Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020
Emerg Infect Dis published online August 2020
Current literature suggests that children (< age 9) are infected at a lower rate and play a less significant role in transmission of the virus (Pediatr Adolesc Med published online July 19, 2020: jwatch.org/na52000 and Pediatrics 2020; 146:e20201576). In the current study, investigators analyzed age-specific COVID-19 rates in close to 60,000 contacts, including 10,600 household contacts, of almost 6000 patients with confirmed COVID-19 in South Korea during a 2-month period. Contacts were tested for SARS-CoV-2 if they were in a high-risk group or were symptomatic; other contacts self-quarantined and were observed for symptoms for 14 days. They reported the following:

- Twelve percent of household contacts developed COVID-19.
- Two percent of nonhousehold contacts developed COVID-19.
- Nineteen percent of household contacts of the 124 10-to-19-year-old COVID-19 index cases developed COVID-19 compared with only 5% who were in household contact with 1 of the 29 index cases who were aged ≤9 years.
- As expected, the detection rate among nonhousehold contacts was lower than among household contacts in all age groups.

Comment: This is a vigorous contact trace study that confirms both the risk of household contacts, but also the role of older children. As other studies have suggested younger children represent smaller percentage of index cases and transmit at a lower rate compared to older adults. This information may help determine how best to re-open schools with perhaps bringing the youngest children back first.

Novel Coronavirus Infection in Febrile Infants Aged 60 Days and Younger
Pediatrics published online August 2020
This is a case series describing the clinical course and outcomes of 7 febrile infants aged ≤60 days infected with confirmed SARS-CoV-2. No infant had severe outcomes, including the need for mechanical ventilation or ICU level of care. Two infants had concurrent urinary tract infections, which were treated with antibiotics.

Comment: Although a small series, the data suggest that febrile infants with SARS-CoV-2 infections often have mild illness. Most case series have either combined the results of all infants <1 year of age or excluded infants. Given how small the sample it limits the generalizability of their findings. SARS-CoV-2 testing was reserved for children requiring hospitalization; therefore, some febrile infants did not undergo testing and may have been missed. Lastly, they did not have information regarding maternal SARS-CoV-2 status at the time of delivery.

Early Identification of COVID-19 Cytokine Storm and Treatment with Anakinra or Tocilizumab
Int J Infect Dis published online August 3, 2020
COVID-19-related cytokine storm appears to start 8 to 10 days after symptom onset and is characterized by high fevers, dyspnea, hypoxemia, and bilateral pulmonary infiltrates, and can progress rapidly to acute respiratory distress syndrome and multisystem organ failure with or without hypercoagulability and, ultimately, death.

This article described their initial experience with tocilizumab and anakinra (IL-1 receptor antagonist) for the treatment of patients with COVID-19-related cytokine storm at 15 Kaiser Permanente hospitals in southern California. The authors noted that treatment options for cytokine storm initially included tocilizumab without corticosteroids (and no anakinra). However, clinicians wanted to identify early

cytokine storm through laboratory abnormalities in patients with increasing oxygen requirements and to initiate combined treatment with anakinra and corticosteroids. Between March 1, 2020, and April 13, 2020, 52 patients received 1 to 4 doses of tocilizumab a median 14 days after symptom onset, and 41 patients received anakinra a median of 13 days after symptom onset, respectively. Most tocilizumab-treated patients received 1 dose. The median duration of anakinra treatment was 9 days and the median cumulative dose was 1,500 mg. All patients had bilateral infiltrates on chest x-ray or CT, and all non-intubated patients had increasing supplemental oxygen requirements at the time of treatment initiation. Concomitant corticosteroids were used in only 7 tocilizumab-treated patients, although 12 others received rescue treatment with steroids later in their hospital course. In contrast, allanakinra-treated patients received concomitant corticosteroids. Of the patients treated with tocilizumab, 20 also received remdesivir, as did 16 patients in the anakinra group. Hydroxychloroquine was administered to 34 anakinra-treated patients and 48 tocilizumab-treated patients. The risk of death was lower in the anakinra group (22.0%) than the tocilizumab group (46.2%). Among the 18 non-intubated patients at anakinra start, 14 never required intubation, 3 were subsequently intubated (1 extubated and 2 still intubated), 11 (47.8%) were extubated at last follow-up compared with 20 (40%) of the 50 intubated patients at tocilizumab initiation. After accounting for differences in disease severity at treatment initiation, this apparent superiority of anakinra over tocilizumab was no longer statistically significant (propensity score-adjusted hazards ratio = 0.46; 95% confidence interval, 0.18-1.20). Identify COVID-19-related cytokine storm earlier in the disease course, prior to intubation, through a combination of laboratory abnormalities and respiratory deterioration was explored. They accomplished this by standardizing early ordering and interpretation of inflammatory markers and the subsequent treatment of patients with cytokine storm with corticosteroids and anakinra. (These COVID19-CS laboratory criteria are as follows: 1) ferritin >2000ng/mL and one other abnormal inflammatory marker; or 2) ≥4 abnormal inflammatory markers, including C-reactive protein >70mg/L; ferritin>700ng/mL, D-dimer>1000ng/mL, triglycerides >265mg/dL, AST >59u/L, LDH >300IU/L, lymphopenia 8000cells/uL.)This approach resulted in better outcomes compared to the early tocilizumab-treated patients, but our analyses suggest that this could be due to earlier identification and treatment of COVID-19-related cytokine storm rather than superior efficacy of anakinra compared with tocilizumab. In addition, concomitant treatment with corticosteroids may have contributed to the better response observed in the anakinra-treated group.

Comment: Not measuring inflammatory markers and delayed treatment, including with corticosteroids, may have contributed to worse outcomes in the tocilizumab-treated patients. Tocilizumab is not preferred in MAS/HLH because it increases the risk of bacterial infections, has a long half-life, and blunts CRP and ferritin levels in the absence of clinical response, which can lead to confusion and delays in escalating treatment. Their results support the RECOVERY Trial on the use of steroids; however, randomized controlled trials of targeted anti-cytokine treatments are needed and should report duration of elevated cytokine storm inflammatory markers in addition to clinical severity at randomization. The main limitation of this study is the possibility of unmeasured confounding that is present in all observational studies. This and other observational studies show how difficult it is to determine efficacy of IL-6 and IL-1 inhibitors. Hopefully, the RECOVERY RCT on tocilizumab may shed light of this intervention.

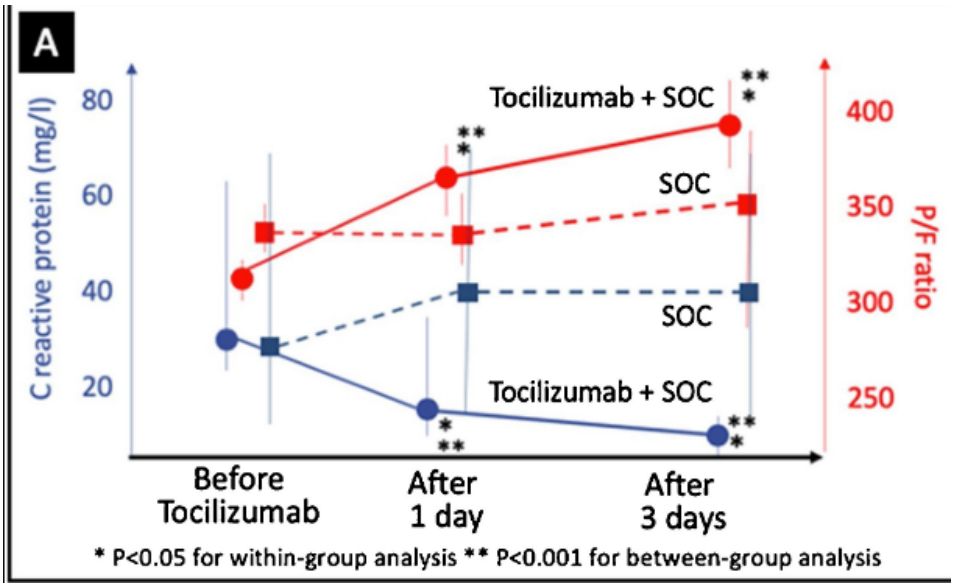
Low-Dose Subcutaneous Tocilizumab to Prevent Disease Progression in Patients with Moderate COVID-19 Pneumonia and Hyperinflammation

Int J Infect Dis published online August 5, 2020

The authors retrospectively analyzed clinical characteristics and outcomes of patients with laboratory-confirmed bilateral COVID-19 pneumonia, hyperinflammation (C reactive protein ≥20 mg/dl), no hypoxemia (oxygen saturation >90%) and no contra-indications to TCZ, who were treated with

subcutaneous TCZ (324 mg) administered within 48 hours from hospitalization on top of standard of care (SOC), and compared them with matched controls treated with SOC only before TCZ was available at our center. Clinical data were available for all patients until death or, for those discharged from hospital, until day 35.

Ten consecutive patients (6 males, median age 55 years) treated with TCZ on top of SOC, and ten patients (6 males, median age 56 years) treated with SOC only were included. TCZ was well-tolerated, with no clinically relevant adverse events. TCZ was associated with a reduction in CRP at day 1 (−50%, IQR −28 to −80) and day 3 (−89%, IQR −79 to −96; P = 0.005 for within-group), whereas there was no significant change in CRP values in the SOC group (P < 0.001 for between-groups comparisons at both time points). TCZ resulted in a parallel improvement of oxygenation, as assessed by the ratio of partial pressure of oxygen to fraction of inspired oxygen (P/F) ratio, which increased at day 1 (+11%, IQR + 6 to +16; P = 0.005 for within-group, and P = 0.006 for between-groups comparisons), and day 3 (+23%, IQR + 16 to +34; P = 0.005 for within-group, and P = 0.003 for between-groups comparisons). None of the TCZ-treated patients had disease progression defined as requirement of oxygen therapy or mechanical ventilation, whereas progression occurred in 5 (50%) patients among the SOC group.



Comment: This is a very small series using TCZ early to prevent progression in patients who had elevated CRPs. The trial was non-randomized and subject to unmeasured confounders. However, their findings suggest that early IL-6 receptor blockade with TCZ may reduce the risk of progression to severe disease in hospitalized patients with moderate COVID-19 pneumonia and hyperinflammation. Is this the same effect we see with use of dexamethasone?

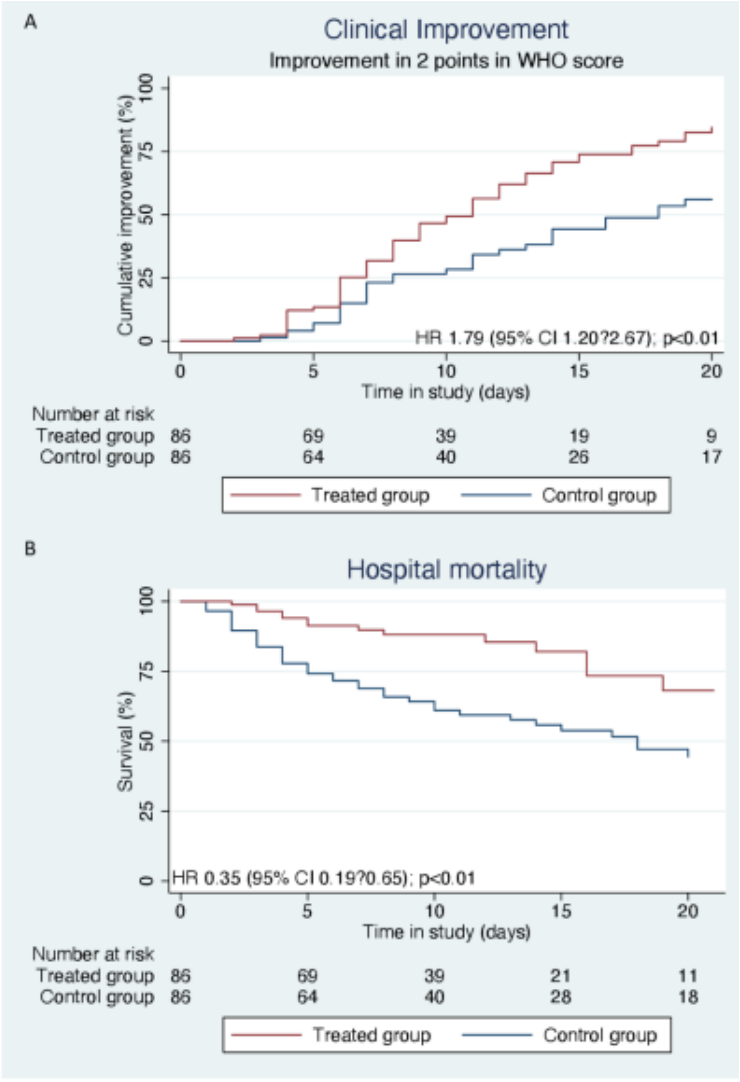
Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome (CSS): results of the CHIC study

Ann Rheum Dis published online August 2020

From 1 April 2020, patients with COVID-19- associated CSS, defined as rapid respiratory deterioration plus at least two out of three biomarkers with important elevations (C-reactive protein >100 mg/L; ferritin >900 µg/L; D-dimer >1500 µg/L), received high-dose intravenous methylprednisolone for 5

consecutive days (250 mg on day 1 followed by 80 mg on days 2–5). If the respiratory condition had not improved sufficiently (in 43%), the interleukin-6 receptor blocker tocilizumab was added on or after day 2. Control patients with COVID-19-associated CSS (same definition) were retrospectively sampled from the pool of patients (n=350) admitted between 7 March and 31 March and matched one to one to treated patients on sex and age. The primary outcome was ≥2 stages of improvement on a 7-item WHO-endorsed scale for trials in patients with severe influenza pneumonia, or discharge from the hospital. Secondary outcomes were hospital mortality and mechanical ventilation. All patients received ceftriaxone (2g every 24 hours for 7 days) and up to 11 May 2020 in the presence of oxygen saturation <90% chloroquine 300mg every 12 hours following a loading dose of 600mg unless the corrected QT interval on an ECG was prolonged (>500ms)

At baseline all patients with COVID-19 in the treatment group (n=86) and control group (n=86) had symptoms of CSS and were at risk for acute respiratory failure. Treated patients had 79% higher likelihood on reaching the primary outcome (HR: 1.8; 95% CI 1.2 to 2.7) (7 days earlier), 65% less mortality (HR: 0.35; 95% CI 0.19 to 0.65) and 71% less invasive mechanical ventilation (HR: 0.29; 95% CI 0.14 to 0.65). Treatment effects remained constant in confounding and sensitivity analyses.



Comment: This study was not a RCT. Efforts were to match the control patients as closely as possible to the treated patients. Residual confounding by unmeasured variables cannot be ruled out. While patients were almost perfectly matched for age and gender and efforts, diabetes and obesity were slightly more prevalent in the control patients and some biomarkers of CSS were slightly higher too. Cardiovascular comorbidity and arrhythmias, on the other hand, were more prevalent in the treated patients. The results of this study also suggest that the timely administration of high-dose GCs alone may provide significant benefit in more than half of the patients and that TCZ is only needed in those cases that had insufficient clinical improvement on MP alone.