A Study on the Role of Pharmacovigilance and Benefit-Risk Assessment of the drug Tocilizumab used in COVID-19 patients

*Masheer A. Khan, Aakash Jain, Purva Pandya, Riddhi Bokil, Udita Shiromani, and Vartika Saxena

*Corresponding Author, School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore, India

ABSTRACT

Background: The aim of our project is to "study the role of Pharmacovigilance and Benefit-Risk assessment of the drug tocilizumab used in COVID-19 patients". The purpose of the survey is to check the awareness of pharmacovigilance, ADR, and its reporting among medical professionals during an emergency use of the medication, tocilizumab in COVID-19 as they were the ones prescribing and administering the drug and had maximum information regarding the dose, regimen, and side effects of it.

Result: A questionnaire consisting of 20 questions was formulated including questions corresponding to basic awareness of Pharmacovigilance, suspected ADRs due to the medication, it's reporting, and whether the benefit of tocilizumab outweighs the risk. Also, we have studied the measures to enhance ADR reporting.

Conclusion: This study depicted that, medical professionals have a fundamental knowledge of Pharmacovigilance and the importance of ADR reporting. More emphasis should be put on the awareness programs for the target groups and extensive training should be conducted for the concerned professionals. From a future perspective, our study could be used to evaluate the benefits and risks associated with the use of tocilizumab in COVID19 and its occurrence with it. This study would also assist in understanding the practicality of a pandemic and the emergency use of medications in it followed by the significance of pharmacovigilance in healthcare.

Keywords: Pharmacovigilance, COVID-19, ADRs, Tocilizumab

Background:

The term 'Pharmacovigilance' is derived from pharmakon (Greek for drug) and "vigilare" (Latin for to keep watch). Pharmacovigilance is an important part of clinical research that deals with adverse drug reactions and adverse drug events of any drug from its discovery to post-marketing surveillance. According to WHO Pharmacovigilance has been described as– the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine vaccine-related problems [1].

Need for Pharmacovigilance:

Medications are needed for the diagnosis, prevention, and treatment of diseases. However, these products may cause some undesirable events. Thus, to identify and control them Pharmacovigilance is needed. It ensures the safety and quality of medicinal products and prevents adverse effects [2].

Objectives of Pharmacovigilance:

The main objectives of Pharmacovigilance are to promote safety and efficacy of drugs and other health care products. It creates awareness about ADR among healthcare professionals, to promote understanding, knowledge, and education about pharmacovigilance among healthcare professionals and promotes safe and rational use of medicine.

Pharmacovigilance Methods:

Pharmacovigilance methods can be categorized as: **Passive Surveillance** and includes, Spontaneous Reporting in which Suspected ADRs are reported by the healthcare professional or consumer to the regulatory authority and Case series in which a series of case reports that provides evidence of an association between a drug and an adverse event and is used for hypothesis generation.

Stimulated Reporting: includes online reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method.

Active Surveillance including Sentinel Sites: in which a review of the reported ADR data and survey is done and Drug event monitoring in which patients are identified by electronic prescription data and health insurance claims. Also includes Registry which is based on similar characteristics like specific disease or exposure.

Comparative Observational Studies: Cross-sectional Studies: It involves analyzing data from a group of populations at a specific point in time. Case-control Studies: Here, a control group with no exposure to disease and a test group with exposure are compared. Cohort Studies: Here, a population at risk for the disease is followed over time for the occurrence of the outcome of interest.

Descriptive Studies are important to detect the natural history of the disease and the incidence of adverse events [3].

TOCILIZUMAB:

Tocilizumab is a drug sold under the brand name Actemra. It belongs to the drug category, DMARDs (Disease-modifying Anti-Rheumatic Drugs) and falls under the classification of biologic immunomodulators [4]. It is a humanized monoclonal antibody that is an Interleukin 6 (IL-6) Receptor Blocker. Interleukin 6 (IL-6) is a cytokine that has a vital role in immune response and is implicated in the pathogenesis of various diseases, such as autoimmune diseases and several types of myelomas and cancers. It is primarily used to treat rheumatoid arthritis and systemic juvenile arthritis, a severe form of arthritis in children [5].

Dose and Marketed Products of Tocilizumab:

S.No.	Brand Name	Contents	Dose	Route of Administration	Manufacturer
1.	Tocira-400	Tocilizumab	400 mg	Intravenous	Hetero
2.	Actemra	Tocilizumab	80 mg	Intravenous	Cipla

It is available as an injectable solution administered sub-cutaneously via:

1. Injection
   20 mg/ml (4 ml, 8 ml, and 20 ml single-dose vials)
2. Single-use autoinjector (ACTPen)
   162 mg/0.9 ml
3. Single-use prefilled syringe
   162 mg/0.9 ml

The Emergency use (EUA) dose of Tocilizumab indicated was 8 mg/kg IV; not to exceed 800 mg/dose. Subcutaneous administration was not authorized for the treatment of COVID-19. One additional IV infusion may be administered 8 hours post the first infusion in the case of unimproved clinical signs [6].

Mechanism of Action of Tocilizumab:

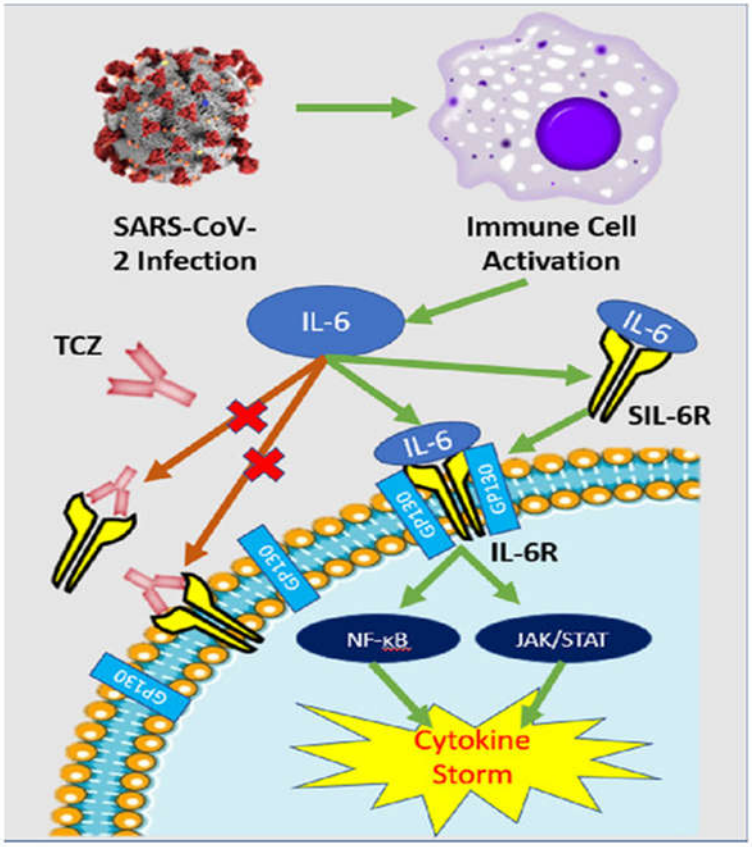


Figure 1: IL-6 pathway and TCZ mechanism of action. DOI: 10.7717/peerj.10322/fig-3

Tocilizumab molecule is a genetically-engineered monoclonal antibody. TCZ is a competitive inhibiter of IL-6 receptors. This results in a plummet in cytokine's pro-inflammatory response. IL-6 is a T-cell-derived factor. It induces the B cells to differentiate into antibody-producing cells. It also prompts angiogenesis by bringing about the Vascular Endothelial Growth Factor (VEGF) expression where the inflammatory cells secrete pro-and anti-inflammatory cytokines. To conclude, IL-6 trans-signaling Pathway substantiates the pro-inflammatory activity of Interleukin 6. TCZ acts as a neutralizing antibody against IL-6 and IL-6R and blocks the trans-signaling pathways [7].

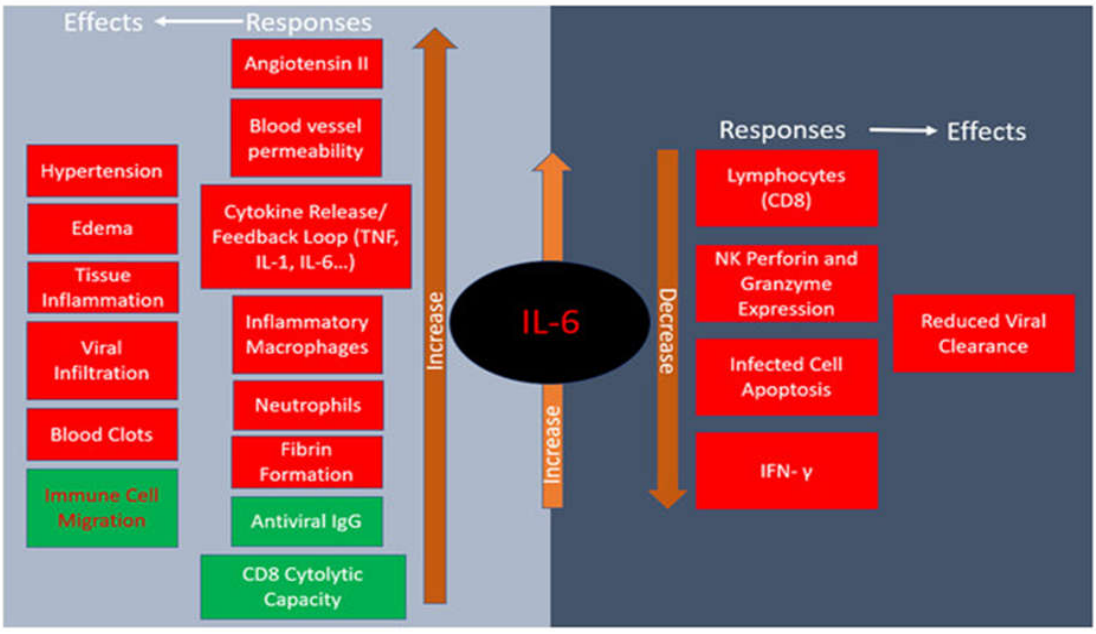


Figure 2: Responses to IL-6 release and their physiological effects.
Red indicates negative consequences of IL-6 increase while green designates positive ones in COVID-19. DOI: 10.7717/peerj.10322/fig-2

RHEUMATOID ARTHRITIS:

Rheumatoid Arthritis or RA is an autoimmune disease [8]. The most predominant manifestations of RA are inflammatory arthritis of peripheral joints and cardiovascular, hematologic, neurological, and pulmonary abnormalities [9]. The treatment of RA constitutes the use of medications that defer and prevent joint deformity, called the Disease-Modifying Anti-Rheumatic Drugs (DMARDs) which include Tocilizumab and Sulfasalazine [8].

Role of Pharmacovigilance in COVID-19:

The robust clinical research to develop the novel coronavirus vaccine has been plausible. Still, there are loopholes in the process that need to be checked as patient health is the priority. Pharmacovigilance activities despite clinical trials must be undertaken to address any adverse drug events [10]. The predominant issue was medicine and vaccine-related threat [11]. In the case of hydroxychloroquine, which was extensively administered but its efficacy was not proven in the case of COVID-19. It was evident that it led to inefficient control of symptoms [12] [13]. The World Health Organization took an initiative to ensure global vaccine safety.

The objective involves standardized reporting of,

1. Adverse events following immunization,
2. Adverse events of special interest [14].

COVID-19 (SARS-CoV-2):

Novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a major public health crisis and initiated a pandemic in December 2019. With its first case in Wuhan city, China, it spread globally as a life-threatening surge [15].

The virus is communicated through inhalation of infected droplets or physical contact with infected droplets. Some symptoms observed during mild infection included fever, cough, dyspnoea, malaise, fatigue, breathlessness, loss of taste or smell, etc. Disease advanced to pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction in severe infection cases. Several cases were asymptomatic [16-18]. COVID-19 diagnosis is based on two diagnostic methods i.e. Clinical (Radiography and Chest CT Scan) and In-vitro diagnostics (Nucleic acid amplification tests (NAATs) and serological antigen and antibody-based assays) [19-21].

COVID-19 Outbreak:

In late December 2019, various health centers in Wuhan, China witnessed a surge in severe pneumonia cases with unknown causes [22]. Several initial cases were epidemiologically associated with Huanan Seafood Wholesale Market [23] [24]. Fig.3 illustrates the timeline of the outbreak of COVID with emphasis on the major events.

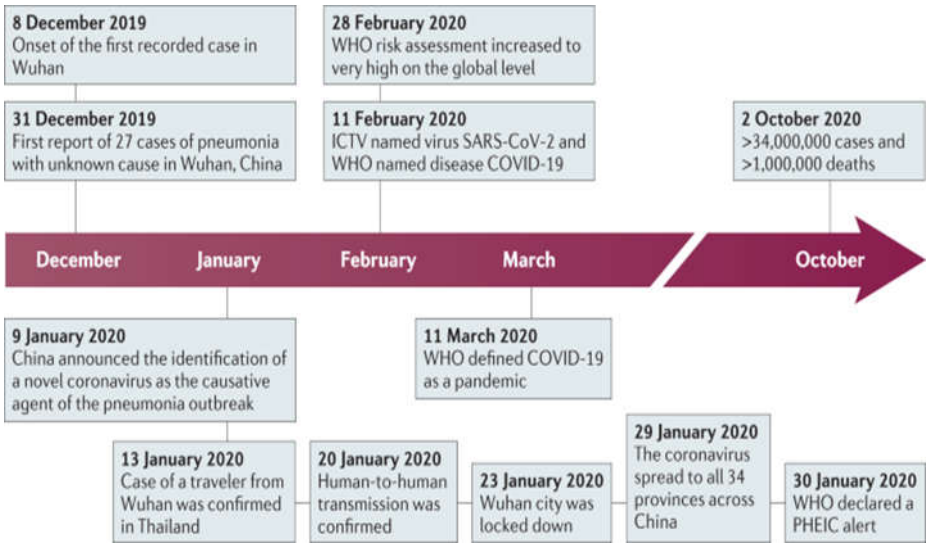


Fig. 3: Timeline of key events of the COVID-19 outbreak
https://www.nature.com/articles/s41579-020-00459-7#ref-CR9

Indications of COVID-19:

Variable indications are observed in COVID-19 ranging from an asymptomatic state to acute respiratory distress syndrome and finally multi-organ dysfunction [25]. The incubation period is up to 14 days from exposure with 4-5 days on average [26-28]. As noted by the U.S. CDC, clinical features seen in patients include-Fever or chills, myalgia, dyspnoea, sore throat, cough, congestion or runny nose, nausea or vomiting, fatigue, loss of sense of taste (anosmia) or smell (ageusia), diarrhea, and headache [29]. Acute strokes and myocardial infarctions were also reported, signifying multi-organ participation, which was ascertained in many studies [30-31]. Fever and cough were the most recorded indications as suggested by hospital data [26] [32-33]. Updated WHO interim guidance of 7th August 2020, highlighted anosmia and ageusia as COVID-19 specific [34-35]. Here, patients have ordinary or low white platelet counts, lymphopenia or thrombocytopenia, and raised C-responsive protein levels [36-38]. On average, symptoms progressed to dyspnea within 5 days, hospitalization after a week and

ARDS developed in 8 days. Complications encountered were acute lung injury, ARDS, and shock. The average hospitalized duration was 10 days. The mortality rates were higher in the elderly and patients with comorbidities.

TOCILIZUMAB IN COVID-19:

IL-6 is produced in response to tissue damage and infections, and it aids in the protection of the host by activating immunological responses and stimulating acute phase reactions. Tocilizumab, an anti-IL-6 receptor antibody, has been created because IL-6 is important in the pathophysiology of several inflammatory disorders, including infectious inflammations linked with tissue fibrosis. IL-6 binds to its receptor (IL-6R), which is exclusively found on hepatocytes and some leukocytes initiating a classical signaling pathway [39-40].

As illustrated by Fig.4, Tocilizumab blocks the IL-6-receptor, a critical cytokine that can trigger an inflammatory storm, leading to increased alveolar-capillary blood-gas exchange dysfunction, particularly decreased oxygen transport, and finally pulmonary fibrosis and organ failure. Tocilizumab has been tested for the treatment of COVID-19 due to its capacity to downregulate the immune system. Tocilizumab has been linked to improvements in inflammatory indicators, clinical response, and survival in studies [41].

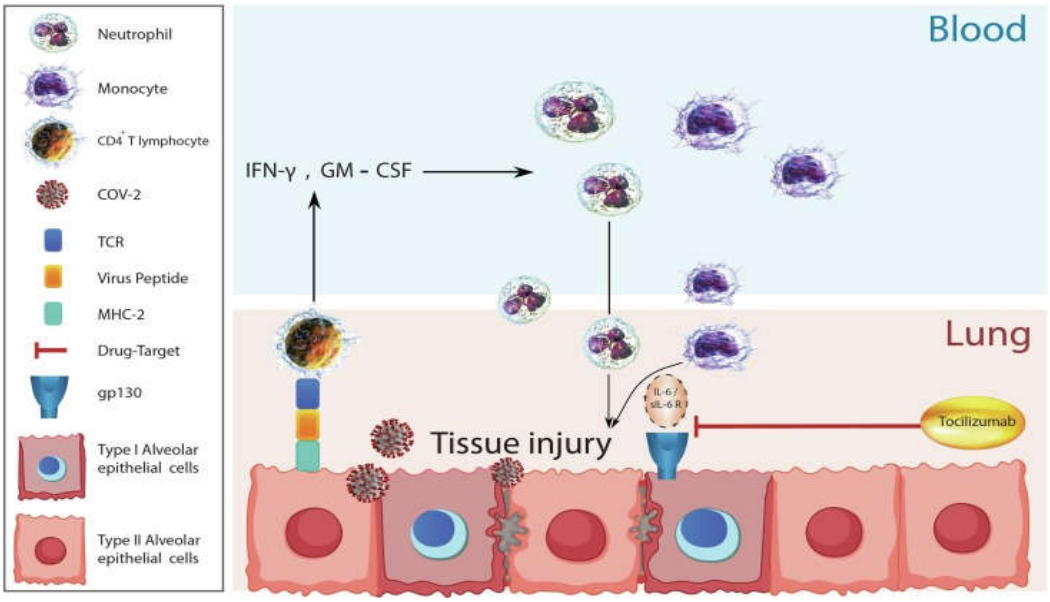


Fig. 4: Mechanism of Tocilizumab in Lung Injury
Int Immunopharmacol. 2020 Dec; 89: 107018.
Published online 2020 Sep 16. DOI: 10.1016/j.intimp.2020.107018

Tocilizumab, in addition to the routine care patients receive for COVID-19 treatment, which includes corticosteroid therapy, was shown in clinical trials of hospitalized patients with COVID-19 to reduce the risk of death and decrease the number of time patients remained hospitalized after 28 days of follow-up. During the 28-day follow-up period, the likelihood of patients being placed on ventilators or dying was also reduced. The immune system can become hyperactive in the event of COVID-19 infection, which can lead to disease progression. SARS-COV-2 is not directly targeted by tocilizumab. The FDA has approved the emergency use of tocilizumab for the treatment of COVID-19 in selected hospitalized patients under the terms of today's EUA [42].

On June 24, 2020, an Emergency use authorization (EUA) was issued by the FDA for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and paediatric patients (aged >2 years) who are receiving systemic corticosteroids and require supplemental oxygen [43].

Side Effects, ADRs, and ADEs of Tocilizumab:

They can be divided into four categories:

1) Common side effects
   Respiratory tract Infections, Headaches, Hypertension, and an increase in liver enzymes.
2) Injection Site Reactions
   Rashes, Redness, Swelling, Itching
3) Associated Serious Infection
   Tuberculosis, Sepsis, and Fungal Infection
4) Side effects reported in studies
   Hypersensitivity Reactions, Developed cancer, Reactivation of Herpes Zoster, Gastrointestinal Perforation in patients with diverticulitis [44].

Ethics Statement:

PROJECT STUDY

The survey was conducted with a perspective to know the awareness, knowledge, and application methods of Pharmacovigilance in the group of respondents consisting of medical professionals from India as well as abroad. This is because, during the pandemic, they were on the front line and were generally the ADRs/ AEs respondents. They also received training to accurately diagnose and report ADRs and AEs. They play an important role in the interaction between clinical departments and patients. They are also a valuable source of ADR compilation, analysis, and reporting.

MATERIALS

STUDY CENTRE

The study was conducted at the School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore, M.P which is an educational center with comprehensive facilities for education, and research, and the institute provides full-time graduate, postgraduate and doctoral courses in Pharmacy.

STUDY DESIGN

A retrospective cohort study was carried out to determine awareness and need for Pharmacovigilance among healthcare professionals.

STUDY DURATION

This study was conducted for 20 days (APRIL 14 - MAY 4).

STUDY POPULATION

The survey questionnaire was distributed to approx. 120 healthcare professionals. However, the total numbers of respondents were 105.

STUDY TOOLS

The questionnaire was prepared after an extensive literature review and discussion with mentors and colleagues. The survey questions were analyzed and the response was calculated in data percentage.

DISTRIBUTION AND COLLECTION OF DATA

The questionnaire was surfaced online using Google forms and was subsequently distributed to various medical centers all over India as well as abroad. The objectives of the study were briefed and the respondents were asked to fill up the survey.

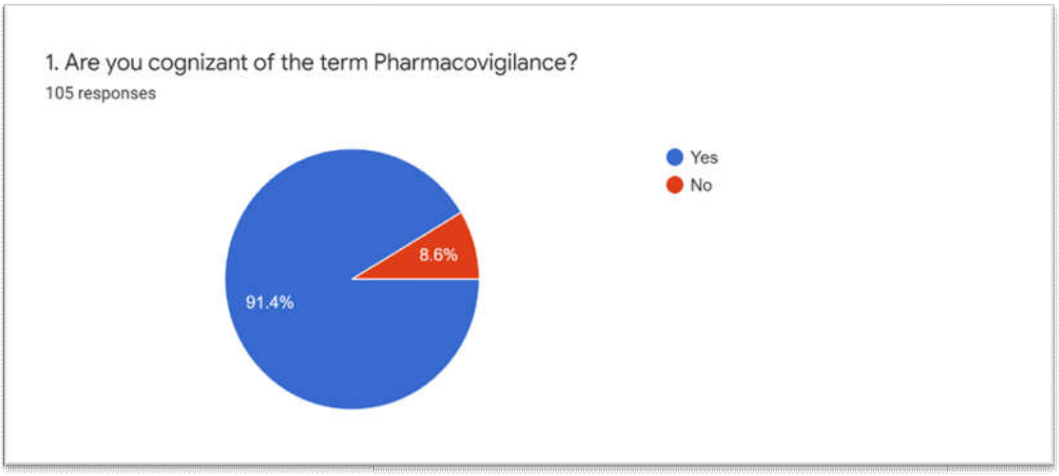
RESULTS

GENERAL INFORMATION

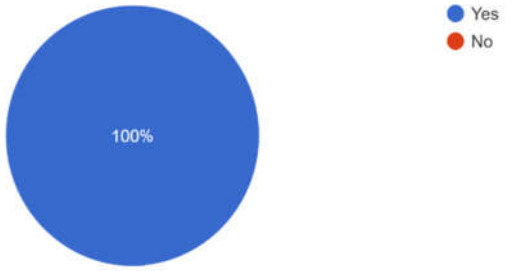
In this study, we evaluated the awareness, knowledge, and application methods of pharmacovigilance among medical professionals as respondents. Out of 120 professionals, 105 doctors participated in the study.

QUESTIONS ON THE STUDY ON THE ROLE OF PHARMACOVIGILANCE AND BENEFIT-RISK ASSESSMENT OF THE DRUG TOCILIZUMAB USED IN COVID-19 PATIENTS:

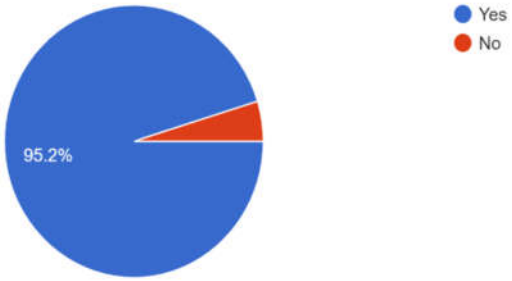
The findings from our study indicate that: -



2. Are you aware of the term ADVERSE DRUG REACTIONS (ADRs) and ADVERSE EVENTS(AEs)?
105 responses

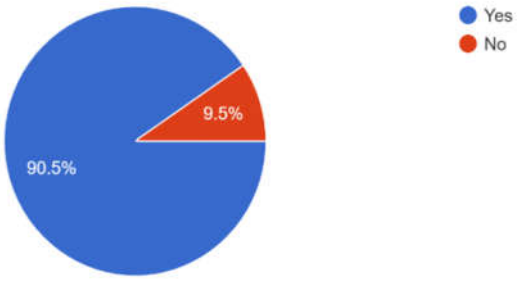


3. Do you feel that ADR Reporting plays a vital role in Pharmacovigilance during an emergency use of a drug?
105 responses

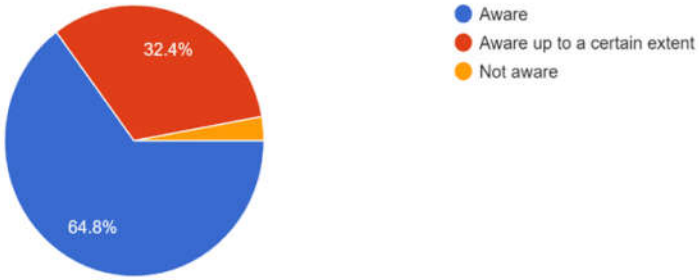


4. Do you think that a medical professional's assistance is helpful in the detection, reporting, and management of an Adverse Drug Reaction or Adverse Event?
105 responses

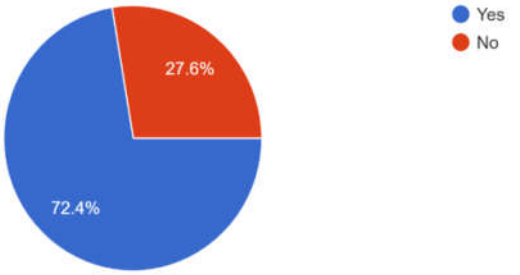
5. Are you aware that all severe ADR/ADE is to be reported in a case reporting format?
105 responses

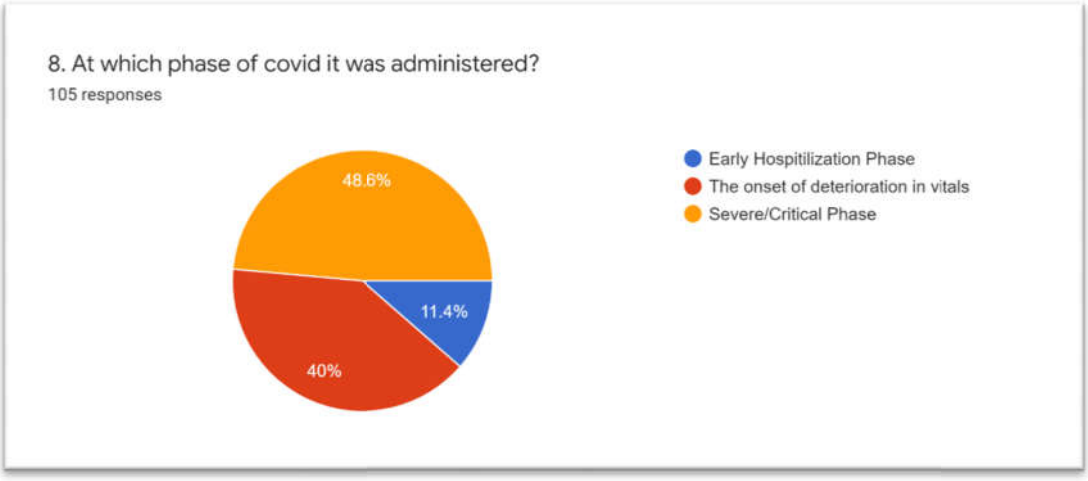


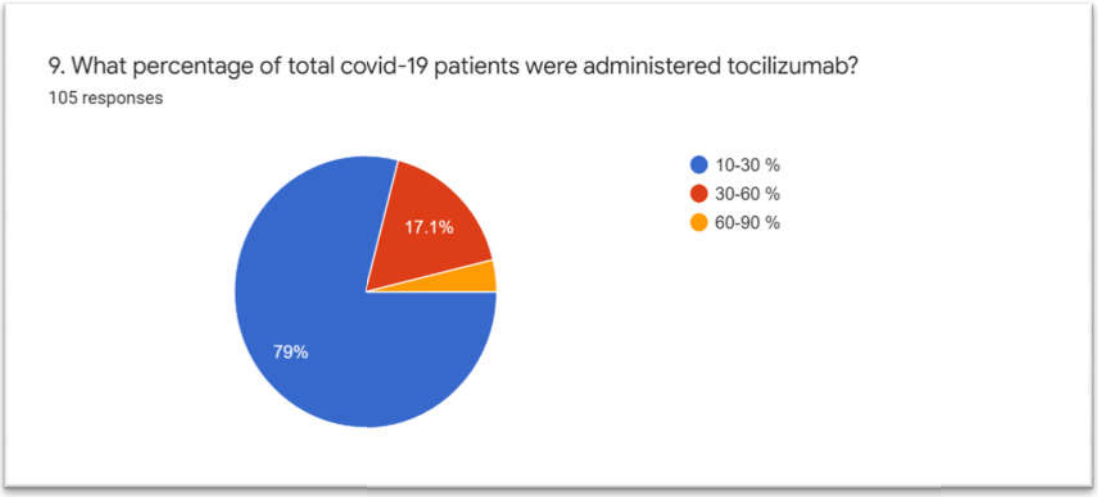
6. Are you aware that Tocilizumab is an immunosuppressant (IL-6 receptor blocker) and was used in COVID-19 in the case of multiple organ failure?
105 responses

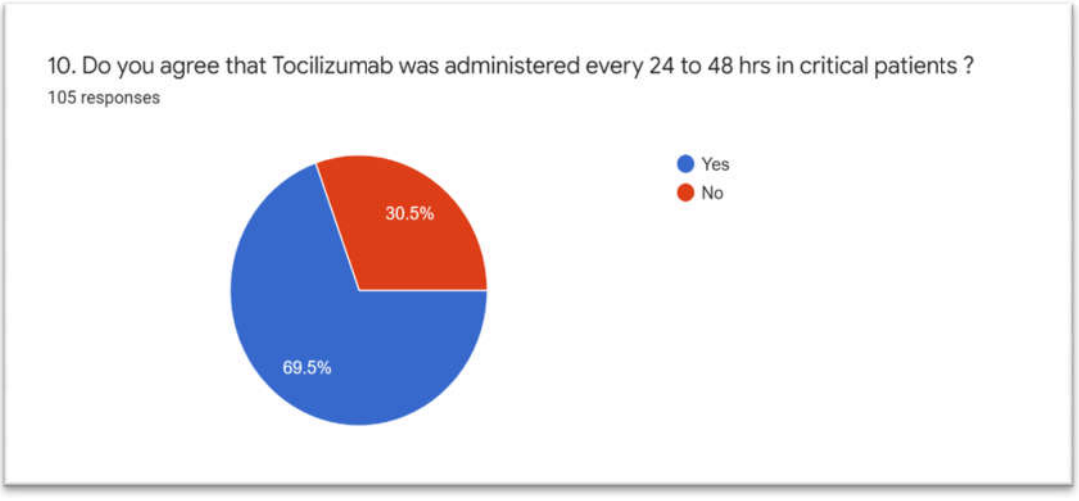


7. Do you feel that the administration of tocilizumab in COVID patients was successful in reducing mortality rates ?
105 responses



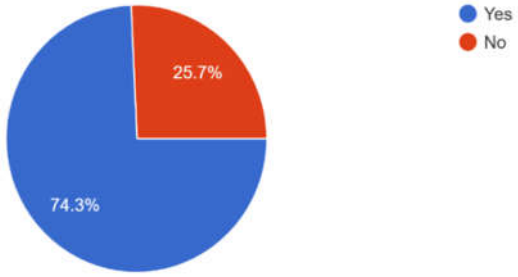

8. At which phase of covid it was administered?
105 responses
48.6%
11.4%
40%
Early Hospitilization Phase
The onset of deterioration in vitals
Severe/Critical Phase


9. What percentage of total covid-19 patients were administered tocilizumab?
105 responses
17.1%
79%
10-30 %
30-60 %
60-90 %


10. Do you agree that Tocilizumab was administered every 24 to 48 hrs in critical patients ?
105 responses
30.5%
69.5%
Yes
No

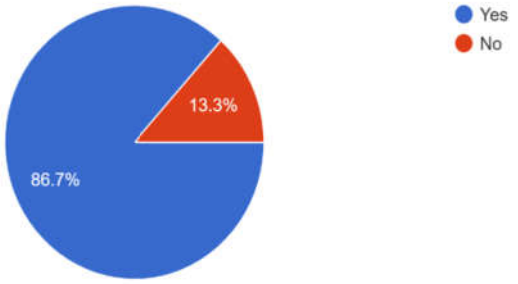
11. Do you agree that with systemic corticosteroids tocilizumab demonstrated the maximum activity?

105 responses



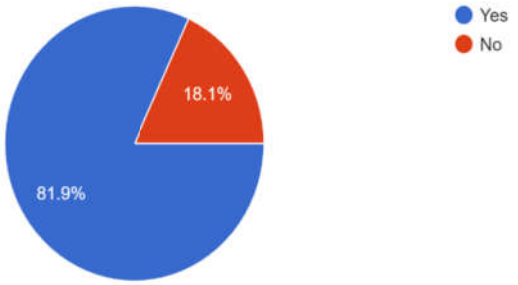
12. Do you think that there was a high risk of contraindication from Tocilizumab in patients with underlying comorbidities like Cardiovascular Disease, Diabetes, and Liver Dysfunction?

105 responses



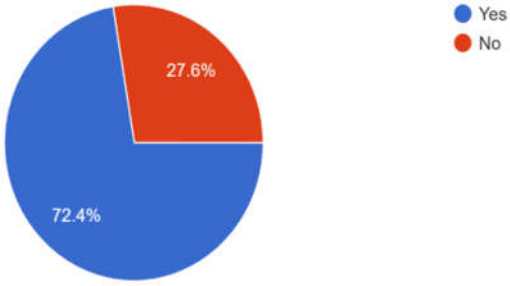
13. Are you aware that Tocilizumab was not approved by the FDA but was allowed to be used in emergency cases for COVID-19?

105 responses



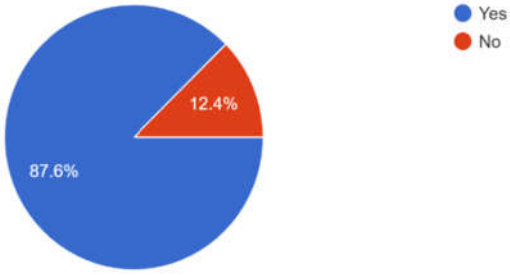
14. Do you agree that the following side effects: Hypertension, Fungal Infection(Mucormycosis), Gastrointestinal Perforation, and Hypersensitivity ...dministration of tocilizumab in COVID-19 patients?

105 responses



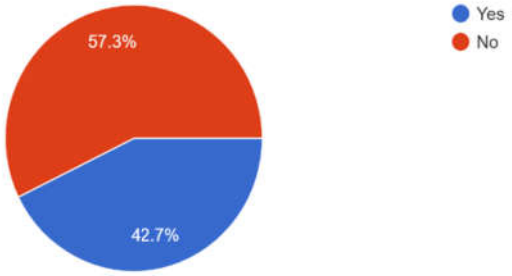
15. Do you agree that the following ADRs: Severe neutropenia, Cardiac Abnormalities, Haematological complications, and Hepatitis were ...ministration of tocilizumab in COVID-19 patients?

105 responses



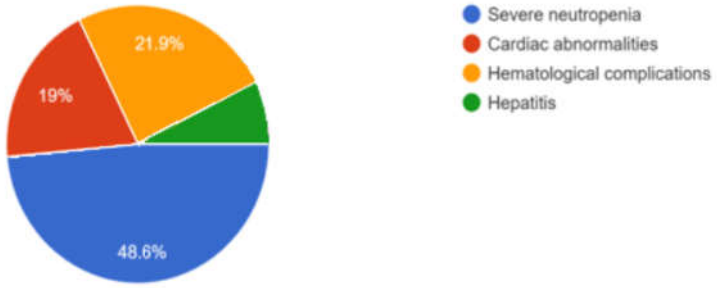
16. Do you agree that the above-mentioned ADRs were reported efficiently?

103 responses



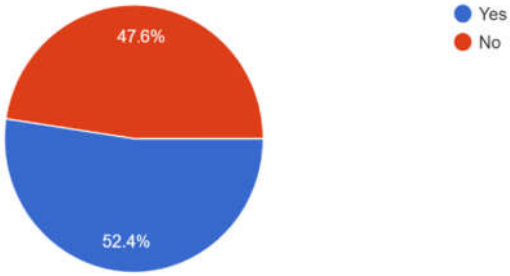
17. According to your knowledge which of the ADRs were frequent in tocilizumab-administered patients?

105 responses



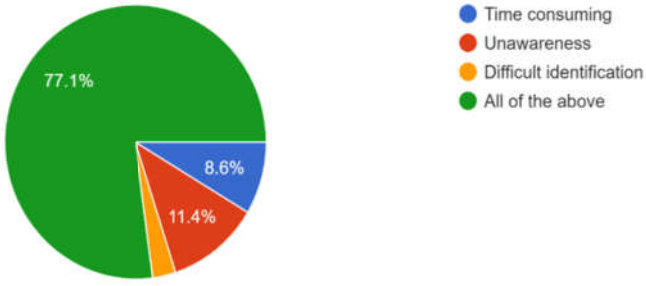
18. Do you agree that there were a greater number of ADR incidences in males as compared to females for tocilizumab in covid-19?

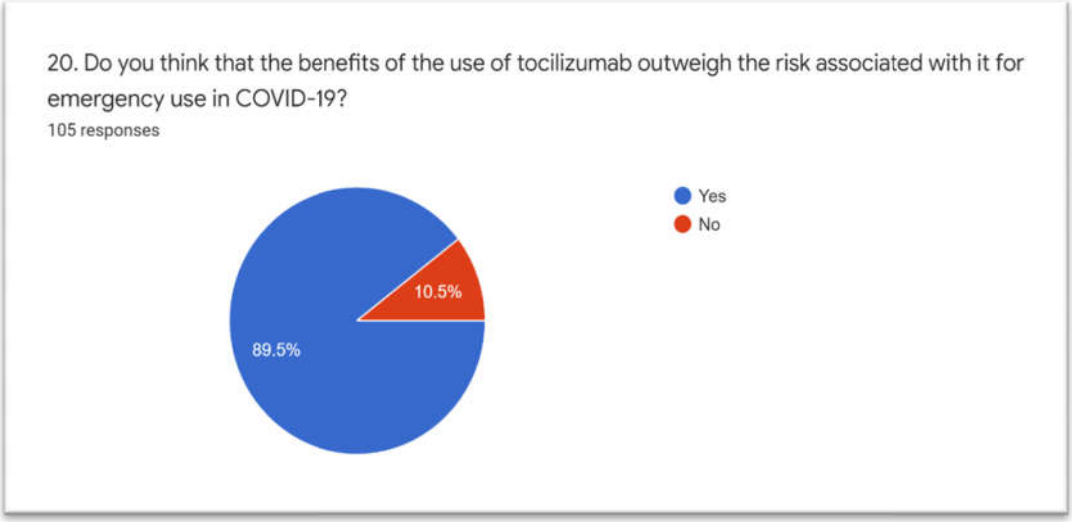
105 responses



19. What do you think is the reason behind low ADR reporting during the COVID-19 pandemic?

105 responses





DISCUSSION

In this study, we evaluated the benefit and risks associated with the immunosuppressant drug, TOCILIZUMAB administered during the COVID-19 pandemic. It was accomplished by assessing the cognizance of the medical professionals through a series of questions. The fact behind choosing this group was that they were the front-line workers during the pandemic and the primary link between the patient and the medication for its prescription and administration. They play a vital role in ADR identification, analysis, and reporting. Our research illustrates that 91.4 % of our study group knew the term 'Pharmacovigilance', and significantly all of them knew about the Adverse Drug Reactions and Adverse Events. 95.2 % of the respondents felt that ADR reporting plays an essential role in Pharmacovigilance. Also, 90.5 % of participants were aware that ADR/ADE is to be reported in a case reporting format.

About 64.8 % of respondents were aware of the drug Tocilizumab is an immunosuppressant and was used in COVID-19 in the case of multiple organ failure. Almost a quarter of the study group believed that administration of tocilizumab in COVID patients gave positive results in reducing mortality rates. It is evident from the study that this drug was administered in severe cases. 79 % of respondents believed that tocilizumab was administered in 10-30 % of the patients admitted for COVID. 69.5 % of medica;l professionals agreed that tocilizumab was administered every 24-48 hours as indicated by the WHO. 74.3 % of people were in favor of the statement that tocilizumab demonstrated maximum activity with systemic corticosteroids as prescribed by the WHO in combination therapy. Maximum medical professionals felt tocilizumab was risky for patients with underlying comorbidities like cardiovascular disease, diabetes, and liver dysfunction. 81.9 % of people in the study group knew that this drug was not approved by the FDA but was allowed to be used in emergency cases. 87.6 % of professionals agreed that ADRs like severe neutropenia, cardiac abnormalities, hematological complications, and hepatitis were observed post-administration with severe neutropenia being reported the highest. Maximum medical professionals believed that the above-mentioned ADRs were not reported efficiently due to the time-consuming process, unawareness among the group, and difficult identification. It was also apparent that

52.4 % of respondents believed that the ADR incidences were more in males as compared to females.

Finally, 89.5 % of medical professionals were in favor of the statement that the benefits of the use of tocilizumab outweigh the risk associated with it for emergency use in COVID-19.

Our observations indicate that maximum medical professionals were aware of pharmacovigilance and its importance in ADR reporting. However, ADR reporting in India is still wanting and serious steps should be taken to enhance it. These measures include efficient decentralization of pharmacovigilance cells at the district level. These cells should be integrated on a central level for an efficient ADR database for the country.

Pharmacovigilance awareness programs should be held during internships, in training programs in industries, and at professional institutions to enhance the workforce for surveillance and reporting. A post-discharge team should be appointed in hospitals to keep a check on the long-term side effects of medications on patients. More and more awareness programs should be conducted for the general public for efficient ADR reporting which they can be a part of. Additionally, medical professionals should advise the patient to take precautions and report the adverse reactions to them firsthand if found. These measures would aid the Pharmacovigilance Programme of India in achieving maximum ADR reporting.

SUMMARY

S. NO.	STATEMENT	YES	NO
1.	Are you cognizant of the term Pharmacovigilance?	91.4 %	8.6 %
2.	Are you aware of the term ADVERSE DRUG REACTIONS (ADRs) and ADVERSE EVENTS(AEs)?	100 %	-
3.	Do you feel that ADR Reporting plays a vital role in Pharmacovigilance during an emergency use of a drug?	95.2 %	4.8 %
4.	Do you think that a medical professional's assistance is helpful in the detection, reporting, and management of an Adverse Drug Reaction or Adverse Event?	99 %	1 %
5.	Are you aware that all severe ADR/ADE is to be reported in a case reporting format?	90.5 %	9.5 %
6.	Are you aware that Tocilizumab is an immunosuppressant (IL-6 receptor blocker) and was used in COVID-19 in the case of multiple	a. 64.8 % b. 32.4 %	

	organ failure? a. Aware b. Aware up to a certain extent c. Not Aware	c. 2.8 %	
7.	Do you feel that the administration of tocilizumab in COVID patients was successful in reducing mortality rates?	72.4 %	27.6 %
8.	At which phase of covid it was administered? a. Early Hospitalization Phase b. The onset of deterioration in vitals c. Severe/Critical Phase	a. 11.4 % b. 40 % c. 48.6 %	
9.	What percentage of total covid-19 patients were administered tocilizumab? a. 10-30 % b. 30-60 % c. 60-90 %	a. 79 % b. 17.1 % c. 3.9 %	
10.	Do you agree that Tocilizumab was administered every 24 to 48 hrs in critical patients?	69.5 %	30.5 %
11.	Do you agree that with systemic corticosteroids tocilizumab demonstrated the maximum activity?	74.3 %	25.7 %
12.	Do you think that there was a high risk of contraindication from Tocilizumab in patients with underlying comorbidities like Cardiovascular Disease, Diabetes, and Liver Dysfunction?	86. 7 %	13.3 %
13.	Are you aware that Tocilizumab was not approved by the FDA but was allowed to be used in emergency cases for COVID-19?	81.9 %	18.1 %
14.	Do you agree that the following side effects: Hypertension, Fungal Infection (Mucormycosis), Gastrointestinal Perforation, and Hypersensitivity were caused after the administration of tocilizumab in COVID-19 patients?	72.4 %	27.6 %
15.	Do you agree that the following ADRs: Severe neutropenia, Cardiac Abnormalities, Haematological complications, and Hepatitis were observed post the administration of tocilizumab in COVID-19 patients?	87.6 %	12.4 %
16.	Do you agree that the above-mentioned ADRs	42.7 %	57.3 %

	were reported efficiently?		
17.	According to your knowledge which of the ADRs were frequent in tocilizumab-administered patients? a. Severe neutropenia b. Cardiac abnormalities c. Hematological complications d. Hepatitis	a. 48.6 % b. 19 % c. 21.9 % d. 10.5 5	
18.	Do you agree that there were a greater number of ADR incidences in males as compared to females for tocilizumab in covid-19?	52.4 %	47.6 %
19.	What do you think is the reason behind low ADR reporting during the COVID-19 pandemic? a. Time consuming b. Unawareness c. Difficult identification d. All of the above	a. 8.6 % b. 11.4 % c. 2.9 % d. 77.1 %	
20.	Do you think that the benefits of the use of tocilizumab outweigh the risk associated with it for emergency use in COVID-19?	89.5 %	10.5 %

CONCLUSION

To conclude, 89.5 % of respondents in the survey conducted were in favor of the statement that the benefits of the use of tocilizumab outweigh the risk associated with it for emergency use in COVID-19. This depicted that medical professionals have a fundamental knowledge of Pharmacovigilance and the importance of ADR reporting. However, there is a dire need for systematic and efficient reporting and analysis of ADRs. This would pave the way to measure the co-morbidities and casualties associated with a particular medication. It would help in primary studies of ADR by effective and correct data generation and review. More emphasis should be put on the awareness programs for the target groups and extensive training should be conducted for the concerned professionals. From a future perspective, our study could be used to evaluate the benefits and risks associated with the use of tocilizumab in COVID19 and the ADRs occurring with it.

ACKNOWLEDGEMENT:

We would like to express our heartfelt gratitude towards our esteemed institution, School of Pharmacy, Devi Ahilya Vishwavidyalaya, and our Head of Department, for providing us with this felicitous opportunity to work on this project entitled" A study on Role of Pharmacovigilance and Benefit-Risk Assessment of the drug Tocilizumab used in COVID-19 patients ". In addition, we would like to thank our project mentor, for

entrusting us with this. We would like to thank all the medical professionals from various states of India as well as from U.S and Canada who participated in our survey by taking out some time from their busy schedules and abetted us to gain insight regarding our project.

LIST OF ABBREVIATIONS:

WHO: World Health Organisation

FDA: Food and Drug Administration

ADR: Adverse Drug Reactions

AE: Adverse Events

SARS: Severe Acute Respiratory Syndrome

EUA: Emergency Use Authorization

DMARD: Disease-Modifying Antirheumatic Drugs

IL-6: Interleukin 6

VEGF: Vascular Endothelial Growth Factor

RA: Rheumatoid Arthritis

CDC: Centre for Disease Control and Prevention

ARDS: Acute Respiratory Distress Syndrome

NAAT: Nucleic Acid Amplification Test

REFERENCES:

1. https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance

2. Mantasha Sultan, Divya Kukreja, Aditi Vyas, Shweta Thakur, Pooja Singh and Dr. Masheer A. Khan, A study on awareness about "Adverse drug reaction & Pharmacovigilance Practices" among Medical students, World Journal of Pharmacy and Pharmaceutical Sciences, Vol.10, Issue 1, 288-299, 2021, ISSN 2278-4357.

3. Masheer A. Khan, Kriti Shrivastava, Neeta Chhabra, Priyal Jain, Priyanka Parmar And Tasneem Singaporewala, "A Study on the awareness of Vaccine Pharmacovigilance and its need during COVID-19 pandemic among some Medical Students, Pharmacy Students and Healthcare Professionals" Zeichen Journal, Volume 7, Issue 8, 2021, Page No. 284-303, ISSN: 0932-4747, UGC CARE Group II Journal (Scopus Indexed)

4. https://www.rxlist.com/actemra-drug.htm
5. Markus Harwart (2008). "Die Entwicklung von Tocilizumab" [The development of tocilizumab] (in German). Krankenpflege-Journal. Archived from the original on 15 October 2018. Retrieved 30 April 2016.
6. https://reference.medscape.com/drug/actemra-tocilizumab-999419
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5612212/
8. https://www.cdc.gov/arthritis/basics/rheumatoid-arthritis.html
9. Mohan Harsh, Textbook of Pathology, Jaypee Brothers Publications, 6th edition, Pg-851-852
10. Desai MK. Pharmacovigilance and assessment of drug safety reports during COVID 19. Perspect Clin Res. 2020 Jul-Sep;11(3):128-131. DOI: 10.4103/picr.PICR_171_20. Epub 2020 Jul 6. PMID: 33033703; PMCID: PMC7513786.
11. World Health Organization (2020). Risk Communication and Community Engagement Readiness and Response to Coronavirus Disease (COVID-19)
12. Liu, M., Caputi, T. L., Dredze, M., Kesselheim, A. S., and Ayers, J. W. (2020). Internet Searches for Unproven COVID-19 Therapies in the United States. JAMA Intern. Med. 180 (8), 1116–1118. Doi:10.1001/jamainternmed.2020.1764
13. Niburski, K., and Niburski, O. (2020). Impact of Trump's Promotion of Unproven COVID-19 Treatments on social media and Subsequent Internet Trends: Observational Study. J. Med. Internet Res. 22 (11), e20044. Doi:10.2196/20044
14. Report of the 7th global vaccine safety initiative (GVSI) meeting. [cited 2021 Mar 24]. Available from: https://www.who.int/publications/i/item/WHO-MVP-EMP-SAV-2019.01
15. Wang Chen, Horby Peter W, Hayden Frederick G, Gao George F. A novel coronavirus outbreak of global health concern. The Lancet. 2020;395(10223):470–473. DOI: 10.1016/S0140-6736(20)30185-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7090728/
16. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
17. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Inter Med. (2020). 172:577–82. DOI: 10.7326/M20-0504

18. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. (2020) 382:1199–207. DOI: 10.1056/NEJMoa2001316 https://doi.org/10.3389/fmed.2021.615099
19. Carter LJ, Garner L V, Smoot JW, Li Y, Zhou Q, Saveson CJ, et al. Assay techniques and test development for COVID-19 diagnosis. ACS Cent Sci. (2020) 6:591–605. DOI: 10.1021/acscentsci.0c00501
20. Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M, et al. Diagnostic testing for severe acute respiratory syndrome-related coronavirus 2: a narrative review. Ann Inter Med. (2020) 172:726–34. DOI: 10.7326/M20-1301 https://doi.org/10.3389/fmed.2021.615099
21. Vashist SK. In vitro diagnostic assays for COVID-19: recent advances and emerging trends. Diagnostics. (2020) 10:202. DOI: 10.3390/diagnostics10040202 https://doi.org/10.3389/fmed.2021.615099
22. Zhu, N. et al. A Novel Coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733(2020). CAS https://www.nature.com/articles/s41579-020-00459-7#ref-CR9
23. Deng, S. Q. & Peng, H. J. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J. Clin. Med. 9, 575 (2020). https://www.nature.com/articles/s41579-020-00459-7#ref-CR9
24. Jiang, S., Du, L. & Shi, Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg. Microbes Infect. 9, 275–277 (2020). https://www.nature.com/articles/s41579-020-00459-7#ref-CR9
25. Rothe Camilla, Schunk Mirjam, Sothmann Peter, Bretzel Gisela, Froeschl Guenter, Wallrauch Claudia, Zimmer Thorbjörn, Thiel Verena, Janke Christian, Guggemos Wolfgang, Seilmaier Michael, Drosten Christian, Vollmar Patrick, Zwirglmaier Katrin, Zange Sabine, Wölfel Roman, Hoelscher Michael. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. New England Journal of Medicine. 2020;382(10):970–971. doi: 10.1056/NEJMc2001468. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7090728/
26. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032

27. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Inter Med. (2020). 172:577–82. DOI: 10.7326/M20-0504
28. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. (2020) 382:1199–207. DOI: 10.1056/NEJMoa2001316
29. CDC. Symptoms of Coronavirus (COVID-19). National Center for Immunization and Respiratory Diseases (2020) Available online at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html (accessed August 26, 2020)
https://doi.org/10.3389/fmed.2021.615099
30. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun. (2020) 87:115–9.
DOI: 10.1016/j.bbi.2020.04.077
31. Stefanini GG, Matteo M, Daniela T, Daniele A, Giuseppe F, Marco A, et al. ST-Elevation myocardial infarction in patients with COVID-19. Circulation. (2020) 141:2113–6. DOI: 10.1161/CIRCULATIONAHA.120.047525
https://doi.org/10.3389/fmed.2021.628370
32. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. (2020) 395:514–23. DOI: 10.1016/S0140-6736(20)30154-9
33. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. (2020) 323:1061–9. DOI: 10.1001/jama.2020.1585
34. World Health Organization. Public Health Surveillance for COVID-19: Interim Guidance. WHO (2020). Available online at: https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.
35. Gourtsoyannis Y. Olfactory and gustatory symptoms in European COVID-19 cohorts. Clin Infect Dis. (2020) 71:3017–8. DOI: 10.1093/cid/ciaa685
36. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. (2020) 395:497–506. DOI: 10.1016/S0140-6736(20)30183-5

37. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect. (2020) 80:656–65. DOI: 10.1016/j.jinf.2020.03.041
38. Hurley MM, Kream BE, Raisz LG. Structural determinants of the capacity of heparin to inhibit collagen synthesis in 21-day fetal rat calvariae. J Bone Miner Res. (1990) 5:1127–33. DOI: 10.1002/jbmr.5650051106
39. Saito F., Tasaka S., Inoue K., Miyamoto K., Nakano Y., Ogawa Y., Yamada W., Shiraishi Y., Hasegawa N., Fujishima S., Takano H., Ishizaka A. Role of interleukin-6 in bleomycin-induced lung inflammatory changes in mice. *Am. J. Respir. Cell Mol. Biol.* 2008;38(5):566–571. DOI: 10.1165/rcmb.2007-0299OC.
40. Le T.T., Karmouty-Quintana H., Melicoff E., Le T.T., Weng T., Chen N.Y., Pedroza M., Zhou Y., Davies J., Philip K., Molina J., Luo F., George A.T., Garcia-Morales L.J., Bunge R.R., Bruckner B.A., Loebe M., Seethamraju H., Agarwal S.K., Blackburn M.R. Blockade of IL-6 Trans signaling attenuates pulmonary fibrosis. *J. Immunol.* 2014;193(7):3755–3768. DOI: 10.4049/jimmunol.1302470.)
41. Medical reviewed by John P. Cunha, DO, FACOPE, FDA prescribing information for Actemra. 41
42. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19
43. https://reference.medscape.com/drug/actemra-tocilizumab-999419
44. Price CC, Altice FL, Shyr Y, et al. Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019: survival and clinical outcomes. Chest. 2020 Oct;158(4):1397–1408. Samaee H, Mohsenzadegan M, Ala S, et al. Tocilizumab for treatment patients with COVID-19: recommended medication for novel disease. Int Immunopharmacol. 2020 Sep 16;89(Pt A):107018.