before irreversible respiratory failure, especially in patients at an inflammatory stage could be the key to successful outcome.

KEYWORDS
anti-interleukin-6, coronavirus disease 2019, randomised clinical trial, review, tocilizumab

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, Coronavirus disease 2019; CRP, C-reactive-protein; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL-6, interleukin-6; OR, odds ratio; RCTs, randomised clinical trials; SARS-CoV-2, acute respiratory syndrome coronavirus 2.

1 | INTRODUCTION

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread around the world making more than one hundred million of infected people and at least 2.7 million deaths.[1] Until now, corticosteroids have been the only treatment proven to reduce mortality with strong evidence.[2] Death due to SARS-CoV-2 mainly results from acute respiratory distress syndrome (ARDS).[3] Markers of inflammation such as C-reactive-protein (CRP), ferritin, and interleukin-6 are significantly associated with mortality.[4,5] Coronavirus disease 2019 (COVID-19)-related multiple-organ failure and ARDS are mainly caused by cytokine storm.[6] Post-viral hyper-inflammation, which begins in the second week of the disease explains disease severity.[7] Cytokine storm reactions are mainly related to inflammatory cytokines, especially to interleukin-6 (IL-6),[8] which play a major role (with IL-1β and IL-8) in mediating acute lung injury[9] leading to ARDS. In our center we managed a cohort of 206 COVID-19 patients using tocilizumab (a recombinant humanized anti-interleukin-6 (IL-6) receptor[10]) which we feel can be an effective treatment to reduce mortality and invasive mechanical ventilation requirement in COVID-19[11]; a meta-analysis of cohort studies supported this impression suggesting an association between tocilizumab and lower mortality.[12] However, since July, the first results of randomised clinical trials (RCTs)[13–15] have not shown an impact on short term mortality. In November, Huang et al.[16] published a meta-analysis of five RCTs and concluded that tocilizumab does not provide mortality benefit for severe COVID-19 patients. In January 2021, we discussed the lack of positive results of these five RCTs which contrast with cohort studies; our main conclusion was that heterogenous population may explain this and tocilizumab should be effective in severe patients.[17] Three new RCTs have now been published or are at a pre-published state.[18–20] Veiga et al.[18] raised the question that tocilizumab may possibly increase the risk of death in opposition to REMAP-CAP and RECOVERY which showed mortality benefit of tocilizumab administration. We think that a deep and updated discussion is necessary. Here we discuss the contradictory results of these eight RCTs[13–15,18–22] especially about the impact of tocilizumab on mortality rate and mechanical ventilation incidence to try to assess if there is an optimal group and timing for tocilizumab administration.

2 | TOCILIZUMAB IMPACT ON MORTALITY RATE

The meta-analysis of Huang et al.[16] showed no effect on short-term mortality (during the first month) of tocilizumab administration in COVID-19 hospitalised patients; thus, the five other RCTs seem to have shown no effect in favour or disfavour of tocilizumab.[13–15,21,22] Moreover, Veiga et al. trial was stopped early in July 2020 after an increase in deaths[23] in contradiction to REMAP-CAP and RECOVERY results.[19,20] These two last RCTs on severe and critical COVID-19 pneumonia showed a positive benefit of tocilizumab on mortality. In REMAP-CAP the hospital mortality was 28% (98/350 patients) for tocilizumab and 36% (142/397 patients) for control with a median adjusted odds ratio (OR) for hospital survival for the tocilizumab arm at 1.64 (95% CrI 1.14, 2.35) compared with control arm, yielding >99.9% posterior probabilities of superiority. In RECOVERY, overall, 596 (29%) of the 2,022 patients allocated tocilizumab and 694 (33%) of the 2,094 patients allocated to usual care died within 28 days (rate ratio 0.86; [0.77–0.96]; $p = 0.007$).

A few assumptions can be discussed to explain this contradiction on mortality effect in these in RCTs results.

Firstly, a lack of statistical power seems manifest in some RCTs. For example, Stone et al. and Salvarini et al.[14,15] had a mortality rate <5% in their population and the required number of patients to assess mortality was not reached[24]; any conclusions should be taken with caution and must not be generalised to the overall COVID-19 population.

Secondly, we only have the results of short-term mortality, after a follow-up of one month after administration. We can expect that tocilizumab may decrease the risk of long-term complications and possibly death by reducing incidence or Intensive Care Unit (ICU) admissions.[12] For example, in COVACTA,[13] at day 28 26% (115/438) of patients were still hospitalised and 72% (83/115) of these 115 patients required high flow oxygen or noninvasive ventilation or mechanical ventilation. Furthermore, they were 17% (50/294) in the tocilizumab arm versus 23% (33/144) in the placebo arm; we can possibly expect a lower number of deaths in the tocilizumab arm in long-term mortality. We are looking for the results of long term follow-up concerning mortality in these trials.

Thirdly, these RCTs included heterogenous populations which may explain variability of results.[17,24] Veiga et al.[18] raised the question that tocilizumab may possibly harm and increase the risk of death. If on the one hand tocilizumab could possibly increase the risk of death in a population with a majority (60%) of non ICU patients[18] but on the other hand tocilizumab decreased the risk of death in a majority of ICU patients[17,19] we would not see an impact on mortality in a heterogenous population as it is in most RCTs.[13–15,21,22] Subgroup analyses are imperatives.[17,24] Veiga et al. results must be interpreted with caution due to the sample size of the trial; finally, they was no significant difference on mortality at day 28 and their results have never been confirmed in another trial. We have recently defined the optimal group which is likely to have the greatest benefit from tocilizumab as severe/critical COVID-19 (except patients after some time of mechanical ventilation).[17] In COVACTA[13] if we choose this population, the category four and five of the seven-category ordinal scale (Table 1) the number of deaths is clearly lower for tocilizumab than placebo (17% [24/139] vs. 28% [15/54]). A mortality rate at 17% is extremely low in this ICU population and contrasts with the medical literature, which is usually around 30%[25] and reached 60% in the beginning of the pandemic.[26] A mortality rate of 17% corresponds more to the in-hospital mortality; for example, Kim et al. showed that the in-hospital mortality among COVID-19 hospitalised adults in United States is 17%.[27]

The heterogenous population included in RCTs probably explains the heterogeneity of the results on mortality.[17,24] A meta-analysis of

TABLE 1 Categories of the seven-category ordinal scale in COVACTA study

Categories	
1	Discharged or ready for discharge
2	Hospitalisation in a non-intensive care unit (ICU) without supplemental oxygen
3	Non-ICU hospitalisation with supplemental oxygen
4	ICU or non-ICU hospitalisation with noninvasive ventilation or high-flow oxygen
5	ICU hospitalisation with mechanical ventilation
6	ICU hospitalisation with extracorporeal membrane oxygenation or mechanical ventilation and additional organ support
7	Death

retrospective cohort studies suggests a possible association between tocilizumab and lower mortality.[12] Our assumption to explain the disparity between RCTs and retrospective cohort studies is that retrospective cohort populations were more homogenous than RCTs population. In fact, tocilizumab was mainly used as an off label rescue treatment in critical COVID-19 patients in retrospective cohorts. For example in Italy, in Brescia, in a cohort of 100 patients, tocilizumab was often used in ICU beds and sometimes in the general ward as no ICU beds were available[28]; or in France, in the *Nord Franche-Comté Hospital*, in our cohort of 206 patients, among the 30 patients in the tocilizumab group the mean oxygen therapy flow at tocilizumab onset was 10.5 L/min and most patients were not admitted in ICU in regard to their comorbidities and tocilizumab was used as a rescue treatment.[11] We do not think that methodological bias only, is enough to explain the gap that tocilizumab efficacy showed in retrospective cohort studies and the conclusions in the first RCTs,[12,17,24] the difference in populations may also explain this contrast and sub-group analyses in severe/critical COVID-19 patients are imperatives in RCTs.

3 | TOCILIZUMAB IMPACT ON MECHANICAL VENTILATION INCIDENCE

A meta-analysis on the five RCTs conducted by Tleyjeh et al.[12] showed that tocilizumab decreased the incidence of mechanical ventilation in COVID-19 hospitalised patients (with a low risk of bias). Among these five RCTs the two RCTs[14,15] which did not show benefit of tocilizumab used on mechanical ventilation incidence in COVID-19 pneumonia had wide confidence intervals (about comparisons on mechanical ventilation incidence) and benefits cannot be ruled out. Furthermore, they focus on a selected population of moderate COVID-19 pneumonia. In Stone et al.[14] trial >95% of patients had a level of O_2 < 6 L/min delivered by nasal cannula or no oxygen administration at baseline. In Salvarani et al. trial[15] we do not have the detailed description of respiratory support at baseline; however, the median PaO_2/FiO_2 was >250 mmHg (at 264.5 mmHq) and patients had a very low level of systemic inflammation with a median of C-reactive protein (CRP) at 8,2 mg/l. This selected population of moderate COVID-19 at baseline pneumonia is confirmed by the low mortality rate in the total population in these two trials (≤5%), this, in contrast to a proportion of 10–32% deaths in the total population of the six other RCTs[13,18,19,21,22] (Table 2). Conclusions about these two trials might not be generalised to severe and critical COVID-19 pneumonia. Gordon's (REMAP-CAP), Horby's (RECOVERY) and Veiga et al.'s trials[18,19] were not included in the meta-analysis[12] because their results were not published at this date. Likewise, Veiga et al.[18] showed a lower number of mechanical ventilation patients at day 15 in the tocilizumab arm than in the placebo arm (11% vs. 17%, respectively) but we do not have the results of the cumulative incidence of mechanical ventilation at day 28. In REMAP-CAP[19] we also do not have the results of the cumulative incidence of mechanical ventilation restricted to patients not intubated at baseline but a composite criteria about progression to mechanical ventilation, ECMO or death, in this group was lower for tocilizumab than placebo: 41% (100/242) versus 53% (144/273) with a median adjusted OR at 1.69 (CI 95%; 1.17–2.42) with a probability of superiority to control at 99.8%. In RECOVERY[20] the progression to mechanical ventilation was lower for tocilizumab than placebo: 12% (215/1754) versus 15% (273/1800) with a median adjusted OR at 0.81 (CI 95%; 0.68–0.95; $p = 0.01$).

RCTs confirm retrospective cohorts and the fact that tocilizumab decreased the incidence of mechanical ventilation in COVID-19 hospitalised patients.[12] In countries facing a huge challenge in terms of ICU beds while dealing with this outbreak, tocilizumab may be helpful to manage the crisis in term of public health. For example, the UK government was the first government to make tocilizumab available to patients with severe COVID-19.[29]

4 | OPTIMAL GROUP AND TIMING OF TOCILIZUMAB ADMINISTRATION

Finding the optimal group of patients likely to have the greatest benefit is probably the main challenge. *Primum non nocere*! That way, tocilizumab administration to patients with a low level of oxygen requirement seems to be ineffective according to Stone et al. and Salvarini et al. conclusions.[14,15] However, as we discussed above, the mortality rates in these two studies were <5% and any conclusions should be taken with caution. In Veiga et al. trials[18] we do not have

TABLE 2 Main characteristics and results of tocilizumab randomised controlled trials

	Salvarini et al.[15]	Stone et al.[14]	Salama et al.[22]	Hermine et al.[21]	Veiga et al.[18]	Rosas et al.[13]	Horby et al.[20]	Gordon et al.[19]
Study characteristics								
Study design	Randomised, open-label, controlled trial	Randomised, double-blind, placebo-controlled trial	Randomised, double-blind, placebo-controlled trial	Randomised, open-label, controlled trial	Randomised, open-label, controlled trial	Randomised, double-blind, placebo-controlled trial	Randomised, open-label, controlled trial	Randomised, open-label, controlled trial
Country	Italy, 24 sites	United States	Six countries in America and Africa	France, nine sites	Brazil, nine sites	Nine countries in Europe and North America	United Kingdom	Europe, Oceania and North America
Number of patients	126 patients (60 in TCZ arm)	243 patients (161 in TCZ arm)	389 patients (249 in TCZ arm)	131 patients (63 in TCZ arm)	129 patients (65 in TCZ arm)	444 patients (294 in TCZ arm)	4116 patients (2022 in TCZ arm)	755 patients (353 in TCZ arm)
TCZ regimen[1]	Two doses (2nd dose 12 h later)	Single dose	Single dose. Possibility of a 2nd dose 8–24 h later	Single dose. Possibility of a 2nd dose 48 h later	Single dose	Single dose	Single dose. Possibility of a 2nd dose 12–24 h later	Single dose. Possibility of a 2nd dose 12-24 h later
Population characteristics								
Respiratory support at baseline in TCZ arm	Not detailed but 72% of patients (43/60) had a $PaO_2/FiO_2 \geq 250$ mmHg (so a O_2 flow $\leq$ 3 L/min)	Ordinal scale score[2a] 2: 14% (23/161) 3: 83% (133/161) 4: 3% (5/161)	Ordinal scale score[2c] 2: 9% (24/249) 3: 65% (161/249) 4: 26% (64/249)	WHO-CPS-score (0-10)[3]: 5: 100% (63/63)	Ordinal scale score[2b] 4: 60% (39/65) 5: 23% (15/65) 6: 17% (11/65)	Ordinal scale score[2d] 2: 3% (9/294) 3: 27% (78/294) 4: 32% (94/294) 5: 15% (45/294) 6 : 23% (68/294)	Respiratory support: Low flow O_2[4]: 46% (935/2022) NIV or HFNC: 41% (819/2022) IMV: 13% (268/2022)	Respiratory support:[5] HFNC: 29% (101/353) NIV: 42% (147/353) IMV: 29% (104/353)
Excluded criteria on respiratory support	ICU admission NIV or IMV	O_2 flow >10 L/min	NIV or IMV or HFNC	O_2 flow $\leq$ 3 L/min NIV or IMV or HFNC	IMV > 24 h			IMV > 24h

TABLE 2 (Continued)

		Salvarini et al.[15]	Stone et al.[14]	Salama et al.[22]	Hermine et al.[21]	Veiga et al.[18]	Rosas et al.[13]	Horby et al.[20]	Gordon et al.[19]
Essay of classification	O_2 ≤3 L/min or no O_2	72%	97%	9%	0%	60%	3%	46%	0,3%
	3 L/min < O_2 ≤ 6L/min	28%		65%	100%		27%		
	O_2 > 6L/min	0%	3%						
	HFNC, NIV, IMV <24 h	0%	0%	26%	0%	40%	32%	44%	99,7%
	IMV more than 24 h	0%	0%	0%	0%	0%	38%		0%
Mortality rate (TCZ arm)		2% (3%)	5% (6%)	10% (10%)	12% (11%)	16% (21%)	20% (20%)	31% (29%)	32% (28%)
Significant results[6]									
Mortality at day 28		No	No	No	No	No	No	In favour for TCZ	In favour for TCZ
MV or ICU incidence		No	No	In favour for TCZ	In favour for TCZ	No	No	In favour for TCZ	In favour for TCZ
Hospitalisation characteristics		No	No	In favour for TCZ	In favour for TCZ	In favour for TCZ	In favour for TCZ	In favour for TCZ	In favour for TCZ
Safety		No	In favour for TCZ	No	In favour for TCZ	No	No	No	No
RCT risk of bias[7]		Some concerns	Low	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns

Note: Bold represents results with significant differences. There were no significant results in favour for control in any of these five categories.

Abbreviations: HFNC, high flow nasal cannula; ICU, Intensive Care Unit; IMV, invasive mechanical ventilation; NA, not applicable; NIV, non-invasive ventilation; RCT, randomised clinical trial; TCZ, tocilizumab.

[1]All doses were tocilizumab intravenous infusion of 8 mg/kg (maximum 800 mg), except for the second dose of Hermine et al. which was a fixed dose of 400 mg.

[2]The ordinal scale score range from 1 to 7 for each study but was defined differently.

[2a]2 – not receiving supplemental oxygen, 3 – receiving supplemental oxygen ≤6 L/min, 4 – receiving high flow oxygen >6 and ≤10 L/min delivered by any device.

[2b]4 – receiving supplemental oxygen, 5 – receiving NIV or high flow oxygen through a nasal cannula, 6 – receiving IMV.

[2c]2 – not receiving supplemental oxygen, 3 – receiving supplemental oxygen, 4 – receiving NIV or high flow oxygen.

[2d]2 – not receiving supplemental oxygen, 3 – receiving supplemental oxygen, 4 – receiving NIV or high flow oxygen, 5 – receiving IMV, 6 – receiving ECMO or IMV and additional organ support.

[3]Score 5 of the World Health Organization (WHO) clinical progression scale was defined by: hospitalised; oxygen by mask or nasal prongs.

[4]Less than nine patients without respiratory O_2 support at baseline.

[5]Only one patient was with supplemental O_2 only or none respiratory support at baseline.

[6]We noticed a result in favour of TCZ or in favour of control if they were at least one statistically significant result for the category concerned. The 'Hospitalization characteristics' category included clinical evolution on ordinal scale score, duration of hospitalisation and duration of ICU or IMV.

[7]We used the RoB 2: the revised Cochrane risk-of-bias tool for randomised trials.

the detailed oxygen flow of patients but we know that in the tocilizumab arm the majority (60%) of patients were not ICU patients; also, we do not have the detailed ordinal scale on day 28 (according to baseline ordinal scale category) which would be interesting to analyze in which group most of deaths occur. In contrast, in a more homogenous population (all ICU patients at baseline) REMAP-CAP[19] shows that tocilizumab reduces mortality in patients with a high requirement of oxygen: 29% were at intubation stage with mechanical ventilation and 71% were before intubation stage (29% high flow nasal cannula and 42% with non-invasive ventilation only). Hermine et al. and Salama et al. RCTs[21,22] met their primary composite endpoint and concluded that tocilizumab may have some benefit in severe COVID-19 pneumonia. At baseline, in Hermine et al. trial[21] all patients had severe pneumonia with a level ≥3L of 02 (but no patients on mechanical ventilation); in Salama et al. trial,[22] patients received supplemental oxygen (we do not have the detailed about oxygen flow at tocilizumab onset) or noninvasive ventilation or high flow oxygen (before invasive mechanical ventilation). In RECOVERY,[20] in the subgroup of patients with mechanical ventilation the efficacy remains unclear: the mortality rate at day 28 was 47% (125/268) for tocilizumab versus 48% (142/294) for placebo with a median adjusted OR at 0.94 (CI 95%; 0.73–1.19).

The optimal group of patients likely to have a benefit after tocilizumab administration seems to be severe and critical COVID-19 patients.[13] In this population finding the optimal timing for tocilizumab administration is crucial. Hermine et al.[21] reported efficacy in patients with an O_2 flow >3 L/min. In COVACTA[17] the only category (among seven categories) which has significantly improved their clinical status on day 14 compared with placebo: 2.0 (1.0–4.0) for tocilizumab and 5.0 (3.0–6.0) for placebo (OR, 2.10 [1.07–4.10]) is the category four of the seven-category ordinal scale: ICU or non–ICU hospital ward, requiring high-flow oxygen or noninvasive ventilation). They were no benefit of tocilizumab used for patients at intubation stage at baseline (category five and six of the seven-category ordinal scale with an OR at 0.89 [0.30–2.57] and 1.00 [0.50–2.02], respectively) as in RECOVERY.[20] In REMAP-CAP[19] we do not have the detailed outcome according to baseline category to analyze if there are any difference of response between intubated patients or patients before intubation stage at baseline; this would be interesting. In REMAP-CAP[19] it is interesting to note that patients had to be enrolled within 24 h after starting organ support.[19] COVACTA[13] did not have this deadline of 24 h as an inclusion criterion. Concerning biological findings, in REMAP-CAP,[19] a secondary analysis of primary outcome according to CRP tercile subgroups shows that the optimal response was found in the CRP highest tercile (OR, 1.92 [1.12–3.34] with a probability of superiority to control at 99.1%). In RECOVERY[20] all patient had a CRP level ≥75 mg/L. Treating critically ill patients early, before CRP decreases seems to be important.

To conclude, tocilizumab appears to reduce mortality and mechanical ventilation requirement in severe/critical COVID-19 pneumonia. Due to heterogenous populations in RCTs, secondary analyses of subgroups are needed and further subgroup analyses are likely to be helpful as more results are reported to define the optimal group and timing for tocilizumab benefit. Currently, we think that tocilizumab has a place in treatment of severe/critical COVID-19 pneumonia with a high level of O_2 flow (possibly as of >3 L/min or at least at a level of oxygen flow ≥6 L/min) or noninvasive ventilation or high flow nasal cannula and possibly early after intubation in patients on mechanical ventilation, especially in patients at an inflammatory stage. Initiating tocilizumab in critically ill patients early before irreversible respiratory failure could be the key.

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CONFLICTS OF INTEREST

All authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Timothée Klopfenstein and Souheil Zayet drafted the manuscript. Vincent Gendrin, N'dri Juliette Kadiane-Oussou and Thierry Conrozier revised the final manuscript.

PATIENT CONSENT STATEMENT

Due to the retrospective nature of the study, the Ethics & Scientific Committee *of Nord Franche Comté Hospital* determined that patients consent was required only for the off-label use Tocilizumab. We make sure to keep patient data confidential and in compliance with the Declaration of Helsinki.

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