International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 838-842 www.ijprajournal.com ISSN: 2249-7781

A Review on: Tocilizumab in COVID-19 treatment

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Date Of Submission: 01-05-2021 Date Of Acceptance: 12-05-2021

ABSTRACT: The number of cases in the COVID-19 pandemic is rapidly increasing. There hasn't been a single proven effective medication for COVID-19 disease.The subjects who develop acute respiratory disease have the highest mortality rate (ARDS). Histopathological analysis of lung specimens has given rise to theories that suggest cytokine release syndrome plays a major role in the development of ARDS. IL-6 levels have frequently been found to be elevated in patients with severe disease. Tocilizumab is a selective inhibitor of the IL-6 pathway that has been approved for the treatment of a variety of rheumatological diseases. Its use in COVID-19 has been assessed in light of the success of other immunosuppressive drugs such as steroids. There is a lack of data to support its use in COVID19. Similarly, the risk of early and delayed infections following tocilizumab treatment in COVID-19 is unknown. Despite numerous studies, its safety and efficacy in COVID-19 are unknown. Caution should be exercised regarding the timing and role of IL-6 levels in disease monitoring.

Keywords: Tocilizumab, COVID-19, Cytokine release syndrome, Polyarticular Juvenile Idiopathic Arthritis(PJIA).

I. INTRODUCTION

More than 1.57 billion people have been infected by the COVID-19 pandemic worldwide. So far, it has resulted in 3.284.031 deaths. There are mainly 5 brands of vaccines developed till date that has been shown to be effective in treating or preventing human coronavirus Infection with the SARS-CoV-2 virus.

The COVID-19 disease's most serious and deadly complication is acute respiratory distress syndrome (ARDS). The main responsible etiologies for pulmonary involvement in COVID-19 disease have been identified as inflammation and cytokine storm. In its most serious form, cytokine release syndrome (CRS) is a life-threatening acute systemic inflammatory syndrome accompanied by multiorgan failure and fever. In the pathogenesis of SARS-CoV-2 infection, it is important.

Increased levels of cytokines, especially interleukin-6 (IL-6), were found to be a key factor of inflammation in COVID-19 severe disease. The growing importance of immunosuppressive drugs like steroids, as well as their possible mortality benefits, has sparked interest in the role of targeted cytokine inhibitor therapy, such as tocilizumab.

Tocilizumab is a recombinant humanised monoclonal antibody that binds to the IL-6 receptor in both membrane-bound and soluble forms. Tocilizumab was first discovered and used to treat rheumatoid arthritis and chimeric antigen receptor T (CAR T) cell therapies. Tocilizumab is medication used to treat various inflammatory conditions of the joints (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis), skin(psoriasis), and bowel (ulcerative colitis, Crohn's disease). It reduces swelling in these conditions by blocking Tumour Necrosis Factor alpha (TNF alpha). It is administered by a healthcare professional and cannot be self administered. To get the most out of it, you can use it on a daily basis and at the same time per day. Even if you feel better, continue to use it as directed by your doctor and finish the whole dose. Tocilizumab improves clinical signs and symptoms, prevents the radiographic progression of systemic joint injury, and improves health status in adults with rheumatoid arthritis (RA). Tocilizumab is approved for polyarticular and systemic juvenile idiopathic arthritis in paediatric patients 2 years and older.

Headache, high blood pressure, upper respiratory tract infection, elevated liver enzymes, and nasopharyngitis are the most common side effects associated with this medication (pain or irritation in the throat). If any of the side effects

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linger or annoy you, talk to your doctor. Your doctor will be able to advise you about how to ease or avoid these symptoms. You may also be more susceptible to infections when taking this medication. If you experience signs of an infection such as fever, cough, rash, loose stools, or flu-like symptoms, call your doctor right away.

Uses of Tocilizumab in various diseases

Approved: cytokine release syndrome, polyarticular juvenile idiopathic arthritis, rheumatoid arthritis, systemic juvenile idiopathic arthritis. temporal arteritis.

Unapproved: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, scleroderma (systemic sclerosis).

Mechanism of Action-

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist. Endogenous IL-6 is activated by inflammatory stimuli and mediates a wide range of immune responses. Tocilizumab inhibits IL-6 receptors, resulting in a decrease in cytokine and acute phase reactant production.

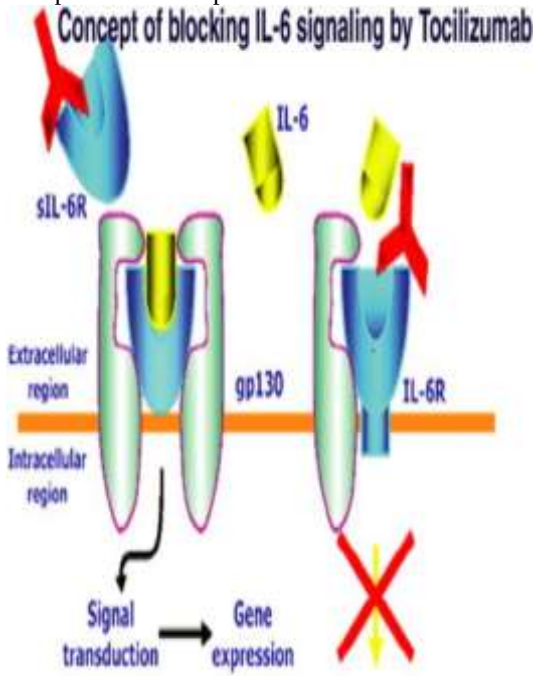

Fig 1: Blockade of IL-6 signals by anti IL-6 receptor antibody.

II. POTENCY OF TOCILIZUMAB IN COVID19

Tocilizumab, which is commonly used to treat IL-6-induced CRS, is being tested as an off-label treatment for moderate to severe COVID-19 disease. Tocilizumab's safety and efficacy in the treatment of COVID-19 patients have yet to be established. Because of the rapidly changing evidence surrounding COVID-19, there is limited data on the use of tocilizumab in COVID-19. Neither safety nor efficacy have been tested prospectively in well-designed trials. However, only a few centres have reported on the use of tocilizumab in COVID-19 patients and its efficacy. Toniati et al. reported on 100 subjects from Italy who used tocilizumab. They were able to show that tocilizumab could reduce the Brescia COVID respiratory severity score (BCRSS) significantly in short period of time. However, the index study's main flaws were its single centre and lack of control arms. Similarly, Guaraldi et al. discovered that tocilizumab was associated with significantly lower deaths as well as the need for invasive mechanical ventilation in a retrospective study. The use of mechanical ventilation and survival in these cases were influenced by an algorithm that included the use of tocilizumab for CRS targeting. The preliminary results of the COVACTA trials were recently released. Despite being a World Health Organization (WHO)-approved double-blind, randomised controlled trial with a large number of participants, tocilizumab failed to improve clinical status or mortality when compared to the standard of care control. The subgroup analysis and detailed results have yet to be completed. Tocilizumab use was associated with lower mortality (9.1 percent vs 57.1 percent, p = 0.001) and lower need for therapy escalation (22.7 percent vs 65.1 percent, p = 0.001). Likewise, biomarkers of inflammation and CRS were lower in the tocilizumab group versus the control group. These findings support the role of tocilizumab therapy in the treatment of COVID-19 disease.

The criteria for using tocilizumab in COVID-19 have varied, but the majority of them include the following:

- Extensive and bilateral lung disease in critically ill patients with high IL-6 levels
- Alternatively, a high level of D-dimer and/or C-reactive protein (CRP) and/or ferritin and/or progressively increasing fibrinogen may be present.
- deterioration of respiratory exchanges to the point where noninvasive or invasive ventilation support is required

Tocilizumab should only be used in a significant number of patients. The timing of the

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drug's administration is critical. However, evidence on the proper timing of administration is also uncertain. Tocilizumab, based on current data, should be used in patients with moderately or severely ill patients with elevated IL-6 level, and significant lung involvement. If no clinical improvement is seen, a different dose can be used. Despite the fact that lower doses of tocilizumab have been tried in various studies, their efficacy in severe disease is limited. However, the effectiveness and safety against intravenous administration is unknown.

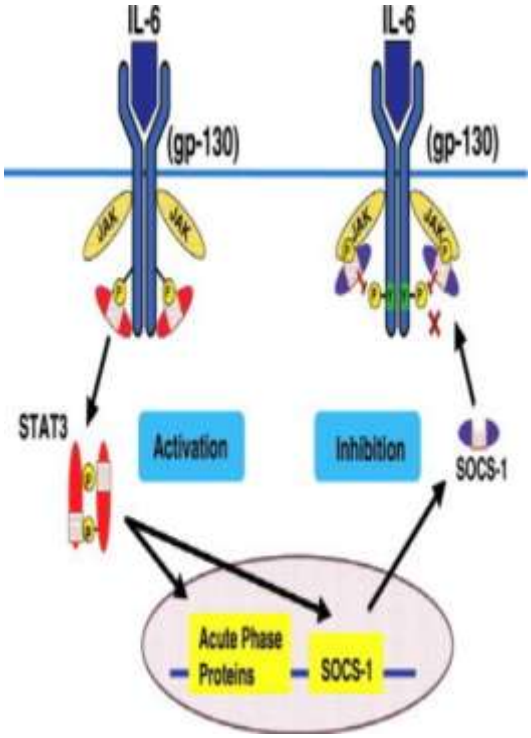

Fig 2:- feedback regulation in IL-6 signaling by SOCS. Il -6, interlukin-6-receptors.

III. TREATMENT

Rheumatoid arthritis- Adults with moderately to seriously active rheumatoid arthritis who have not responded well to one or more Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Intravenous Dosage Adults- Every four weeks, a 4 mg/kg IV infusion is administered over an hour. If required, raise the dose to 8 mg/kg IV every four weeks; doses exceeding 800 mg per infusion are not recommended. Including as a stand alone treatment or in combination with methotrexate or other non- biological DMARDs. Avoid using anakinra, rituximab, ofatumumab, and abatacept along with biological DMARDs including TNF modifiers, anakinra, rituximab, ofatumumab, and abatacept.

Adults weight less than 100 kg- 162 mg subcutaneously every other week as monotherapy or concomitantly with methotrexate or other nonbiologic DMARDs. Increase to 162 mg subcutaneously once weekly based on clinical response. If transitioning from IV tocilizumab, give the first subcutaneous dose instead of the next scheduled IV dose.

Polyarticular juvenile idiopathic arthritis- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis

Intravenous Dosage Children and Teenagers (Weight 30 kg or more)- Every 4 weeks, administer 8 mg/kg/dose IV over 1 hour. Do not significantly change your dose solely based on a single visit body weight measurement, as weight can fluctuate. Use as a single agent or in combination with methotrexate.

Children and Teenagers (Weight less than 30kg)- Every 4 weeks, administer 10 mg/kg/dose IV over 1 hour. Do not significantly change your dose solely based on a single visit body weight measurement, as weight can fluctuate. Use as a single agent or in combination with methotrexate.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel severe acute respiratory syndrome coronavirus. It was first isolated from three people with pneumonia connected to the cluster of acute respiratory illness cases in Wuhan. All structural features of the novel SARS-CoV-2 virus particle occur in related coronaviruses in nature.

Intravenous Dosage Adults- There is a limited data available, and efficacy has yet to be established. The National Institutes of Health (NIH) COVID-19 treatment guidelines do not recommend or discourage the use of IL-6 receptor inhibitors such as tocilizumab due to a lack of clinical data. 4–8 mg/kg/dose (Usual dose: 400 mg; Max dose: 800 mg) IV once a week is being tested in conjunction with antiviral therapy. In patients who do not respond clinically to the first infusion, a second dose administered 8 to 12 hours later may be considered (i.e., continued fever). According to one protocol, a third dose administered 16 to 24 hours after the first dose is possible.

Recommended Intravenous PJIA Dosage Every 4 Weeks

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Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

IV. TOXICITY AND SAFETY STUDIES-

Tocilizumab's adverse reactions for chronic administration were initially evaluated only in rheumatological disease. In a double-blind, randomised study of 623 RA patients given tocilizumab vs placebo, it was discovered that serious infections are more common with tocilizumab. It was discovered that serious adverse events, such as infections, were common, as were mild abnormalities in the lipid profile or the liver function test. Tocilizumab's most common side effect is an increase in serum cholesterol, AST, ALT, and injection site reaction. Tocilizumab's safety and toxicity in other diseases aid in the development of potential exclusion criteria in COVID-19 treatment. Among infections, reactivation of latent tuberculosis is a common risk following tocilizumab administration.

Tocilizumab patients are at an increased risk of developing serious infections that can lead to hospitalisation or death. The majority of patients who developed these infections were taking immunosuppressants at the same time, such as methotrexate or corticosteroids. If a serious infection develops, treatment of tocilizumab aws dechallenged until the infection is under control.

Reported infections include:

- Active tuberculosis that can manifest as pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before and during treatment with tocilizumab. Prior to using tocilizumab, treatment for latent infection should be initiated.
- Invasive fungi, such as candidiasis, aspergillosis, and pneumocystis. Invasive fungal infections can cause disseminated disease rather than regional disease.
- Infections caused by opportunistic pathogens such as bacteria, viruses, and others.

The risks and benefits of treatment with tocilizumab should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Conflict of interest: none.

V. CONCLUSION:

To date, data on the use of tocilizumab in the treatment of acute lung injury in COVID19 patients are insufficient to draw a conclusion. More large and welldesigned randomized controlled clinical trials are required to confirm the efficacy and safety of tocilizumab in COVID19 developed ARDS patients. Future research could also provide a score for determining the indication for tocilizumab based on disease severity, the extent of lung injury, the presence of risk factors, and levels of inflammatory markers, particularly IL6. It would assist clinicians in determining which populations benefit the most from the drug. Due to a lack of data at this time, clinical considerations about the use of tocilizumab in patients with COVID19 should be taken in terms of patient selection, treatment dose, combination with other therapies, and safety issues until the results of ongoing clinical trials are determined.

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