

Tocilizumab in the treatment of adult patients with COVID-19

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Useful elements are provided below to guide the prescription and to define a relationship between the benefits and risks of the medicine for the individual patient.	
<i>For which patients is it recommended?</i>	<p>Based on current knowledge, the use of tocilizumab can be reimbursed by the National Health Service for the treatment of hospitalised adults with severe COVID-19 and/or high levels of systemic inflammation indices.</p> <p>In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered candidates for treatment with tocilizumab:</p> <ul style="list-style-type: none"> • Recently hospitalised patients admitted to intensive care for less than 24/48 hours who receive mechanical ventilation or high flow oxygen; or recently hospitalised patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥ 75 mg/L). • Patients hospitalised in rapid clinical progression after 24/48 hours of use of dexamethasone, or other cortisone. Rapid clinical progression means rapidly increasing oxygen requirements, even without the need for non-invasive ventilation or high flow oxygen, and with high levels of inflammation indices (CRP ≥ 75 mg/L)
<i>At what dosages is it preferably prescribed and in what forms?</i>	<p><i>Recommended dosage</i></p> <p>The recommended dosage of tocilizumab in adult patients is 8 mg/kg to be administered as a 60-minute intravenous infusion.</p> <p>In the absence of clinical improvement in signs and symptoms after the first dose, a second dose may be given at a minimum interval of at least 8 hours. Doses above 800 mg per infusion are not recommended.</p> <p>For special situations, refer to the technical data sheet of the RoActemra[®] medicine.</p>
<i>Who can prescribe the medicine in this emergency phase?</i>	<p>Tocilizumab (RoActemra[®]) is a prescription-only hospital medicine. For the indication admitted for reimbursement by Law 648/96, the prescription is limited to clinicians operating in the centers indicated by the Region for the management of COVID-19.</p>
<i>What are the greatest risks in terms of adverse reactions?</i>	<p>Warnings (from data sheet):</p> <ul style="list-style-type: none"> • Current active infections (other than COVID-19) that could worsen with the use of tocilizumab • history of intestinal ulceration or diverticulitis • active liver disease and hepatic impairment <p>For more safety information, please see the recently published data sheet and studies: https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_it.pdf</p>

<p><i>Can it be prescribed together with other medicines?</i></p>	<p>Main Interactions (from data sheet):</p> <p>When starting or discontinuing tocilizumab therapy, patients receiving medicinal products whose dosage needs to be adjusted on an individual basis and which are metabolised by CYP450 3A4, 1A2 or 2C9 (such as methylprednisolone, dexamethasone, (with the possibility of oral glucocorticoid suspension), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, cyclosporine or benzodiazepines) should be monitored, as their dose may need to be increased to maintain the therapeutic effect. In view of its long elimination half-life (t_{1/2}), the effect of tocilizumab on the activity of the CYP450 enzyme may persist for several weeks after discontinuation of therapy.</p> <p>For further information on medicine interactions, please see the technical data sheet and consult the website: https://www.covid19-druginteractions.org/.</p>
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Background

Tocilizumab (RoActemra® concentrate solution for infusion 20 mg/ml) is a humanised monoclonal antibody capable of non-specifically binding to both soluble (sIL-6R) and membrane (mIL-6R) IL-6 receptors and shown to inhibit signals mediated by them.

Tocilizumab (TCZ) is indicated for the following clinical conditions:

- severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX);
- moderate to severe RA in adult patients who have not responded adequately or are intolerant to previous therapy with one or more Disease Modifying Antirheumatic Drugs (DMARDs) or anti-TNF;
- active systemic juvenile idiopathic arthritis (JIA) in patients ≥ 2 years of age who have not responded adequately or are intolerant to previous therapies with NSAIDs or systemic corticosteroids;
- juvenile idiopathic polyarthritis (JIA; rheumatoid factor positive or negative and extensive oligoarthritis), in combination with MTX, in patients ≥ 2 years of age who have not responded adequately to previous MTX therapy;
- severe or life-threatening cytokine release syndrome (CRS) induced by Chimeric Antigen Receptor T-Cell Therapies (CAR-T) lymphocytes in adults and paediatric patients ≥ 2 years of age.

Rationale

The rationale for using TCZ in complex patients with SARS-CoV-2 infection is based on the ability to block the IL-6 receptor (IL-6R), thus preventing the effects of activating the pro-inflammatory cascade.

IL-6 represents the target of a potential therapeutic strategy in the treatment of severe and critical cases of patients affected by COVID-19. SARS-CoV-2 infection induces an excessive and aberrant host immune response associated with acute respiratory distress syndrome and, in most critically ill patients, a "cytokine storm" (increased plasma and tissues of various cytokines that produce long-term damage and fibrosis of the lung tissue). Numerous studies have shown a correlation between IL-6 levels and faster progression of SARS-CoV-2 disease (Mojtabavi H et al. 2020). It has been hypothesized that therapies that target the cytokines involved in this aberrant inflammatory response (including IL-6) may have an important therapeutic role in delaying lung damage in patients with SARS-CoV2 infection.

Main evidence available

Randomised clinical trials

In recent months, the results of 9 randomised controlled clinical trials have been made available, published in major international journals, aimed at evaluating the efficacy and safety of TCZ in the treatment of COVID. The main results are summarised below in chronological order:

- 01/05/2021: the results are published, available in pre-print form from February 2021, relating to the treatment with tocilizumab obtained in the RECOVERY (Randomized Evaluation of COVID-19 thERapY) study, a large multi-arm adaptive trial aimed to evaluate the efficacy of different therapeutic options for hospitalised COVID-19 patients (RECOVERY Trial, 2021). Patients hospitalised with hypoxia (SaO₂ <92% or requiring oxygen therapy) and with high inflammatory rates (CRP > 75mg/L) were randomised to tocilizumab in addition to standard therapy or standard treatment (SOC). 4,116 subjects (2,022 in the TCZ arm and 2,094 in the SOC arm) were randomised: 45% received low-flow oxygen therapy, 41% were on non-invasive respiratory support, and 14% were on invasive mechanical ventilation; in addition, 82% of the participants received corticosteroids upon enrolment. Overall, death occurred in 621 / 2,022 (31%) of patients assigned to TCZ and 729 / 2,094 (35%) of patients in the SOC group (RR 0.85; 95% CI 0.76-0.94; p = 0.0028). Consistent results were observed across all pre-specified patient subgroups. In particular, a clear mortality benefit was observed in those taking systemic corticosteroids. Patients assigned to tocilizumab were also more likely to be discharged alive from the hospital within 28 days (57% vs 50%; RR 1.22; 95% CI 1.12-1.34; p <0.0001). By narrowing the analysis to the subgroup of those who did not receive invasive mechanical ventilation at baseline, patients assigned to TCZ were less likely to achieve the composite endpoint of invasive mechanical ventilation or death (35% vs 42%; RR 0.84; CI 95 % 0.77-0.92; p <0.0001). In a meta-analysis on mortality results that the authors conducted including also other 7 studies, the authors reported a reduction in relative terms of about 14% in the risk of death (RR 0.86; 95% CI 0.78-0.94; P = 0.0017).
- 04/03/2021: *Soin AS et al – COVINTOC Study – Lancet Respir Med 2021*: the results of a small randomized, open-label study conducted in India between May and August 2020 are published online. The study involved the enrolment of adult subjects with moderate to severe disease according to the Indian local classification and the randomisation to treatment with tocilizumab (6 mg/kg) vs the standard of care (SOC). Study groups were not perfectly balanced at baseline as a greater proportion of subjects with severe COVID were randomised to the tocilizumab treatment group; and percentages of subjects receiving corticosteroids (91%) and remdesivir (43% and 41%, respectively) were well balanced between the two groups. Although the primary endpoint (moderate to severe or severe clinical progression to death at 14 days) was achieved in fewer subjects in the tocilizumab group (8/91, 9%) than in the SOC (11/88, equal to 13%), this difference was not statistically significant (-3.71; 95% CI -18.23; 11.19; p=0.42). In a post-hoc analysis relating exclusively to subjects with severe COVID, the difference between the two groups in terms of disease progression at 14 days was statistically significant in favour of the tocilizumab arm (8/50 vs 14/41).
- 25/02/2021: *Gordon AC et al for the REMAP-CAP Investigators; NEJM 2021*: Results are published for the immunomodulatory therapy (anti-IL-6) domain of the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial, a large open-label, multi-domain, adaptive trial platform designed to evaluate the efficacy of different treatment options for COVID-19 inpatients. The immunomodulatory therapy domain enrolled adult ICU inpatients who were randomised to tocilizumab (8mg/kg; n=353), sarilumab (400 mg; n=48), or standard non-immunomodulatory therapy (n=402) within 24 hours of initiation of organ support therapy. All but 3 subjects received respiratory support at enrolment: high-flow nasal canula in 29% of cases, non-invasive or invasive mechanical ventilation in 42% and 29% of subjects, respectively.

With respect to the primary endpoint (represented by an ordinal scale combining hospital mortality and days without organ support up to day 21 of observation), the study data produced an estimated odds ratio of 1.46 (95%CI 1.25-2.24) and 1.76 (95%CI 1.17-2.91) for higher efficacy associated with tocilizumab and sarilumab compared to no immune modulation respectively, with a high degree of statistical certainty (with a probability of being superior to no immune modulation of 99.9% for tocilizumab and 99.5% for sarilumab). Specifically, the number of days without organ support was 10 (IQR, -1 to 16) in the tocilizumab-treated group, 11 (IQR, 0-16) in the sarilumab-treated group, and 0 (IQT, -1 to 15) in the placebo group. Hospital mortality was 28% (98/350) for TCZ, 22.2% (10/45) for sarilumab and 35.8% (142/397) for the control group (statistically significant difference).

- 25/02/2021: *Rosas IO et al. 2020 (COVACTA Study)*: The COVACTA study is a double-blind randomised trial vs placebo, conducted in 9 countries in Europe, US and Canada, which involved randomisation in a 2:1 ratio to IV tocilizumab (8 mg/kg up to a maximum of 800 mg repeatable 8-24 hours after the previous one in case of non-response) or placebo. The study enrolled adults with severe pneumonia ($\text{SaO}_2 < 93\%$ and $\text{Pa/Fi} < 300$ mmHg); the endpoint was clinical status at day 28 based on the WHO 7-category scale. A total of 438 subjects were enrolled in the study (294 in the TCZ treatment arm and 144 in the placebo arm). It should be noted that subjects randomised to TCZ had lower proportions of subjects treated with steroids and antivirals. There were no statistically significant differences in clinical status or 28-day mortality (19.7% vs 19.4%) between the two study groups, but shorter discharge times (20 vs 28 days) and ICU stays (9.8 vs 15.5 days).
- 20/01/2021: *Veiga VC et al. 2021 (TOCIBRAS Study)*: this is a small study conducted in Brazil that enrolled subjects on oxygen therapy or mechanical ventilation and with at least 2 altered biomarkers of inflammation (among CRP, D dimer, LDH and ferritin) and randomized them to TCZ (8 mg/kg; n=65) or standard of care (n=64). The primary endpoint was originally clinical status at 51 days on the WHO 7-category ordinal scale, but later, due to the inability to demonstrate the assumption of proportionality of probabilities, the primary endpoint was changed to a composite endpoint of mortality and mechanical ventilation. The study was stopped early by the DSMB after enrolment of 129 subjects due to an excess of deaths in the active treatment group: 18/65 (28%) in the TCZ group and 13/64 (20%) in the SOC group (OR 1.54; 0.66-3.66). In particular, the number of deaths was higher in the TCZ treatment (17%) than in the SOC treatment (3%). However, these data are difficult to interpret due to the early discontinuation of the study, the small number of subjects enrolled and the large margins of uncertainty in the estimation of the effect.
- 17/12/2020: *Salama C et al. 2021 (EMPACTA Study)*: This is a randomised, double-blind, placebo-controlled trial. The study enrolled adults admitted for pneumonia with $\text{SaO}_2 < 94\%$ but not requiring C-PAP or mechanical ventilation. A total of 249 subjects were enrolled in the TCZ group and 128 subjects in the placebo group. The primary endpoint was the composite endpoint of mortality and mechanical ventilation at day 28 and was achieved in 12.0% of TCZ-treated subjects and 19.3% of the placebo group (HR 0.56; CI 95% 0.33- 0.97; P = 0.04 at log-rank test). Death from any cause by day 28 occurred in 10.4% of patients in the tocilizumab group and 8.6% of those in the placebo group (non-significant difference between groups).
- 20/10/2020 *Hermine O et al. 2020 (CORIMUNO Trial)*: randomised, open-label study with Bayesian analysis design, conducted in France in adult subjects with COVID-19 pneumonia requiring oxygen at flows $> 3\text{L/min}$ but not on mechanical ventilation or admitted to the ICU. Participants were randomised to TCZ (n=64) or standard treatment (n=67). The study had two primary endpoints of achieving a WHO Clinical Progression Scale (WHO-CPS) 10-point score of > 5 at day 4 and survival without mechanical ventilation at 14 days. A WHO-CPS score was obtained in 12 subjects treated with TCZ and in 19 subjects in the control group, with an *a posteriori* probability that did not reach the 95% threshold. In contrast, at day 14, significantly fewer TCZ-treated subjects required

mechanical ventilation compared to the control (24% vs 36%) with an a posteriori probability greater than 95%.

A subsequent analysis of data from the CORIMUNO study with a longer follow-up (Meriette et al. 2021), at 90 days, showed a statistically significant difference in terms of mortality reduction in the tocilizumab arm compared to standard treatment (7/63 or 11% vs 11/67 or 18%; HR 0.64; 95% CI, 0.25-1.65).

- 20/10/2020: *Salvarani C t al. 2020*: Italian, multicentre, randomised, open-label study. The study involved 24 Italian clinical centres and enrolled subjects with COVID-19 pneumonia with a Pa/FiO₂ ratio between 200-300 mmHg and an inflammatory phenotype defined as fever and elevated CRP levels. Subjects were randomised to receive tocilizumab or standard treatment (subjects in the control group were eligible for TCZ therapy when they worsened). The primary endpoint of the study was a composite endpoint of use of invasive mechanical ventilation, death or worsening with Pa/FiO₂<150 mmHg. The study was discontinued by the DSMB prematurely, after 126 patients (one third of the planned cohort) were enrolled for futility following an interim analysis that showed no significant differences in clinical progression between the two study groups (28.3% vs 27.0%).
- 21/20/2020: *Stone JH et al. 2020*: Randomised double-blind, controlled vs placebo study in which subjects with COVID-19 pneumonia, SatO₂<92%, inflammatory status were enrolled. The primary endpoint was the combined endpoint of time to death or intubation. The study enrolled 243 subjects (161 in the TCZ group and 82 in the placebo group) and the two groups did not differ in terms of time to death or intubation. At 14 days, 18.0% of patients in the tocilizumab group and 14.9% of patients in the placebo group had worsened disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8-7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8-7.8) in the placebo group (P = 0.69).

Overall, data deriving from the randomised clinical trials are not easy to interpret due to the remarkable differences between the different studies in terms of the population studied (by seriousness, concomitant treatments and timing of commencement of therapy) and the different outcomes assessed (*Angriman F et al. 2021*). An in-depth analysis of the populations included in the clinical studies shows that tocilizumab is more effective within patients with severe COVID-19 and/or with high levels of systemic inflammation indices. In particular, hospitalised patients with rapidly worsening clinical conditions who have received mechanical ventilation or high-flow oxygen for less than 24/48 hours, or in rapidly worsening clinical conditions requiring non-invasive mechanical ventilation or high-flow oxygen, in the presence of high levels of inflammation indices (CRP≥75 mg/L). The use can also be considered in hospitalised subjects in rapid clinical progression despite the use of dexamethasone who require a rapidly increasing supplemental oxygen without the need for non-invasive ventilation or high-flow oxygen, and with high levels of inflammation indices (CRP≥75 mg/L).

Observational studies

Numerous observational studies, both prospective and retrospective, have been conducted which have evaluated the use of tocilizumab in subjects with COVID-19.

In particular, a meta-analysis was recently published in which 10 observational studies were evaluated for a total of 1,358 treated subjects (Malgie J et al. 2020). The quality of the studies was considered adequate for

9/10 studies and the results showed, in the group of subjects treated with TCZ, a 12% lower mortality compared to the control group (95% CI 4.6% -20%), with a NNT equal to 11, in the case of the most conservative estimate and adjusting for heterogeneity.

Scientific reviews and meta-analyses

Scientific reviews and meta-analyses updated in real time have been made available (“*living systematic review and network meta-analysis*”) which have been conducted by important research groups in which the results of the clinical studies were summarised as available at any given time.

- In one of the main available living systematic reviews, edited by the Cochrane in collaboration with several universities and research bodies (https://covid-nma.com/living_data/index.php), the analysis of the available data deriving from RCT, updated on 11/04/2021 and also including data from the RECOVERY study, confirms a protective effect of tocilizumab on mortality outcomes (RR 0.89; 95% CI 0.82-0.97) and time to clinical improvement (RR 1.27; 95% CI 1.13-1.43).
- 16/04/2021 – *Selveraj V et al. 2021*: a meta-analysis that considered 9 randomized controlled trials with a total of 6,490 subjects including: 3,358 subjects treated with tocilizumab and 3,132 treated with standard care/placebo. The pooled analysis showed a significantly reduced risk of all-cause mortality (RR 0.89; 95% CI 0.80-0.98, $p = 0.02$) and progression to mechanical ventilation (RR 0.80, 95% CI 0.71-0.89, $p < 0.0001$) in the tocilizumab group compared to standard therapy or placebo. Furthermore, a trend was highlighted of an improvement in median time to hospital discharge (RR 1.28, 95% CI 1.12-1.45, $p = 0.0002$).
- 18/03/2021- *Ghosn L et al. 2021*: a review is published by the Cochrane group on the use of IL-6 inhibitors for COVID-19. Data analysis from 8 randomized trials with a total of 6,363 participants shows that use of tocilizumab reduces all-cause mortality at 28 days compared to standard of care or placebo (RR 0.89; 95% CI 0.82-0.97; high-certainty evidence), while the effect on other outcomes is still uncertain.
- 12/02/2021 – *Khan FA et al. 2021*: a systematic review and meta-analysis in which different immunomodulatory treatments were considered: anakinra, sarilumab, siltuximab, and tocilizumab. 71 studies (including 6 RCTs) were considered, with a total of 22,058 subjects. Tocilizumab was the most studied drug (60/71 studies). In the context of prospective studies, TCZ was associated with improved survival in an uncontrolled analysis (unadjusted-RR 0.83, 95% CI 0.72-0.96, $I^2 = 0.0\%$). In retrospective assessments, TCZ was associated with lower severity using as an endpoint an ordinal disease severity scale (OR 1.34, 95% CI 1.10-1.64, $I^2 = 98\%$) and a reduced risk of death (AdjHR 0.52, 95% CI 0.41-0.66, $I^2 = 76.6\%$). However, the retrospective studies were burdened by a relevant heterogeneity, which makes the results obtained difficult to interpret.
- 30/12/2020 – *Kim MS et al. 2020*: a systematic review and network meta-analysis (NMA) to systematically evaluate the comparative efficacy and safety of pharmacological interventions for COVID-19 and the level of evidence underlying each treatment regimen in different clinical settings. A total of 110 studies (40 RCTs and 70 observational studies) were included in the review. In the analyses that also included the observational studies, tocilizumab was associated with reduced mortality both in the setting of non-hospitalized subjects in intensive care (OR 0.43, 95% CI 0.30 to 0.60, $p < 0.001$) and in subjects with severe disease (OR 0.62, 95% CI 0.42 to 0.90, $p = 0.012$).

Recommendations of international organisations

- **National Institutes of Health (NIH)**: NIH has updated its recommendations following the availability of data relating to the REMAP-CAP and RECOVERY studies [Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (last update of the specific section: 21 April 2021)].

The panel recommends the use of tocilizumab (single intravenous dose of 8 mg / kg effective body weight, up to 800 mg) in combination with dexamethasone (6 mg daily for up to 10 days) in hospitalized patients presenting with rapid respiratory failure due to COVID-19. Patients included in this population are:

- Recently hospitalised (within 3 days) patients who have been admitted to an intensive care unit (ICU) within the previous 24 hours and who require invasive mechanical ventilation, non-invasive mechanical ventilation (NIV), or high-flow nasal tube oxygen (HFNC) (> 0.4 FiO₂/30 L/min of oxygen flow) (BIIa); or
- Recently hospitalized (within 3 days) non-ICU patients with rapidly increasing oxygen supplementation who require NIV or HFNC and with significantly increased inflammation markers (BIIa) (Note: the RECOVERY study inclusion criterion for inflammation was C-reactive protein [CRP] ≥75 mg/L).

For hospitalized patients with hypoxemia requiring conventional oxygen supplementation, the available evidence is not sufficient to identify individuals who may benefit most from adding tocilizumab. Some panel members recommend use of tocilizumab also in patients showing a rapidly increasing oxygen supplementation during treatment with dexamethasone and with a CRP ≥75 mg/L, but not requiring yet NIV or HFNC.

- **Infectious Diseases Society of America (IDSA):** the American society publishes the Guidelines on Treatment and Management of Patients with COVID-19 (last update of the specific section: 17/02/2021). For hospitalised patients with rapidly evolving severe or critical COVID-19, the IDSA guideline panel suggests using tocilizumab in addition to standard of care (i.e. steroids) rather than just standard of care. (Conditional recommendation, poor certainty of evidence).
- **NHS Interim Position Statement:** Interleukin-6 inhibitors (tocilizumab or sarilumab) for patients admitted to ICU with COVID-19 pneumonia (adults) - 22 February 2021 (<https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/02/C1143-interim-clinical-commissioning-policy-tocilizumab-rps-v2.pdf>):

“Clinicians should consider prescribing intravenous tocilizumab following the criteria outlined below for ICU patients. Intravenous sarilumab could be considered as an alternative (if available)”.

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Eligibility criteria:

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Patients are eligible to be considered for tocilizumab or sarilumab if:

- COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that COVID-19 is the most likely diagnosis **AND**
- They are receiving dexamethasone or an equivalent corticosteroid **AND**
- With a CRP level ≥ 75mg/L; AND SaO₂<92% on room air OR requirement for supplemental O₂ **OR**
- If an IL-6 inhibitor has not been already administered for COVID-19 during this admission and within 24-48 hours of commencement of respiratory support (highflow nasal oxygen, continuous positive airway pressure (CPAP) or invasive/non-invasive mechanical ventilation).

Exclusion criteria:

- Known hypersensitivity to tocilizumab or sarilumab [REMAP-CAP and SmPC contraindications]
- Co-existing infection that might be worsened by tocilizumab or sarilumab [SmPC contraindication]

- More than 24 hours have elapsed since ICU admission or more than 24 hours after commencement of respiratory support (whichever is greater) [REMAP-CAP]
- A baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal (caution is advised if the hepatic enzymes are more than 1.5 times the upper limit of normal) [REMAP-CAP and SmPC special warning and precautions for use]
- A baseline platelet count below $50 \times 10^9 / L$ [REMAP-CAP and SmPC special warning and precautions for use]
- Absolute neutrophil count at baseline below $2 \times 10^9 / L$ [SmPC special warning and precautions for use]
- A pre-existing condition or treatment resulting in ongoing immunosuppression [SmPC special warning and precautions for use].”

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