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A Mini Review on the Clinical Studies of Tocilizumab for COVID-19 Conducted in Selected Asian Countries

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ABSTRACT:

The primary purpose of this short review article is to give adequate data and information on many clinical studies undertaken in Asian countries on the utilzation of the recombinant drug, Tocilizumab for Coronavirus disease 2019 (COVID-19). It is caused by severe acute respiratory syndrome coronavirus 2, which has spread around the globe in recent years. Vaccines and antiviral drugs were being explored for efficacy in order to reduce disease transmission. Tocilizumab, a recombinant monoclonal antibody, is being evaluated to treat COVID-19 infections. Some nations, such as the Canada, Denmark, France, Germany, Italy, Netherlands, Spain, United Kingdon and United States, conducted clinical trials to determine the efficacy of this agent against COVID-19. Asian nations that took part in the tocilizumab clinical trials included China, Japan, India, Pakistan, and Saudi Arabia. In the testings, flat doses ranging from flat 4 – 8 mg/kg IV and maximum doses of 200-800 mg/kg for severe infection were used and some countries whose trials were in combination with Dexamethasone. These doses are well tolerated and no significant adverse effects were noted. As a result, Tocilizumab is a promising medication that is being developed with the goal of treating and preventing COVID-19 infections.

1. Introduction

COVID-19, or Coronavirus illness in 2019, is a global health crisis that occurred in the fourth quarter of 2019. It is caused by SARS-COV-2, also known as Severe/Acute Respiratory Syndrome Coronavirus 2. This disease's primary symptoms are fever, a dry cough, diarrhea, and sore throat. It expanded around the globe in the early months of 2020, affecting all industries of several countries [1, 2].

Biological products such as vaccines and antiviral medicines were developed to combat COVID-19. The majority of them have undergone clinical testing. Remdesivir is an antiviral medication for COVID-19 that has been shown to be effective. Other medications, such as Molnupiravir and Baricitinib, are successful in treating COVID-19 infections. All of the above Pharmaceutical agents have undergone clinical trials for the aforementioned condition [3,4]. Tocilizumab is one of the current medications approved for COVID-19, particularly in severe cases. This has been used to treat rheumatologic diseases and T cell-induced cytokine release syndrome. It is a humanized recombinant anti-IL-6 receptor monoclonal antibody that reduces inflammation by inhibiting the IL-6 receptor. It was recently authorized by the US Food and Drug Administration, and a number of European and Asian nations have already granted emergency use authorization for hospitalized patients receiving COVID-19 therapy [5,6]. Tocilizumab is in late-stage clinical studies in the United States and a few European nations. Asian nations such as China, Japan, and India were also active participants in the clinical trials for this COVID-19 medication [7]. This review study highlights the outcomes and conclusions from a brief literature analysis of several clinical trials in selected Asian regions on the use of Tocilizumab for COVID-19 infections in hospitalized patients.

2. Methods

This study was done utilizing journal databases such as BMJ, Directory of Open Access, Elsevier, Google Scholar, The Lancet Journals, and the Wiley Online Library. A search strategy was developed for

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publications in each database, with no restrictions on language or duration of the research. The pursuit began in April 2024. The search terms used were Tocilizumab, Monoclonal Antibodies, COVID-19, Tocilizumab clinical trials, or a combination of these terms. Appropriate studies or articles were classified using specific criteria as follows: articles focused on clinical trials on Tocilizumab, articles related to reports of different trials conducted or participated in by a specific Asian country, and research studies related to clinical outcomes of Tocilizumab for COVID-19. Other characteristics assessed were the trial design, intervention, population size, and the presence of any adverse or side effects from the antiviral medicine. The clinical studies cited were confirmed using clinicaltrials.gov as a reference. There was no online review for this study that took place [8].

3. Results and Discussion

Tocilizumab, frequently referred to as Actemra as its proprietary name, is a monoclonal antibody that targets the interleukin-6 receptor. Interleukin-6 is a cytokine that has a role in a variety of inflammatory processes and is linked to disorders including rheumatoid arthritis and cytokine release syndrome. Its invention and use in clinical medicine have considerably improved the management of various disorders. It is a recombinant humanized monoclonal antibody that selectively binds to soluble and membrane-bound IL-6 receptors. It prevents IL-6 from connecting with its receptors, inhibiting the ensuing signaling cascade that causes the inflammatory response. This inhibition of IL-6 signaling can lower inflammation and alter the course of inflammatory disorders [9,10].

The justification for administering Tocilizumab in COVID-19 is based on higher IL-6 levels in individuals with severe illness. This cytokine rush was linked to acute respiratory distress syndrome, multiple organ failure, and higher death. Tocilizumab, which inhibits IL-6, intended to reduce these severe inflammatory reactions. Tocilizumab is usually given intravenously in a single dose of 4 to 8 mg/kg (with a maximum dose of 400 to 800 mg). If clinical symptoms persist, a second dose may be administered. The timing of dosing is essential, with the optimum results seen when administered early in the inflammatory phase of severe COVID-19. [11].

Tocilizumab has demonstrated efficacy in lowering death rates in severe COVID-19 patients, reducing the requirement for mechanical breathing, and minimizing hospital stays for individuals with severe symptoms. Yet its effectiveness appears to be evident in individuals who are seriously ill with high inflammatory markers [12]. Phase III clinical studies are now underway, with participation from several nations worldwide. Canada, the United States of America, and several European nations, including Denmark, France, Germany, Italy, the Netherlands, Spain, and the United Kingdom, are among them. Asian nations that participate in the clinical investigations include China, Japan, India, Pakistan, and Saudi Arabia [13].

A clinical trial in China with the initiaitive of Xiaoling Xu and colleagues evaluated the effectiveness of tocilizumab in treating COVID-19 patients with severe symptoms in China and looked for a potential treatment plan. Between February 5 and 14, 2020, tocilizumab was administered in addition to regular therapy to patients diagnosed with severe or critical COVID-19 at Anhui Provincial Hospital, The First Affiliated Hospital of University of Science and Technology of China, and Anhui Fuyang Second People's Hospital. A retrospective analysis was conducted on the variations in laboratory tests, computed tomography (CT) scan images, and clinical symptoms. Fever returned to normal on the first day, and other symptoms recovered impressively within a few days. Of the 20 patients, 15 (75.0%) reduced their oxygen intake within 5 days of starting tocilizumab, and 1 patient did not require oxygen therapy. CT scans showed that in 19 patients, or 90.5%, the lung lesion opacity had absorbed. On the fifth day following treatment, 52.6% of patients (10/19) had their peripheral blood lymphocyte percentage return to normal, whereas it had decreased in 85.0% of patients (17/20) prior to treatment (mean, 15.52 ± 8.89%). In 84.2% of patients (16/19), abnormally elevated C-reactive protein significantly decreased. There were no overt negative effects noted. After receiving tocilizumab, all patients were released from the hospital on average 15 days later. Based on preliminary data, Tocilizumab is an effective treatment to lower mortality because it immediately improved the clinical outcome in severe and critical COVID-19 patients [14].

In 2020 in Japan with 49 patients enrolled in a clinical study, Tocilizumab Intravenous Infusion 80 mg, 200 mg,

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and 400 mg is a humanized anti-human IL-6 receptor monoclonal antibody used in a Phase III clinical research on patients with pneumonia related to COVID-19. Of the 48 patients treated with Tocilizumab, 35 (72.9%) were released or prepared for discharge from the hospital at 28 days post-treatment, while 5 (10.4%) had a tragic result. When comparing day 28 results to the prior therapy, 39 patients (81.3%) showed improvement in at least one category on the 7-Category Ordinal scale. Twelve percent of the patients had worsened on at least one category [15].

In 2020, Gokhale and colleagues did an observational study in India that included patients with chronic hypoxia and severe COVID-19 pneumonia. The trial comprised 269 individuals with chronic hypoxia and severe COVID-19 pneumonia; 151 of these patients received tocilizumab, while the remaining 118 patients served as historical controls. The recombinant medication tocilizumab was associated with increased survival; patients who got it had a considerably higher median survival of 18 days compared to 9 days in the control group. Even with the best supportive treatment, tocilizumab shows a substantial survival advantage in COVID-19 patients with persistent hypoxia, suggesting its potential as a therapeutic intervention [16].

From May 3, 2020, to October 3, 2020, Malik and colleagues carried out a single-center, randomized, double-blind, placebo-controlled phase 2 study in Pakistan. During severe acute respiratory syndrome-coronavirus-2 infection, the purpose of this clinical research was to evaluate the safety and effectiveness of tocilizumab as a treatment. Using critically sick adult COVID-19 patients, the study carried out a phase 2 randomised, double-blind, placebo-controlled experiment. Standard medical care plus the prescribed dosage of either Tocilizumab or a placebo medicine were given to the participants in a 4:1 random assignment. There were layers to the randomization. After receiving either a placebo or tocilizumab, the main result was either recovery or death. Secondary outcomes included clinical recuperation or worsening of symptoms and inflammatory indicators, as well as hospital release. Of the 190 participants included in this study, 152 received Tocilizumab and 38 received a placebo. The interventional group's hospital stay was 12.9 ± 9.2, while the placebo group had a longer stay (15.6 ± 8.8). The mortality ratio for the primary endpoint, i.e., death or recovery in the Tocilizumab group, was 17.8% (p = 0.58 by log-rank test). The mortality rate in the placebo group was 76.3% (p = 0.32 using the log-rank test). By day 16, the Tocilizumab group had considerably lower levels of inflammatory markers than the placebo group. Tocilizumab treatment was linked to lower mortality, quicker improvement of inflammatory markers, and a shorter hospital stay in patients with severe COVID-19 [17].

In a retrospective, single-center cohort study carried out in Saudi Arabia by AlQahtani and associates, adult patients hospitalized between June and October 2020 who had a PCR test confirming SARS-CoV-2 infection were included. Following their hospital discharge or death, a retrospective evaluation was conducted on the 135 patients who had severe to critical COVID-19 and had been treated with tocilizumab, corticosteroids, or dexamethasone. The patients in the cohort were split into two groups: N = 100 got Tocilizumab ± corticosteroid, whereas N = 35 received Dexamethasone medication. Hospital mortality was examined for each group. Hospital mortality rates were 36% in the Tocilizumab group and 37% in the Dexamethasone group (p = 0.91). A greater death rate was linked to age 60 and beyond, with OR = 1.030 and 95% CI = (1.004, 1.057). In both groups, more than 50% of patients needed MV. Following immunomodulator use, the development of bacterial or fungal infections was comparable in the Tocilizumab and Dexamethasone groups (29% vs. 31.4%). According to their clinical study, regardless of the kind of immunomodulator medication, the only predictor linked to a greater death rate is being older than 60. The results of this trial also showed that there was no interaction between tocilizumab and dexamethasone in terms of reducing hospital mortality [18,19].

Various clinical studies keep advancing to refine the scientific knowledge of Tocilizumab's role in COVID-19 treatment, including optimal timing and patient selection for administration, xombination therapies with other immunomodulators and antiviral agents, and long-term outcomes of Tocilizumab-treated COVID-19 patients [20].

4. Conclusion

Tocilizumab has emerged as a major treatment option for treating severe COVID-19, particularly in patients who have a hyperinflammatory response. Its capacity to

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inhibit IL-6 and decrease inflammation has resulted in considerable therapeutic advantages, including lower mortality and faster recovery periods. While it is not a cure-all, its efficacy in treating severe COVID-19 emphasizes the necessity of focused immunomodulation in controlling the disease's complicated pathology. Further research and clinical studies will help to clarify its optimal use and long-term safety in Asian and global settings.

Disclosure of conflict of interest

The author declare that he has no conflict of interest.

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