Actemra Use in Coronavirus Disease 2019 (COVID-19)

This responds to your request for information on the use of Actemra™ (tocilizumab) in patients with coronavirus disease 2019 (COVID-19).

In Brief

- Preliminary case study/series exploring the use of Actemra for treatment of patients with severe respiratory complications and COVID-19 have been reported from various parts of the world. Actemra was included in the 7th updated Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia issued by China's National Health Commission on March 3, 2020.

- At present, there is no robust published clinical trial evidence evaluating the safety or efficacy of Actemra for treatment of COVID-19. (March 19, 2020). Results from a retrospective, single-arm observational study of 21 patients with severe or critical COVID-19 pneumonia have been posted the study investigators on ChinaXiv, an open repository and distribution server for unpublished but complete manuscripts (preprints).

- A Phase 3, randomized, double-blind, placebo-controlled study is being conducted to assess the efficacy and safety of Actemra compared with placebo in combination with Standard of Care in approximately 330 hospitalized adult patients with severe COVID-19 pneumonia. Patients in the Actemra treatment arm will receive 1 infusion of Actemra 8 mg/kg, with a maximum dose of 800 mg. One additional Actemra infusion can be given 8-12 hours after the initial infusion if the clinical signs and symptoms worsen or do not improve.

- Actemra is approved for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA), giant cell arteritis (GCA), and chimeric antigen receptor T cell-induced cytokine release syndrome (CRS).

- Please refer to the locally approved product label for important safety information, including Warnings, Precautions, and Contraindications.

- We fully respect the clinical decision and independent choice of healthcare providers and medical institutions.

Abbreviations

CAR=chimeric antigen receptor
CDC=Centers for Disease Control and Prevention
COVID-19=Coronavirus Disease 2019
CRS=cytokine release syndrome
GCA=giant cell arteritis
ICU=intensive care unit
IL=interleukin
pJIA=polyarticular juvenile idiopathic arthritis
RA=rheumatoid arthritis arthritis
SOC=standard of care
sJIA=systemic juvenile idiopathic
WHO=World Health Organization

Background Information

High concentrations of cytokines have been reported in severely- or critically-ill patients infected with COVID-19, though the role of IL-6 in mediating cytokine storm associated with COVID-19 remains unclear.[1,2]

In a recent Lancet publication, a retrospective, multicenter, cohort study of 191 hospitalized patients with COVID-19 from Wuhan observed that age, lymphopenia, leukocytosis, and elevated levels of ALT, lactate dehydrogenase, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6 prothromobin time, creatinine, and procalcitonin were associated with death (univariable analysis).[1] In a temporal analysis, elevated levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and IL-6 were observed in non-survivors compared with survivors throughout the clinical

course, and increased with illness deterioration. The authors noted a number of study limitations, including the difficulty in assessing host risk factors for disease severity and mortality with multivariable-adjusted methods due to the small sample size.

In another Lancet publication describing 41 patients in Wuhan hospitalized for COVID-19, there was no evidence of marked IL-6 elevation between ICU and non-ICU patients.[2]

Actemra, an IL-6 inhibitor, is approved for the treatment of RA, pJIA, sJIA, GCA, and CAR T cell-induced CRS. The risks and benefits of treatment should be considered prior to initiating Actemra in patients with COVID-19. Please refer to the locally approved product label for important safety information of Actemra, including Warnings, Precautions, and Contraindications.

Use in Coronavirus Disease 2019 (COVID-19)

Preliminary case study/series describing the use of Actemra in patients with COVID-19 have been reported from various parts of the world. At present, there is no robust published clinical trial evidence evaluating the safety or efficacy on the use of Actemra for treatment of COVID-19. (March 19, 2020)

The World Health Organization (WHO) has gathered and complied the latest scientific findings and knowledge on COVID-19 in a database. Interested clinicians can search the WHO database of publications on COVID-19 at www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov (accessed March 13, 2020).

Centers for Disease Control and Prevention (CDC) & China's National Health Commission

Actemra is not indicated for the treatment of COVID-19. There is very limited evidence to evaluate the potential benefit or safety risks in these patients. The risks and benefits of treatment should be considered prior to initiating Actemra in patients with COVID-19. We fully respect the clinical decision and independent choice of healthcare providers and medical institutions.

Information adapted from the current guidance and treatment plan from the United States' Centers for Disease Control and Prevention and China's National Health Commission on management of COVID-19 are summarized below. These summaries are provided for informational purposes and should not be interpreted as recommendations from Genentech/Roche on management of COVID-19.

The Centers for Disease Control and Prevention

In the current *Interim Clinical Guidance for Management of Patients with Confirmed COVID-19* by the CDC, the following is stated[3] (assessed March 19, 2020):

- "No specific treatment for COVID-19 is currently available. Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated."
- At present, Actemra is not mentioned for management of COVID-19.

The National Health Commission of the People's Republic of China

Actemra was included in the 7th update *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)* released by the National Health Commission & State Administration of Traditional Chinese Medicine on March 3, 2020 (Chinese only)[4]. In a translation organized by the WHO China Office, Actemra was mentioned as a treatment of severe and critical cases:

- "3.7 Immunotherapy: For patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in laboratory testing, Tocilizumab can be used for treatment. The initial dose is 4-8 mg/kg with the recommended dose of 400mg diluted with 0.9% normal saline to 100ml. The infusion time should be more than 1 hour. If the initial medication is not effective, one extra

administration can be given after 12 hours (same dose as before). No more than two administrations should be given with the maximum single dose no more than 800 mg. Watch out for allergic reactions. Administration is forbidden for people with active infections such as tuberculosis."

Case Series

Preliminary results from a preprint shared in ChinaXiv, an open repository and distribution server for unpublished but complete manuscripts (preprints), are summarized below. Preprints are preliminary reports of work that have **not been peer-reviewed**. They should not be relied on to guide clinical practice. As such, results from preprints should be interpreted with caution.

In a retrospective, single-arm observation study, the use of Actemra was reported in 21 patients diagnosed with severe or critical COVID-19 defined by the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th interim edition)* by China's National Health Commission.[5] Patients were classified as having severe COVID-19 if any of the following was present: respiratory rate ≥30 breaths/min, SpO2 ≤93% while breathing room air, or PaO2/FiO2 ≤ 300 mmHg. Patients were classified as having critical COVID-19 if any the following was present: respiratory failure requiring mechanical ventilation, shock, or other organ failure requiring admittance to an ICU. All patients received one dose of Actemra IV (400mg) between February 5, 2020 and February 14, 2020 along with standard care as defined by the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th interim edition)*, which includes methylprednisolone, lopinavir, oxygen therapy, and other symptom relievers.

The average age of patients was 56.8±16.5 years (range, 25 to 88 years).[5] Eighteen patients were male and 3 were female. Seventeen patients were assessed as severe and 4 were critical. Of the 21 patients, 18 patients received Actemra 400 mg IV x1 and 3 patients received a second dose of Actemra IV (400 mg) within 12 hours because of fever. Body temperature returned to normal in all patients on Day 1 and remained stable through Day 5. Fifteen patients had lowered oxygen intake and 1 patient was off oxygen therapy. Lung lesion opacity were absorbed on CT scans in 19 patients. Nineteen patients were discharged an average of 13.5 day after treatment with Actemra along with the standard care. Laboratory test results before and after Actemra are shown in the table below:

Laboratory Tests before and after Actemra[5]

	Range	Mean ± SD (abnormal no./total no., %)			
		Before Actemra	After Actemra		
			Day 1	Day 3	Day 5
White blood cell count, $x10^9$/L	3.5-9.5	6.3±2.77 (4/20, 20%)	8.05±4.39 (8/18, 44.4%)	6.02±3.05 (9/21, 42.9%)	5.25±2.11 (2/19, 10/5%)
Lymphocyte percentage, %	20-50	15.52±8.89 (17/20, 85%)	11.78±11.36 (16/18, 88.9%)	16.93±13.59 (14/21, 66.7%)	22.62±13.48 (9/19, 47.4%)
C-reactive protein, mg/L	0-5	75.06±66.8 (20/20, 100%)	38.13±54.21 (17/18, 94.4%)	10.61±13.79 (10/20, 50%)	2.72±3.6 (3/19, 15.8%)
Procalcitonin, mg/ml	0-0.5	0.33±0.78 (2/20, 10%)	0.21±0.35 (2/16, 12.5%)	0.09±0.13 (1/19, 5.3%)	0.12±0.15 (1/18, 5.6%)

Abbreviation: SD=standard deviation.

No details were provided regarding the dose or duration of treatment for other drugs (i.e. methylprednisolone and lopinavir) that may have been used.[5] The authors reported that no obvious adverse events were observed. A number of study limitations were noted by the authors, including a single-arm observation study with a limited number of patients and potential significant bias, and the study observations should be confirmed by additional studies.

Clinical Trials

Randomized, Double-blind, Placebo-controlled, Phase 3 Study

On March 23, 2020 Genentech, a member of the Roche Group, announced that the company initiated a randomized, double-blind, placebo-controlled Phase 3 clinical trial in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), a part of the U.S. Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR), to evaluate the safety and efficacy of Actemra plus SOC in approximately 330 hospitalized adult patients with severe COVID-19 pneumonia compared to placebo plus SOC.[6,7] This study is expected to begin enrolling as soon as possible in early April globally, including the United States.

Key inclusion criteria includes ≥18 years of age, confirmed COVID-19 infection per the WHO criteria (including a positive PCR of any specimen) and evidenced by chest X-ray or CT scan, and SpO_2≤93% or PaO_2/FiO_2 <300 mmHg) despite being on SOC.[8] Key exclusion criteria includes active tuberculosis or suspected active bacterial, fungal, viral or other infection (besides COVID-19), oral anti-rejection or immunomodulatory drugs (including Actemra) within the past 6 months, or any serious abnormality of clinical laboratory tests that, in the investigator's judgement, precludes the patient's safe and participation in and completion of the study. Patients will be randomized to receive either Actemra or placebo, respectively, in combination with SOC. Patients randomized to Actemra arm will receive Actemra 8 mg/kg IV (maximum dose of 800 mg). One additional Actemra infusion can be given 8-12 hours after the initial infusion if the clinical signs and symptoms worsen or do not improve. The primary and secondary endpoints include clinical status, mortality, mechanical ventilation and ICU variables. Patients will be followed for 60 days post-randomization, and an interim analysis will be conducted to look for early evidence of efficacy.

Additional Studies

Researchers around the world are independently exploring the efficacy and safety of Actemra for COVID-19. Interested clinicians can access the following website for additional clinical trials information:

- The World Health Organization International Clinical Trials Registry Platform (ICTRP), a searchable portal of COVID-19 trials at www.who.int/ictrp/en/ (accessed March 13, 2020).
- ClinicalTrials.gov, a web-based resource by the National Library of Medicine at the National Institutes of Health at https://clinicaltrials.gov/.

Additional Resources

In addition to local Public Health guidance, or local guidance specifically issued by medical or patient associations, more information about COVID-19 can be found on the World Health Organization (WHO) and the Centers for Control of Disease and Prevention (CDC) websites:

- WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
- CDC: https://www.cdc.gov/coronavirus/2019-ncov/index.html

Actemra Use in Coronavirus Disease 2019 (COVID-19) References

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