Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19)

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ARTICLE

Immunotherapy

We performed a meta-analysis to determine safety and efficacy of tocilizumab in persons with coronavirus disease-2019 (COVID-19). We searched PubMed, Web of Science and Medline using Boolean operators for studies with the terms coronavirus OR COVID-19 OR 2019-nCoV OR SARS-CoV-2 AND tocilizumab. Review Manager 5.4 was used to analyze data and the modified Newcastle–Ottawa and Jadad scales for quality assessment. We identified 32 studies in 11,487 subjects including three randomized trials and 29 cohort studies with a comparator cohort, including historical controls (N = 5), a matched cohort (N = 12), or concurrent controls (N = 12). Overall, tocilizumab decreased risk of death (Relative Risk [RR] = 0.74; 95% confidence interval [CI], 0.59, 0.93; P = 0.008; I² = 80%) but not of surrogate endpoints including ICU admission (RR = 1.40 [0.64,3.06]; P = 0.4; I² = 88%), invasive mechanical ventilation (RR = 0.83 [0.57,1.22]; P = 0.34; I² = 65%) or secondary infections (RR = 1.30 [0.97,1.74]; P = 0.08; I² = 65%) and increased interval of hospitalization of subjects discharged alive (mean difference [MD] = 2 days [<1, 4 days]; P = 0.006; I² = 0). RRs of death in studies with historical controls (RR = 0.28 [0.16,0.49]; P < 0.001; I² = 62%) or a matched cohort (RR = 0.68 [0.53, 0.87]; P = 0.002; I² = 42%) were decreased. In contrast, RRs of death in studies with a concurrent control (RR = 1.10 [0.77, 1.56]; P = 0.60; I² = 85%) or randomized (RR = 1.18 [0.57,2.44]; P = 0.66; I² = 0) were not decreased. A reduced risk of death was not confirmed in our analyses which questions safety and efficacy of tocilizumab in persons with COVID-19.

Introduction

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease-2019 (COVID-19), an important pathogenetic component of which is cytokine release syndrome (CRS). CRS is mediated, at least in part, by interleukin-6 (IL-6). Tocilizumab, a humanized monoclonal antibody, selectively targets the interleukin-6 receptor (IL-6r) [1, 2] and is reported safe and effective in other settings such as after chimeric antigen receptor (CAR)–T-cell therapy, rheumatoid arthritis, and giant cell arteritis [3, 4].

Data from 11 uncontrolled studies [5–16] and most prior meta-analyses [17–24] claim tocilizumab is safe and effective in persons with COVID-19. However, data from three recent randomized controlled trials (RCTs) question this conclusion [25–27].

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We conducted a systematic review and meta-analysis of 32 studies of safety and efficacy of tocilizumab in persons with COVID-19 which had a comparator cohort. Overall, we found tocilizumab decreased risk of death but not rates of intensive care unit (ICU) admission, invasive mechanical ventilation, secondary infections, and increased interval of hospitalization in persons discharged alive. However, a reduced risk of death was not confirmed in our analyses of studies with concurrent controls nor randomized trials. These data question safety and efficacy of tocilizumab in persons with COVID-19.

**Methods**

**Search strategy and selection criteria**

PubMed, Web of Science and Medline were searched using Boolean operators for studies with the terms coronavirus OR COVID-19 OR 2019-nCoV OR SARS-CoV-2 AND tocilizumab. Start and stop dates were 2020/1/1 and 2020/10/27. Two investigators independently reviewed abstracts of identified citations and selected articles for full review. Discordances were resolved by a third reviewer. Results were also manually searched and reviewed. We found 1492 articles excluding 914 duplicates. After further review we focused on 32 studies, 29 non-randomized comparator studies, and three RCTs [1, 2, 25–52]. A flow diagram of the search strategy and article selection is displayed in Fig. 1. Review Manager 5.4 was used to analyze data and the modified Newcastle-Ottawa score (NOS) and Jadad scale for quality assessment.

**Inclusion and exclusion criteria**

Inclusion criteria included English language reports of clinical trials and observational studies with a comparator cohort and with outcomes reporting, but not limited to, survival. Reviews and case reports were excluded as were studies with a NOS < 6.

**Data extraction**

For each selected article we extracted (1) first author, (2) publication year, (3) country, (4) study-design, (5) number of subjects, (6) comparator cohort, (7) baseline subject clinical and laboratory co-variates, (8) details of tocilizumab use, (9) concurrent interventions, and (10) outcomes, including: (1) survival, (2) rates of ICU admission, (3) invasive mechanical ventilation, (4) secondary infection, and (5) interval of hospitalization. The study used
anonymized, published data with no requirement for Ethics Committee approval. (Table 1; Supplement Table 1)

Risk of bias assessment

Risk of bias was assessed using the Jadad scale in four domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants, and (4) complete reporting of withdrawals and dropouts [53]. Methodological quality of comparator studies was assessed using the modified Newcastle–Ottawa scale (NOS) [54, 55] consisting of three domains: (1) subject selection, (2) comparability of the study groups, and (3) outcomes assessment. A score of 0–9 was allocated to each relevant study. Observational studies with a NOS score <6 (N = 1) were excluded [56].

Statistics

We pooled data and utilized Relative Risks (RRs) and Confidence Intervals (CIs) to describe dichotomous outcomes, including risk of death, ICU admission, invasive mechanical ventilation, secondary infection. We used mean difference (MD) and CIs for continuous outcomes including interval of hospitalization. We grouped the cohort studies into unmatched historical controls and concurrent controls, matched and unmatched or subgroup analyses. A fixed-effects model was used when $I^2 \leq 50\%$ and the Cochran Q statistic $P > 0.1$ and a random-effects model when $I^2 > 50\%$ and Q statistic $P \leq 0.1$. Funnel plots were used to screen for potential publication bias. Statistical analyses were carried out with Review Manager 5.4 (Cochrane Collaboration).

Results

We included 11,487 subjects from 29 studies (NOS scores 6–9) with a comparator cohort including historical controls (N = 5) [1, 30, 32, 35, 43], a matched cohort (N = 12) [2, 28, 29, 33, 40, 44–47, 49, 50, 57] or concurrent controls (N = 12) [31, 34, 36–39, 41, 42, 48, 51, 52, 58] and three randomized controlled trials (Jadad scales 4–5). We excluded some studies because they were uncontrolled (N = 11) [5–16] and/or different study-entry severities of COVID-19 between treated subjects and controls (N = 1) [59]. Two studies reported only a composite endpoint (ICU admission, use of mechanical ventilation or death) [57, 58]. These were included in the systemic review but not used to estimate RRs for specific endpoints.

Survival

To test the impact of tocilizumab on survival we included 30 studies, three RCTs and 27 other comparator studies of 10,054 subjects. [1, 2, 25–52] Relative Risk (RR) of death = 0.74 (95% Confidence Interval [CI], 0.59, 0.93; $P = 0.008$; $I^2 = 80\%$). Studies with historical controls (RR = 0.28 [0.16, 0.49]; $P < 0.001$; $I^2 = 62\%$) or with an otherwise matched cohort (RR = 0.68 [0.53, 0.87]; $P = 0.002$; $I^2 = 42\%$) reported significant survival improvement. In contrast, RRs of death in studies with concurrent controls (RR = 1.10 (0.77, 1.56; $P = 0.60$; $I^2 = 85\%$; Table 2, Fig. 2) and randomized trials (RR = 1.18 (0.57, 2.44; $P = 0.66$; $I^2 = 0$; Table 2, Fig. 2) showed no significant improvement in survival.

Surrogate clinical endpoints

To test the efficacy of tocilizumab on rate of ICU admission we included seven studies [25–27, 31, 41, 42, 45] of 2017 subjects. RR = 1.40 (0.64, 3.06; $P = 0.4$; $I^2 = 88\%$). RR for RCTs and for studies with concurrent controls were RR = 0.80 (0.49, 1.33; $P = 0.39$; $I^2 = 26\%$) and RR = 1.91 (0.47, 7.69; $P = 0.36$; $I^2 = 89\%$; Table 2, Fig. 3). (There was only one study with a matched cohort and no study with a
Fig. 2 The effect of tocilizumab on survival. Risk of death.
4.1.1 RCT

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Hermine 2020      | 11 60 22 64 | 15.2%  0.53 [0.28, 1.00] |
| Salvarani 2020    | 6 60 5 63 12.4%  1.26 [0.41, 3.91] |
| Stone 2020        | 25 157 12 76 15.2%  1.01 [0.54, 1.90] |
| Subtotal (95% CI) | 277 203 | 42.8%  0.80 [0.49, 1.33] |
| Total events      | 42 39 |
| Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.71, df = 2 (P = 0.26); I^2 = 26% |
| Test for overall effect: Z = 0.86 (P = 0.39) |

4.1.2 Retrospective study (Matched)

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Pereira 2020      | 18 29 8 29 15.1%  2.25 [1.17, 4.33] |
| Subtotal (95% CI) | 29 29 | 15.1%  2.25 [1.17, 4.33] |
| Total events      | 18 8 |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 2.43 (P = 0.02) |

4.1.3 Retrospective study (Pure concurrent control)

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Colaneri 2020     | 3 21 12 91 12.2%  1.08 [0.34, 3.50] |
| Martinez-Sanz 2020| 50 260 32 969 16.1%  5.82 [3.82, 8.88] |
| Masia 2020        | 9 76 8 62 13.8%  0.92 [0.38, 2.24] |
| Subtotal (95% CI) | 357 1122 | 42.1%  1.91 [0.47, 7.69] |
| Total events      | 62 52 |
| Heterogeneity: Tau^2 = 1.33; Chi^2 = 18.17, df = 2 (P = 0.0001); I^2 = 89% |
| Test for overall effect: Z = 0.91 (P = 0.36) |

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Total (95%)       | 663 1354 100.0%  1.40 [0.64, 3.06] |
| Total events      | 122 99 |
| Heterogeneity: Tau^2 = 0.94; Chi^2 = 50.70, df = 6 (P < 0.0001); I^2 = 88% |
| Test for overall effect: Z = 0.85 (P = 0.40) |

Fig. 3 The impact of tocilizumab on ICU admission. Risk of ICU admission.

4.1.1 RCT

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Hermine 2020      | 3 63 8 67 5.7%  0.40 [0.11, 1.44] |
| Stone 2020        | 11 61 8 81 9.0%  1.83 [0.78, 4.26] |
| Subtotal (95% CI) | 124 148 | 14.8%  0.92 [0.21, 4.10] |
| Total events      | 14 16 |
| Heterogeneity: Tau^2 = 0.86; Chi^2 = 3.80, df = 1 (P = 0.05); I^2 = 74% |
| Test for overall effect: Z = 0.11 (P = 0.92) |

4.1.2 Retrospective (Historical control)

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Campochiaro 2020  | 9 64 29 64 10.9%  0.31 [0.16, 0.60] |
| Capra 2020        | 5 62 4 23 6.1%  0.46 [0.14, 1.58] |
| De Rossi 2020     | 13 90 6 68 8.4%  1.64 [0.66, 4.09] |
| Guandalini 2020   | 33 179 57 365 13.9%  1.18 [0.80, 1.74] |
| Menzel 2020       | 9 41 12 38 10.1%  0.70 [0.33, 1.46] |
| Subtotal (95% CI) | 436 558 | 49.4%  0.74 [0.40, 1.37] |
| Total events      | 69 108 |
| Heterogeneity: Tau^2 = 0.34; Chi^2 = 14.81, df = 4 (P = 0.005); I^2 = 73% |
| Test for overall effect: Z = 0.96 (P = 0.34) |

4.1.3 Retrospective (matched)

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Albertini 2020    | 3 22 6 22 5.9%  0.50 [0.14, 1.75] |
| Canziani 2020     | 0 32 1 33 1.3%  0.34 [0.01, 8.13] |
| Eimer 2020        | 18 22 21 22 15.5%  0.86 [0.69, 1.06] |
| Klopfenstein 2020 | 0 30 39 176 1.7%  0.97 [0.00, 1.15] |
| Pereira 2020      | 18 29 6 29 9.8%  3.00 [1.39, 6.46] |
| Potere (2) 2020   | 0 10 2 10 1.6%  0.20 [0.01, 3.70] |
| Subtotal (95% CI) | 145 292 | 35.8%  0.77 [0.33, 1.80] |
| Total events      | 39 75 |
| Heterogeneity: Tau^2 = 0.56; Chi^2 = 15.56, df = 5 (P = 0.008); I^2 = 68% |
| Test for overall effect: Z = 0.61 (P = 0.54) |

| Study or Subgroup | Tocilizumab | Control | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
|                   | Events Total | Events Total | Weight |                      |
| Total (95%)       | 705 998 100.0%  0.83 [0.57, 1.22] |
| Total events      | 122 199 |
| Heterogeneity: Tau^2 = 0.23; Chi^2 = 34.59, df = 12 (P = 0.0005); I^2 = 65% |
| Test for overall effect: Z = 0.96 (P = 0.34) |
| Test for subgroup differences: Chi^2 = 0.07, df = 2 (P = 0.96), I^2 = 0% |

Fig. 4 The association of tocilizumab and invasive mechanical ventilation. Risk of invasive mechanical ventilation.
To test the efficacy of tocilizumab on rate of invasive mechanical ventilation we included 13 studies \([1, 2, 25, 27, 28, 30, 32, 33, 35, 40, 43, 45, 47, 56]\) of 1703 subjects. RR \(= 0.83 \ (0.57, 1.22; \ P = 0.34; \ I^2 = 65\%\). RR of studies with historical controls (RR \(= 0.74 \ (0.40, 1.37); \ P = 0.34; \ I^2 = 73\%\)), those with a matched cohort (RR \(= 0.77 \ (0.33, 1.80); \ P = 0.54; \ I^2 = 68\%\) and RCTs (RR \(= 0.92 \ (0.21, 4.10); \ P = 0.92; \ I^2 = 74\%\) are indicated. (There were no studies with concurrent controls; Table 2; Fig. 4). To test the effect of tocilizumab on rate of secondary infections we included 10 studies \([1, 2, 26, 29, 35, 37, 38, 45, 51, 58]\) of 5495 subjects. RR \(= 1.30 \ (0.97, 1.74; \ P = 0.08; \ I^2 = 65\%\). RR for studies with a historical controls (RR \(= 2.18 \ (0.68, 6.98); \ P = 0.19; \ I^2 = 64\%\)), those with a matched cohort (RR \(= 1.12 \ (0.77, 1.62); \ P = 0.56; \ I^2 = 35\%)\) and those with concurrent controls (RR \(= 1.27 \ (0.85, 1.89); \ P = 0.25; \ I^2 = 66\%\) were indicated in Fig. 5. (There was only one RCT). To test the impact of tocilizumab on hospitalization interval we included seven studies \([30, 32, 38, 40, 42, 51, 52]\) of 1041 subjects. Mean difference in subjects discharged from hospital was 2 days \(<1, 4\) days; \(P = 0.006; \ I^2 = 0\); Supplement Fig. 1).

**Discussion**

Increased concentrations of inflammatory cytokines (IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF) and tumor necrosis factor-a (TNF-a) are reported in persons with COVID-19 \([60, 61]\). IL-6 is produced by diverse immune cells and implicated in development of acute respiratory distress syndrome (ARDS) and CRS.

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### Fig. 5 The correlation between tocilizumab and secondary infection. Risk of secondary infection.

| Study or Subgroup | Tocilizumab | Control | Weight | Risk Ratio | Risk Ratio |
|-------------------|-------------|---------|--------|------------|------------|
|                   | Events      | Total   | Total  | M-H, Random. 95% CI | M-H, Random. 95% CI |
| 5.1.1 RCT         |             |         |        |             |             |
| Salvarani 2020    | 1           | 60      | 4      | 1.7%       | 0.26 [0.03, 2.28] |
| Subtotal (95% CI) | 60          | 4       | 63     | 1.7%       | 0.26 [0.03, 2.28] |
| Total events      | 1           | 4       |        |             |             |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.21 (P = 0.23) |

| 5.1.2 Retrospective study (Historical control) | |
|-----------------------------------------------|------|
| Campochiaro 2020                              | 4    |
| Guarnieri 2020                                | 24   |
| Subtotal (95% CI)                             | 211  |
| Total events                                  | 28   |
| Heterogeneity: Tau^2 = 0.47; Chi^2 = 2.74, df = 1 (P = 0.10); I^2 = 64% |
| Test for overall effect: Z = 1.31 (P = 0.19) |

| 5.1.3 Retrospective study (Matched) | |
|------------------------------------|------|
| Biran 2020                         | 36   |
| Canziani 2020                      | 20   |
| Pereira 2020                       | 10   |
| Subtotal (95% CI)                  | 303  |
| Total events                       | 66   |
| Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.07, df = 2 (P = 0.22); I^2 = 35% |
| Test for overall effect: Z = 0.59 (P = 0.56) |

| 5.1.4 Retrospective study (Pure concurrent control) | |
|-----------------------------------------------------|------|
| Gupta 2020                                          | 140  |
| Kewan 2020                                          | 5    |
| Rodriguez-Bano 2020                                 | 11   |
| Somers 2020                                         | 42   |
| Subtotal (95% CI)                                   | 627  |
| Total events                                        | 198  |
| Heterogeneity: Tau^2 = 0.10; Chi^2 = 8.91, df = 3 (P = 0.03); I^2 = 66% |
| Test for overall effect: Z = 1.15 (P = 0.25) |

| Total (95% CI)                                      | 1201 |
| Total events                                        | 293  |
| Heterogeneity: Tau^2 = 0.11; Chi^2 = 25.89, df = 9 (P = 0.002); I^2 = 65% |
| Test for overall effect: Z = 1.76 (P = 0.08) |
| Test for subgroup differences: Chi^2 = 3.11, df = 3 (P = 0.38); I^2 = 3.5% |
Some data suggest increased IL-6 concentrations correlate with risk of death [61, 64]. Several meta-analyses claim tocilizumab is safe and effective in COVID-19 [17, 21, 23, 24]. Most studies we include gave tocilizumab to subjects with evidence of inflammation including a CRP concentration >100 mg/L, a ferritin concentration >900 ng/ml and/or a D-dimer concentration >1500 μg/L [1].

Evaluating all 32 studies we found tocilizumab reduced risk of death but not several surrogate endpoints, including ICU admission, invasive mechanical ventilation, and secondary infections. Hospitalization interval was significantly increased. However, in our analysis of RCTs and studies with a concurrent control cohort we could not confirm a decreased risk of death. This conclusion differs from most prior meta-analyses [17–24] which failed to analyze outcomes by study-design (Table 3). A recent meta-analysis concluded an association between tocilizumab and lower mortality by low certainty evidence from cohort studies [22]. Our data contradict this assumption. Two recent analyses which included only studies with a comparator cohort support our conclusion [65, 66]. Also, Mao and colleagues reported use of tocilizumab did not decrease risk of death possibly because of an increased risk of secondary bacterial infections [67].

There are important limitations to our study. Firstly, subjects were heterogeneous in COVID-19 severity although most had severe to critical COVID-19. Secondly, many studies were observational and lacked an appropriate control cohort. We tried to overcome potential biases in these studies by analyzing outcomes by study-type.

### Table 3 Previous meta-analyses.

| Ref | N studies | N subjects | Studies included | RR or OR of death (95% CI) |
|-----|-----------|------------|------------------|---------------------------|
| [19] | 13 | 766 | 2 historical controls 1 matched control 4 concurrent controls 6 no control | RR = 0.56 [0.34, 0.92] |
| [17] | 23 | 6279 | 4 historical controls 5 matched controls 14 concurrent controls | RD = −0.06 [−0.12, −0.01] |
| [18] | 16 | 3641 | 4 historical controls 3 matched controls 9 concurrent controls | OR = 0.57 [0.36–0.92] |
| [20] | 7 | 592 | 1 historical control 3 matched controls 3 concurrent controls | RR = 0.62, [0.31,1.22] |
| [21] | 10 | 1358 | 3 historical controls 1 matched control 6 concurrent controls | RR = 0.27 [0.12, 0.59] |
| [22] | 23 | 11346 | 3 historical controls 6 matched controls 8 concurrent controls 1 no control 5 RCTs | RR for cohort studies = 0.58 [0.51–0.66] RR for RCTs = 1.09 [0.80,1.49] |
| [23] | 10 | 1675 | 3 historical controls 2 matched controls 5 concurrent controls | OR = 0.47 [0.36, 0.60] |
| [24] | 19 | 2285 | 4 historical controls 4 matched controls 5 concurrent controls 6 no controls | OR = 0.44 [0.36, 0.55] |

**RR** relative risk, **OR** odds ratios, **RD** risk differences, **RCTs** randomized controlled trials.
In conclusion, tocilizumab decreased risk of death but not rates of surrogate endpoints including ICU admission, invasive mechanical ventilation, secondary infections and did significantly alter interval of hospitalization. A reduced risk of death was not confirmed in our meta-analysis of randomized trials or studies with a concurrent control cohort. These data question safety and efficacy of tocilizumab in persons with COVID-19.

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**Author contributions** YL, RPG, and CXC designed study. CXC and FH searched databases and processed analysis. CXC, FH, LTY, TMW, JW, YL, and RPG drafted the typescript. YL, RPG, CXC, LTY, TMW, and JW revised the final typescript. YL and RPG are responsible for the paper.

**Compliance with ethical standards**

**Conflict of interest** RPG is a consultant to: BeiGene Ltd., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Pharmaceuticals Inc. and CStone Pharmaceuticals. Advisor: Antegen Biotech LLC, Medical Director: FFF Enterprises Inc. Partner: AZACA Inc. Board of Directors: RakFond Foundation for Cancer Research Support. Scientific Advisory Board, StemRad Ltd. All other authors declare no competing interests.

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