**Philippine Rheumatology Association (PRA) Guidance Statement**

# Repurposed Anti-rheumatic Drugs for the Treatment of Cytokine Storm Syndrome Secondary to COVID-19 Pneumonia

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## Key Recommendations:

1. Cytokine Storm Syndrome (CSS) is an exaggerated host immune response to the SARS-CoV-2 infection. It is characterized by acute respiratory distress that could culminate in a fulminant hypercytokinemia, multi-organ failure, and death, especially in genetically predisposed individuals. Because of its multiple organ involvement and multi-factorial pathogenesis, a multidisciplinary approach to its management is recommended. This approach may entail the collaboration of infectious disease, pulmonary, and intensive care specialists with other experts such as rheumatologists, hematologists, and others.

2. Several drugs for autoimmune inflammatory rheumatologic diseases have been repurposed to treat CSS secondary to COVID-19 pneumonia. Some of them have been proven to improve clinical outcomes. A multidisciplinary discussion on the timely initiation of treatment and monitoring of these agents should be sought.

3. Dexamethasone or an equivalent glucocorticoid is recommended as standard of care for oxygen-requiring COVID-19 pneumonia with or without a consideration of CSS.

4. The anti-cytokine monoclonal antibody tocilizumab (TCZ) is recommended for the treatment of COVID-19 pneumonia with a consideration of CSS in addition to usual care.

4. Baricitinib or, if unavailable, tofacitinib, both oral small molecule Janus kinase (JAK) inhibitors, is recommended as an alternative to TCZ for the treatment of COVID-19 pneumonia with a consideration of CSS in addition to usual care.

6. Due to limited resources and availability of these drugs, measures that will optimize outcomes are recommended. These measures include judiciously evaluating a patient's condition and following the best available evidence to choose the most appropriate therapy and to give it in a timely manner.

## Background

The clinical manifestations of most patients with COVID-19 are like common viral respiratory infections. A majority have a self-limiting course without the need for advanced medical care. In a small proportion of patients however, the virus is not eliminated or controlled, triggering an exaggerated immune response. As SARS-CoV-2 binds to alveolar epithelial cells, it activates the innate and adaptive immune system resulting in the release of a large number of cytokines, including IL-6. These pro-inflammatory factors increase vascular permeability which flood the alveoli with fluid and blood cells, resulting in dyspnea and respiratory failure (1).

Cytokine storm syndrome secondary to COVID-19 pneumonia is a potentially fatal immune disease characterized by excessive local release of cytokines. Left unabated, this hyperinflammatory syndrome leads to multi-organ failure and death. The same findings parallel those found in established hyperinflammatory syndromes, namely, chimeric antigen receptor therapy-related (CAR-T) cytokine storm, hemophagocytic histiolymphocytosis, and macrophage activation syndrome. Consequently, the newly labeled entity of COVID-19-related CSS and CSS in general have been used interchangeably (2).

It manifests in a similar manner to acute respiratory distress syndrome (ARDS) (3). COVID-19 patients such as the elderly and those with comorbidities are at risk for disease progression, COVID-19-associated ARDS (CARDS), and the eventual multi-organ dysfunction syndrome (MODS) brought about by multisystemic end-organ inflammation.

It has been postulated to cause death in healthy young individuals in the 1918 pandemic. Cases in the SARS, MERs-CoV and AH1N1 epidemics have been similarly described (4). Early in the COVID-19 pandemic in China and Italy, young patients have shown findings similar to CSS. These reports also offer insights into disease characteristics and trajectories, and timely interventions.

To address the impact of COVID-19 pneumonia and CSS, several anti-rheumatic drugs have been repurposed for COVID-19 therapy (5). These agents range from common anti-inflammatory medications like glucocorticoids and colchicine to monoclonal antibodies and oral small molecule inhibitors. Two of these drugs address specific

inflammatory pathways, prevent organ damage, and improve clinical outcomes in CSS secondary to COVID-19 pneumonia: inhibitors of interleukin 6 (IL-6) and Janus Kinase (JAK). These drugs are part of the standard of care treatment for rheumatoid arthritis (RA), the prototypical systemic autoimmune inflammatory arthritis.

The United States Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for these repurposed agents for use in the pandemic (6,7). In the Philippines the only anti-IL-6 available with an FDA-issued certificate of product registration (CPR) is the intravenous and subcutaneous preparation of TCZ. The JAK inhibitors available with CPR are baricitinib and tofacitinib. These agents have since been given to COVID-19 patients nationwide under an off-label indication or compassionate special permits (CSP) issued to certain institutions by the Philippine FDA.

Early in the pandemic in April 2020, the Philippine Rheumatology Association (PRA), together with the national societies of pulmonologists and nephrologists, issued the joint declaration of support for the use of TCZ in CSS secondary to COVID-19 pneumonia (8). This recommendation was further reinforced by the inclusion of TCZ in the updated clinical management guidelines for COVID-19 by the Philippine Society for Microbiology and Infectious Diseases in July 2020 (9).

This year the Health Technology Assessment Council (HTAC) recommended the use of TCZ, in addition to systemic glucocorticoids, for patients showing respiratory deterioration or elevated markers of inflammation and requiring high doses of oxygen. HTAC is an independent advisory body created under Republic Act 11223, otherwise known as the Universal Health Care Act, with the overall role of providing guidance to the Department of Health (DOH) and the Philippine Health Insurance Corporation (PhilHealth) on the coverage of health interventions and technologies to be funded by the government. It also recommended baricitinib in combination with the antiviral remdesivir in hospitalized patients with COVID-19 who require oxygen and in whom glucocorticoids are contraindicated (10).

The US National Institute of Health has updated and revised the recommendations for these agents. Baricitinib is now indicated for hospitalized patients with COVID-19 who have rapidly increasing oxygen requirements and require non-invasive ventilation such as high-flow oxygen. The same recommendation applies to TCZ. Also, TCZ is indicated

for patients who are within 24 hours of admission to the ICU and require invasive mechanical ventilation or extracorporeal membrane oxygenation. Any one of these agents should be given together with dexamethasone and with or without remdesivir (11).

The DOH and Philhealth classification likely suffering from CSS falls under the severe to critical illness spectrum (12, 13).

Cytokine storm syndrome may show up in the labs before it appears clinically. Patients with laboratory evidence of CSS exhibit a higher risk of progression to CARDS, shock, and MODS (14). Lab findings suggestive of CSS may, therefore, merit early consideration of these agents.

Although the following laboratory markers are consistent with CSS-related COVID-19 pneumonia, these are not specific to CSS and clinical correlation is advised. Some patients may not reach the cut-off values for these markers so treatment decisions should be individualized taking into account the whole clinical picture, including results from other exams such as imaging (15).

1. C-reactive protein (CRP) >50 mg/L
2. At least two of the following:

a) Ferritin >500 ng/mL
b) Lactate dehydrogenase (LDH) >300 U/L
c) D-dimer >1000 ng/mL

Periodic monitoring of these markers should be done in suspected or confirmed CSS. The cut-off values taken in isolation are not as significant as the trends of these markers and should approximate response or resistance to treatment with these agents.

**Rationale for the use of glucocorticoids in COVID-19 pneumonia requiring oxygen supplementation**

The glucocorticoid cortisone was first used in 1948 by Nobel Laureate and then chief rheumatologist at Mayo clinic Philip Hench on a 29-year-old woman with RA. Since then, glucocorticoids have been part of the standard of care of inflammatory rheumatic conditions (16). Patients who develop ARDS benefit from the early use of glucocorticoids. (17).

Trials on glucocorticoids for COVID-19 pneumonia have shown benefit in terms of arresting disease progression or preventing death.

The RECOVERY trial has shown that dexamethasone decreased the incidence of death in those on invasive ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and non-invasive ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not those without ventilatory support (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55) (18).

The CoDEX trial enrolled adults who had confirmed or suspected COVID-19 infection and were receiving mechanical ventilation within 48 hours of meeting the criteria for moderate to severe ARDS (Pao2/Fio2 $\leq$ 200). They were randomized to receive 5 days of 20 mg dexamethasone followed by 10 mg dexamethasone or to standard care. The dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) in the first 28 days compared to the standard care group (difference, 2.26; 95% CI, 0.2-4.38; P=0.04) with 4.0 ventilator-free days (95% CI, 2.9-5.4). Less patients in the dexamethasone group, compared to the standard care group, had secondary infection, 33 (21.9%) versus 43 (29.1%) or experienced serious adverse events, 5 (3.3%) versus 9 (6.1%) (19).

**Rationale for the use of TCZ in CSS secondary to COVID-19 pneumonia**

Interleukin-6 activates T cells and macrophages and plays a dominant role in inflammation. It is a potent inflammatory mediator that cascades signals to other pro-inflammatory cytokines. Historically, the anti-IL-6 TCZ was approved for CAR-T-related cytokine storm (20). Tocilizumab is the first humanized anti-IL-6 receptor subunit alpha monoclonal antibody approved for the treatment of RA refractory to methotrexate and tumor necrosis factor inhibitors (TNFi). TCZ inhibits both the cis- and trans-signaling cascades involving the JAK signal transducer and activator of transcription pathway, playing a crucial role in modulating not only joint inflammation but also extra-articular manifestations (21). In COVID-19 elevated levels of IL-6 have been shown to correlate with severe disease manifestation (22). Interleukin-6 inhibition prevents T cell activation and halts the inflammatory cascade and is, therefore, considered protective.

The World Health Organization, relying on their meta-analysis, made a strong case for TCZ use in severe and critical COVID-19 (23). Two large pivotal trials, REMAP-CAP and RECOVERY, paved the way for the widespread use of TCZ in COVID-19. These

trials have shown a mortality benefit for TCZ use in patients with rapid respiratory decompensation and high oxygen requirements using high-flow oxygen. Glucocorticoids were also given in these studies. (24, 25)

In the REMAP-CAP trial, patients admitted to an ICU with severe to critical COVID-19 and rapid respiratory decompensation were randomized to receive open-label TCZ or usual care. Compared to usual care, the use of TCZ reduced in-hospital mortality (28% vs. 36%) and increased the median number of days free of respiratory and cardiovascular organ support over 21 days of follow-up (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days) suggesting benefit of TCZ use in patients experiencing rapid respiratory decompensation. Therapeutic benefit was stronger for recipients on high-flow oxygen or non-invasive ventilation than for those on mechanical ventilation. However, the lack of a formal subgroup analysis by oxygen requirement is a notable limitation of this study.

The RECOVERY trial also suggested a mortality benefit for TCZ plus dexamethasone in patients on high-flow oxygen or noninvasive ventilation. A subset of participants with hypoxemia and C-reactive protein levels ≥ 75 mg/L were randomized to receive TCZ or usual care. Tocilizumab reduced all-cause mortality in these patients. By day 28, 33% of participants in the usual care arm had died compared to only 29% in the TCZ arm (rate ratio 0.86; 95% CI, 0.77–0.96).

**Rationale for the use of JAK Inhibitors in CSS secondary to COVID-19 pneumonia**

Many pro-inflammatory cytokines require members of the JAK family of protein tyrosine kinases to carry their signals across cell membranes (26). The inhibitors of these signalling molecules target downstream receptors that several inflammatory cytokines commonly use. Two JAK inhibitors are locally available. They have the potential to treat COVID-19, obviate the need for oxygen, and decrease the incidence of death.

The RA drug baricitinib is one of the JAK inhibitors. (27). It is a selective and reversible inhibitor of JAK1 and JAK2, which belong to the JAK family of protein tyrosine kinases. It modulates the JAK and signal transducers and activators of transcription (STAT) pathway by transiently occupying the ATP binding pocket of JAK. This action inhibits the

phosphorylation of JAKs and the subsequent phosphorylation and activation of STATs (28). It was identified as a potential intervention for COVID-19 pneumonia (29).

The ACTT-2 trial demonstrated that baricitinib in combination with remdesivir improved time to recovery in hospitalized patients with COVID-19. The effect was most pronounced on patients receiving noninvasive ventilation. Although patients on glucocorticoids were excluded from the ACTT-2 trial, the study nevertheless supported the view that baracitinib may have a clinical benefit on patients who were not on glucocorticoids (30).

The COV-BARRIER trial randomized 1,525 hospitalized patients with COVID-19 and an elevation of one or more inflammatory markers into baricitinib 4 mg once daily or placebo in addition to usual care for up to 14 days or until hospital discharge. There was no difference in the primary endpoint of progression to use of non-invasive ventilation and invasive ventilation or death by day 28 between baricitinib (27.8% of patients) and placebo (30.5% of patients; OR 0.85; 95% CI, 0.67–1.08; P = 0.18). All-cause mortality was 13.1% for placebo and only 8.1% for baricitinib, a 38.2% reduction in mortality in the baricitinib group overall (HR 0.57; 95% CI, 0.41–0.78; nominal P = 0.002). Across all disease severity subgroups, mortality estimates were lower for baricitinib than for placebo. The difference in mortality was most pronounced in 370 patients receiving high-flow oxygen or non-invasive ventilation at baseline (17.5% died in the baricitinib arm vs. 29.4% in the placebo arm; HR 0.52; 95% CI, 0.33–0.80; nominal P = 0.007). Adverse events, serious adverse events, serious infections, and venous thromboembolic events were comparable in both arms (31).

Tofacitinib is a selective inhibitor of JAK1 and JAK3. It has only functional selectivity for JAK2. It inhibits cytokine formation and may modulate the action of interferons and IL-6. In the double-blind placebo-controlled STOP-COVID trial, use of tofacitinib given at 10 mg twice daily for 14 days was associated with a decreased risk in the composite outcome of respiratory failure or death (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days was 5.5 % in the placebo group (n=145) and only 2.8% in the tofacitinib group (n= 144) (HR 0.49; 95% CI, 0.15–1.63). Approximately 80% of participants in each group also received glucocorticoids. Serious adverse events occurred in 14.2% in the tofacitinib group and 12.0% in the placebo group (32).

**Treatment dosing and precautions (adapted from US NIH)**

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| **Baricitinib** | Dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge | eGFR $\geq$ 60mL/min/1.73m$^2$: 4 mg PO once daily<br>eGFR 30 to <60mL/min/1.73m$^2$: 2 mg PO once daily<br>eGFR 15 to $\leq$ 30mL/min/1.73m$^2$: 1 mg PO once daily<br>eGFR $\leq$ 15mL/min/1.73m$^2$: not recommended |
| **Tofacitinib** | 10 mg PO twice daily for up to 14 days or until hospital discharge | Use as an alternative if baricitinib is not available or not feasible to use<br>eGFR $\leq$ 60mL/min/1.73m$^2$: 5 mg PO twice daily |
| **Tocilizumab** | 8mg/kg actual body weight, (up to 800mg) administered as a single IV dose | In clinical trials, a third of the participants received a second dose of tocilizumab 8 hours after the first dose if no clinical improvement was observed |

It is recommended to give these agents to COVID-19 patients with normal procalcitonin and for those with elevated procalcitonin to be cleared by an infectious disease specialist prior to use.

Contraindications to drug administration:

a. Absolute neutrophil count < 1000 cells/microliter
b. ALT > 5x upper limit of normal
c. Active tuberculosis
d. Bacterial sepsis

Around the world these repurposed agents have been granted EUAs and CSPs and adapted into international and local COVID-19 treatment guidelines, including the one promoted by DOH (33). It is imperative to the treating physician to practice the medical bioethical principles of patient autonomy, justice, non-maleficence and beneficence in the use and allocation of these timely therapeutic interventions. Clinicians experienced in treating patients with COVID-19 and in using these immunomodulators must guide the administration of these agents and monitor for untoward safety signals.

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