Genentech
A Member of the Roche Group

Dear Healthcare Professional:

The attached letter responds to your request for information on Actemra® (tocilizumab) in patients with COVID-19 infection.

The information provided is a summary of the best available clinical data selected using principles of evidence-based medicine and may include uses that have not been approved by the US Food and Drug Administration. It is being provided to enable you to make informed individual patient treatment decisions and should not be construed as a recommendation to use Actemra for nonapproved uses.

Please refer to the Actemra Full Prescribing Information for the most current information on the risks and benefits associated with Actemra across its approved indications. You may access the prescribing information here.

If you have questions, you may contact the Genentech Medical Information Department at either 1-800-821-8590 or online at http://medinfo.gene.com. Alternatively, click here to request an office visit from a Genentech Medical Science Liaison.

Actemra Use in Coronavirus Disease 2019 (COVID-19)

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

This response was developed according to principles of evidence-based medicine and includes data from two randomized, double-blind, placebo-controlled, Phase 3 trials as well as published prospective studies (N>50) and retrospective studies (N>1000).

In Brief

- Actemra is not indicated for the treatment of COVID-19 pneumonia. 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.
    - Actemra is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and chimeric antigen receptor T cell-induced cytokine release syndrome.
    - Actemra has a safety warning for risk of serious infections. Please refer to the product label for important safety information, including Warnings, Precautions, and Contraindications.
- In EMPACTA (Evaluating Minority Patients with Actemra), a randomized, double-blind, placebo-controlled Phase 3 trial of Actemra in hospitalized patients with COVID-19 pneumonia, 379 patients were randomized to receive Actemra 8 mg/kg IV or placebo along with current standard of care (SOC).
    - The primary endpoint was met. Patients who received Actemra plus SOC were 44% less likely to progress to mechanical ventilation or death compared to placebo plus SOC (log-rank p-value=0.0348, HR [95%CI] = 0.56 [0.32, 0.97]. The cumulative proportion of patients who progressed to mechanical ventilation or death by Day 28 was 12.2% in the Actemra group vs 19.3% in the placebo group.
    - The difference in time to hospital discharge or “ready for discharge” to Day 28 was not significant: median days = 6 for the Actemra group, median days = 7.5 for the placebo group, log-rank p-value=0.2456, HR [95%CI] = 1.16 [0.90, 1.48].
    - The difference in time to improvement in ordinal clinical status to Day 28 was not significant: median days = 6 for the Actemra group, median days = 7 for the placebo group, log-rank p-value=0.2597, HR [95% CI] =1.15 [0.90, 1.47].
    - Time to clinical failure to Day 28 was longer in the Actemra group compared to the placebo group (median days = not estimable for both groups, log rank p-value=0.0217, HR [95% CI] =0.55 [0.33, 0.92]. The difference cannot be considered statistically significant as other key secondary endpoints were not met.
    - There was no statistical difference in mortality between patients who received Actemra or placebo by Day 28. The mortality rate was 10.4% in the Actemra group and 8.6% in the placebo group, p=0.5146, Difference [95% CI]= 2.0% [-5.2%, 7.8%].
    - The most common adverse events in patients who received Actemra were constipation (5.6%), anxiety (5.2%), and headache (3.2%).

- At Day 28, the incidence of infections were 10% and 11% in the Actemra and placebo arms, respectively, and the incidence of serious infections were 5.0% and 6.3% in the Actemra and placebo arms, respectively. The EMPACTA study did not identify any new safety signals for Actemra.

- In COVACTA, the randomized, double-blind, placebo-controlled, Phase III study of Actemra in hospitalized adult patients with severe COVID-19 associated pneumonia, 452 patients were randomized to receive Actemra 8 mg/kg IV (maximum dose of 800 mg) or placebo along with current standard of care.

  - The primary endpoint of improved clinical status at Week 4 was not met. The difference in clinical status between Actemra and placebo in patients assessed using a 7-category ordinal scale at Week 4 was not statistically significant (p=0.36; odds ratio [95% CI] = 1.19 [0.81, 1.76]).

  - There was no difference between Actemra and placebo in the percentage of patients that died by week 4 (19.7% vs 19.4%, respectively with a difference [95% CI] of 0.3% [-7.6%, 8.2%], p=0.94).

  - Time to hospital discharge was shorter in patients treated with Actemra than in those treated with placebo. The median time to discharge was 20 days (95% CI, 17.0, 27.0) for Actemra and 28 days (95% CI, 20.0, NE) (p=0.04) for placebo. Because the primary endpoint was not met, the difference cannot be considered statistically significant.

  - The difference in ventilator-free days between Actemra and placebo was not statistically significant (median of 22 days for Actemra and 16.5 days with placebo, difference in medians [95% CI] = 5.5 [-2.8, 13.0], p=0.32).

  - The most common adverse events in patients who received Actemra were COVID-19 associated pneumonia (10.5%), hypertension (6.4%), pneumonia (5.8%), acute kidney injury (5.8%) and diarrhea (5.8%).

  - At Week 4, rates of infections were 38.3% and 40.6% in the Actemra and placebo arms, respectively, and the rates of serious infections were 21.0% and 25.9% in the Actemra and placebo arms, respectively. The COVACTA study did not identify any new safety signals for Actemra.

- Additional data from prospective studies and retrospective, observational studies are summarized in this response.

Abbreviations

AE=adverse event
ALT=alanine aminotransferase
ANC=absolute neutrophil count
ARDS=acute respiratory distress syndrome
AST=aspartate aminotransferase
BIPAP=bilevel positive airway pressure
BMI=body mass index
CAR=chimeric antigen receptor
CDC=Centers for Disease Control and Prevention
CKD=chronic kidney disease
COVID-19=Coronavirus Disease 2019
CPAP=continuous positive airway pressure
CRP=C-reactive protein
CRS=cytokine release syndrome
ECMO= extracorporeal membrane oxygenation
ESRD=end-stage renal disease
FiO_2=percentage of inspired oxygen
GCA-giant cell arteritis
HR=hazard ratio
HRow=Hazard Ratio by a propensity score weighted Cox regression analysis
hsCRP=high sensitivity C-reactive protein
HTN=hypertension
ICU=intensive care unit
IL=interleukin
IQR=interquartile range
LFT=liver function tests
LMWH=low molecular weight heparin
NE=Non Evaluable
PaO_2=partial pressure of oxygen
PICU=pediatric intensive care unit
pJIA=polyarticular juvenile idiopathic arthritis
RA=rheumatoid arthritis
RCC=renal cell carcinoma
SC=subcutaneous
SOC=standard of care
SOFA=subsequent organ failure assessment
sJIA=systemic juvenile idiopathic arthritis
TB=tuberculosis
WHO=World Health Organization

Background

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 Lancet publication, a retrospective, multicenter, cohort study of 191 hospitalized patients with COVID-19 from Wuhan, China 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 prothrombin 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. Due to the retrospective study design, not all laboratory tests, including IL-6, were done in all patients. Several factors that may have contributed to the poor clinical outcomes in some patients, such as delayed transfer to hospitals, lack of effective antivirals, inadequate adherence to standard support therapy and use of high-dose corticosteroids.

In a letter to the editors in Intensive Care Medicine, investigators informed a retrospective study of 68 death cases and 82 discharged cases with laboratory-confirmed COVID-19 from 2 hospitals in Wuhan, China.[3] Patients who died were statistically significantly older in age and had a greater proportion of underlying disease and secondary infections compared with those in the discharged group. There was no statistical difference in the time from onset of symptoms to laboratory testing between the 2 groups. Significant differences in the white blood cell counts, absolute values of lymphocytes, platelets, albumin, total bilirubin, blood urea nitrogen, blood creatinine, myoglobin, cardiac troponin, CRP and IL-6 (mean 11.4 vs 6.8 ng/mL, $p<0.001$) were observed between those who died vs those who were discharged.

In another Lancet publication describing 41 patients in Wuhan, China hospitalized for COVID-19, there was no evidence of marked IL-6 elevation between patients requiring ICU admission (n=13) and those who did not (n=28) (p=0.13).[2] Due to the small sample size, there was difficulty assessing host risk factors for disease severity and mortality with multivariable-adjusted methods

Actemra, an IL-6 inhibitor, is approved for the treatment of RA, pJIA, sJIA, GCA, and CAR T cell-induced CRS. Actemra has a safety warning for risk of serious infections. Serious infections leading to hospitalization or death including tuberculosis, bacterial, invasive fungal, viral, and other opportunistic

infections have occurred in patients receiving Actemra. 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)

Actemra is not indicated for the treatment of COVID-19 pneumonia. 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.

Health Authorities

Information from health authorities for the treatment of COVID-19 infection is provided for informational purposes and should not be interpreted as recommendations from Genentech/Roche on management of COVID-19.

National Institutes of Health (NIH)

The NIH "recommends against the use of anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) for the treatment of COVID-19, except in a clinical trial."[4]

Clinical Experience

Randomized, Double-blind, Placebo-controlled, Phase 3 Study (EMPACTA)

Study Design

EMPACTA – Evaluating Minority Patients with Actemra (ClinicalTrials.gov Identifier: NCT04372186) was a randomized, double-blind, placebo-controlled Phase 3 clinical trial that evaluated the safety and efficacy of Actemra plus SOC in hospitalized patients with COVID-19 pneumonia.[5–7] Patients were recruited at trial sites known to provide critical care to underserved and minority populations that often do not have access to clinical trials.

Methods

Inclusion criteria include age ≥18 years, confirmed COVID-19 infection by PCR of any specimen and evidenced by CT scan or chest X-ray, and SpO_2<94% while on ambient air.[5–7] Key exclusion criteria include the following: requirement for CPAP, BIPAP or invasive mechanical ventilation, imminent death (within 24 hours) as deemed by investigator, suspected active bacterial, fungal or viral infection other than COVID-19, ANC <1000/mL, platelet count <50,000/mL.

Three hundred seventy-nine patients were randomized to receive Actemra 8 mg/kg IV or placebo with current SOC.[5] One additional Actemra infusion can be given.

The primary endpoint is the cumulative proportion of patients who died or required mechanical ventilation by Day 28 (time to event analysis).[5–7] Key secondary endpoints include time to hospital discharge or "ready to discharge", time to improvement in ordinal clinical status to Day 28, time to clinical failure up to Day 28, and difference in mortality rate by Day 28.

Results

The efficacy results are summarized in the table below.[6,7]

Table 1. Efficacy Endpoints (modified ITT population)[6,7]		
	Actemra (n=249)	**Placebo (n=128)**
Primary Endpoint – Cumulative proportion of patients who died or required mechanical ventilation by Day 28 (time to event analysis)	12.2%	19.3%
p value*	p=0.0348	
Hazard ratio (95% CI)	0.56 [0.32, 0.97]	
Time to hospital discharge or "ready to discharge" up to Day 28†		
Median time to event (days)	6	7.5
p value*	p=0.2456	
Hazard ratio (95% CI)	1.16 [0.90, 1.48]	
Time to improvement in ordinal clinical status to Day 28‡		
Median time to event (days)	6	7
p value*	p=0.2597	
Weighted difference in % (95% CI)§, p value	1.15 [0.90, 1.47]	
Time to clinical failure up to Day 28‖		
Median time to event in days	NE	NE
Cumulative proportion of events	13.8%	21.6%
p value*	p=0.0217	
Hazard ratio (95% CI)	0.55 [0.33, 0.92]	
Difference in mortality rate by Day 28		
Mortality Rate	10.4%	8.6%
p value	p=0.5146	
Difference in mortality rate by Day 28	2.0 [-5.2%, 7.8%]	

Notes:
*Based on log-rank test
†Defined as time to hospital discharge or "ready for discharge" up to Day 28 on the 7-category ordinal scale
‡Defined as time to at least a 2-category (or 1-category if baseline ordinal scale is 2) improvement in the 7-category ordinal scale up to Day 28. The 7-category ordinal scale is defined as follows: 1=discharged or ready for discharge, 2=non-ICU hospital ward, not requiring supplemental oxygen, 3=non-ICU hospital ward, requiring supplemental oxygen, 4=ICU or non-ICU hospital ward, requiring noninvasive ventilation/ high-flow oxygen, 5=ICU, requiring intubation and mechanical ventilation, 6=ICU, requiring ECMO or mechanical ventilation and additional organ support, 7=death
‖Defined as the time to death, mechanical ventilation, ICU admission or withdrawal (whichever occurs first)

Abbreviations: ITT=intent-to-treat, NE=not estimable

The most common adverse events in patients who received Actemra were constipation (5.6%), anxiety (5.2%), and headache (3.2%).[6,7] At Day 28, the incidence of infections were 10% and 11% in the Actemra and placebo arms, respectively, and the incidence of serious infections were 5.0% and 6.3% in the Actemra and placebo arms, respectively. The EMPACTA study did not identify any new safety signals for Actemra.

Randomized, Double-blind, Placebo-controlled, Phase 3 Study (COVACTA)

Study Design and Methods

COVACTA (ClinicalTrials.gov Identifier: NCT04320615) was a randomized, double-blind, multicenter, placebo-controlled Phase 3 clinical trial evaluating the safety and efficacy of Actemra plus SOC adult patients with severe COVID-19 pneumonia.[8–11] To be eligible for inclusion, patients had to have ≤93% blood oxygen saturation or fraction of inspired oxygen/ partial pressure of oxygen <300mg Hg. Eligible patients with confirmed PCR for COVID-19 and bilateral chest infiltrates on chest x-ray or were randomized 2:1 to receive Actemra 8 mg/kg IV (maximum dose of 800 mg) or placebo with current SOC. Exclusion criteria included active TB, bacterial, fungal or viral infection other than COVID-19, and imminent death (within 24 hours) as deemed by treating physician. SOC was defined per local practice and may have included antivirals, low-dose steroids, convalescent plasma and supportive care. With the exception of antivirals, concomitant use with other investigational drugs were not permitted; use of immunomodulatory drugs were also not permitted. One additional Actemra infusion could be given 8-24 hours after the initial infusion if the clinical signs and symptoms worsen or do not improve, defined as

worsened ordinal scale clinical status or persistent fever. The primary analysis was conducted on Day 28, and patients were followed for 60 days.

The primary endpoint was improved clinical status at Day 28 as measured by a 7-category ordinal scale, which tracked patients' clinical status based on the need for intensive care and/or ventilator use, as well as supplemental oxygen requirements.[11] Key secondary endpoints included the following:

- Clinical status at Day 14 on the 7-category ordinal scale
- Mortality at Day 28
- Ventilator-free days to Day 28
- Time to improvement from baseline in at least 2 categories on the 7-category ordinal scale
- Time to hospital discharge (or ready to discharge), defined as normal respiratory rate, body temperature and stable oxygen saturation/ on ambient air or ≤2 L supplemental oxygen

Results

The efficacy results are summarized in the table below.[11]

Table 2. COVACTA Efficacy Endpoints (modified ITT population)[11]

	Actemra (n=294)	Placebo (n=144)
Primary Endpoint - Clinical status based on 7-category ordinal scale* at Day 28, median (95% CI)	1.0 (1.0 to 1.0)	2.0 (1.0 to 4.0)
Difference (95% CI), p value†	-1.0 (-2.5 to 0.0), p=0.36	
Odds ratio (95% CI)‡	1.19 (0.81 to 1.76)	
Clinical status at Day 14 based on 7-category ordinal scale* at Day 14, median (95% CI)	3.0 (2.0 to 4.0)	4.0 (3.0 to 5.0)
Difference (95% CI), p value†	-1.0 (-2.0 to 0.5), p=0.05	
Odds ratio (95% CI)‡	1.42 (0.99 to 2.05)	
Mortality at Day 28, n (% [95% CI])	58 (19.7 [15.2 to 24.3])	28 (19.4 [13.0 to 25.9])
Weighted difference in % (95% CI)§, p value	0.3 (-7.6 to 8.2), p=0.94	
Time to hospital discharge or ready for discharge in days, median (95% CI)	20.0 (17.0 to 27.0)	28.0 (20.0 to NE)
p value‖	p=0.04	
Hazard ratio (95% CI), reference: placebo¶	1.35 (1.02 to 1.79)	
Time to improvement of at least 2 categories on 7-category ordinal scale of clinical status in days, median (95%CI)	14.0 (12.0 to 17.0)	18.0 (15.0 to 28.0)
p value‖	p=0.08	
Hazard ratio (95% CI), reference: placebo¶	1.26 (0.97 to 1.64)	
Ventilator-free days to Day 28, median (95% CI)	22.0 (18.0 to 28.0)	16.5 (11.0 to 26.0)
Difference in medians (95% CI), p value†	5.5 (-2.8 to 13.0), p=0.32	

Notes:
*Defined as follows: 1=discharged or ready for discharge, 2=non-ICU hospital ward, not requiring supplemental oxygen, 3=non-ICU hospital ward, requiring supplemental oxygen, 4=ICU or non-ICU hospital ward, requiring noninvasive ventilation/ high-flow oxygen, 5=ICU, requiring intubation and mechanical ventilation, 6=ICU, requiring ECMO or mechanical ventilation and additional organ support, 7=death
† Based on van Elteren test, stratified by mechanical ventilation and region at randomization
‡ Based on ordinal logistic regression analysis, adjusted for mechanical ventilation and region at randomization
§ Based on extended Cochran-Mantel-Haenszel test, stratified by mechanical ventilation and region at randomization
‖ Based on log-rank test,
¶ Cox proportional hazards model, stratified by mechanical ventilation and region at randomization

Abbreviations: ECMO=extracorporeal membrane oxygenation, ITT=intent-to-treat, NE=non evaluable

The safety findings are summarized in the table below.[11] The most common adverse events in patients who received Actemra were COVID-19 associated pneumonia (10.5%), hypertension (6.4%), pneumonia (5.8%), acute kidney injury (5.8%) and diarrhea (5.8%).[9,10] At Week 4, rates of infections were 38.3% and 40.6% in the Actemra and placebo arms, respectively, and the rates of serious infections were 21.0% and 25.9% in the Actemra and placebo arms, respectively. The COVACTA study did not identify any new safety signals for Actemra.

Table 3. Safety Up to Day 28 (safety population)[11]

	Actemra (n=295)	Placebo (n=143)
Patients with ≥1 AE, n(%) Total AE, n	228 (77.3) 778	116 (81.1) 360
Patients with ≥1 SAE, n(%) Total SAE, n	103 (34.9) 160	55 (38.5) 101
Deaths, n(%)	58 (19.7)	28 (19.6)
Patients with adverse events of special interest, n (%)		
Infections Serious Infections Opportunistic infections*	113 (38.3) 62 (21.0) 1 (0.3)	58 (40.6) 37 (25.9) 1 (0.7)
Medically confirmed malignancies	1 (0.3)	0
Hypersensitivity†	19 (6.4)	4 (2.8)
Anaphylaxis per Sampson criteria	0	1 (0.7)
Hepatic events	5 (1.7)	3 (2.1)
Laboratory criteria of Hy's Law‡	3 (1.0)	3 (2.1)
Myocardial infarction	3 (1.0)	2 (1.4)
Stroke	3 (1.0)	2 (1.4)
Bleeding events Serious bleeding events	45 (15.3) 13 (4.4)	16 (11.2) 5 (3.5)
Serious infections reported in >1% of patients in the Actemra group or in the Placebo group		
Death caused by COVID-19	39 (13.2)	18 (12.6)
Septic shock	7 (2.4)	6 (4.2)
Pneumonia	7 (2.4)	4 (2.8)
Bacterial Pneumonia	6 (2.0)	2 (1.4)
Sepsis	3 (1.0)	4 (2.8)
Bacteremia	2 (0.7)	3 (2.1)

Notes:
*Candida sepsis occurred in the Actemra group, and respiratory moniliasis occurred in the placebo group
†Defined as all events that occurred within 24 hours of infusion and were not deemed "unrelated to study treatment" by the investigator, regardless of whether the events were clinically consistent with hypersensitivity
‡Alanine aminotransferase or aspartate aminotransferase levels >3 times upper limit of normal with either bilirubin level >2 times upper limit of normal

Abbreviations: AE=adverse events, SAE=serious adverse events

Prospective Studies (N>50)

Toniati et al. conducted a prospective study evaluating the use of Actemra in 100 patients with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support.[12] Actemra was given at 8 mg/kg IV q12h x 2 followed by a third dose 24 hours after the second infusion, based on clinical response. The primary outcome was improvement in ARDS based on the Brescia COVID Respiratory Severity Score at 24-72 hours and 10 days after Actemra. The median age was 62 years (IQR, 57-71 years), 88% were male, and comorbidities included HTN (46%), obesity (31%), diabetes (17%), and cardiovascular disease (16%). Majority of patients received 2 doses of Actemra (87%) with the remaining receiving 3 doses (13%). All patients had elevated inflammatory markers (CRP, fibrinogen, ferritin and IL-6). At 24-72 hours, 58 patients demonstrated clinical and respiratory improvement, 37 were stable, and 5 deteriorated, of whom 4 died. By 10 days, 15 patients were discharged and 23 patients worsened. A total of 20 patients died. C-reactive protein, fibrinogen, and ferritin decreased in patients who had improved clinical status, while

IL-6 and D-dimer increased in both improved and worsened patients. Serious adverse events included septic shock (n=2; both died) and GI perforation (n=1).

In another single-arm, prospective study, Sciascia et al. reported the use of Actemra in 63 hospitalized patients with confirmed COVID-19 infection.[13] All patients were required to have marked elevation of at least 3 of the following inflammatory markers: CRP, ferritin, D-dimer, or LDH. IL-6 levels were also measured. The primary endpoint was safety, and secondary endpoints were improvement in respiratory and laboratory status (data collected at baseline and on Days 1, 2, 7, and 14). Actemra was administered at 8 mg/kg IV (n=34) or 324 mg SC (n=29). Among 31 patients who received IV for their first dose, 91% received a second dose (IV, n=25; SC at 162 mg, n=6). Twenty-one patients in the SC group received a second dose of Actemra 162 mg SC. An improvement in CRP, ferritin, D-dimer and lymphocyte counts were observed and respiratory parameters as measured by PaO_2/FiO_2, were also improved. At Day 14, a total of 7 (11.5%) patients died. No difference in mortality was observed between those who received IV (12.9%) vs SC (10.3%) administration. Five patients required mechanical ventilation on admission, and by Day 14, 2 patients remained on mechanical ventilation and 1 patient died. All patients who died received 2 doses of Actemra and death occurred within the first week of receiving Actemra (mean 5±1.5 days). Baseline D-dimer levels were predictive of death (HR=5.01; 95% CI, 1.04-29.17). The use of Actemra within 6 days of hospital admission was associated with an increased chance of survival (HR=2.2; 95% CI, 1.3-6.7; p<0.05). No moderate to severe AEs related to Actemra were reported.

In an open-label prospective study, Morena et al. reported the clinical characteristics and outcomes of 51 patients with confirmed, severe COVID-19 pneumonia treated with Actemra.[14] All patients were required to have an IL-6 level of >40 pg/mL. The primary endpoints were death or hospital discharge. Secondary endpoints included change in disease severity and change in oxygen requirements at different timepoints after Actemra administration. Actemra 400 mg IV q12h x2 or 8 mg/kg IV q12h x2 (for patients ≥60 kg) was administered. A total of 18 (35%) patients received the fixed dose of Actemra and 33 (65%) received the 8 mg/kg doses. Two patients did not receive a second dose of Actemra (due to death and rash, respectively). Select baseline characteristics include (median values): 60 years (IQR, 50-70); majority male (78.4%); history of cardiovascular disease (49%), HTN (29.4%) and diabetes (11.8%); CRP of 189 mg/L (IQR, 138-268 mg/L); d-dimer of 1706 pg/L (IQR, 860-5261 pg/mL); and IL-6 of 116 pg/mL (IQR, 65-180). Concomitant medications included hydroxychloroquine (98%), lopinavir/ritonavir (84%), remdesivir (45%), and antibiotics (76%). At baseline, 84% of patients were classified as severe and 12% as critically severe. After a median follow-up of 34 days (IQR, 32-37 days) after the first dose of Actemra, 31 (61%) patients were discharged, 14 (27%) died, and 2 (12%) remain hospitalized. The mortality rate was 27% (14/51), of which 83% (5/6) were receiving mechanical ventilation and 20% (9/45) were receiving non-invasive oxygen support (p=0.0001). The multivariate Cox proportional hazard model showed mechanical ventilation at time of treatment was associated with an increased risk of death (HR=7.18; 95% CI, 2-25; p=0.002). The most common cause of death was ARDS; 4 patients had concomitant septic shock and multi-organ failure. Thirty-four (67%) patients experienced an improvement in their clinical severity, while 16 (33%) patients had no change in status, and no patients on mechanical ventilation were extubated. Laboratory parameters showed a decrease in CRP and a significant increase in transaminases within 7 days of Actemra administration. C-reactive protein levels returned to normal in 36 (71%) patients. The most common AEs were increased hepatic enzymes ≥3xULN (29%), thrombocytopenia (14%), neutropenia (6%), and cutaneous rash (2%). Fourteen (27%) patients experienced bacteremia (median time to onset from Actemra administration, 11 days, IQR, 9-13 days).

In an observational study, Somers et al. assessed the safety and effectiveness of Actemra in patients with COVID-19 pneumonia requiring mechanical ventilation.[15] The primary endpoint was post-intubation survival probability and a key secondary endpoint included clinical status on Day 28, which included bloodstream infection and pneumonia. A multivariable Cox regression with propensity score inverse probability weighting (IPTW) was used to compare 78 patients treated with Actemra to 76 patients who did not (control). Actemra was administered at 8 mg/kg (max 800 mg) once. Additional doses were discouraged. Baseline characteristics were well-balanced between both groups except Actemra-treated patients were younger (55 years vs 60 years; p=0.05) and had lower median d-dimer (2.4 mg/dL vs 6.5 mg/dL; p=0.005) and higher mean serum albumin concentrations (3.5 g/dL vs 3.1 g/dL; p<0.001). Based on Kaplan-Meier estimates, patients treated with Actemra had an improved survival compared to those

who did not (p=0.0189). Actemra was also associated with a lower hazard of death when adjusted for demographics (HR=0.54, 95% CI, 0.29-1.00), complete laboratory data (n=116; HR=0.55; 95% CI, 0.33-0.90), and missing laboratory data (HR=0.54; 95% CI, 0.35-0.84). Patients treated with Actemra had higher rates of superinfections compared to control (54% vs 26%; p<0.001), which was driven by an increase in ventilator-associated pneumonia (45% vs 20%; p<0.001).

Retrospective Studies (N>1000)

Outcomes of 2,512 hospitalized, confirmed COVID-19 patients were reviewed in a retrospective, observational cohort study using electronic medical records data.[16] The primary objective was to evaluate the effect of hydroxychloroquine in hospitalized patients. A secondary, exploratory objective was to evaluate the effect of Actemra in ICU patients. The primary endpoint was mortality. Data for the Actemra group are presented here. Age, gender, COPD, and renal failure were included in the propensity score model for Actemra using a multivariate logistic regression. Patients receiving Actemra in the ICU were compared to control patients in the ICU who did not receive Actemra. Out of 198 patients who received Actemra, 134 patients received the first dose of Actemra in the ICU and comprised the Actemra exploratory treatment cohort. A total of 413 patients served as the control group. The median age of patients in the Actemra group was 62 years (range, 53-70) and 28% were male. Actemra was administered as a single dose in 104 (78%) patients (400 mg, 96%; 800 mg, 1%, 4 mg/kg, 1%, missing dose, 1%). Treatment with Actemra in the ICU setting trended towards improved survival (HR=0.76; 95% CI, 0.57-1.00). The unadjusted 30-day mortality rate was 46% in the Actemra group and 56% in the control group. Eighteen (13%) patients in the Actemra group and 44 (11%) patients in the control group experienced secondary bacteremia. Twelve (9%) patients in the Actemra group and 25 patients (6%) in the control group developed secondary pneumonia.

Clinical Trials

Genentech/Roche-Sponsored Clinical Trials

Randomized, Double-blind, Placebo-controlled, Phase 3 Study (REMDACTA)

REMDACTA (ClinicalTrials.gov Identifier: NCT04409262) is a randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the safety and efficacy of Actemra plus remdesivir in approximately 450 hospitalized patients with severe COVID-19 pneumonia.[17,18] Eligible patients will be randomized to receive a remdesivir loading dose, followed by 1 infusion of Actemra 8 mg/kg IV (maximum dose of 800 mg) on Day 1, and a once-daily maintenance dose of remdesivir from Days 2-10 or remdesivir plus placebo. The primary endpoint is clinical status on Day 28. Key secondary endpoints include time to improvement of clinical status, time to clinical failure, mechanical ventilation, ICU care, mortality, and time to discharge.

Randomized, Open-Label, Phase 2 Study (MARIPOSA)

MARIPOSA (ClinicalTrials.gov Identifier: NCT04363736) is a randomized, open-label Phase 2 clinical trial investigating the pharmacodynamics, pharmacokinetics, safety and efficacy of Actemra in approximately 100 hospitalized patients with moderate to severe COVID-19 pneumonia.[19] Eligible patients will be randomized to receive Actemra 8 mg/kg or 4 mg/kg IV in addition to current SOC. The key primary and secondary endpoints include concentrations of CRP, IL-6, ferritin, clinical status, mortality, mechanical ventilation, and additional ICU variables.

Additional Clinical Trial Resources

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/.

- ClinicalTrials.gov, a web-based resource by the National Library of Medicine at the National Institutes of Health at https://clinicaltrials.gov/.

The WHO has also gathered and compiled 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.

Actemra Use in Coronavirus Disease 2019 (COVID-19)

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