Chapter

A Clinical Update on Employing Tocilizumab to Fight COVID-19

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Abstract

SARS-CoV-2 infection or COVID-19, currently regarded as 'terror' worldwide, has spread uncontrollably as a serious menace. Till date, limited effective medicines or treatments are available. The mortality and morbidity rates have increased considerably, which have been aggravated by acute respiratory distress syndrome (ARDS) and new and old cardiovascular injuries. To control COVID-19, many drugs have been taken into consideration, like ACE2 blockers, anti-inflammatory drugs, antibodies against IL-1 and anti-IL-6, Remdesivir, Dexamethasone, Hydroxychloroquine and vaccines. In this chapter, preference is given to Tocilizumab with the latest status of clinical research update available. Despite several clinical research attempts, some have yielded promising results, others are inconclusive.

Keywords: COVID-19, Tocilizumab, Clinical Studies, Antiviral drugs, Public Health

1. Introduction

Since December 2019, the outbreak of the novel coronavirus (SARS-CoV-2) infection (i.e. COVID-19), from Wuhan, China as a pandemic, has posed a serious threat towards mankind, treatment of which is still unknown [1]. In Jan 30, 2020, the novel coronavirus disease 2019 (COVID-19), was declared as the Sixth public health emergency epidemic by the World Health Organization [WHO] [2]. Till date there is no single drug to control it. Despite Remdesivir being used extensively for the treatment, it is still under clinical trials [3] and not beyond question [4]. The elderly, immune-compromised or people having co-morbidities led to acute respiratory distress syndrome (ARDS), cardiovascular (CV) complications, and multi-organ failure [2, 5]. Common symptoms of the disease include fever, cough, myalgia, malaise, breathlessness and diarrhea [2]. Tocilizumab (a humanized anti-IL-6 receptor antibody) is one of drugs used for the treatment of COVID-19 hospitalized patients [6]. This article summarizes all critical clinical trials to evaluate the efficacy of Tocilizumab.

2. About the molecule

Tocilizumab is an Interleukin-6 Receptor Inhibitor, having a molecular formula of [C6428H9976N1720O2018S42]. Its molecular mass is of [145.0 kDa], CAS number: [375823-41-9]. It is a recombinant humanized monoclonal antibody used in the

treatment of inflammatory and autoimmune conditions like Rheumatoid arthritis, multiple myeloma and prostate cancer, nowadays used extensively for COVID-19 treatment [7–11].

3. Tocilizumab as drug

Tocilizumab, an immunosuppressive monoclonal antibody drug having the traditional name Actemra and Atlizumab, has been reported to be effective against COVID-19 in several countries such as China, France, Italy, Switzerland and Qatar Xiaoling [12, 13]. The drug is known to treat patients with hyperinflammatory syndrome and acute respiratory failure [14]. The drug is sold in the European Union (EU) under the trade name RoActemra and in the United States as Actemra [15, 16]. The drug was first approved in 2005 as an orphan drug in Japan, used in the treatment of Castleman's disease [17]. Nowadays, Tocilizumab has acquired license for EU, to be used alone or in combination with DMARDs [disease-modifying antirheumatic drugs]. This combined therapy is used in the treatment of rheumatic arthritis in adults, systemic form of juvenile idiopathic arthritis (sJIA) in children above 2 years and with the polyarticular form of juvenile idiopathic arthritis (pJIA) in children more than 2 years of age [17]. This drug displays a long elimination half-life. Several studies were conducted to find out whether the drug is useful or not.

In a single centre study in Brescia [Italy], having an gathering of 100 patients, 8 mg/kg [max 800 mg] of the drug was advised to be given to patients by two consecutive intravenous infusions 12 hr. apart. Significant clinical improvement was observed in this case [18]. In another study by Alattar et al. [19] at Quatar, 25 patients having COVID-19 were administered with Tocilizumab, one to three median doses of the drug individually [4.8 mg/kg]. Tocilizumab was associated with dramatic decline in inflammatory markers, radiological improvement and reduced ventilatory support requirements [19]. In a 61-year-old man with COVID-19 symptoms, with a history of kidney transplantation, 324 mg Tocilizumab was administered via subcutaneous route along with hydroxychloroquine that helped in prevention of the disease and did not require mechanical ventilation [20]. However, contrary reports do exist, that reports that Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 [21].

4. USFDA approval

The drug Actemra (tocilizumab, Genentech, Inc., South San Francisco, CA) was approved by USFDA to be used for the treatment of Rheumatoid Arthritis (RA), Giant Cell Arthritis (GCA), Polyarticular Juvenile Idiopathic Arthritis (PJIA), Systemic Juvenile Idiopathic Arthritis (SJIA) and Cytokine Release Syndrome (CRS) [22]. However, despite of recommendation of NIH on usage of Tocilizumab for COVID-19 treatment, it has not yet received approval of USFDA.

5. Dosage of tocilizumab for COVID-19 treatment

The use of Tocilizumab is recommended as per the US NIH guidelines only for clinical trial studies [23]. The preference is mainly given to hospitalized patients with increasing oxygen demand with or without elevated markers of systemic inflammation. As per the recommendations, Tocilizumab (single intravenous [IV]

dose of tocilizumab 8 mg/kg actual body weight up to 800 mg) in combination with dexamethasone (6 mg daily for up to 10 days) is advised to be administered in certain hospitalized patients experiencing rapid respiratory decompensation due to COVID-19 [24].

6. Storage

This drug should be stored refrigerated at 2 to 8° C (36 to 46 F).

7. Plausible mechanism of tocilizumab against COVID-19

According to a study, by the team of Haiming Wei [25], after the SARS-CoV-2 infection, CD4 + T lymphocytes are activated to become pathogenic T helper cells, generating GM-CSF (Granulo Macrophage Colony Stimulating Factor]. This leads to severe inflammatory storm created by CD14 + CD16+ inflammatory monocytes with elevated expression of IL-6. These excessive immune cells usually invade the pulmonary circulation and cause damage to the immune system, thus leading to functional disability of lungs and mortality. Therefore, drugs like Tocilizumab are administered to prevent the cytokine storm. Tocilizumab has yielded effective results as an IL-6R antagonist.

Excessive stimulation of IL-6 can cause CRS [Cytokine Release Syndrome] in hospitalized patients. The higher the level of CRS, higher is the serum peak concentration of IL-6. IL-6 binds to its receptor IL-6R and a complex is formed. IL-6R then binds to the signal transducer glycoprotein 130 (gp-130) to cause signal transduction. Two types of IL-6R are there, one is the Soluble form (sIL-6R) and the other is Membrane bound form [mIl-6R]. In classical signal transduction pathway, IL-6 binds to mIL-6R [transmembrane integral protein], and forms a complex, which then prohibits the connection of IL-6R with gp130 [integral membrane protein]. Thus no cytokine storm is produced. In the trans-signaling pathway, binding of Tocilizumab to sIl-6R, prevents the binding of IL-6R to gp130 [present on the membrane of monocytes, macrophages, dendritic cells] and thus hinders release of inflammatory storm. JAK/STAT tyrosine kinase system mediates one pathway, while Ras/mitogen-activated protein kinase (MAPK)/ NF-κB-IL-6 pathway mediates the other. Tocilizumab [humanized anti-IL-6R monoclonal antibody], is thus considered a potential drug in COVID-19 treatment [26, 27].

8. Other clinical considerations

Tocilizumab is contraindicated in immunocompromised individuals, those who use biologic immunomodulating drugs, and in patients having alanine aminotransferase >5 times the upper limit of normal; patients with gastrointestinal perforation; those having uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection; absolute neutrophil count <500 cells/μL; platelet count <50,000 cells/μL. The drug should also be avoided in individuals having a known hypersensitivity to it [28]. It has been recommended to administer Dexamethasone [or an alternative corticosteroid of dosage equal to dexamethasone 6 mg] simultaneously in patients receiving Tocilizumab [9]. A patient's clinical response to dexamethasone is initially accessed before administering Tocilizumab [29]. The combination therapy yields an adverse

effect in the form of severe and disseminated strongyloidiasis infestation. Therefore, Ivermectin should be used as a prophylactic treatment [30].

9. Side effects

The common side effects include respiratory tract infections, headache, hypertension, elevation in liver test. Rashes, erythema, oedema, itching can occur at the infection site [31]. Tuberculosis, sepsis and fungal infection are the associated infections that can occur. Hypersensitivity reactions, cancer, reactivation of herpes zoster, gastrointestinal perforation in patients with diverticulitis are also seen in some patients, though not significant [32].

10. Clinical trial status

The process of systemic review was followed and effectiveness of the drug analyzed from the NIH, US National Library of Medicine Clinical Trial Registry (ClinicalTrials.gov). At present (till May 2021), 81 clinical studies could be traced in the name Toclilizumab [until May 2021]. 33 studies have been excluded due to non-relevance. 48 records are included in this study. Some of the studies have yielded promising initial results yet require more time for validation and declared to be effective or safe. Among the 48 trials done on Tocilizumab, 17 are in Recruiting stage, 12 trials have been concluded, 5 have been terminated, 1 has been withdrawn, 5 trials are in not yet recruiting stage and 6 are active but non recruiting. 1 among the 47 trials is in phase 1, 16 trials are in phase 2, 14 are in phase 3 trial. Analyzing the clinical trials from **Table 1**, it is evident that there is attempt to use Toclizumab alone or in combination with other drugs looks promising for the treatment of COVID 19 (**Figure 1**).

11. Comparing tocilizumab with other drugs involved in COVID-19 treatment

Several drugs employed for the treatment of COVID-19 through clinical trials are: Remdesivir, Tocilizumab, Baricitinib, Sarilumab and Hydroxychloroquine. In terms of clinical research output Remdesivir emerges as frontrunner, while Tocilizumab may be considered as a potential drug candidate against COVID-19. Despite the initial attempt of drug repurposing by using Hydroxychloroquine to treat COVID-19, there were limited encouraging results for which, its administration was removed from the line of treatment in various countries. A comparison between Tocilizumab and other drugs involved in the treatment of COVID-19 is presented in **Table 2**.

12. Summarizing prominent publications on tocilizumab related to COVID treatment

Apart from several clinical research outcomes (summarized in **Table 1**) there has been several publications revealing scientific information on the mechanism, application and prospect of the drug candidate Tocilizumab for COVID-19 treatment. There are more than 30 publications found in PubMed (https://pubmed.ncbi.nlm.nih.gov/) in the year 2021 among which few significant ones are summarized in following **Table 3**.

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
1	The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation	To assess the therapeutic value of intravenous tocilizumab administered as single 8 mg/Kg dose in patients affected by SARS-CoV2 infection with a pulmonary manifestation causing hypoxia.	Interventional	Recruiting	Apr-20	May-21	Phase 4	Not Available	Hadassah Medical Center	NCT04377750	Nil
2	Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis	To establish proof of concept that tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalized, non-critically ill patients	Interventional	Completed	Apr-20	Jun-20	Phase2	Not Available	University of Chicago	NCT04331795	Nil
3	Low-dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19 [COVIDOSE-2]	To establish whether low-dose tocilizumab reduces the time to clinical recovery in patients with COVID-19 pneumonitis and hyperinflammation, when compared to a tocilizumab-free	Interventional	Recruiting	Sep-20	Dec-20	Phase 2	Not Available	University of Chicago	NCT04479358	[33]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		standard of care and to establish whether low-dose tocilizumab is near-equivalent to high-dose tocilizumab (400 mg or 8 mg/kg) in reducing the time to clinical recovery in patients with COVID-19 pneumonitis and hyperinflammation.									
4	Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (TOCIVID-19)	This study project includes a single-arm phase 2 study and a parallel cohort study, enrolling patients with COVID-19 pneumonia.	Interventional	Active not recruiting	March 19, 2020	December 19, 2022	Phase 2	Not Available	National Cancer Institute, Naples	NCT04317092	[34–36]
5	Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalized COVID-19 Patients With High Risk of Progression	This study aims to compare the efficacy and safety of Methylprednisolone versus Tocilizumab in improving clinical outcomes and reducing the need for ventilator support in COVID-19 patients with moderate COVID-19 disease at risk for	Interventional	Not yet recruiting	April 15, 2020	October 31, 2020	Phase 3	Not Available	University of Malaya	NCT04345445	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		complications of cytokine storm.									
6	Clinical Efficacy of Heparin and Tocilizumab in Patients With Severe COVID-19 Infection: a Randomized Clinical Trial (HEPMAB)	To study the use of heparin and tocilizumab to potencially reduce inflammation and thrombogenesis in patients with severe COVID-19 infection, improving patients outcomes and survival.	Interventional	Recruiting	November 10, 2020	December 31, 2021	Phase 3	Not Available	Ludhmila Abrahão Hajjar, University of Sao Paulo	NCT04600141	Nil
7	Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01) (COVITOZ-01)	To study the unicenter, randomized, open-label clinical trial on the efficacy of tocilizumab in modifying the inflammatory parameters of patients with COVID-19.	Interventional	Recruiting	May 4, 2020	August 4, 2020	Phase 2	Not Available	Jose A Perez Molina, Hospital Universitario Ramon y Cajal	NCT04435717	Nil
8	Trial of Tocilizumab for Treatment of Severe COVID-19: ARCHITECTS (ARCHITECTS)	The overall objective is to evaluate the clinical efficacy and safety of tocilizumab relative to placebo among approximately 300	Interventional	Recruiting	June 12, 2020	December 31, 2021	Phase 3	Not Available	Queen's Medical Centre	NCT04412772	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		hospitalized adult patients who have severe COVID-19									
9	TOCILIZUMAB - An Option for Patients With COVID-19 Associated Cytokine Release Syndrome; A Single Center Experience	To analyze the effectiveness of Tocilizumab in moderate to severe Covid-19 participants on the basis of predefined assessment criteria.	Interventional	Completed	May 12, 2020	June 12, 2020	Phase 4	Not Available	Aijaz Zeeshan Khan Chachar, FMH College of Medicine and Dentistry	NCT04730323	Nil
10	Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID)	To evaluate the use of Tocilizumab in combination with hydroxychloroquine and azithromycin for the treatment of hospitalized adult patients with COVID-19.	Interventional	Recruiting	April 2, 2020	Oct-20	Phase 2	Not Available	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	NCT04332094	Nil
11	Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia	To evaluate the effectiveness and safety of IV tocilizumab in patients with COVID-19 severe pneumonia who are currently hospitalized or admitted to ICU.	Interventional	Completed	May 22, 2020	December 23, 2020	Phase 2	Not Available	Fundacion SEIMC-GESIDA	NCT04445272	[7]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
12	Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection	The purpose of this study is to find out whether the study drug tocilizumab is an effective treatment for COVID-19 infection.	Interventional	Active, not recruiting	May 1, 2020	May 1, 2022	Phase 2	Not Available	Memorial Sloan Kettering Cancer Center	NCT04377659	Nil
13	COVID-19: Salvage Tocilizumab as a Rescue Measure (COVIDSTORM)	To Evaluate the efficacy of Tocilizumab in hospitalized patients in the inflammatory phase of COVID-19.	Interventional	Recruiting	August 14, 2020	December 31, 2021	Phase 3	Not Available	Jarmo Oksi, Turku University Hospital	NCT04577534	Nil
14	Serum IL-6 and Soluble IL-6 Receptor in Severe COVID-19 Pneumonia Treated With Tocilizumab (UHID-COVID19)	To assess the role of interleukin-6 (IL-6) and soluble interleukin 6 receptor (sIL-6R) as predictors of efficacy and safety outcomes in patients with severe coronavirus disease (COVID-19) pneumonia treated with tocilizumab.	Observational	Recruiting	June 16, 2020	May 15, 2021	case only	Not Available	University Hospital for Infectious Diseases, Croatia	NCT04359667	Nil
15	A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation, to Compare Standard-	The study is designed as a randomized, controlled, single-center open-label trial to compare standard-of-care (SOC) treatment	Interventional	Recruiting	June 11, 2020	Feb-21	Phase 2	Not Available	Jonas Sundén-Cullberg, Karolinska University Hospital	NCT04412291	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
	of-care With Anakinra and Tocilizumab Treatment The Immunomodulation-CoV Assessment (ImmCoVA) Study	with SOC + anakinra or SOC + tocilizumab treatment in hospitalized adult subjects who are diagnosed with severe COVID 19.									
16	A Trial Using ANAKINRA, TOCILIZUMAB Alone or in Association With RUXOLITINIB in Severe Stage 2b and 3 of COVID19-associated Disease (INFLAMMACOV)	To use biological drugs currently available for inhibition of IL-1 (anakinra), IL-6 (tocilizumab) or IFNg signaling (ruxolitinib) in the severe forms of COVID19-associated disease.	Interventional	Not yet recruiting	September 1, 2020	November 1, 2022	Phase 3	Not Available	Assistance Publique Hopitaux De Marseille	NCT04424056	Nil
17	Tocilizumab Versus Methylprednisolone in the Cytokine Release Syndrome of Patients With COVID-19	This study compare the efficacy and safety of tocilizumab versus methylprednisolone in the cytokine release syndrome of patients with COVID-19	Interventional	Not yet recruiting	May-20	Aug-20	Phase 2	Not Available	José Raimundo Araujo de Azevedo, Hospital Sao Domingos	NCT04377503	[8, 37–43]
18	Tocilizumab in the Treatment of Coronavirus Induced Disease (COVID-19) (CORON-ACT)	To evaluate whether treatment with TCZ reduces the severity and mortality in	Interventional	Terminated	April 26, 2020	September 27, 2020	Phase 2	Not Available	University Hospital Inselspital, Berne	NCT04335071	[2, 9, 10, 28, 43–53]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		patients with COVID-19.									
19	A Study to Investigate Intravenous Tocilizumab in Participants With Moderate to Severe COVID-19 Pneumonia (MARIPOSA)	To Investigate Intravenous Tocilizumab in Participants With Moderate to Severe COVID-19 Pneumonia	Interventional	Completed	May 5, 2020	August 12, 2020	Phase 2	Not Available	Hoffmann-La Roche	NCT04363736	Nil
20	Efficacy and Safety of Tocilizumab in the Treatment of SARS-Cov-2 Related Pneumonia (TOSCA)	This is a prospective observational clinical study and it is aimed at verifying tocilizumab efficacy and safety in patients with COVID-19 complicated by acute distress respiratory syndrome (ARDS) and CRS.	Observational	Recruiting	April 1, 2020	March 31, 2021	Observational Model: Cohort	Not Available	Prof. Roberto Giacomelli, University of L'Aquila	NCT04332913	[2, 9, 12, 28, 54–62]
21	Efficacy of Tocilizumab on Patients With COVID-19	To test the effect of Tocilizumab on multi-organ dysfunction in a phase 3 randomized controlled trial among hospitalized patients with COVID-19 infection.	Interventional	Completed	April 20, 2020	August 27, 2020	Phase 3	Tocilizumab provided no benefit in prevention of death (the primary outcome) or reducing the risk of clinical worsening (secondary outcomes).	Stone, John H, M.D., M.P.H, Massachusetts General Hospital	NCT04356937	[21]
22	A Study to Evaluate the Safety and	This study will evaluate the efficacy,	Interventional	Completed	April 3, 2020	July 28, 2020	Phase 3	No difference was noticed between	Hoffmann-La Roche	NCT04320615	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
	Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)	safety, pharmacodynamics, and pharmacokinetics of tocilizumab (TCZ) compared with a matching placebo in combination with standard of care (SOC) in hospitalized patients with severe COVID-19 pneumonia.						tocilizumab and placebo for clinical status (including death) at Day 28 (the primary outcome), but tocilizumab exhibited a shorter time to recovery and shorter length of ICU stay (secondary outcomes).			
23	Efficacy and Safety of Remdesivir and Tociluzumab for the Management of Severe COVID-19: A Randomized Controlled Trial	To evaluate the efficacy of Remdesivir and Tocilizumab as a treatment for severe Acute Respiratory Distress Syndrome (ARDS) caused by Coronavirus disease 2019 (COVID-19).	Interventional	Completed	August 15, 2020	February 10, 2021	Phase 3	Not Available	Abu Taiub Mohammed Mohiuddin Chowdhury, First Affiliated Hospital Xi'an Jiaotong University	NCT04678739	Nil
24	A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (EMPACTA)	This study (EMPACTA) will a) evaluate the efficacy and safety of tocilizumab (TCZ) compared with a placebo in combination with standard of care (SOC) in	Interventional	Recruiting	May 14, 2020	December 1, 2021	Phase 3	Tocilizumab lowered rates of mechanical ventilation or death by Day 28 but provided no benefit in 28-day mortality.	Genentech, Inc.	NCT04372186	[63]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		hospitalized participants with COVID-19 pneumonia, and b) include an optional substudy to explore the long-term sequelae of resolved COVID-19 pneumonia.									
25	A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia (REMDACTA)	This study will evaluate the efficacy and safety of combination therapy with remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized patients with COVID-19 pneumonia.	Interventional	Completed	June 16, 2020	March 8, 2021	Phase 3	Not Available	Hoffmann-La Roche	NCT04409262	Nil
26	Safety and Efficacy of Tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers (TOCIBRAS)	To evaluate the efficacy and safety of Tocilizumab, which rapidly reduces the inflammation process through inhibition of IL-6 in patients with moderate to severe COVID-19 with increased	Interventional	Terminated	May 8, 2020	July 21, 2020	Phase 3	Tocilizumab showed no benefit in this study	Dr Rozana Mesquita Ciconelli, Beneficência Portuguesa de São Paulo	NCT04403685	[64]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		inflammatory markers.									
27	Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure (TOCIVID)	To compare the effect of either one of three IL-6 inhibitor administrations, relative to the standard of care, on time to independence from supplementary oxygen therapy, measured in days from baseline to day 28, in patients with severe SARS-CoV-2 pneumonia.	Interventional	Terminated	April 5, 2020	October 8, 2020	Phase 2	Not Available	Marius Henriksen, Frederiksberg University Hospital	NCT04322773	Nil
28	Treatment of COVID-19 Patients With Anti-interleukin Drugs (COV-AID)	To test the safety and effectiveness of individually or simultaneously blocking IL-6 and IL-1 versus standard of care on blood oxygenation and systemic cytokine release syndrome in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic	Interventional	Active, not recruiting	April 3, 2020	Mar-21	Phase 3	Not Available	Bart N. Lambrecht, University Hospital, Ghent	NCT04330638	[65]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		cytokine release syndrome									
29	CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) (CORIMUNO-TOC)	To determine the therapeutic effect and tolerance of Tocizilumab in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19)	Interventional	Active, not recruiting	March 30, 2020	December 31, 2021	Phase 2	In COVID-19 Patients Tocilizumab led to improved ventilator-free survival at Day 14 suggesting possible benefit, but the clinical implications are unclear as there was no difference in survival for tocilizumab vs. usual care through Day 28.	Assistance Publique - Hôpitaux de Paris	NCT04331808	[66]
30	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan	To study the role of Investigational Therapies Alone or in Combination to Treat Moderate, Severe and Critical COVID-19	Interventional	Completed	April 1, 2020	July 20, 2020	Not applicable	Not Available	sultan mehmood kamran, UNICEF	NCT04492501	[67–73]
31	Tocilizumab in Coronavirus-19 Positive Patients	To determine the impact of adjunctive Tocilizumab (TCZ) to standard of care on the reduction of hyperinflammation-related mortality in COVID-19.	Interventional	Not yet recruiting	July 30, 2020	Jun-21	Phase 3	Not Available	University of Calgary	NCT04423042	[8, 71, 74]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
32	Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-19 (SARS-CoV-2 Infection)	TO compare the effect of adding tocilizumab to standard of care versus standard of care alone in treating cytokine release syndrome (CRS) in patients with SARS-CoV-2 infection. CRS is a potentially serious disorder caused by the release of an excessive amount of substance that is made by cells of the immune system (cytokines) as a response to viral infection	Interventional	Withdrawn	April 7, 2020	June 2, 2020	Phase 3	Not Available	Ajay Nooka, Emory University	NCT04361552	Nil
33	Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients With Covid-19 (TOCIDEX)	To determine the therapeutic effect and tolerance of Tocilizumab combined with Dexamethasone in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19).	Interventional	Recruiting	July 16, 2020	December 31, 2021	Phase 2	Not Available	Assistance Publique - Hôpitaux de Paris	NCT04476979	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
34	Toclizumam Versus Dexamethasone in Severe Covid-19 Cases	To study randomized controlled trial comparing survival benefit of Tocilizumab therapy with dexamethasone in patients with severe COVID 19	Interventional	Completed	March 1, 2020	August 5, 2020	Not applicable	Not Available	Alaa Rashad, South Valley University	NCT04519385	Nil
35	Tocilizumab for SARS-CoV2 (COVID-19) Severe Pneumonitis	To test the hypothesis that an anti-IL6 treatment can be effective in calming the virus-induced cytokine storm, blocking deterioration of lung function or even promoting a rapid improvement of clinical conditions, preventing naso-tracheal intubation and/or death.	Interventional	Active, not recruiting	March 12, 2020	May-20	Phase 2	Not Available	Armando Gabrielli, Università Politecnica delle Marche	NCT04315480	[75–79]
36	Personalized Immunotherapy for SARS-CoV-2 (COVID-19) Associated With Organ Dysfunction (ESCAPE)	To conduct one trial of personalized immunotherapy in patients with SARS-CoV-2 (COVID-19) associated with organ dysfunction and with laboratory findings of macrophage activation syndrome	Interventional	Completed	April 2, 2020	January 8, 2021	Phase 2	Not Available	Hellenic Institute for the Study of Sepsis	NCT04339712	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
		or immune dysregulation.									
37	Theranostic Implication of Complementary Medicines Against Interleukin Receptors and Gp-130 Proteins	To estimate the relationship of severity of disease with gp-130 and IL-6	Interventional	Completed	July 23, 2020	December 10, 2020	Not Applicable	Not Available	Dr Muhammad Mansoor Hafeez, University of Lahore	NCT04690920	Nil
38	Tocilizumab vs. CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS)	To study Tocilizumab associated with better clinical outcomes, such as decreased systemic inflammation, improved survival rate, better hemodynamic and improved of respiratory distress.	Observational	Recruiting	February 20, 2020	June 20, 2020	Cohort	Not Available	YIKAI YU, Tongji Hospital	NCT04306705	Nil
39	Tocilizumab for Patients With Cancer and COVID-19 Disease	To enhance access to tocilizumab for patients who cannot participate in the randomized COVACTA trial with specific emphasis on patients with cancer, especially those who belong to high-risk and minority populations and children.	Interventional	Terminated	May 28, 2020	January 14, 2021	Phase 2	Not Available	National Cancer Institute (NCI)	NCT04370834	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
40	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	To evaluate the efficacy and safety of favipiravir combined with tocilizumab in the treatment of corona virus disease 2019	Interventional	Recruiting	March 8, 2020	May-20	Not Applicable	Not Available	Guiqiang Wang, Peking University First Hospital	NCT04310228	Nil
41	Tocilizumab in COVID-19 Lahore General Hospital (TC19LGH)	This is intervention single-center study, done at Lahore General Hospital in which 95 beds are allocated for COVID-19 patients including ICUs and HDUs.	Interventional	Recruiting	May 1, 2020	December 30, 2020	Phase 1	Not Available	Dr. M.Irfan Malik, Lahore General Hospital	NCT04560205	[80–83]
42	Comparison of Tocilizumab Versus Tocilizumab/ Infliximab in Patients With COVID-19-associated Cytokine Storm Syndrome	To compare the outcomes of a large cohort of patients with moderate and severe COVID-19 pneumonia treated with tocilizumab in addition to standard management, with those of concomitantly hospitalized patients who received infliximab and tocilizumab in addition to standard management.	Observational	Recruiting	December 1, 2020	June 1, 2021	Cohort	Not Available	Neven Sarhan, Misr International University	NCT04734678	Nil

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
43	Assessment of Efficacy and Safety of Tocilizumab Compared to DefeROxamine, Associated With Standards Treatments in COVID-19 (+) Patients Hospitalized In Intensive Care in Tunisia (TRONCHER)	To study the assessment of Efficacy and Safety of Tocilizumab Compared to DefeROxamine, associated with standards treatments in COVID-19 (+) patients, Hospitalized In Intensive care in Tunisia.	Interventional	Not yet recruiting	September 4, 2020	October 4, 2020	Phase 3	Not Available	Dr Jalila Ben Khelil, Abderrahmane Mami Hospital	NCT04361032	Nil
44	Tocilizumab Treatment in Patients With COVID-19	To study the impact of the administration of Tocilizumab on the evolution of the acute respiratory distress syndrome (ARDS) in patients with severe or critical SARS-CoV-2 infection	Interventional	Active, not recruiting	June 1, 2020	August 1, 2021	Phase 2	Not Available	Oscar Gerardo Arrieta Rodríguez, Instituto Nacional de Cancerologia de Mexico	NCT04363853	[1, 2, 5, 54, 77, 84–91]
45	Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care (POPS) (POPS or POP02)	To evaluate the PK of understudied drugs currently being administered to children per SOC as prescribed by their treating provider.	Observational	Recruiting	March 5, 2020	April 24, 2024	Prospective	Not Available	Duke University	NCT04278404	[92–142]

Sl. no.	Clinical trial	Primary objectives	Study type	Status	Study start date	Study completion date	Phase	Observation/ interpretation	Studied by:	Reference	Publication
46	Efficacy of Early Administration of Tocilizumab in COVID-19 Patients	To study early administration of Tocilizumab compared to late administration of Tocilizumab can reduce the number of patients with COVID-19 pneumonia who require mechanical ventilation.	Interventional	Terminated	March 31, 2020	June 6, 2020	Phase 2	Not Available	Azienda Unità Sanitaria Locale Reggio Emilia	NCT04346355	[143]
47	Comparative Therapeutic Efficacy and Safety of Different Antiviral and Anti Inflammatory Drugs in COVID-19 Patients.	To study the comparison of the outcomes of a large cohort of moderate and severe COVID-19 patients received different Antiviral and Anti Inflammatory Drugs.	Interventional	Recruiting	October 1, 2020	April 5, 2021	Phase 4	Not Available	Ahmed Essam, October 6 University	NCT04779047	Nil
48	Anti-IL6 and Corticosteroid Monotherapy vs. Combination in COVID-19	To evaluate the safety and efficacy of anti-IL6 alone vs. anti-IL6 corticosteroid combination in patients with COVID-19 pneumonia	Observational	Recruiting	July 22, 2020	July 22, 2021	Other	Not Available	King Faisal Specialist Hospital & Research Center	NCT04486521	[144]

Table 1.
Update of the status of clinical trials for the use of tocilizumab in the treatment of COVID-19.

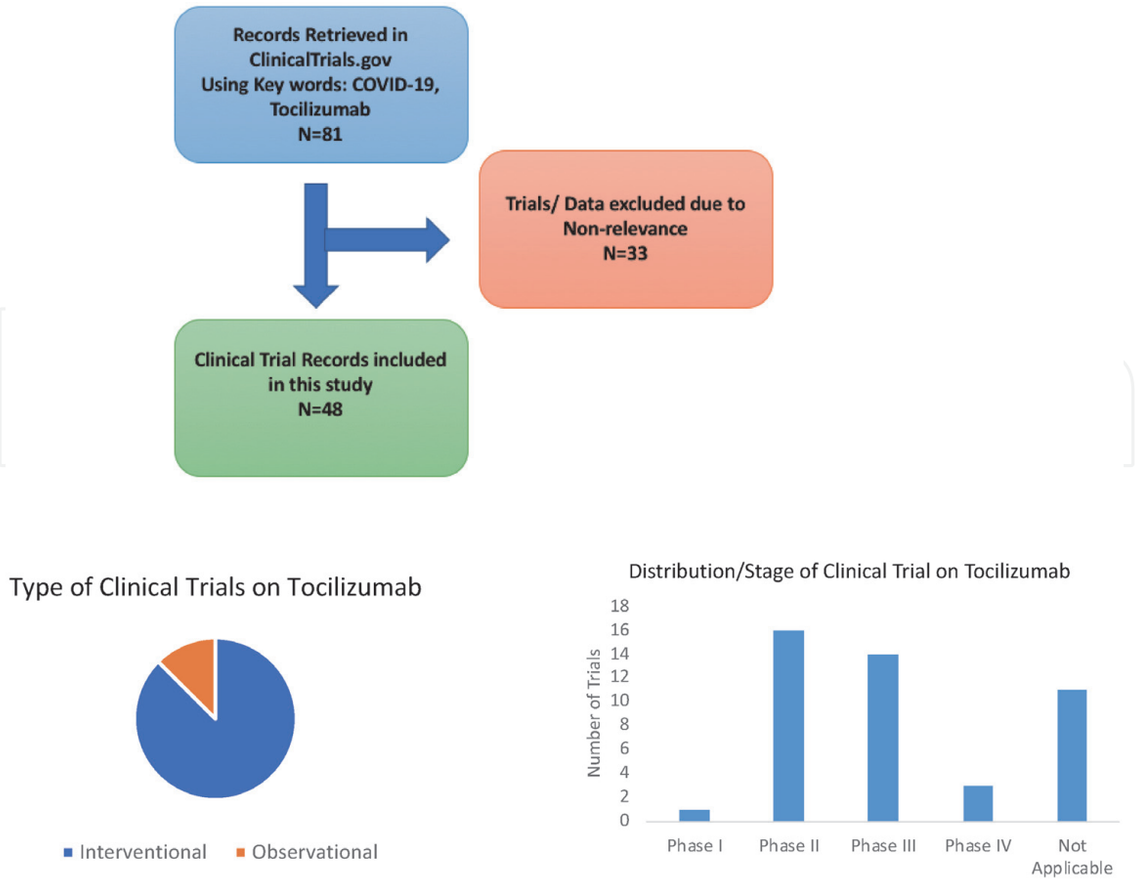

Figure 1.
Status of clinical trials and stage: tocilizumab.

Sl. no.	Name of the drug	Mechanism of action	Clinical trial status	Significant findings	References
1	Tocilizumab	Tocilizumab has rendered effective results as an IL-6R antagonist, to prevent the cytokine storm.	At present, 87 clinical studies could be traced in the name Tocilizumab. Out of which, 1 is in early phase 1; 3 are in phase1; 33 are in phase 2; 24 are in phase 3; and 4 are in phase 4.	Although Tocilizumab is approved by the USFDA (Not for COVID-19 treatment), still its positive effects cannot be predicted in all patients. Among some hospitalized patients with severe or critical COVID-19,a shorter time to recovery and shorter length of ICU stay was seen in those who received this drug. It still it cannot be referred to as an anti-viral drug	—

Sl. no.	Name of the drug	Mechanism of action	Clinical trial status	Significant findings	References
				and may only be effective in patients having inflammation and lung damage caused by the coronavirus.	
2	Remdesivir	The drug inhibits the synthesis of viral RNA by delayed chain termination method.	At present, 110 clinical studies could be traced in the name Remdesivir. Of which 1 study is in early phase 1; 9 are in phase 1; 35 are in phase 2; 41 are in phase 3; 3 are in phase 4.	The USFDA approved drug Remdesivir has been used alone or in combination with other drugs to curb the severity of COVID-19. However it still needs to be administered to a large mass to predict the significant outcomes.	[3, 4]
3	Baricitinib	Baricitinib is an inhibitor of JAK-1 and JAK-2, which dampens the proinflammatory cytokine signaling. It also inhibits AP2-associated protein kinase [AAK-1].	At present, 20 studies could be traced in the name of Baricitinib. Out of which, 10 are in phase2; 11 are in phase 3; and 1 is in phase 4	The USFDA approved drug appears to be relatively safe and well tolerated when used for rheumatoid arthritis. Nowadays they are used for COVID-19 treatment, combined with Remdesivir. Mortality rates have been significantly lowered.	[145, 146]
4	Sarilumab	Sarilumab is a human recombinant IgG1 antibody that binds to both forms of IL-6R, inhibiting the IL-6 mediated signaling.	At present, 17 clinical studies could be traced in the name Sarilumab, out of which 1 is in phase1; 6 are in phase 2; 1 is in phase 2,3; 3 are in phase 1 and 1 is in phase 4.	The drug has been already approved by USFDA for treatment of patients with COVID-19.No benefit of Sarilumab with respect to time to clinical improvement or mortality was observed in case of this drug.	[147]

Sl. no.	Name of the drug	Mechanism of action	Clinical trial status	Significant findings	References
5	Hydroxychloroquine	The drug increases endosomal pH, interferes with the glycosylation of cellular receptors of SARS-COV and blocks viral infection.	At present, 281 clinical studies could be traced in the name Hydroxychloroquine. Out of which 5 studies are in early phase 1; 14 are in phase 1; 88 are in phase 2; 116 are in phase 3; 24 are in phase 4.	The drug has not been approved by FDA for treatment of COVID-19 patients. No significant observation can be noted, as trials are still ongoing.	

Table 2.
Comparing tocilizumab with other drugs employed for COVID-19 treatment.

Sl. no.	Year of publication	Title of publication	Significant observation	Reference
1	2020	Tocilizumab in patients hospitalized with Covid-19 Pneumonia	This trial consisted of more than 25% of the patients who were older than 65 years of age, more than 75% having at least one coexisting disease condition, and greater than 80% were in a minority racial or ethnic group. Scientists found that the possibility of progression to mechanical ventilation or death by day 28 was considerably lower among patients who received tocilizumab plus standard care in comparison to those who received placebo plus standard care.	[148]
2	2020	Tocilizumab in patients with severe COVID-19: a retrospective cohort study	This trial consisted of 1351 patients who were admitted to the recruiting centres. 544 (40%) patients with severe pneumonia were also taken into consideration. There were 359 (66%) male patients, with a median age of 67 years. Tocilizumab [administered intravenously or subcutaneously] plus standard care could reduce the mortality rate or curb the usage of mechanical ventilation in severe COVID-19 patients compared to those who received only standard care as per shown in this study.	[149]
3	2020	Impact of tocilizumab administration on mortality in severe COVID-19.	In this trial 84 patients were administered with tocilizumab and 190 patients were not treated with tocilizumab. Scientists could not predict or conclude any favorable outcome from this trial.	[150]

Sl. no.	Year of publication	Title of publication	Significant observation	Reference
4	2020	Why Tocilizumab could an effective treatment for severe COVID-19?	The IL-6 antagonist, Tocilizumab is highly recommended by scientists to curb the mortality of severe COVID-19. Scientists hope this drug could be beneficial in curbing the severity of COVID-19 pandemic. This study analyses the beneficial effects of this drug.	[151]
5	2020	Effective treatment of severe COVID-19 patients with Tocilizumab.	The average age of the subjects in this study were 56.8 ± 16.5 y and ranged from 25 to 88 years. Out of them in 21 patients, improvement of the rate of deterioration of COVID-19 patients was observed by scientists, which suggested that this drug could be effective enough to treat patients with COVID-19.	[152]
6	2020	Hydroxychloroquine and tocilizumab therapy in COVID-19 patients- An observational study.	In this retrospective observational cohort study consisting of 2512 patients hospitalized COVID-19 patients, within a 13- hospital network, scientists could not predict any favorable outcome. On the contrary, the use of Tocilizumab alone yielded effective results, that is, it helped in reducing the death rate.	[153]
7	2020	Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia.	The efficacy of the drug was unclear from this study compared to other observational studies.	[154]
8	2021	Tocilizumab in COVID-19: some clarity amid controversy.	The recovery trial showed some evidence regarding the use of Tocilizumab in COVID-19 patients. Scientists found that only 31% of the population receiving Tocilizumab showed promises of recovery as compared to those receiving placebo. Still, this drug therapy needs to be combined with other drugs for better outcomes.	[155]
9	2021	Effectiveness of Tocilizumab in patients hospitalized with COVID-19.	Scientists found that Tocilizumab may be effective in diminishing the health hazards of patients with moderate to severe COVID-19 – associated pneumonia and elevated CRP level. Yet it needs to be administered to a large mass to fathom its efficacy.	[156]
10	2021	Tocilizumab in hospitalized patients with severe Covid-19 Pneumonia.	Scientists could not gather any significant clinical status or predict any lowering of mortality rate in comparison to placebo at 28 days.	[157]

Table 3.
Prominent publications reporting the treatment of COVID-19 using Tocilizumab.

13. Conclusion

Although the drug Tocilizumab has shown to reduce mortality and morbidity, still it cannot be referred to as an anti-COVID drug and may only be effective in patients having inflammation and lung damage caused by the coronavirus. Moreover the sensitivity of the drug limits its usage to a specific age and certain patients. Moreover, Tocilizumab is not-yet approved by the USFDA. This drug brings a ray of hope, as it's very much effective in mitigating immune damage, lung functional injuries and arterial oxygen saturation. Scientists therefore hope that this drug could be beneficial to a large mass of population in diminishing the adverse effects of the pandemic.

Conflict of interest

The authors declare that they neither have any conflict of interest nor is involved directly or indirectly with any clinical trials of any of the drugs mentioned in the chapter.

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