We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

A Clinical Update on Employing Tocilizumab to Fight COVID-19

Nilanjana Dhara, Sumana Saha and Saptarshi Chatterjee

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 anti-rheumatic 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]
A 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 Tocilizumab [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 Tocilizumab 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. | Intervventional | 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 | Intervventional | Completed  | Apr-20           | Jun-20                 | Phase 2 | Not Available             | University of Chicago              | NCT0434795 | 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 approach | Intervessional | 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 |
|--------|----------------|-------------------|------------|--------|------------------|-----------------------|-------|---------------------------|-------------|-----------|-------------|
| 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                  |
|--------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------|--------------|------------------|-----------------------|--------|---------------------------|--------------------------------------------------------------------------------|--------------|-----------------------------|
| 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 potentially 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 Albrâão 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 uncenter, 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 patients. | 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 |
|--------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------|------------|------------------|------------------------|-------|--------------------------|-------------------------------------------------------|-----------|-------------|
| 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 Oksa, 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 |
|--------|----------------|-------------------|------------|--------|------------------|-----------------------|-------|---------------------------|------------|-----------|-------------|
| 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 |
|--------|----------------|-------------------|------------|--------|-----------------|-----------------------|-------|---------------------------|------------|-----------|-------------|
| 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 | Intervventional | 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 | NCT0432913 [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 Efficacy of Tocilizumab in Patients With COVID-19 | 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 |
|--------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------|------------------|------------------------|--------------------------|---------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------|-----------|-------------|
| 22     | 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. | Intervventional   | Completed        | August 15, 2020       | February 10, 2021        | Phase 3            | 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). | Abu Taiub Mohammed Mohiuddin Chowdhury, First Affiliated Hospital Xi’an Jiaotong University | NCT04678739 | Nil         |
| 23     | Efficacy and Safety of Remdesivir and Tocilizumab 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). | Intervenional     | 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]        |
| 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 | Intervenional     | 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 |
|--------|----------------|--------------------|------------|--------|-----------------|----------------------|-------|---------------------------|-------------|-----------|-------------|
| 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 |
|-------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------|----------------|------------------|----------------------|-------|---------------------------|----------------------------------------------------------------------------|-----------|-------------|
| 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 | [65]        |
| 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 inflammatory markers. | 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 |
|--------|----------------|--------------------|------------|--------|-----------------|-----------------------|-------|--------------------------|------------|-----------|-------------|
| 29     | CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) (CORIMUNO-TOC) | To determine the therapeutic effect and tolerance of Tocilizumab 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     | Tocilizumab 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 |
|--------|----------------|--------------------|------------|--------|------------------|-----------------------|-------|---------------------------|------------|----------|-------------|
| 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 | Intervenional | 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 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. | Intervenional | 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. | Intervventional | Not yet recruiting | September 4, 2020 | October 4, 2020 | Phase 3 | Not Available | Dr. Jalila Ben Khelif, 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 | Intervventional | Active, not recruiting | June 1, 2020 | August 1, 2021 | Phase 2 | Not Available | Oscar Gerardo Arrieta Rodríguez, Instituto Nacional de Cancerología de México | 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.
Table 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 phase 1; 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 cannot be referred to as an anti-viral drug. | — |
| Sl. no. | Name of the drug | Mechanism of action | Clinical trial status | Significant findings | References |
|--------|-------------------|---------------------|-----------------------|----------------------|------------|
| 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 phase 2; 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 phase 1; 6 are in phase 2; 3 are in phase 2; 3 are in phase 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] |
### 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 $56.8 \pm 16.5$ 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.
References

[1] Lu, H., Stratton, C. W., & Tang, Y. W. (2020). Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. Journal of medical virology, 92(4), 401–402. https://doi.org/10.1002/jmv.25678

[2] Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England), 395(10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

[3] Chatterjee S. (2021). Remdesivir: Critical Clinical Appraisal for COVID 19 Treatment. Drug research, 71(3), 138–148. https://doi.org/10.1055/a-1288-4078

[4] Chatterjee S. (2021). Status of Remdesivir: Not Yet Beyond Question!. Archives of medical research, 52(1), 102–103. https://doi.org/10.1016/j.arcmed.2020.09.004

[5] Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA, 323(11), 1061–1069. https://doi.org/10.1001/jama.2020.1585

[6] Frey N., Grange S., Woodworth T. Relationship between serum concentrations of the interleukin-6 receptor inhibitor tocilizumab and C-reactive protein reduction in RA patients: 6 months’ data from a phase 3 study. Arthritis Rheum. 2007;56:148–149.

[7] Maude, S. L., Barrett, D., Teachey, D. T., & Grupp, S. A. (2014). Managing cytokine release syndrome associated with novel T cell-engaging therapies.

[8] Zhang, C., Wu, Z., Li, J. W., Zhao, H., & Wang, G. Q. (2020). Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. International journal of antimicrobial agents, 55(5), 105954. https://doi.org/10.1016/j.ijantimicag.2020.105954

[9] Le, R. Q., Li, L., Yuan, W., Shord, S. S., Nie, L., Habtemariam, B. A., Przepiorka, D., Farrell, A. T., & Pazdur, R. (2018). FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. The oncologist, 23(8), 943–947. https://doi.org/10.1634/theoncologist.2018-0028

[10] Richter, A., Listing, J., Schneider, M., Klopsch, T., Kapelle, A., Kaufmann, J., Zink, A., & Strangfeld, A. (2016). Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Annals of the rheumatic diseases, 75(9), 1667–1673. https://doi.org/10.1136/annrheumdis-2015-207838

[11] Stone, J. H., Tuckwell, K., Dimonaco, S., Klearman, M., Aringer, M., Blockmans, D., Brouwer, E., Cid, M. C., Dasgupta, B., Rech, J., Salvarani, C., Schett, G., Schulze-Koops, H., Spiera, R., Unizony, S. H., & Collinson, N. (2017). Trial of Tocilizumab in Giant-Cell Arteritis. The New England journal of medicine, 377(4), 317–328. https://doi.org/10.1056/NEJMoa1613849

[12] Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., & Wei, H. (2020). Effective treatment of
severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences of the United States of America, 117(20), 10970–10975. https://doi.org/10.1073/pnas.2005615117

[13] Michot, J. M., Albiges, L., Chaput, N., Saada, V., Pommeret, F., Griscelli, F., Balleyguier, C., Besse, B., Marabelle, A., Netzer, F., Merad, M., Robert, C., Barlesi, F., Gachot, B., & Stoclin, A. (2020). Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Annals of oncology: official journal of the European Society for Medical Oncology, 31(7), 961–964. https://doi.org/10.1016/j.annonc.2020.03.300

[14] Toniati, P., Piva, S., Cattalini, M., Garrafa, E., Regola, F., Castelli, F., Franceschini, F., Airò, P., Bazzani, C., Beindorf, E. A., Berlendis, M., Bezzì, M., Bossini, N., Castellano, M., Cattaneo, S., Cavazzana, I., Contessi, G. B., Crippa, M., Delbarba, A., De Peri, E., ... Latronico, N. (2020). Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmunity reviews, 19(7), 102568. https://doi.org/10.1016/j.autrev.2020.102568

[15] Assessment Report For RoActemra [Internet] 1st ed. London: European Medicines Agency; 2009. [accessed 2017January3]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment.report/human/000955/WC500054888.pdf

[16] RoACTEMRA [Internet] F Hoffmann-La Roche Ltd; c2017 [accessed 2017January2]. http://www.roche.com/products/product-details. htm?productlid=30d444d8-7658-469e-9fce-f4de549c00c4

[17] Venkiteshwaran A. (2009). Tocilizumab. mAbs, 1(5), 432–438. https://doi.org/10.4161/mabs.1.5.9497

[18] Luo, P., Liu, Y., Qiu, L., Liu, X., Liu, D., & Li, J. (2020). Tocilizumab treatment in COVID-19: A single center experience. Journal of medical virology, 92(7), 814–818. https://doi.org/10.1002/jmv.25801

[19] Alattar, R., Ibrahim, T., Shaar, S. H., Abdalla, S., Shukri, K., Daghfal, J. N., Khatib, M. Y., Aboukamar, M., Abukhattab, M., Alsoub, H. A., Almaslamani, M. A., & Omrani, A. S. (2020). Tocilizumab for the treatment of severe coronavirus disease 2019. Journal of medical virology, 92(10), 2042–2049. https://doi.org/10.1002/jmv.25964

[20] Fontana, F., Alfano, G., Morì, G., Amurri, A., Tei, L., Ballestri, M., Leonelli, M., Facchini, F., Damiano, F., Magistrini, R., & Cappelli, G. (2020). COVID-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 20(7), 1902–1906. https://doi.org/10.1111/ajt.15935

[21] Stone, J. H., Frigault, M. J., Serling-Boyd, N. J., Fernandes, A. D., Harvey, L., Foulkes, A. S., Horick, N. K., Healy, B. C., Shah, R., Bensaci, A. M., Woodley, A. E., Nikiforow, S., Lin, N., Sagar, M., Schrager, H., Huckins, D. S., Axelrod, M., Pincus, M. D., Fleisher, J., Sacks, C. A., ... BACC Bay Tocilizumab Trial Investigators (2020). Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. The New England journal of medicine, 383(24), 2333–2344. https://doi.org/10.1056/NEJMoa2028836

[22] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf

[23] Bhimraj, A., Morgan, R. L., Shumaker, A. H., Lavergne, V., Baden,
L., Cheng, V. C., Edwards, K. M., Gandhi, R., Muller, W. J., O’Horo, J. C., Shoham, S., Murad, M. H., Mustafa, R. A., Sultan, S., & Falck-Ytter, Y. (2020). Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, ciaa478. Advance online publication. https://doi.org/10.1093/cid/ciaa478

[24] https://www.covid19treatmentguidelines.nih.gov/immunomodulators/interleukin-6-inhibitors/

[25] Yonggang Zhou, Binqing Fu, Xiaohu Zheng, Dongsheng Wang, Changcheng Zhao, Yingjie Qj, Rui Sun, Zhigang Tian, Xiaoling Xu, Haiming Wei. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients, National Science Review, 7:6 2020, 998–1002, https://doi.org/10.1093/nsr/nwaa041

[26] Tanaka, T., Narazaki, M., & Kishimoto, T. (2016). Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy, 8(8), 959–970. https://doi.org/10.2217/int-2016-0020

[27] Braun, G. S., Nagayama, Y., Maruta, Y., Heymann, F., van Roeyen, C. R., Klinkhammer, B. M., Boor, P., Villa, L., Salant, D. J., Raffetseder, U., Rose-John, S., Ostendorf, T., & Fleige, J. (2016). IL-6 Trans-Signaling Drives Murine Crescentic GN. Journal of the American Society of Nephrology: JASN, 27(1), 132–142. https://doi.org/10.1681/ASN.2014111147

[28] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England), 395(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

[29] Rosas, I. O., Bräu, N., Waters, M., Go, R. C., Hunter, B. D., Bhagani, S., Skiest, D., Aziz, M. S., Cooper, N., Douglas, I. S., Savic, S., Youngstein, T., Del Sorbo, L., Cubillo Gracian, A., De La Zerda, D. J., Ustianowski, A., Bao, M., Dimonaco, S., Graham, E., Matharu, B., ... Malhotra, A. (2021). Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. The New England journal of medicine, 384(16), 1503–1516. https://doi.org/10.1056/NEJMoA2028700

[30] Lier, A. J., Tuan, J. J., Davis, M. W., Paulson, N., McManus, D., Campbell, S., Peaper, D. R., & Topal, J. E. (2020). Case Report: Disseminated Strongyloidiasis in a Patient with COVID-19. The American journal of tropical medicine and hygiene, 103(4), 1590–1592. https://doi.org/10.4269/ajtmh.20-0699

[31] Oldfield, V., Dhillon, S., & Plosker, G. L. (2009). Tocilizumab: a review of its use in the management of rheumatoid arthritis. Drugs, 69(5), 609–632. https://doi.org/10.2165/00003495-200969050-00007

[32] Sebba A. (2008). Tocilizumab: the first interleukin-6-receptor inhibitor. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists, 65(15), 1413–1418. https://doi.org/10.2146/ajhp070449

[33] Strohbehn, G. W., Reid, P. D., & Ratain, M. J. (2020). Applied Clinical Pharmacology in a Crisis: Interleukin-6 Axis Blockade and COVID-19. Clinical pharmacology and therapeutics, 108(3), 425–427. https://doi.org/10.1002/cpt.1931

[34] Perrone, F., Piccirillo, M. C., Ascierto, P. A., Salvarani, C., Parrella, R., Marata, A. M., Popoli, P., Ferraris, ... DOI: http://dx.doi.org/10.5772/intechopen.99785
L., Marrocco-Trischitta, M. M., Ripamonti, D., Binda, F., Bonfanti, P., Squilace, N., Castelli, F., Muiesan, M. L., Lichtner, M., Calzetti, C., Salerno, N. D., Attripaldi, L., Cascella, M., ... TOCIVID-19 investigators, Italy (2020). Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. Journal of translational medicine, 18(1), 405. https://doi.org/10.1186/s12967-020-02573-9

[35] Chiodini, P., Arenare, L., Piccirillo, M. C., Perrone, F., & Gallo, C. (2020). A phase 2, open label, multicenter, single arm study of tocilizumab on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia (TOCIVID-19 trial): Statistical analysis plan. Contemporary clinical trials communications, 20, 100665. https://doi.org/10.1016/j.conctc.2020.100665

[36] Piccirillo, M. C., Ascieto, P., Atripaldi, L., Cascella, M., Costantini, M., Dolci, G., Facciolongo, N., Fraganza, F., Marata, A., Massari, M., Montesarchio, V., Mussini, C., Negri, E. A., Parrella, R., Popoli, P., Botti, G., Arenare, L., Chiodini, P., Gallo, C., Salvarani, C., ... Perrone, F. (2020). TOCIVID-19 - A multicenter study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia. Study protocol. Contemporary clinical trials, 98, 106165. https://doi.org/10.1016/j.cct.2020.106165

[37] Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., Li, S. Y., ... China Medical Treatment Expert Group for Covid-19 (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine, 382 (18), 1708–1720. https://doi.org/10.1056/NEJMoa2002032

[38] Grasselli, G., Zanigrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., Cereda, D., Coluccello, A., Foti, G., Fumagalli, R., Iotti, G., Latronico, N., Lorini, L., Merler, S., Natalini, G., Piatti, A., Ranieri, M. V., Scandroglio, A. M., Storti, E., Cecconi, M., ... COVID-19 Lombardy ICU Network (2020). Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted To ICUs of the Lombardy Region, Italy. JAMA, 323 (16), 1574–1581. https://doi.org/10.1001/jama.2020.5394

[39] Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., & HLH Across Speciality Collaboration, UK (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England), 395(10229), 1033–1034. https://doi.org/10.1016/S0140-6736(20)30628-0

[40] Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. The Journal of infection, 80(6), 607–613. https://doi.org/10.1016/j.jinf.2020.03.037

[41] Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., Yuan, Y., ... Wang, C. (2020). A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. The New England journal of medicine, 382(19), 1787–1799. https://doi.org/10.1056/NEJMoa2001282

[42] Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F. X., Nicastrì, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Berritt, J., Chelliah, D., Chen, D., ... Flanagan, T. (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. The New England journal of medicine, 382(24), 2327–2336. https://doi.org/10.1056/NEJMoa2007016
Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., ... Song, Y. (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine, 180(7), 934–943. https://doi.org/10.1001/jamainternmed.2020.0994

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England), 395 (10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Morrondo, C. D., Zarza, L. P., Gil, J. G., Pinto Tasende, J. A., Diez, P. D., & López, J. M. (2016). Benefit of Tocilizumab Therapy for Adult-Onset Still Disease Complicated With Acute Respiratory Distress Syndrome. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases, 22(5), 291–293. https://doi.org/10.1097/RHU.0000000000000374

Shakoory, B., Carcillo, J. A., Chatham, W. W., Amdur, R. L., Zhao, H., Dinarello, C. A., Cron, R. Q., & Opal, S. M. (2016). Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical care medicine, 44(2), 275–281. https://doi.org/10.1097/CCM.0000000000001402

Neuenschwander, B., Capkun-Niggli, G., Branson, M., & Spiegelhalter, D. J. (2010). Summarizing historical information on controls in clinical trials. Clinical trials (London, England), 7(1), 5–18. https://doi.org/10.1177/1740774509356002

Khanna, D., Denton, C. P., Jahreis, A., van Laar, J. M., Frech, T. M., Anderson, M. E., Baron, M., Chung, L., Fierbeck, G., Lakshminarayanan, S., Allanore, Y., Pope, J. E., Riemekasten, 31

[43] Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., ... Song, Y. (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine, 180(7), 934–943. https://doi.org/10.1001/jamainternmed.2020.0994

[44] Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England), 395 (10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

[45] Morrondo, C. D., Zarza, L. P., Gil, J. G., Pinto Tasende, J. A., Diez, P. D., & López, J. M. (2016). Benefit of Tocilizumab Therapy for Adult-Onset Still Disease Complicated With Acute Respiratory Distress Syndrome. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases, 22(5), 291–293. https://doi.org/10.1097/RHU.0000000000000374

[46] Shakoory, B., Carcillo, J. A., Chatham, W. W., Amdur, R. L., Zhao, H., Dinarello, C. A., Cron, R. Q., & Opal, S. M. (2016). Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical care medicine, 44(2), 275–281. https://doi.org/10.1097/CCM.0000000000001402

[47] Neuenschwander, B., Capkun-Niggli, G., Branson, M., & Spiegelhalter, D. J. (2010). Summarizing historical information on controls in clinical trials. Clinical trials (London, England), 7(1), 5–18. https://doi.org/10.1177/1740774509356002

[48] Jones, G., Sebba, A., Gu, J., Lowenstein, M. B., Calvo, A., Gomez-Reino, J. J., Siri, D. A., Tomsic, M., Alecock, E., Woodworth, T., & Genovese, M. C. (2010). Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Annals of the rheumatic diseases, 69(1), 88–96. https://doi.org/10.1136/ard.2008.105197

[49] Stone, J. H., Tuckwell, K., Dimonaco, S., Klearman, M., Aringer, M., Blockmans, D., Brouwer, E., Cid, M. C., Dasgupta, B., Rech, J., Salvarani, C., Schett, G., Schulze-Koops, H., Spiera, R., Unizony, S. H., & Collinson, N. (2017). Trial of Tocilizumab in Giant-Cell Arteritis. The New England journal of medicine, 377(4), 317–328. https://doi.org/10.1056/NEJMoa1613849

[50] Villiger, P. M., Adler, S., Kuchen, S., Wermelinger, F., Dan, D., Fiege, V., Bütikofer, L., Seitz, M., & Reichenbach, S. (2016). Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet (London, England), 387(10031), 1921–1927. https://doi.org/10.1016/S0140-6736(16)00560-2

[51] Yang, S., Cao, P., Du, P., Wu, Z., Zhuang, Z., Yang, L., Yu, X., Zhou, Q., Feng, X., Wang, X., Li, W., Liu, E., Chen, J., Chen, Y., & He, D. (2020). Early estimation of the case fatality rate of COVID-19 in mainland China: a data-driven analysis. Annals of translational medicine, 8(4), 128. https://doi.org/10.21037/atm.2020.02.66

[52] Khanna, D., Denton, C. P., Jahreis, A., van Laar, J. M., Frech, T. M., Anderson, M. E., Baron, M., Chung, L., Fierbeck, G., Lakshminarayanan, S., Allanore, Y., Pope, J. E., Riemekasten, 31
G., Steen, V., Müller-Ladner, U., Lafyatis, R., Stifano, G., Spotswood, H., Chen-Harris, H., Dziadek, S., ... Furst, D. E. (2016). Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet (London, England), 387(10038), 2630–2640. https://doi.org/10.1016/S0140-6736(16)00232-4

[53] Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine, 46(5), 846–848. https://doi.org/10.1007/s00134-020-05991-x

[54] Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet. Respiratory medicine, 8(5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

[55] Hays, P., Costello, C., & Asudani, D. (2019). Clinical care of chimeric antigen receptor T-cell patients and managing immune-related adverse effects in the ambulatory and hospitalized setting: a review. Future oncology (London, England), 15(36), 4235–4246. https://doi.org/10.2217/fon-2019-0467

[56] Hunter, C. A., & Jones, S. A. (2015). IL-6 as a keystone cytokine in health and disease. Nature immunology, 16(5), 448–457. https://doi.org/10.1038/ni.3153

[57] Pathan, N., Hemingway, C. A., Alizadeh, A. A., Stephens, A. C., Boldrick, J. C., Oragu, E. E., McCabe, C., Welch, S. B., Whitney, A., O’Gara, P., Nadel, S., Relman, D. A., Harding, S. E., & Levin, M. (2004). Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet (London, England), 363(9404), 203–209. https://doi.org/10.1016/S0140-6736(03)15326-3

[58] Salehi, S., Abedi, A., Balakrishnan, S., & Gholamrezanazhad, A. (2020). Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. AJR. American journal of roentgenology, 215(1), 87–93. https://doi.org/10.2214/AJR.20.23034

[59] Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M., Stemmler, H. J., Schloëßer, H. A., Schlaak, M., Kochanek, M., Böll, B., & von Bergwalt-Baldion, M. S. (2018). Cytokine release syndrome. Journal for immunotherapy of cancer, 6(1), 56. https://doi.org/10.1186/s40425-018-0343-9

[60] van der Stegen, S. J., Davies, D. M., Wilkie, S., Foster, J., Sosabowski, J. K., Burnet, J., Whilding, L. M., Petrovic, R. M., Ghaem-Maghami, S., Mather, S., Jeannot, J. P., Parente-Pereira, A. C., & Maher, J. (2013). Preclinical in vivo modeling of cytokine release syndrome induced by ErbB-retargeted human T cells: identifying a window of therapeutic opportunity?. Journal of immunology (Baltimore, Md.: 1950), 191(9), 4589–4598. https://doi.org/10.4049/jimmunol.1301523

[61] Winkler, U., Jensen, M., Manzke, O., Schulz, H., Diehl, V., & Engert, A. (1999). Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood, 94(7), 2217–2224.

[62] Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet. Respiratory medicine, 8(4),
A Clinical Update on Employing Tocilizumab to Fight COVID-19
DOI: http://dx.doi.org/10.5772/intechopen.99785

420–422. https://doi.org/10.1016/S2213-2600(20)30076-X

[63] Salama, C., Han, J., Yau, L., Reiss, W. G., Kramer, B., Neidhart, J. D., Criner, G. J., Kaplan-Lewis, E., Baden, R., Pandit, L., Cameron, M. L., Garcia-Diaz, J., Chávez, V., Mekebeb-Reuter, M., Lima de Menezes, F., Shah, R., González-Lara, M. F., Asman, B., Freedman, J., & Mohan, S. V. (2021). Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. The New England journal of medicine, 384(1), 20–30. https://doi.org/10.1056/NEJMoa2030340

[64] Veiga, V. C., Prats, J., Farias, D., Rosa, R. G., Dourado, L. K., Zampieri, F. G., Machado, F. R., Lopes, R. D., Berwanger, O., Azevedo, L., Avezum, Á., Lisboa, T. C., Rojas, S., Coelho, J. C., Leite, R. T., Carvalho, J. C., Andrade, L., Sandes, A. F., Pintão, M., Castro, C. G., Jr, ... Coalition covid-19 Brazil VI Investigators (2021). Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ (Clinical research ed.), 372, n84. https://doi.org/10.1136/bmj.n84

[65] Maes, B., Bosteels, C., De Leeuw, E., Declercq, J., Van Damme, K., Delporte, A., Demeyer, B., Vermeersch, S., Vuylstke, M., Willaert, J., Bollé, L., Vanbiervliet, Y., Decuyper, J., Libeer, F., Vandecasteele, S., Peene, I., & Lambrecht, B. (2020). Treatment of severely ill COVID-19 patients with anti-interleukin drugs (COV-AID): A structured summary of a study protocol for a randomised controlled trial. Trials, 21(1), 468. https://doi.org/10.1186/s13063-020-04453-5

[66] Hermine, O., Mariette, X., Tharaux, P. L., Resche-Rigon, M., Porcher, R., Ravaud, P., & CORIMUNO-19 Collaborative Group (2021). Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA internal medicine, 181(1), 32–40. https://doi.org/10.1001/jamainternmed.2020.6820

[67] Knaup, H., Stahl, K., Schmidt, B., Idowu, T. O., Busch, M., Wiesner, O., Welte, T., Haller, H., Kielstein, J. T., Hoepner, M. M., & David, S. (2018). Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers. Critical care (London, England), 22(1), 285. https://doi.org/10.1186/s13054-018-2220-9

[68] Keith, P., Day, M., Perkins, L., Moyer, L., Hewitt, K., & Wells, A. (2020). A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Critical care (London, England), 24(1), 128. https://doi.org/10.1186/s13054-020-2836-4

[69] Shi, H., Zhou, C., He, P., Huang, S., Duan, Y., Wang, X., Lin, K., Zhou, C., Zhang, X., & Zha, Y. (2020). Successful treatment with plasma exchange followed by intravenous immunoglobulin in a critically ill patient with COVID-19. International journal of antimicrobial agents, 56(2), 105974. https://doi.org/10.1016/j.ijantimicag.2020.105974

[70] Chen, L., Xiong, J., Bao, L., & Shi, Y. (2020). Convalescent plasma as a potential therapy for COVID-19. The Lancet. Infectious diseases, 20(4), 398–400. https://doi.org/10.1016/S1473-3099(20)30141-9

[71] Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., & Wei, H. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences of the United States of America, 117(20),
10970–10975. https://doi.org/10.1073/pnas.2005615117

[72] Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T. F., Parees, R., Sweeney, D. A., Short, W. R., Touloumi, G., ... ACTT-1 Study Group Members (2020). Remdesivir for the Treatment of Covid-19 - Final Report. The New England journal of medicine, 383(19), 1813–1826. https://doi.org/10.1056/NEJMoa2007764

[73] Leng, Z., Zhu, R., Hou, W., Feng, Y., Yang, Y., Han, Q., Shan, G., Meng, F., Du, D., Wang, S., Fan, J., Wang, W., Deng, L., Shi, H., Li, H., Hu, Z., Zhang, F., Gao, J., Liu, H., Li, X., ... Zhao, R. C. (2020). Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging and disease, 11(2), 216–228. https://doi.org/10.14336/AD.2020.0228

[74] Alzghari, S. K., & Acuña, V. S. (2020). Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology, 127, 104380. https://doi.org/10.1016/j.jcv.2020.104380

[75] Tian, S., Hu, W., Niu, L., Liu, H., Xu, H., & Xiao, S. Y. (2020). Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer, 15(5), 700–704. https://doi.org/10.1016/j.jtho.2020.02.010

[76] Ashour, H. M., Elkhatab, W. F., Rahman, M. M., & Elshabrawy, H. A. (2020). Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. Pathogens (Basel, Switzerland), 9(3), 186. https://doi.org/10.3390/pathogens9030186

[77] Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Seminars in immunopathology, 39(5), 529–539. https://doi.org/10.1007/s00281-017-0629-x

[78] Zumla, A., Ippolito, G., Ntoumi, F., Seyfert-Margolies, V., Nagu, T. J., Cirillo, D., Chakaya, J. M., Marais, B., & Mauerer, M. (2020). Host-directed therapies and holistic care for tuberculosis. The Lancet. Respiratory medicine, 8(4), 337–340. https://doi.org/10.1016/S2213-2600(20)30078-3

[79] Sabbatinielli, J., Giuliani, A., Matarcione, G., Latini, S., Laprovitera, N., Pomponio, G., Ferrarini, A., Svegliati Baroni, S., Pavani, M., Moretti, M., Gabrielli, A., Procopio, A. D., Ferracin, M., Bonafé, M., & Olivieri, F. (2021). Decreased serum levels of the inflamming marker miR-146a are associated with clinical non-response to tocilizumab in COVID-19 patients. Mechanisms of ageing and development, 193, 111413. https://doi.org/10.1016/j.mad.2020.111413

[80] Wichmann, D., Sperhake, J. P., Lütgehetmann, M., Steurer, S., Edler, C., Heinemann, A., Heinrich, F., Mushumba, H., Kniep, I., Schröder, A. S., Burdelski, C., de Heer, G., Nierhaus, A., Frings, D., Pfefferle, S., Becker, H., Brederkke-Wiedling, H., de Weerth, A., Paschen, H. R., Sheikhzadeh-Eggers, S., ... Kluge, S. (2020). Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Annals of internal medicine, 173(4), 268–277. https://doi.org/10.7326/M20-2003

[81] Ramos-Casals, M., Brito-Zerón, P., López-Guillermo, A., Khamashta, M. A., & Bosch, X. (2014). Adult
haemophagocytic syndrome. Lancet (London, England), 383(9927), 1503–1516. https://doi.org/10.1016/S0140-6736(13)61048-X

[82] Radbel, J., Narayanan, N., & Bhatt, P. J. (2020). Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome: A Cautionary Case Report. Chest, 158(1), e15–e19. https://doi.org/10.1016/j.chest.2020.04.024

[83] Liu, B., Li, M., Zhou, Z., Guan, X., & Xiang, Y. (2020). Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? Journal of autoimmunity, 111, 102452. https://doi.org/10.1016/j.jaut.2020.102452

[84] Hui, D. S., I Azhar, E., Madani, T. A., Ntoumi, F., Kock, R., Dar, O., Ippolito, G., Mchugh, T. D., Memish, Z. A., Drosten, C., Zumla, A., & Petersen, E. (2020). The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases, 91, 264–266. https://doi.org/10.1016/j.ijid.2020.01.009

[85] Paules, C. I., Marston, H. D., & Fauci, A. S. (2020). Coronavirus Infections-More Than Just the Common Cold. JAMA, 323(8), 707–708. https://doi.org/10.1001/jama.2020.0757

[86] Hu, X., Deng, Y., Wang, J., Li, H., Li, M., & Lu, Z. (2004). Short term outcome and risk factors for mortality in adults with critical severe acute respiratory syndrome (SARS). Journal of Huazhong University of Science and Technology. Medical sciences = Huazhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban, 24(5), 514–517. https://doi.org/10.1007/BF02831124

[87] Schmitt, J., Boutonnet, M., Goutorbe, P., Raynaud, L., Carfantan, C., Luft, A., Pasquier, P., Meaudre, E., & Bordes, J. (2020). Acute respiratory distress syndrome in the forward environment. Retrospective analysis of acute respiratory distress syndrome cases among French Army war casualties. The journal of trauma and acute care surgery, 89(2 Suppl 2), S207–S212. https://doi.org/10.1097/TA.0000000000002633

[88] Ferguson, N. D., Fan, E., Camporota, L., Antonelli, M., Anzueto, A., Beale, R., Brochard, L., Brower, R., Esteban, A.,Gattinoni, L., Rhodes, A., Slutsky, A. S., Vincent, J. L., Rubenfeld, G. D., Thompson, B. T., & Ranieri, V. M. (2012). The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive care medicine, 38(10), 1573–1582. https://doi.org/10.1007/s00134-012-2682-1

[89] Bhattraju, P. K., Ghassemieh, B. J., Nichols, M., Kim, R., Jerome, K. R., Nalla, A. K., Greninger, A. L., Pipavath, S., Wurfel, M. M., Evans, L., Kritek, P. A., West, T. E., Luks, A., Gerbino, A., Dale, C. R., Goldman, J. D., O’Mahony, S., & Mikacenic, C. (2020). Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. The New England journal of medicine, 382(21), 2012–2022. https://doi.org/10.1056/NEJMoa2004500

[90] Wu, Z., & McGoogan, J. M. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA, 323(13), 1239–1242. https://doi.org/10.1001/jama.2020.2648

[91] Wang, W., Tang, J., & Wei, F. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. Journal
of medical virology, 92(4), 441–447. https://doi.org/10.1002/jmv.25689

[92] Benjamin, D. K., Jr, Smith, P. B., Murphy, M. D., Roberts, R., Mathis, L., Avant, D., Califf, R. M., & Li, J. S. (2006). Peer-reviewed publication of clinical trials completed for pediatric exclusivity. JAMA, 296(10), 1266–1273. https://doi.org/10.1001/jama.296.10.1266

[93] Phan, H., Leder, M., Fishley, M., Moeller, M., & Nahata, M. (2010). Off-label and unlicensed medication use and associated adverse drug events in a pediatric emergency department. Pediatric emergency care, 26(6), 424–430. https://doi.org/10.1097/PEC.0b013e3181e057e1

[94] Long, D., Koren, G., & James, A. (1987). Ethics of drug studies in infants: how many samples are required for accurate estimation of pharmacokinetic parameters in neonates? The Journal of pediatrics, 111(6 Pt 1), 918–921. https://doi.org/10.1016/s0022-3476(87)80219-6

[95] European Union. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. (2008). European journal of health law, 15(2), 223–250. https://doi.org/10.1163/157180908x333228

[96] Wade, K. C., Wu, D., Kaufman, D. A., Ward, R. M., Benjamin, D. K., Jr, Sullivan, J. E., Ramey, N., Jayaraman, B., Hoppu, K., Adamson, P. C., Gastonguay, M. R., Barrett, J. S., & National Institute of Child Health and Development Pediatric Pharmacology Research Unit Network (2008). Population pharmacokinetics of fluconazole in young infants. Antimicrobial agents and chemotherapy, 52(11), 4043–4049. https://doi.org/10.1128/AAC.00569-08

[97] de Hoog, M., Schoemaker, R. C., Mouton, J. W., & van den Anker, J. N. (2000). Vancomycin population pharmacokinetics in neonates. Clinical pharmacology and therapeutics, 67(4), 360–367. https://doi.org/10.1067/mcp.2000.105353

[98] García, B., Barcia, E., Pérez, F., & Molina, I. T. (2006). Population pharmacokinetics of gentamicin in premature newborns. The Journal of antimicrobial chemotherapy, 58(2), 372–379. https://doi.org/10.1093/jac/dkl244

[99] Capparelli, E., Hochwald, C., Rasmussen, M., Parham, A., Bradley, J., & Moya, F. (2005). Population pharmacokinetics of cefepime in the neonate. Antimicrobial agents and chemotherapy, 49(7), 2760–2766. https://doi.org/10.1128/AAC.49.7.2760-2766.2005

[100] Pullen, J., Stolk, L. M., Nieman, F. H., Degraeuwe, P. L., van Tiel, F. H., & Zimmermann, L. J. (2006). Population pharmacokinetics and dosing of amoxicillin in (pre)term neonates. Therapeutic drug monitoring, 28(2), 226–231. https://doi.org/10.1097/01.ftd.0000198648.39751.11

[101] Tremoulet, A., Le, J., Poindexter, B., Sullivan, J. E., Laugthon, M., Delmore, P., Salgado, A., Ian-U Chong, S., Melloni, C., Gao, J., Benjamin, D. K., Jr, Capparelli, E. V., Cohen-Wolkowiez, M., & Administrative Core Committee of the Best Pharmaceuticals for Children Act-Pediatric Trials Network (2014). Characterization of the population pharmacokinetics of ampicillin in neonates using an opportunistic study design. Antimicrobial agents and chemotherapy, 58(6), 3013–3020. https://doi.org/10.1128/AAC.02374-13

[102] Hornik, C. P., Benjamin, D. K., Jr, Smith, P. B., Pencina, M. J., Tremoulet, A. H., Capparelli, E. V., Ericson, J. E., Clark, R. H., Cohen-Wolkowiez, M., & Best Pharmaceuticals for Children Act—Pediatric Trials Network (2016).
Electronic Health Records and Pharmacokinetic Modeling to Assess the Relationship between Ampicillin Exposure and Seizure Risk in Neonates. The Journal of Pediatrics, 178, 125–129. e1. https://doi.org/10.1016/j.jpeds.2016.07.011

[103] Le, J., Poindexter, B., Sullivan, J. E., Laughon, M., Delmore, P., Blackford, M., Yogev, R., James, L. P., Melloni, C., Harper, B., Mitchell, J., Benjamin, D. K., Jr, Boakye-Agyeman, F., & Cohen-Wolkowiez, M. (2018). Comparative Analysis of Ampicillin Plasma and Dried Blood Spot Pharmacokinetics in Neonates. Therapeutic drug monitoring, 40(1), 103–108. https://doi.org/10.1097/FTD.0000000000000466

[104] Gonzalez, D., Melloni, C., Yogev, R., Poindexter, B. B., Mendley, S. R., Delmore, P., Sullivan, J. E., Autmizguine, J., Lewandowski, A., Harper, B., Watt, K. M., Lewis, K. C., Capparelli, E. V., Benjamin, D. K., Jr, Cohen-Wolkowiez, M., & Best Pharmaceuticals for Children Act–Pediatric Trials Network Administrative Core Committee (2014). Use of opportunistic clinical data and a population pharmacokinetic model to support dosing of clindamycin for premature infants to adolescents. Clinical pharmacology and therapeutics, 96(4), 429–437. https://doi.org/10.1002/cpt.2014.134

[105] Gonzalez, D., Delmore, P., Bloom, B. T., Cotten, C. M., Poindexter, B. B., McGowan, E., Shattuck, K., Bradford, K. K., Smith, P. B., Cohen-Wolkowiez, M., Morris, M., Yin, W., Benjamin, D. K., Jr, & Laughon, M. M. (2016). Clindamycin Pharmacokinetics and Safety in Preterm and Term Infants. Antimicrobial agents and chemotherapy, 60(5), 2888–2894. https://doi.org/10.1128/AAC.03086-15

[106] Gonzalez, D., Melloni, C., Poindexter, B. B., Yogev, R., Atz, A. M., Sullivan, J. E., Mendley, S. R., Delmore, P., Delinsky, A., Zimmerman, K., Lewandowski, A., Harper, B., Lewis, K. C., Benjamin, D. K., Jr, Cohen-Wolkowiez, M., & Best Pharmaceuticals for Children Act–Pediatric Trials Network Administrative Core Committee (2015). Simultaneous determination of trimethoprim and sulfamethoxazole in dried plasma and urine spots. Bioanalysis, 7(9), 1137–1149. https://doi.org/10.4155/bio.15.38

[107] Autmizguine, J., Melloni, C., Hornik, C. P., Dallefeld, S., Harper, B., Yogev, R., Sullivan, J. E., Atz, A. M., Al-Uzri, A., Mendley, S. R., Poindexter, B., Mitchell, J., Lewandowski, A., Delmore, P., Cohen-Wolkowiez, M., Gonzalez, D., & the Pediatric Trials Network Steering Committee (2017). Population Pharmacokinetics of Trimethoprim-Sulfamethoxazole in Infants and Children. Antimicrobial agents and chemotherapy, 62(1), e01813-17. https://doi.org/10.1128/AAC.01813-17

[108] Dallefeld, S. H., Atz, A. M., Yogev, R., Sullivan, J. E., Al-Uzri, A., Mendley, S. R., Laughon, M., Hornik, C. P., Melloni, C., Harper, B., Lewandowski, A., Mitchell, J., Wu, H., Green, T. P., & Cohen-Wolkowiez, M. (2018). A pharmacokinetic model for amiodarone in infants developed from an opportunistic sampling trial and published literature data. Journal of pharmacokinetics and pharmacodynamics, 45(3), 419–430. https://doi.org/10.1007/s10928-018-9576-y

[109] Hornik, C. P., Gonzalez, D., van den Anker, J., Atz, A. M., Yogev, R., Poindexter, B. B., Ng, K. C., Delmore, P., Harper, B. L., Melloni, C., Lewandowski, A., Gelber, C., Cohen-Wolkowiez, M., Lee, J. H., & Pediatric Trial Network Steering Committee (2018). Population Pharmacokinetics of Intramuscular and Intravenous Ketamine in Children. Journal of clinical pharmacology, 58(8), 1092–1104. https://doi.org/10.1002/jcph.1116
[110] Drolet, B. A., Boakye-Agyeman, F., Harper, B., Holland, K., Lewandowski, A., Stefanko, N., Melloni, C., & Pediatric Trials Network Steering Committee (See Acknowledgments for a listing of committee members.) (2020). Systemic timolol exposure following topical application to infantile hemangiomas. Journal of the American Academy of Dermatology, 82(3), 733–736. https://doi.org/10.1016/j.jaad.2019.02.029

[111] Hornik, C. P., Yogev, R., Mourani, P. M., Watt, K. M., Sullivan, J. E., Atz, A. M., Speicher, D., Al-Uzri, A., Adudarko, M., Payne, E. H., Gelber, C. E., Lin, S., Harper, B., Melloni, C., Cohen-Wolkowiez, M., Gonzalez, D., & Best Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee (2019). Population Pharmacokinetics of Milrinone in Infants, Children, and Adolescents. Journal of clinical pharmacology, 59(12), 1606–1619. https://doi.org/10.1002/jcph.1499

[112] Cohen-Wolkowiez, M., Ouellet, D., Smith, P. B., James, L. P., Ross, A., Sullivan, J. E., Walsh, M. C., Zadell, A., Newman, N., White, N. R., Kashuba, A. D., & Benjamin, D. K., Jr (2012). Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. Antimicrobial agents and chemotherapy, 56(4), 1828–1837. https://doi.org/10.1128/AAC.06071-11

[113] Cohen-Wolkowiez, M., Benjamin, D. K., Jr, Ross, A., James, L. P., Sullivan, J. E., Walsh, M. C., Zadell, A., Newman, N., White, N. R., Kashuba, A. D., & Ouellet, D. (2012). Population pharmacokinetics of piperacillin using scavenged samples from preterm infants. Therapeutic drug monitoring, 34(3), 312–319. https://doi.org/10.1097/FTD.0b013e3182587665

[114] Biomarkers Definitions Working Group. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical pharmacology and therapeutics, 69(3), 89–95. https://doi.org/10.1067/mcp.2001.113989

[115] Kearns, G. L., & Artman, M. (2015). Functional Biomarkers: an Approach to Bridge Pharmacokinetics and Pharmacodynamics in Pediatric Clinical Trials. Current pharmaceutical design, 21(39), 5636–5642. https://doi.org/10.2174/138161282166615091105337

[116] Husain, A., Loehle, J. A., & Hein, D. W. (2007). Clinical pharmacogenetics in pediatric patients. Pharmacogenomics, 8(10), 1403–1411. https://doi.org/10.2217/14622416.8.10.1403

[117] Zheng, H., Webber, S., Zeevi, A., Schuetz, E., Zhang, J., Lamba, J., Bowman, P., & Burckart, G. J. (2002). The MDR1 polymorphisms at exons 21 and 26 predict steroid weaning in pediatric heart transplant patients. Human immunology, 63(9), 765–770. https://doi.org/10.1016/s0198-8859(02)00426-3

[118] Watson, R. S., Crow, S. S., Hartman, E. M., Lacroix, J., & Odetola, F. O. (2017). Epidemiology and Outcomes of Pediatric Multiple Organ Dysfunction Syndrome. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 18(3_suppl Suppl 1), S4–S16. https://doi.org/10.1097/PCC.0000000000001047

[119] Typpo, K. V., Petersen, N. J., Hallman, D. M., Markovitz, B. P., & Mariscalco, M. M. (2009). Day 1 multiple organ dysfunction syndrome is associated with poor functional outcome and mortality in the pediatric intensive care unit. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 10(5), 562–570.
[10] Wang, L., McGregor, T. L., Jones, D. P., Bridges, B. C., Fleming, G. M., Shirey-Rice, J., McLemore, M. F., Chen, L., Weitkamp, A., Byrne, D. W., & Van Driest, S. L. (2017). Electronic health record-based predictive models for acute kidney injury screening in pediatric inpatients. Pediatric research, 82(3), 465–473. https://doi.org/10.1038/pr.2017.116

[11] Kaddourah, A., Basu, R. K., Bagshaw, S. M., Goldstein, S. L., & AWARE Investigators (2017). Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. The New England journal of medicine, 376(1), 11–20. https://doi.org/10.1056/NEJMoa1611391

[12] Ricci, Z., & Goldstein, S. L. (2016). Pediatric Continuous Renal Replacement Therapy. Contributions to nephrology, 187, 121–130. https://doi.org/10.1159/000442370

[13] Hayes, L. W., Oster, R. A., Tofil, N. M., & Tolwani, A. J. (2009). Outcomes of critically ill children requiring continuous renal replacement therapy. Journal of critical care, 24(3), 394–400. https://doi.org/10.1016/j.jcrc.2008.12.017

[14] Nolin, T. D., Aronoff, G. R., Fissell, W. H., Jain, L., Madabushi, R., Reynolds, K., Zhang, L., Huang, S. M., Mehrrota, R., Flessner, M. F., Leypoeldt, J. K., Witcher, J. W., Zineh, I., Archdeacon, P., Roy-Chaudhury, P., Goldstein, S. L., & Kidney Health Initiative (2015). Pharmacokinetic assessment in patients receiving continuous RRT: perspectives from the Kidney Health Initiative. Clinical journal of the American Society of Nephrology: CJASN, 10(1), 159–164. https://doi.org/10.2215/CJN.05630614

[15] Buck M. L. (2003). Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. Clinical pharmacokinetics, 42(5), 403–417. https://doi.org/10.2165/00003088-200342050-00001

[16] Watt, K., Li, J. S., Benjamin, D. K., Jr, & Cohen-Wolkowiez, M. (2011). Pediatric cardiovascular drug dosing in critically ill children and extracorporeal membrane oxygenation. Journal of cardiovascular pharmacology, 58(2), 126–132. https://doi.org/10.1097/FJC.0b013e318213aac2

[17] Goldstein, S. L., & Nolin, T. D. (2014). Lack of drug dosing guidelines for critically ill patients receiving continuous renal replacement therapy. Clinical pharmacology and therapeutics, 96(2), 159–161. https://doi.org/10.1038/clpt.2014.102

[18] Lewis, S. J., & Mueller, B. A. (2014). Antibiotic dosing in critically ill patients receiving CRRT: underdosing is overprevalent. Seminars in dialysis, 27(5), 441–445. https://doi.org/10.1111/sdi.12203

[19] Centers for Disease Control and Prevention (CDC) (2006). Improved national prevalence estimates for 18 selected major birth defects—United States, 1999-2001. MMWR. Morbidity and mortality weekly report, 54(51), 1301–1305.

[20] Pritchard, M., Reeves, R. H., Dierssen, M., Patterson, D., & Gardiner, K. J. (2008). Down syndrome and the genes of human chromosome 21: current knowledge and future potentials. Report on the Expert workshop on the biology of chromosome 21 genes: towards gene-phenotype correlations in Down syndrome. Washington D.C., September 28-October 1, 2007. Cytogenetic and genome research, 121(1), 67–77. https://doi.org/10.1159/000124384

[21] Padmakumar, B., Evans Jones, L. G., & Sills, J. A. (2002). Is arthritis more common in children with Down syndrome?. Rheumatology (Oxford,
Garré, M. L., Relling, M. V., Kalwinsky, D., Dodge, R., Crom, W. R., Abromowitch, M., Pui, C. H., & Evans, W. E. (1987). Pharmacokinetics and toxicity of methotrexate in children with Down syndrome and acute lymphocytic leukemia. The Journal of pediatrics, 111(4), 606–612. https://doi.org/10.1016/s0022-3476(87)80131-2

Peeters, M. A., Rethore, M. O., & Lejeune, J. (1995). In vivo folic acid supplementation partially corrects in vitro methotrexate toxicity in patients with Down syndrome. British journal of haematology, 89(3), 678–680. https://doi.org/10.1111/j.1365-2141.1995.tb08390.x

Jones, J. T., Talib, N., Lovell, D., & Becker, M. L. (2019). Clinical Features and Treatment of Down Syndrome Arthropathy: Experience from Two US Tertiary Hospitals. Paediatric drugs, 21(1), 33–39. https://doi.org/10.1007/s40272-018-0322-0

Foley, C. M., Deely, D. A., MacDermott, E. J., & Killeen, O. G. (2019). Arthropathy of Down syndrome: an under-diagnosed inflammatory joint disease that warrants a name change. RMD open, 5(1), e000890. https://doi.org/10.1136/rmdopen-2018-000890

Blatt, J., Albo, V., Prin, W., Orlando, S., & Wollman, M. (1986). Excessive chemotherapy-related myelotoxicity in children with Down syndrome and acute lymphoblastic leukaemia. Lancet (London, England), 2(8512), 914. https://doi.org/10.1016/s0140-6736(86)90429-0

Taub, J. W., & Ge, Y. (2005). Down syndrome, drug metabolism and chromosome 21. Pediatric blood & cancer, 44(1), 33–39. https://doi.org/10.1002/pbc.20092

Uffmann, M., Rasche, M., Zimmermann, M., von Neuhoff, C., Creutzig, U., Dworzak, M., Scheffers, L., Hasle, H., Zwaan, C. M., Reinhardt, D., & Klusmann, J. H. (2017). Therapy reduction in patients with Down syndrome and myeloid leukemia: the international ML-DS 2006 trial. Blood, 129(25), 3314–3321. https://doi.org/10.1182/blood-2017-01-765057

Taub, J. W., Huang, X., Matherly, L. H., Stout, M. L., Buck, S. A., Massey, G. V., Becton, D. L., Chang, M. N., Weinstein, H. J., & Ravindranath, Y. (1999). Expression of chromosome 21-localized genes in acute myeloid leukemia: differences between Down syndrome and non-Down syndrome blast cells and relationship to in vitro sensitivity to cytosine arabinoside and daunorubicin. Blood, 94(4), 1393–1400.

Ogden, C. L., Carroll, M. D., Curtin, L. R., McDowell, M. A., Tabak, C. J., & Flegal, K. M. (2006). Prevalence of overweight and obesity in the United States, 1999-2004. JAMA, 295(13), 1549–1555. https://doi.org/10.1001/jama.295.13.1549

Sherwin, J., Heath, T., & Watt, K. (2016). Pharmacokinetics and Dosing of Anti-infective Drugs in Patients on Extracorporeal Membrane Oxygenation: A Review of the Current Literature. Clinical therapeutics, 38(9), 1976–1994. https://doi.org/10.1016/j.clinthera.2016.07.169

Srinivasan, V., Nadkarni, V. M., Helfaer, M. A., Carey, S. M., Berg, R. A., & American Heart Association National Registry of Cardiopulmonary Resuscitation Investigators (2010). Childhood obesity and survival after in-hospital pediatric cardiopulmonary resuscitation. Pediatrics, 125(3), e481–e488. https://doi.org/10.1542/peds.2009-1324
[143] Salvarani, C., Dolci, G., Massari, M., Merlo, D. F., Cavuto, S., Savoldi, L., Bruzzi, P., Boni, F., Braglia, L., Turrà, C., Ballerini, P. F., Sciascia, R., Zammarchi, L., Para, O., Scotton, P. G., Inojosa, W. O., Ravagnani, V., Salerno, N. D., Sainaghi, P. P., Brignone, A., ... RCT-TCZ-COVID-19 Study Group (2021). Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA internal medicine, 181(1), 24–31. https://doi.org/10.1001/jamainternmed.2020.6615

[144] Walkey, A. J., Kumar, V. K., Harhay, M. O., Boleta, S., Bansal, V., Gajic, O., & Kashyap, R. (2020). The Viral Infection and Respiratory Illness Universal Study (VIRUS): An International Registry of Coronavirus 2019-Related Critical Illness. Critical care explorations, 2(4), e0113. https://doi.org/10.1097/CCE.0000000000000113

[145] Kalil, A. C., Patterson, T. F., Mehta, A. K., Tomashek, K. M., Wolfe, C. R., Ghazaryan, V., Marconi, V. C., Ruiz-Palacios, G. M., Hsieh, L., Kline, S., Tapson, V., Iovine, N. M., Jain, M. K., Sweeney, D. A., El Sahly, H. M., Branche, A. R., Regalado Pineda, J., Lye, D. C., Sandkovsky, U., Luetkemeyer, A. F., ... ACTT-2 Study Group Members (2021). Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. The New England journal of medicine, 384(9), 795–807. https://doi.org/10.1056/NEJMoa2031994

[146] Azzi, Y., Bartash, R., Scalea, J., Loarte-Campos, F., & Akalin, E. (2021). COVID-19 and Solid Organ Transplantation: A Review Article. Transplantation, 105(1), 37–55. https://doi.org/10.1097/TP.0000000000003523

[147] Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, Patel N, Hagino O; Sarilumab COVID-19 Global Study Group. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021 May;9(5):522-532. doi: 10.1016/S2213-2600(21)00099-0.

[148] Salama, C., & Mohan, S. V. (2021). Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. Reply. The New England journal of medicine, 384(15), 1473–1474. https://doi.org/10.1056/NEJMc2100217

[149] Guaraldi, G., Meschiari, M., Cozzi-Lepri, A., Milic, J., Tonelli, R., Menozzi, M., Franceschini, E., Cuomo, G., Orlando, G., Borghi, V., Santoro, A., Di Gaetano, M., Puzzolante, C., Carli, F., Bedini, A., Corradi, L., Fantini, R., Castaniere, I., Tabbi, L., Girardis, M., ... Mussini, C. (2020). Tocilizumab in patients with severe COVID-19: a retrospective cohort study. The Lancet. Rheumatology, 2(8), e474–e484. https://doi.org/10.1016/S2665-9913(20)30173-9

[150] Tsai, A., Diawara, O., Nahass, R. G., & Brunetti, L. (2020). Impact of tocilizumab administration on mortality in severe COVID-19. Scientific reports, 10(1), 19131. https://doi.org/10.1038/s41598-020-76187-y

[151] Fu, B., Xu, X., & Wei, H. (2020). Why tocilizumab could be an effective treatment for severe COVID-19?. Journal of translational medicine, 18(1), 164. https://doi.org/10.1186/s12967-020-02339-3

[152] Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., & Wei, H. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences of the United States of America, 117(20), 10970–10975. https://doi.org/10.1073/pnas.2005615117
[153] Dong, E., Du, H., & Gardner, L. (2020). An interactive web-based dashboard to track COVID-19 in real time. The Lancet. Infectious diseases, 20(5), 533–534. https://doi.org/10.1016/S1473-3099(20)30120-1

[154] Parr J. B. (2021). Time to Reassess Tocilizumab’s Role in COVID-19 Pneumonia. JAMA internal medicine, 181(1), 12–15. https://doi.org/10.1001/jama.2020.6557

[155] Gupta, S., & Leaf, D. E. (2021). Tocilizumab in COVID-19: some clarity amid controversy. Lancet (London, England), 397(10285), 1599–1601. https://doi.org/10.1016/S0140-6736(21)00712-1

[156] Mariette, X., Hermine, O., Tharaux, P. L., Resche-Rigon, M., Steg, P. G., Porcher, R., & Ravaud, P. (2021). Effectiveness of Tocilizumab in Patients Hospitalized With COVID-19: A Follow-up of the CORIMUNO-TOCI-1 Randomized Clinical Trial. JAMA internal medicine, e212209. Advance online publication. https://doi.org/10.1001/jama.2021.2209

[157] Rosas, I. O., Bräu, N., Waters, M., Go, R. C., Hunter, B. D., Bhagani, S., Skiest, D., Aziz, M. S., Cooper, N., Douglas, I. S., Savic, S., Youngstein, T., Del Sorbo, L., Cubillo Gracian, A., De La Zerda, D. J., Ustianowski, A., Bao, M., Dimonaco, S., Graham, E., Matharu, B., ... Malhotra, A. (2021). Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. The New England journal of medicine, 384(16), 1503–1516. https://doi.org/10.1056/NEJMo2028700