Title:

00636

TOCILIZUMAB (BIOSIMILAR) USE IN CYTOKINE STORM OF SEVERE COVID-19 PNEUMONIA

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BACKGROUND

- Interleukin 6 (IL-6) is a key cytokine involved in cytokine storm of severe COVID-19. Tocilizumab is an IgG1 class humanized monoclonal antibody targeting IL-6 receptor (IL-6R). Tocilizumab down-regulates IL-6 preventing fatal and permanent damage to vital organs, significantly preventing COVID-19 related mortality and morbidity.
- Therefore, this study aimed to compare the efficacy and safety of Tocilizumab (biosimilar) developed by Hetero Biopharma Ltd, India vs Reference Medicinal Product (RMP)-Tocilizumab manufactured by Roche in cytokine storm of severe COVID-19 pneumonia.

METHODS

- This multicenter, randomized, double-blind, active-controlled study enrolled patients aged 18 to 65 years, with laboratory-confirmed, hospitalized, severe COVID-19 disease (RR>30 breaths/min and severe respiratory distress or SpO2<90% in room air) with elevated inflammatory markers (IL-6>40 pg/ml, D-dimer>1.5 µgFEU/ml, CRP>75mg/L or ferritin 5XULN) not on mechanical ventilation.
- This study was approved by local regulatory authorities, ethics committees of participating institutes and registered with Clinical Trial Registry of India, before dosing the patients.
- **Patients randomized in the ratio of** 3:1 (Test-Tocilizumab: RMP-Tocilizumab)
- **Dosing:** 8mg/kg (max. dose 800mg) once on Day 1.
- **Primary Endpoint:** Cumulative proportion of patients requiring mechanical ventilation by Day 14.
- Secondary efficacy endpoints included 28-day mortality rate, proportion of patients with a 2-point decrease in WHO ordinal scale score, time to clinical failure (death or required mechanical ventilation or withdrawn), time to 2-point decrease in ordinal scale, change in inflammatory markers and duration of hospital stay in days.
- Safety assessments included incidence of adverse events, proportion of patients discontinued due to AEs, incidence of any post-treatment bacterial and/or fungal infection. Antidrug antibodies were assessed at the end of study on an exploratory basis.

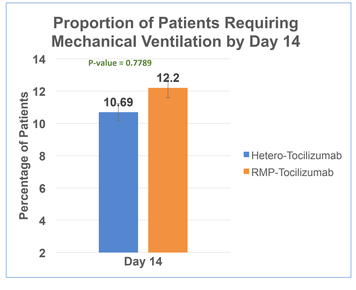
Hetero-Tocilizumab (Biosimilar) is comparable to RMP-Tocilizumab (Roche) in preventing mechanical ventilation in severe COVID19 pneumonia patients with elevated inflammatory markers.

RESULTS

Out of 211 patients screened, 172 patients were eligible and enrolled (131 in Test and 41 in RMP) to receive Tocilizumab 8 mg/kg (Max 800 mg) on Day 1. Out of 172 patients, 24 patients withdrawn from the study (17 in test vs 7 in RMP). All patients were similar in both groups at baseline in terms of age, gender, weight etc.

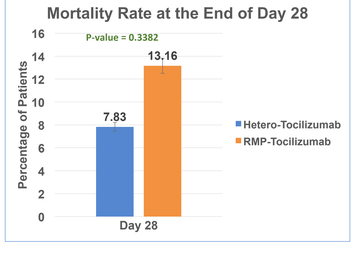
Primary Endpoint Analysis

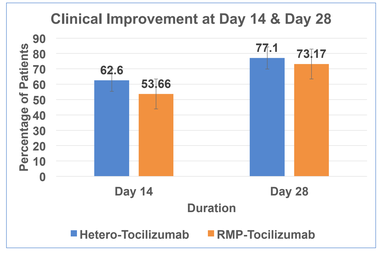
Fourteen (10.69%) patients in Test and 5 (12.20%) patients in RMP progressed to mechanical ventilation by Day 14 (Risk difference 1.5%; 95% CI (-1.1,1.8); p=0.7789). The lower limit of 95% CI lies within the non-inferiority margin of −10%. Hence, Hetero-Tocilizumab (biosimilar) comparable to RMP-Tocilizumab in patients with elevated cytokines due to severe COVID-19 disease in preventing progression to mechanical ventilation.

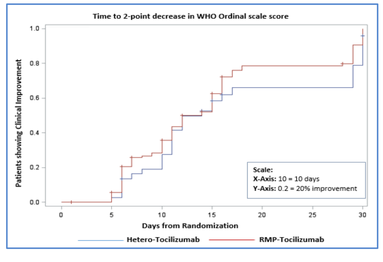


Secondary Endpoint Analysis

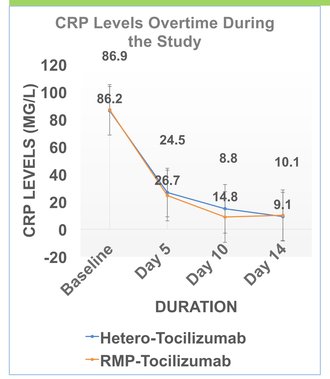
- **Mortality Rate:** Overall, 9 (7.83%) patients died in Test vs 5 (13.16%) in RMP up to 28 days of follow up (p=0.3382).
- **Clinical improvement** was seen in 62.60% and 77.10% vs 53.66% and 73.17% in Test vs RMP at Day 14 and Day 28 respectively.
- **Time to clinical failure** was 6 vs 5 days while **Time to clinical improvement** was 11 vs 11.5 days in Test vs RMP respectively.







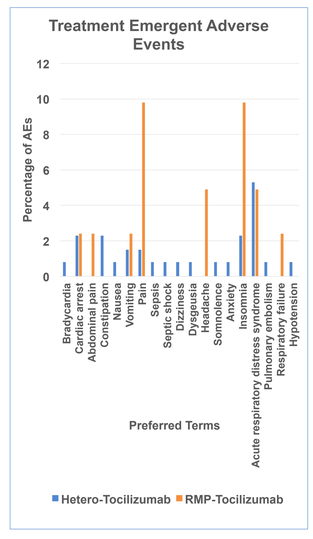
RESULTS (Contd.)



- C-reactive protein (CRP) values showed a significant decrease over time in both treatment groups and were comparable between groups
- The average duration of hospitalization was 12.9 versus 13.8 days in the Test and RMP groups respectively.

Safety Results

- Acute respiratory distress syndrome (7 AEs in Test and 2 in RMP), Insomnia (3 AEs in Test and 4 RMP) and Pain (2 AEs in Test and 4 RMP) were the most frequently reported AEs.
- 7 AEs (3 AEs in Test and 4 RMP) were assessed as related to study drug.
- No post treatment fungal infections reported during 28-day follow up.
- Out of 113 patients, no patient in either arm reported anti-tocilizumab antibodies.



CONCLUSIONS

- Hetero-Tocilizumab (biosimilar) is comparable to RMP-Tocilizumab (Roche) in preventing the progression to mechanical ventilation in severe COVID19 pneumonia patients.
- Hetero-Tocilizumab (biosimilar) is more affordable for usage in an economically challenged patient population worldwide.

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