EXPERT OPINION ON DRUG SAFETY
https://doi.org/10.1080/14740338.2021.1946513

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Tocilizumab in COVID-19: a study of adverse drug events reported in the WHO database

Jaykaran Charan [a], Siddhartha Dutta [a], Rimplejeet Kaur[a], Pankaj Bhardwaj[b], Praveen Sharma [c], Sneha Ambwani[a], Iffat Jahan [d], Abdullahi Rabiu Abubakar[e], Salequl Islam [f], Timothy Craig Hardcastle [g], Nor Azlina A Rahman [h], Halyna Lugova[i] and Mainul Haque [j]

[a]Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; [b]Department of Community and Family Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India; [c]Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India; [d]Department of Physiology, Eastern Medical College, Cumilla, Bangladesh; [e]Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Bayero University, Kano, Nigeria; [f]Department of Microbiology, Jahangirnagar University, Savar, Dhaka, Bangladesh; [g]Department of Surgery, Nelson R Mandela School of Clinical Medicine, University of KwaZulu-Natal, Umbel, Berea, South Africa; [h]Department of Physical Rehabilitation Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Kuantan, Malaysia; [i]Unit of Community Medicine. Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia; [j]Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia

ABSTRACT

Background: Elevated inflammatory cytokines in Coronavirus disease 2019 (COVID-19) affect the lungs leading to pneumonitis with a poor prognosis. Tocilizumab, a type of humanized monoclonal antibody antagonizing interleukin-6 receptors, is currently utilized to treat COVID-19. The present study reviews tocilizumab adverse drug events (ADEs) reported in the World Health Organization (WHO) pharmacovigilance database.

Research design and methods: All suspected ADEs associated with tocilizumab between April to August 2020 were analyzed based on COVID-19 patients' demographic and clinical variables, and severity of involvement of organ system.

Results: A total of 1005 ADEs were reported among 513 recipients. The majority of the ADEs (46.26%) were reported from 18–64 years, were males and reported spontaneously. Around 80%, 20%, and 64% were serious, fatal, and administered intravenously, respectively. 'Injury, Poisoning, and Procedural Complications' remain as highest (35%) among categorized ADEs. Neutropenia, hypofibrinogenemia were common hematological ADEs. The above 64 years was found to have significantly lower odds than of below 45 years. In comparison, those in the European Region have substantially higher odds compared to the Region of Americas.

Conclusion: Neutropenia, superinfections, reactivation of latent infections, hepatitis, and cardiac abnormalities were common ADEs observed that necessitate proper monitoring and reporting.

ARTICLE HISTORY
Received 24 March 2021
Accepted 18 June 2021

KEYWORDS
Tocilizumab; COVID-19; adverse drug event; pharmacovigilance; WHO; monoclonal antibody; interleukin-6

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS - CoV-2) is the pathogen responsible for the current pandemic of coronavirus disease 2019 (COVID -19) [1]. The initial case was identified in December 2019 from Wuhan, China, as several new pneumonia cases, and on 11 March 2020, it was declared a global pandemic by the World Health Organization (WHO) [2]. As of 20 October 2020, WHO has reported that the United States of America is the worst hit, followed by South-East Asia. Globally 40,114,293 people have been infected with COVID-19; the disease has already claimed 1,114,692 lives [3]. A severe form of COVID-19 affects the lungs primarily and is associated with a hyperinflammatory condition, which damages the lungs and leads to pneumonitis and Accute Respiratory Distress Syndrome (ARDS) [4]. Based on the evidence, it is proposed that acute lung injury due to cytokine storm is the pathological basis for lung damage. As reported that in severe cases, the level of interleukins (IL) including IL-2, IL-6, IL-7, IL-10, Macrophage inflammatory protein 1A (MIP-1α/CCL3), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and Interferon gamma-induced protein were raised and lead to a worse prognosis [5–8]. A higher expression of the IL-6 is present in the $CD4^+$ T-cells and monocytes from patients with COVID-19 infection, which points toward the central act of IL-6 in inciting the inflammatory cytokine storm, which potentially damages the lungs and worsens the prognosis of the patient [8–10]. Therefore, IL-6 can be considered a prognostic marker and a crucial target for therapeutic interventions like immunological therapies for SARS-CoV-2 infections. IL-6 can also be used to check the inflammatory lung damage and other multiorgan damage in COVID-19 patients. Henceforth controlling IL-6 should decrease the severity and improve the prognosis in these

CONTACT Jaykaran Charan dr.jaykaran78@gmail.com; Mainul Haque runurono@gmail.com mainul@upnm.edu.com

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14740338.2021.1946513.

Article highlights

- The COVID-19 is associated with severe inflammation and cytokine storm.
- Interleukin 6 is one of the prime mediators culpable for the inflammatory damage to various organs.
- Tocilizumab, an IL-6 receptor blocker primarily approved for inflammatory rheumatic conditions has been found to be effective in reducing the inflammation in COVID-19 patients.
- The suspected adverse drug events from the WHO database were analyzed to assess the safety profile in COVID-19 patients.
- Majorly ADEs were reported from 18–64-year age group and were serious in nature.
- Neutropenia, superinfections, latent infections reactivation and cardiac abnormalities were common suspected ADEs observed.

patients. In support of the fact, IL-6 inhibitors are being used in patients with COVID-19 and have reduced the severity and improved outcomes [11].

1.1. Tocilizumab

Tocilizumab, a type of humanized monoclonal antibody (MAb) that belongs to a class of IL- inhibitors with Anatomical Therapeutic Chemical (ATC) classification code: L04AC07 [12]. It is a MAb that attaches to both soluble and membrane-bound IL-6 receptors (sIL-6 R and mIL-6 R), leading to the blockade of inflammatory signaling pathways associated with IL-6 [13,14]. Tocilizumab was first approved in Japan to manage Multicentric Castleman's Disease in 2007 [15]. It was initially approved for treating Rheumatoid Arthritis by the Food and Drug Administration (FDA) in 2010 [14]. Later on, it was also approved for varied immunological diseases like Systemic Juvenile Idiopathic Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, and lately was approved for managing severe cytokine release syndrome (CRS) due to chimeric antigen receptor T cell therapy [13,14]. The recommended dosage of tocilizumab for various immunological disorders ranges from 4–12 mg per kg and is administered as an intravenous infusion [14].

1.2. Tocilizumab and COVID-19: efficacy and safety

The primary idea of using Tocilizumab in patients of COVID-19 was to curb the inflammatory process and improve the disease outcome. Evidence shows that tocilizumab has effectively improved the prognosis in COVID-19 patients by reducing the inflammatory markers, the severity of the disease, enhancing lung changes, and reducing mechanical ventilation risk [16–24]. On the contrary, some studies have reported no effect of tocilizumab on these patients [25–28]. There is limited data available regarding tocilizumab's safety in COVID-19 patients; hence, chronic use and robust multicentric randomized controlled trials are essential to establish the drug's safety and efficacy and assess and quantify the adverse drug events (ADEs) specific in COVID-19 patients. Its safety analysis in completed trials among COVID-19 patients has shown ADEs like raised liver transaminases, hypertriglyceridemia, increased median QTc interval, severe neutropenia, activation of latent infections [16,18,20,21,23,25,27,29–31]. Tocilizumab is still under investigation and has not been approved for the treatment of COVID-19 patients by FDA but has permitted its emergency use in COVID-19 patients. It is currently being used on an emergency basis by prescribers worldwide to treat COVID-19 patients [14,30]. The ADEs encountered during the therapy have been reported in the global database VigiBase® maintained by WHO [32]. The current study was undertaken to review ADEs' status associated with tocilizumab in managing patients with COVID-19 recorded in the WHO pharmacovigilance database.

2. Methods and materials

The present study was conducted using VigiBase, a global database containing individual case safety reports (ICSRs) of various interventions. This extensive database is maintained by WHO and includes over 20 million reports of suspected adverse effects reported by the WHO Program for International Drug Monitoring member countries since 1968 [32]. VigiBase is an archive of all the alleged ADEs from 130 countries worldwide, reported by respective national pharmacovigilance centers. The reports in the VigiBase are appropriately structured and arranged with details of sociodemographic profile (age, sex, continent, and country), drugs (date of initiation of therapy, last date of treatment, route of administration, and indications), suspected ADEs with their onset date, degree of seriousness, causality, outcome and administrative data which is a type of report and the source of the report. VigiBase allows effortless and pliable extraction and analysis of the data documented over time [33]. In this database, the medicines are coded accordingly as per the WHO Drug Dictionary Enhanced (WHO DDE), and it also encompasses the Anatomical Therapeutic Chemical (ATC) classification [34]. The ADEs were coded using WHO Adverse Reaction Terminology and the Medical Dictionary for Regulatory Authorities (MedDRA) [35,36]. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed MedDRA, which contains distinct standardized medical terminologies to ensure and promote the sharing of regulatory information for medicinal products humans across the countries [35,37]. The hierarchy in MedDRA has five levels and are arranged in order of very specific to very general levels, which are as follows: LTTs (Lowest Level Terms), PTs (Preferred Terms), HLTs (High-Level Terms), HLGTs (High-Level Group Terms), and SOCs (System Organ Classes) . This study uses the PT and SOC information. Preferred Terms are definite terminologies for a symptom, manifestation, diagnosis of a disorder, clinical use, investigation, medical or surgical procedure, and medical social or family history characteristic. Whereas the SOCs are the categorization based on their causality (e.g. infections and infestations), site of manifestation (e.g. gastrointestinal disorders), and indication (e.g. surgical and medical procedures) [37]. Additionally, the SOC also categorizes the issues regarding products and social circumstances [37]. The analysis of all the suspected ADEs from April-2 to August-11, 2020, related to tocilizumab was reported while treating

COVID-19 patients. All ADEs published in the VigiBase refer to a single individual who might have had one or multiple ADEs concomitantly. Due to this, the count of ADEs reported could be higher when equated with patients' numbers. The ADEs were classified according to the MedDRA, grouped at the SOC and individual PT levels. The methodology is summarized (Figure 1).

2.1. Statistical analysis

The data were entered in Microsoft Excel and were reported in frequency and percentages. Descriptive statistics were used for analysis. STATA 15.1, StataCorp, Texas, USA, was used to analyze the data using simple, followed by multiple logistic regression to find the factors associated with the patients' outcome reported with ADESs in this study. The significance level was set at 0.05, where the odds ratio (OR) was reported with its 95% confidence interval (CI). The multiple logistic regression model's fitness was checked using the sensitivity, specificity, and correctly classified outcome. The Pearson and Hosmer-Lemeshow chi-square goodness-of-fit tests confirmed the excellent fit of the model tested. Missing values rendered the adequate sample size reduced to 261 from the original 513 patients included in the initial data analysis.

2.2. Ethical approval

This study was based on the WHO's database and did not involve direct interaction with human participants; hence ethical approval was not required.

3. Results

There were a total of 1005 adverse drug events reported from 513 individuals. On analyzing the data based on number of reported ADEs, the majority of these ADEs were reported from

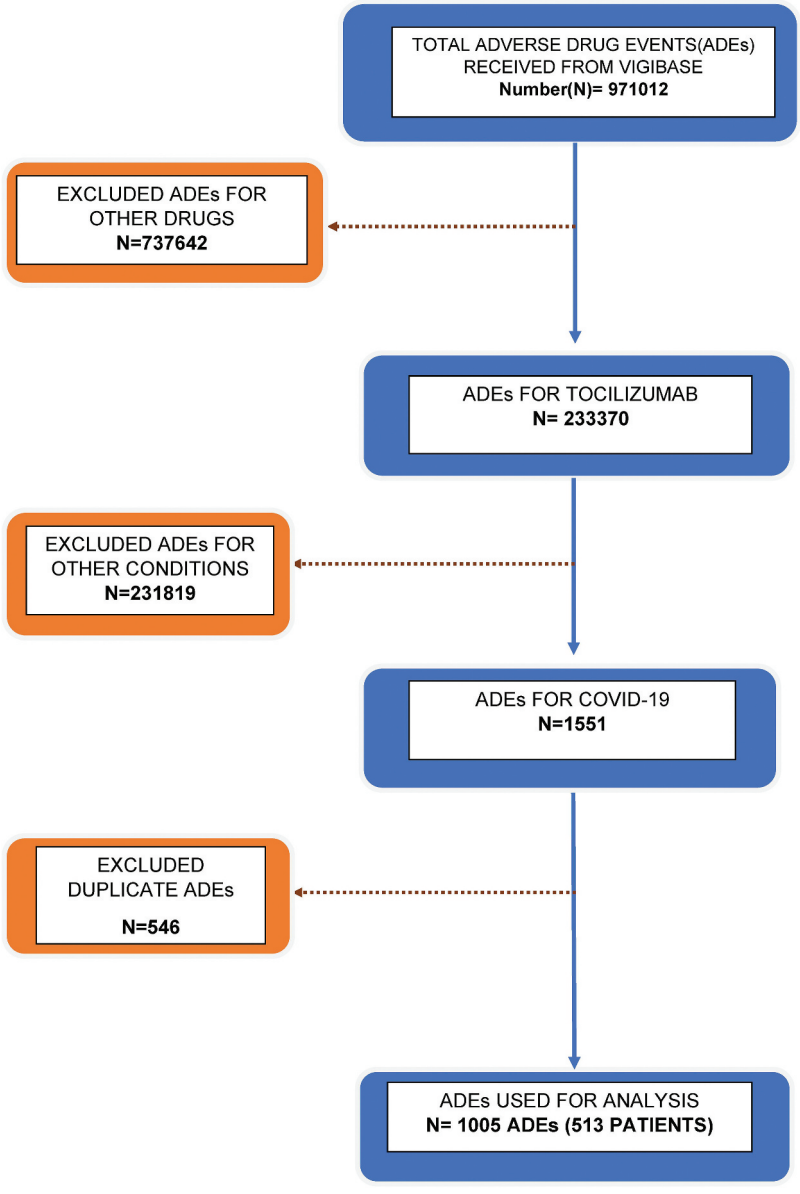

Figure 1. Schematic diagram of Adverse Drug Events selection from VigiBase data used to filter the records.

the age group 18–64 years (46.26%). There were only a few ADEs reported from the age group < 18 years. More than half of the ADEs were reported from the males. Reporting was more from Europe and the Americas as compared to Asia, Africa, and Oceania. Only 12% of the ADEs were reported from the clinical trials, rest were spontaneous reporting. 80% of these ADEs were serious and 20% were fatal. The intravenous route was used for administration of the tocilizumab in around 64% of ADEs. To manage these ADEs, the drug was withdrawn in 17% of ADEs, and Rechallenge was done in 27% of the events. (Table 1)

The distribution of 1005 reported ADEs within the WHO regions is illustrated in Figure 2. Among the various outcomes of 1005 reported ADEs, the majority were unknown (N = 419) followed by fatality (N = 207), recovered or resolved (N = 125), not reported (N = 106), recovering or resolving (N = 91), not recovered or not resolved (N = 56) and recovered or resolved with sequelae (N = 1) (Figure 3). To manage these ADEs, the drug was withdrawn in 17% of ADEs (Figure 4), and following the dechallenge, the reaction was decreased by 20.2% (Figure 5). Rechallenge was attempted in 27% of the events, and most were not reported (Figure 6). Following the rechallenge, the effect was unknown in 26.5% of the events (Figure 7).

On further examining the demographic characteristics data based on number of patients, with 27.9% of unreported age, most of the ADEs were reported in the 45 to 64 years old age group (32.6%). With 26.5% unreported sex, more than half of the ADEs were reported in males (53.2%). Most of the cases were reported from Europe (51.1%) and the Americas (32.0%). Only 11.7% of ADEs were reported from formal clinical trials, while the rest were spontaneous reporting except for 0.8% from other sources. Among the reports, 71.5% of ADEs were serious ADEs. The intravenous route was used for administration of the tocilizumab was 56.8% of the ADEs. The information above is detailed out in Table 2.

Table 1. Characteristics of Adverse Events (1005 AEs reported from 513 Individuals) reported for Tocilizumab in WHO database (N = Number of adverse events).

Parameter		Number of adverse events (%)
Age (N = 1005)	< 18 Years	5 (0.49)
	18–64 Years	465 (46.26)
	≥ 65 Years	320 (31.84)
	Not reported	215 (21.39)
Gender (N = 1005)	Female	220 (21.89)
	Male	572 (56.91)
	Not reported	213 (21.19)
Report Type (N = 1005)	Report from study	122 (12.13)
	Spontaneous	872 (86.76)
	Other	11 (1.09)
Seriousness of Adverse Event (N = 1005)	Serious	803 (79.90)
	Non-Serious	202 (20.09)
Route of Administration (N = 1005)	Intravenous	642 (63.88)
	Subcutaneous	36 (3.58)
	Unknown	289 (28.75)
	Not reported	38 (3.78)

*Number of adverse events reported are more than number of patients.

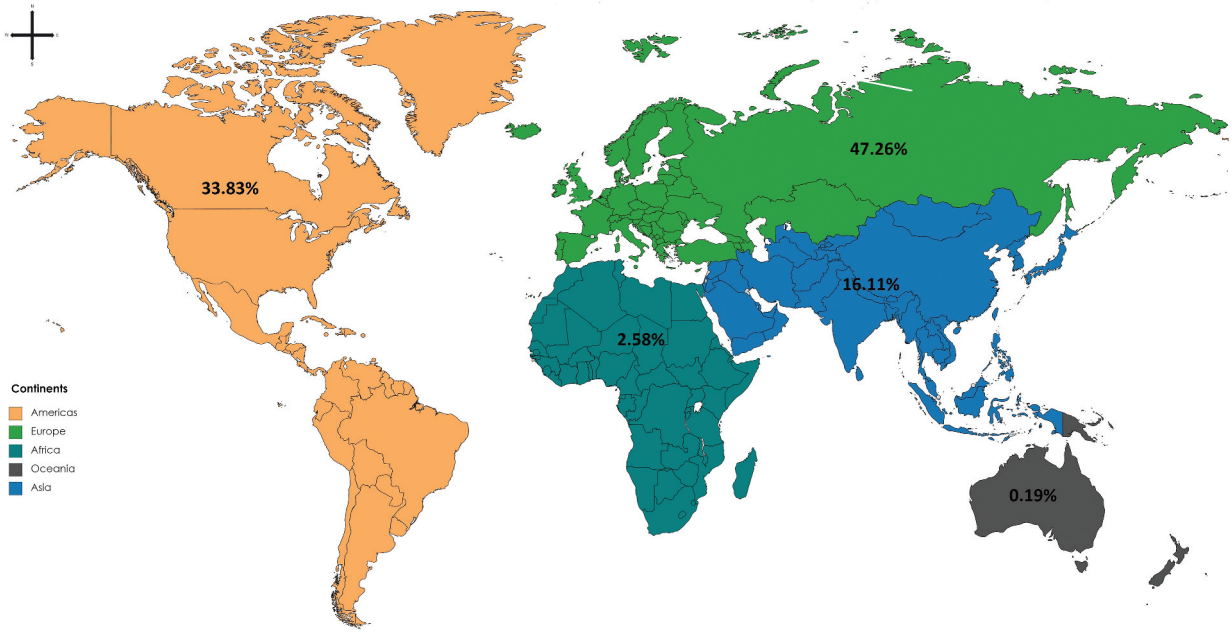

Figure 2. Distribution of Adverse Drug events with Tocilizumab use in COVID-19 across continents.

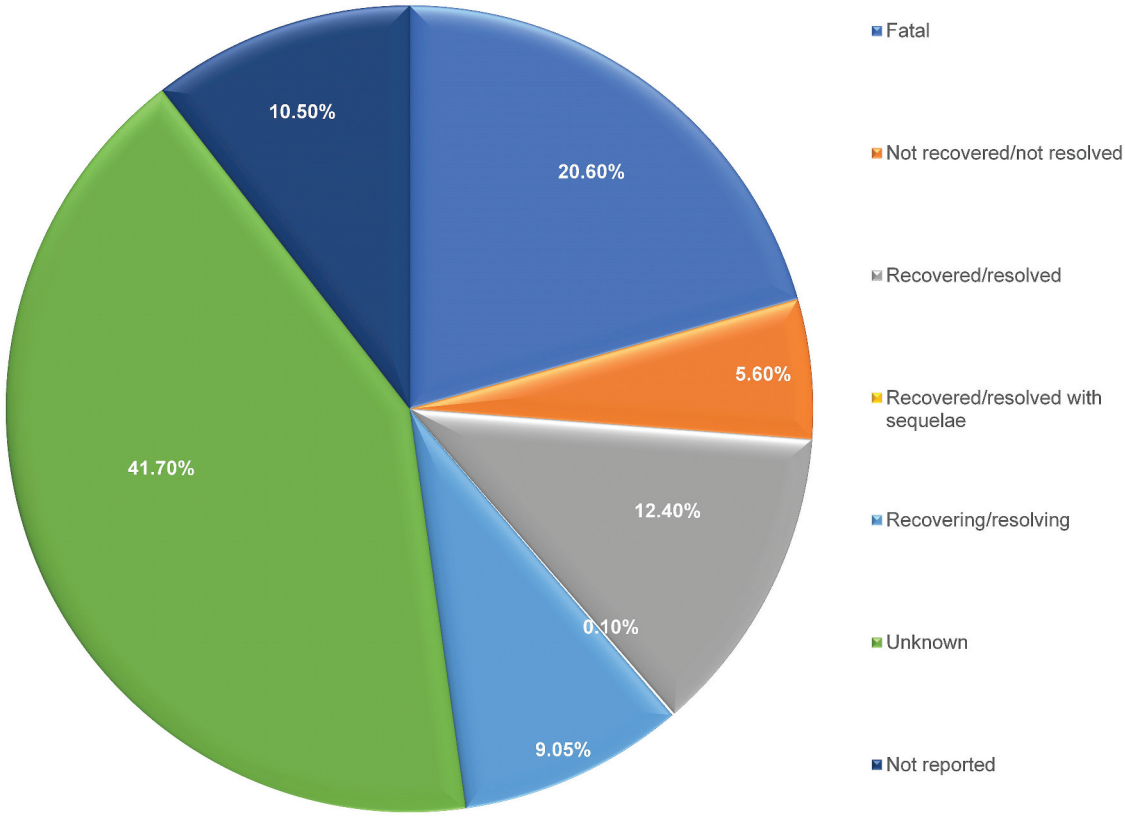

Figure 3. Adverse Drug Event Outcomes of Tocilizumab use in COVID-19.

Examining broad categories, the highest number of ADEs were reported from the 'Injury, Poisoning and Procedural Complications' (35%), followed by 'General Disorders and Administration Site Condition' (17.61%), 'Investigations' (8.6%), and 'Infections and Infestations' (7.8%). In the broad category 'Blood and Lymphatic System Disorders,' the most frequently reported ADEs were neutropenia (1.5%), hypercoagulable state/hypofibrinogenemia (0.80%), and anemia (0.50%). Cardiac arrest (0.90%) and dysrhythmia, including atrial fibrillation and flutter, were common ADEs reported from the broad category 'Cardiac Disorders.' Intestinal perforations (1.2%) and ulcers were commonly reported ADEs from the 'Gastrointestinal Disorders' category. Simultaneously, deterioration of the condition/unexpected therapeutic response was common ADEs from the broad category 'General disorders and administrative site conditions.' More than 50% of ADEs reported from the wide variety 'Hepatobiliary Disorders' were hepatitis, and four ADEs were reported as hypersensitivity from the general category 'Immune System Disorders.' Fungal infections and pneumonia were very commonly reported from the category 'Infections and Infestations.' An increase in the liver enzymes was predominant in the broad category 'Investigations.' There were six acute kidney injury events, four end-stage renal disease events, and four renal failure events in the general category 'Renal and urinary disorders.' Amongst the 'Respiratory, thoracic and mediastinal disorders,' the most frequent ADEs were pulmonary embolism and respiratory failure . The ADEs distribution of tocilizumab use in patients with COVID-19 is summarized (Figure 8). The detailed adverse events are presented in supplementary Table 1.

To assess the factors associated with the outcome (recovered compared to fatal and not recovered as the reference group) in patients with reported ADEs suspected to be caused by tocilizumab used in the treatment of COVID-19 in the WHO database in this study, the simple logistic regression was used, followed by the multiple logistic regression to control for the confounding effects during analysis. The results are reported in Table 3, where the simple logistic regression shows that the sex, age groups, and regions are not significantly associated with the outcome ($p > 0.05$). However, the results of the multiple logistic regression show that the oldest age group (more than 64 years old) has less odds or chance to recover from ADEs (OR = 0.363, 95% CI = 0.153, 0.862, $p = 0.022$) compared to the youngest age group (less than 45 years old). It was also observed from the multiple logistic regression that those from the European Region were more likely to recover compared to those from the Regions of America with the OR of 3.716 (95% CI = 2.018, 6.845, $p < 0.001$).

In a multiple logistic regression model, the seriousness of ADEs ('yes' or 'no') was significantly associated with the age group. The odds of having serious ADEs were more than twice higher in patients aged 65 years and above instead of those aged 44 years and below [OR = 2.09, 95% CI (1.09, 4.00), p = 0.026]. There was a marginally significant association between the seriousness of ADEs and the WHO region.

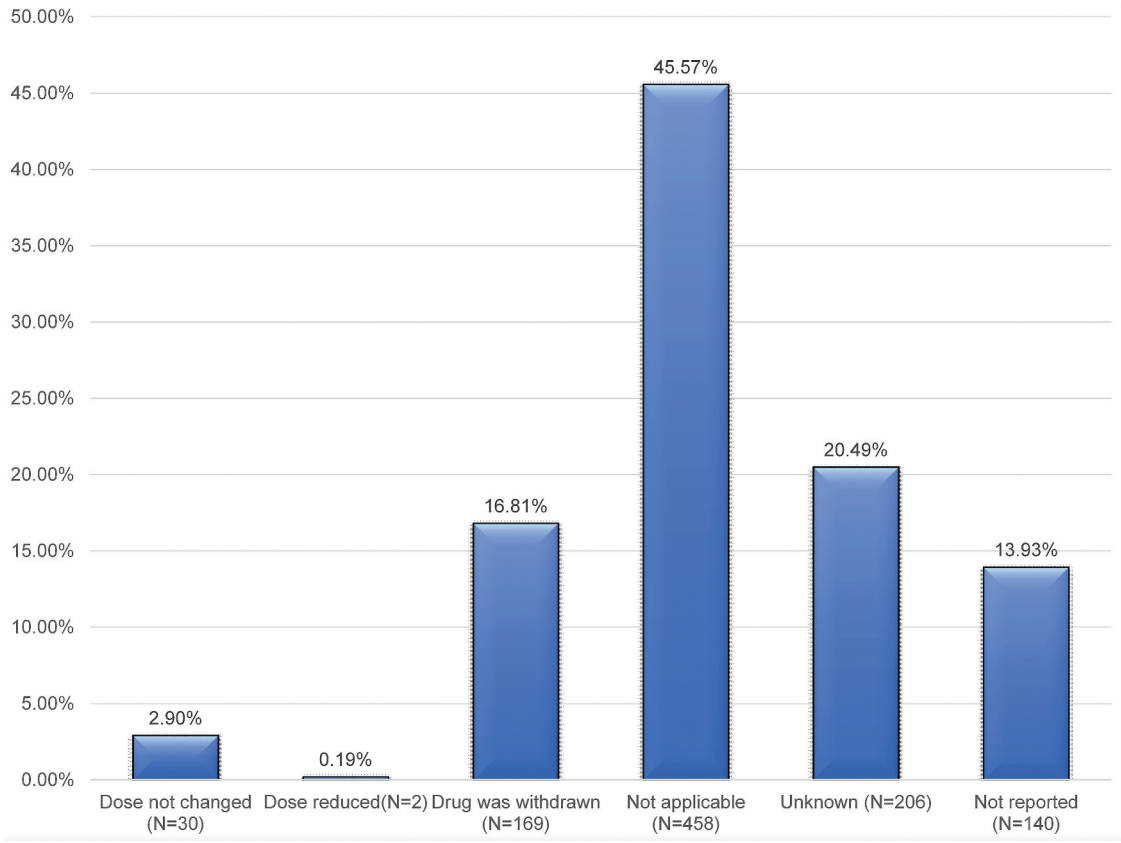

Figure 4. Summary of Dechallenge Action taken on encountering Adverse Drug Events with Tocilizumab use in COVID-19. (N = Number of adverse events with tocilizumab).

Patients from the European region had 39% lower odds of having serious ADEs than those from the Americas [OR = 0.61, 95% CI (0.37, 1.00), p = 0.049]. No significant association was found between the seriousness of ADEs and sex (Table 4).

4. Discussion

The present study was conducted to analyze the ADEs reported in the WHO database. The male sex appears more vulnerable. ADE episodes were reported across a wide age group from below 20-year to over 60-years. A significant chunk of ADEs was reported from Europe, followed by the Americas, and then from elsewhere. Most of the ADEs were reported spontaneously and were observed when tocilizumab was administered intravenously.

Tocilizumab has been used in various immunological disorders, but its use in COVID-19 is either on compassionate grounds or under trial [16–24]. Due to the lack of its extensive usage, limited information about its post-approval safety and efficacy is available [21,25,27,28]. Based on the evidence of use in immunological disorders, the ADEs have been classified into very common ADEs like upper respiratory tract infections and hyperlipidemia [14]. Common ADEs include severe infections due to various pathogens such as bacteria, fungi, viruses, protozoa, or any other opportunistic infections (tuberculosis, cryptococcosis, aspergillosis, candidiasis, etc. Pneumocystis jirovecii pneumonia), which can present as cellulitis, pneumonia, urinary tract infection, herpes zoster, and gastroenteritis [13,14]. Other common ADEs include gastrointestinal diseases such as gastritis, abdominal pain, skin disorders including rashes and itching, headache, dizziness, high blood pressure, cough, respiratory distress, conjunctivitis, along with abnormal laboratory parameters, especially raised liver transaminases, elevated total bilirubin, leukopenia, neutropenia, and low fibrinogen levels. Uncommon ADEs are diverticulitis, renal stones, hypothyroidism, stomatitis, and gastric ulcer were reported [13]. Rare ADEs include severe hypersensitivity reactions (anaphylaxis, Stevens-Johnson-Syndrome) and hepatobiliary disorders (drug-induced liver injury and hepatitis) have been noticed [13,14].

In the present study, neutropenia (1.5%) was the most common blood, and lymphatic system disorder observed, followed by hypofibrinogenemia (0.8%) and thrombocytopenia (0.7%). Higher rates of neutropenia were reported in several previous studies conducted by Price et al. (4%), Morena et al. (6%), Stone et al. (13.7%), and Campochiaro et al. (16%) in tocilizumab treated COVID-19 patients [21,25,27,31]. The rate of thrombocytopenia reported by Stone et al. (0.6%) was comparable to the WHO database (0.7%), whereas Morena et al. (14%) reported a comparatively higher rate [27,31]. Anemia was reported among a few patients (0.5%) in the WHO database, whereas a study performed by Campochiaro et al. reported anemia at 64% as the most frequent ADE [25].

Cytokine storm, which is a fatal occurrence in COVID-19 patients where the immune system is hyperactivated leading to highly elevated levels of cytokines like IL-1β, IL-6, IP-10, TNF,

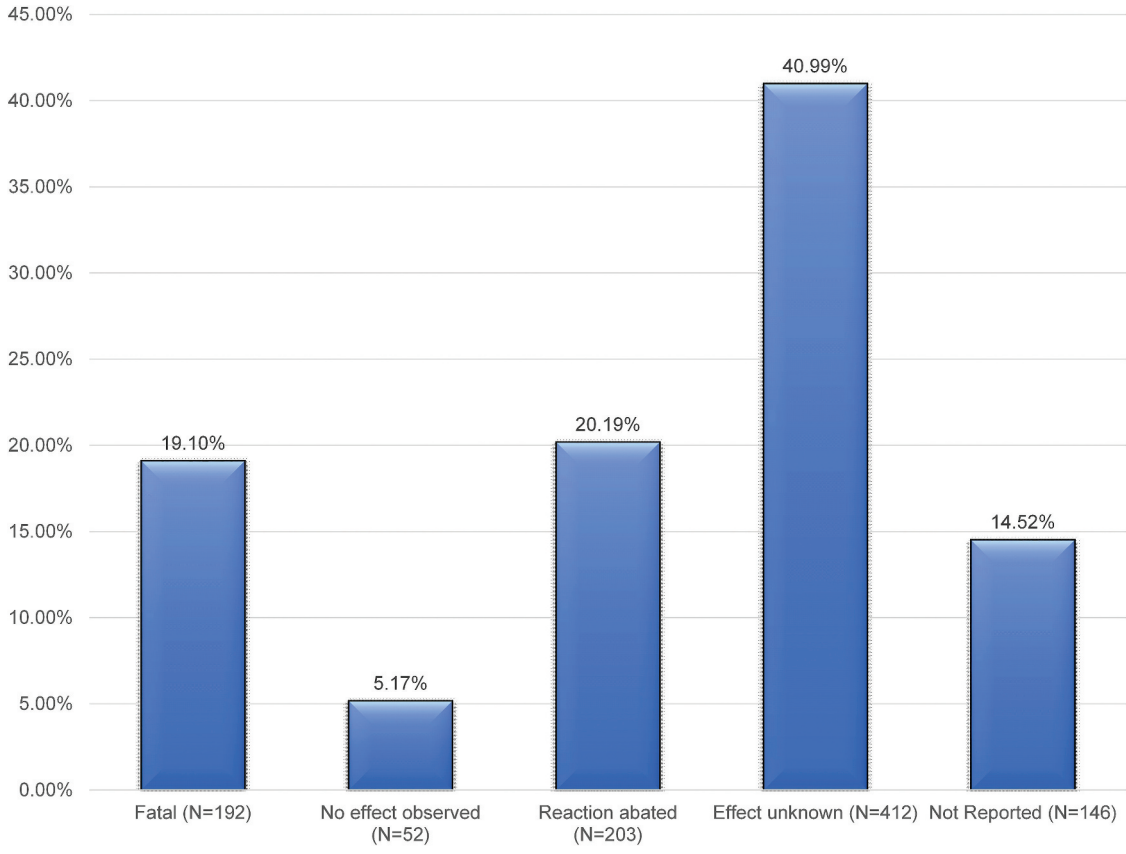

Figure 5. Summary of Dechallenge outcomes of Adverse Drug Events with Tocilizumab use in COVID-19. (N = Number of adverse events with tocilizumab).

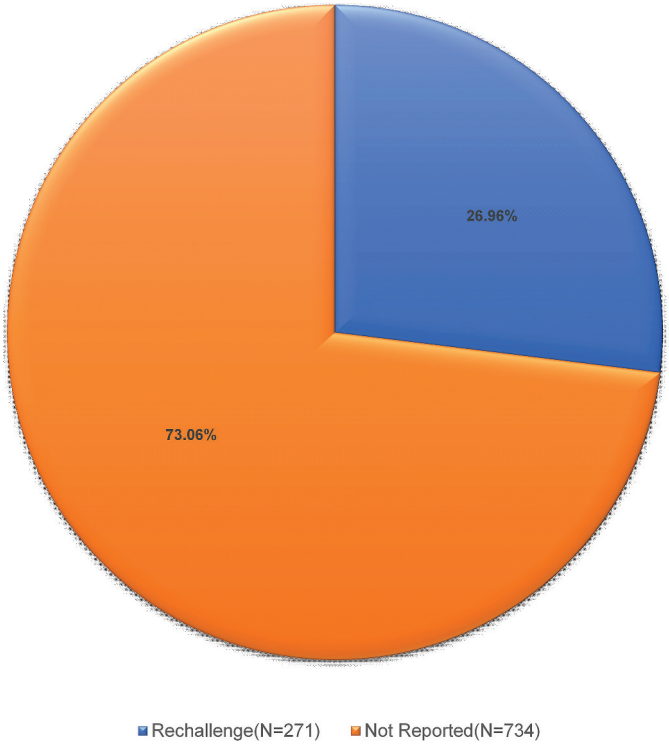

Figure 6. Summary of Rechallenge Action taken with Tocilizumab in COVID-19 patients. (N = Number of adverse events with tocilizumab).

INF-γ, MIP- 1α and 1β [38,39]. The common cells that are involved in the pathogenesis of cytokine storm are neutrophils, macrophages, and natural killer cells. The extracellular webs of DNA/histones synthesized by neutrophils are called Neutrophil extracellular traps (NETs) and helpful in controlling infections and are also responsible for worsening inflammation which can end up into cytokine storm [40,41]. In severe COVID-19 cases, an increased level of NETs have been found and is hypothesized that it is a crucial link inducing release of cytokines further leading to multi-organ damage [41–44]. However, on resolution of the infection or inflammation, the neutrophils undergo apoptosis and necrosis to maintain the homeostasis and prevent the body from prolonged damage by the neutrophils and released granules or reactive oxygen species [45]. This step of death of neutrophils in absence of inciting stimuli is crucial and increased rate of neutrophil clearance might need to neutropenia in certain conditions [46,47]. In the present study, the reasons for the events of neutropenia could not ascertained whether it was because of the resolution of the inflammation/cytokine storm or due to the drug tocilizumab.

Increased hepatic enzyme levels accounted for about 4.68% of the ADEs, whereas hepatitis accounted for 2.49%. The majority of the studies on COVID-19 patients reported higher values as compared to the present study. Campochiaro et al. reported a transient rise in liver enzymes in 15% of the tocilizumab treated patients [25]. Morena et al. had 29% of patients with abnormal hepatic enzymes. In contrast, Alattar et al. reported a rise of Alanine aminotransferase (ALT) in 44% of the patients [27,29].

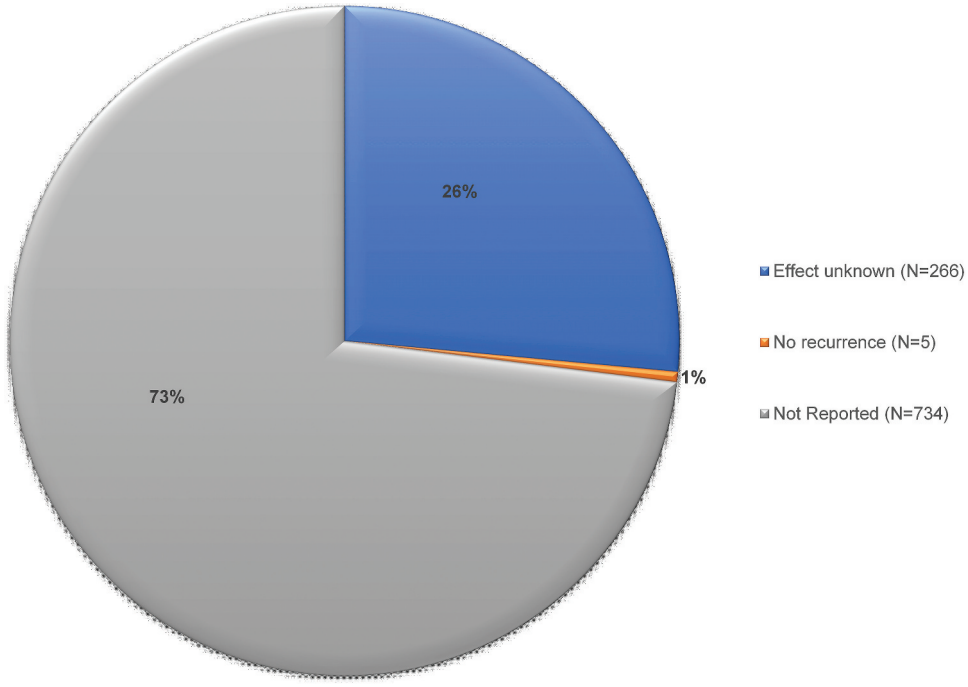

Figure 7. Summary of Rechallenge outcomes with Tocilizumab in COVID-19 patients. (N = Number of adverse events with tocilizumab).

Table 2. Socio-demographic Characteristics of Patients with Reported Adverse Drug Events suspected due to Tocilizumab in the WHO database (n = Number of patients).

Parameter		Number of patients	Percentage
Age (n = 513)	2–44 years old	54	10.5
	45–64 years old	167	32.6
	≥ 65 Years	149	29.0
	Not reported	143	27.9
Sex (n = 513)	Female	104	20.3
	Male	273	53.2
	Not reported	136	26.5
Continents (n = 513)	Americas	164	32.0
	Europe	262	51.1
	Others	87	17.0
Report Type (n = 513)	Report from the study	60	11.7
	Spontaneous	449	87.5
	Other	4	0.8
The seriousness of Adverse Event (n = 513)	Serious	367	71.5
	Non-Serious	146	28.5
Route of Administration (n = 513)	Intravenous	291	56.8
	Subcutaneous	18	3.5
	Unknown	204	39.8

Salvarani et al reported rise in alanine aminotransferase as the most common adverse event with 8% in tocilizumab group in comparison to 3% in standard care group [48]. Rimland et al. reported minimally elevated liver function tests in 64% of the patients, which was higher than other studies [49]. On the contrary, Stone et al. reported a lower rate of ALT (5.0%) and aspartate aminotransferase (AST) rise (3.7%) [31]. In contrast, Guaraldi et al. documented no evidence of AST elevation's differential rate among treatment groups [18]. In a study performed by Gatti et al on the characterization of the adverse events reported with tocilizumab in the FDA Adverse Event Reporting system, several reports of hepatitis fulminant, acute hepatic failure and hepatic necrosis were observed [50].

This study observed varied rates of infections and infestations in the WHO database such as bacteremia (0.3%), Candida Infection (0.5%), Pneumonia of various etiology (1.6%), Staphylococcal Sepsis (0.40%), Septic Shock Syndrome (0.9%) and Staphylococcal Infection (0.4%). Studies conducted on COVID-19 patients using tocilizumab reported varied results. Bacteremia was reported in 27% of patients by Morena et al., 13% of patients by Campochiaro et al., 13% by Ip et al., 13.7% by Stone et al., and <1% by Guaraldi et al. [18,25,27,31,51]. Bacterial infections, superinfections, and related complications were seen in various studies with various proportions. A survey executed by Quartuccio et al. documented that 43% of patients had bacterial complications [30]. In contrast, Gorgolas et al. reported these in 6 · 3% of the patients [52]. Studies were done by Kimmig et al. (64.3% vs. 31.3%), Somers et al. (54% vs.26%), and Menzella et al. reported that patients treated with tocilizumab were almost twice as prone to developing secondary bacterial infections/superinfections as compared to the non-treated group [20,53,54]. Menzella et al. reported that most superinfections were ventilator-associated pneumonia, and Staphylococcus aureus was found to be the pathogen in about 50% of bacterial pneumonia cases [20]. Studies conducted by Ip et al. reported secondary pneumonia in 9% of the cases, and Campochiaro et al., documented cases of candidemia and invasive pulmonary aspergillosis in patients treated with tocilizumab [25,51]. Toniati et al. reported that two patients developed septic shock and later succumbed to it [24]. There were two reported cases of Herpes infection in the WHO database. Alattar et al., in their study, reported one case of herpes simplex virus reactivation [29]. Guaraldi et al., in their research, reported four cases of invasive aspergillosis, one case of hepatitis B virus reactivation, and four cases of

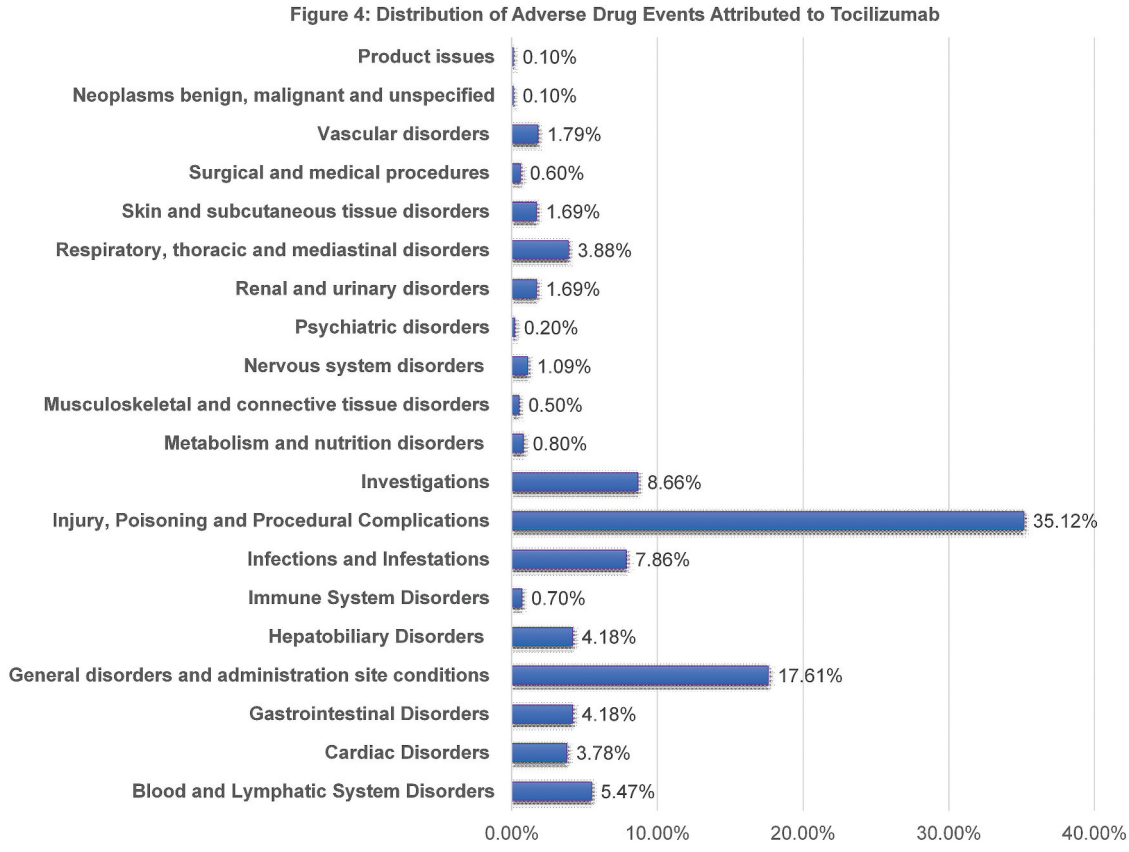

Figure 8. System-wide Distribution of Adverse drug events attributed to Tocilizumab use in COVID-19.

Table 3. Factors Associated with the Outcome (Recovered vs. Fatal/Not Recovered*) Among Patients with Reported Adverse Drug Events Suspected to be Caused by Tocilizumab Used in the Treatment of COVID-19 in the World Health Organization (WHO) Database (n = 261).

	Simple Logistic Regression		Multiple Logistic Regression	
Variables	Odds ratio (95% CI[b])	*p*-value	Odds ratio (95% CI[b])	*p*-value
Sex:				
Male*	0	1.000	0	1.000
Female	1.096 (0.653, 1.839)	0.729	1.217 (0.652, 2.268)	0.538
Age Group (years):				
< 45*	0	1.000	0	1.000
45–64	0.879 (0.436, 1.773)	0.718	0.642 (0.277, 1.485)	0.300
> 64	0.617 (0.304, 1.255)	0.183	0.363 (0.153, 0.862)	0.022
WHO Region:				
Americas*	0	1.000	0	1.000
Europe	1.440 (0.922. 2.248)	0.109	3.716 (2.018, 6.844)	< 0.001
Other regions	0.991 (0.561, 1.753)	0.976	0.964 (0.397, 2.493)	0.887

[a]Controlled for the confounding effect. [b] Confidence interval. * The reference group.

herpes simplex virus reactivation, among which one patient died of severe hepatic failure due to hepatitis owing to severe herpes simplex virus [18].

These infections and superinfections could be due to suppression of the immune system by blocking the IL-6 pathway which is crucial in functioning of immune system by interplay between innate and adaptive immunity [55]. IL-6 as a cytokine which also acts as a differentiation factor for B cells that can instigate the activated B cells to synthesize immunoglobulins [56–58]. As IL-6 is crucial in the synthesis of antibodies which can directly fight against the foreign pathogens like viruses, a drug like tocilizumab which acts via blocking the IL-6 receptors might affect the body's immune defense against the COVID-19 virus by suboptimal formation of immunoglobulins from the B cells [56,57]. However, literature reveals that studies done by Masiá et al. and Başaran et al. reported that tocilizumab administration in the COVID-19 patients did not lead to decreased antibody response to SARS-CoV-2 [56,59]. In support of the findings, Cabanov et al. also reported that tocilizumab do not hamper the production of anti-SARS-CoV-2 antibodies [60]. This finding was supported by previous study conducted by Mori et al. where they reported that tocilizumab did not affect the production of antibodies after influenza vaccination in patients with rheumatoid arthritis [61].

This study identified intestinal perforation in 1.19% of the patients. Toniati et al. reported that one patient developed gastrointestinal perforation while on treatment with tocilizumab [24]. Salvarani reported one serious adverse event in the form of gastrointestinal tract bleeding in patients receiving tocilizumab [48]. Among the skin and subcutaneous tissue disorders, a rash was reported in 0.60% of the cases in the WHO database. Higher numbers were reported by Morena et al., where a cutaneous rash was seen in 2% of the treated patients [27]. In cardiovascular ADEs, QT prolongation was seen in 0.10% and Atrial fibrillation in 0.2% of the patients

Table 4. Predictors of Serious Adverse Drug Events suspected to be caused by Tocilizumab used in treating COVID-19 in the WHO Database.

	Crude		Adjusted	
Variables:	OR (95% CI)	p value	OR (95% CI)	p value
Sex:				
Male	1		1	
Female	0.94 (0.62, 1.42)	0.756	1.22 (0.73, 2.03)	0.457
Age Group:				
≤ 44 years old	1		1	
45–64 years old	1.37 (0.76, 2.48)	0.292	1.52 (0.83, 2.80)	0.174
≥ 65 years old	1.72 (0.93, 3.12)	0.084	2.09 (1.09, 4.00)	0.026
WHO Region:				
Americas	1		1	
Europe	0.92 (0.64, 1.32)	0.637	0.61 (0.37, 1.00)	0.049
Other regions	0.44 (0.28, 0.68)	<0.001	0.76 (0.36, 1.62)	0.480

in the WHO database. Alattar et al., in their study, reported a comparatively higher proportion of QT prolongation in 5 patients (20%) and Atrial fibrillation in one patient in their tocilizumab treated patients [29]. Acute kidney injury was reported in six patients in the WHO database, whereas Alattar et al. documented a single acute kidney injury case in their study [29]. Hypertriglyceridemia was seen in four cases in the WHO database. Alattar et al., in their series, reported two cases of hypertriglyceridemia, and evidence-based on its previous use in immunological disorders, hypercholesterolemia is among very common ADEs of tocilizumab [29].

On the contrary to the above findings, there were studies conducted by Rossi et al., Colaneri et al., Sciascia et al., Xu et al., and Sanchez-Montalvá et al. which concluded that they failed to note any adverse drug reactions deemed to use of tocilizumab in COVID-19 patients [62–65]. In the study performed by Veiga et al, adverse events were reported in 43% participants receiving tocilizumab in comparison to 34% in patients receiving standard care, out of which serious adverse events were in 16% in the tocilizumab group and 11% in the standard care group. However, they did not find any significant difference in the incidence of any specific adverse event between patients receiving tocilizumab and standard care [66].

Even though we do not have enough data regarding the safety of tocilizumab use in COVID-19 patients, safe prescribing in these patients can be predicted based on the previous safety data of its use in immunological diseases. The results in the WHO database and the trials are based on short-term studies on the COVID-19 patients. Extensive trials are essential to assess the safety of tocilizumab in COVID-19 patients. The publication of the results of tocilizumab use in the RECOVERY trial makes this a treatment option of choice.

4.1. Limitation of the study

Tocilizumab has not been used officially and commonly in treating patients with COVID-19 outside the RECOVERY trial; thus, less case information reports are available in the WHO database, which will probably highlight the common ADEs, whereas uncommon ones may be missed. The data in this study was taken from VigiBase where the information comes from varied sources. The probability of a suspected adverse effect to be caused by drug cannot be ascertained in all the cases. The information provided does not represent the opinion of the UMC or the World Health Organization.

5. Conclusion

Tocilizumab appears to be a relatively safe drug based on the WHO database's available data, with small overall numbers of ADEs, reported. Neutropenia, elevated liver enzymes, superinfections, pneumonia, reactivation of herpes simplex, tuberculosis or hepatitis, hypertriglyceridemia, acute kidney injury, pulmonary embolism, rash, and cardiac abnormalities are prevalent ADEs in patients with COVID-19 infection, mostly in mild cases. Therefore, to generate evidence, long-term follow-up studies with a large sample size will enlighten medical science about unknown ADEs associated with tocilizumab in COVID-19 patients. According to this study, the findings suggest there are numerous adverse effects. Reports from randomized, double-blind controlled clinical trials will provide more safety information to enable evidence-based decision-making on the use of tocilizumab to treat patients with COVID-19.

In conclusion, tocilizumab is one of the drugs supported by trial data for the treatment of COVID–19. It is essential to assess tocilizumab's efficacy and safety in COVID-19 based on available data from the trials and spontaneous reports. Patients given tocilizumab should be adequately monitored for altered full blood count, altered liver function, superinfections, and ECG changes during the treatment.

6. Recommendation

Clinicians using tocilizumab should monitor for the presence of neutropenia, changes in cellular blood values, rise in hepatic enzymes, the possibility of superinfection, reactivation of latent infections, and alteration ECG and plausible drug interactions and drug-disease interaction during the treatment to avoid adverse events and obtain better clinical outcomes.

Acknowledgments

We want to acknowledge 'mapchart.net' to prepare a map diagram for our study, a free service.

Author contributions

Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: JC, SD, RK, PB, PS, SA, IJ, ARA, SI, TCH, NAAR, HL, MH; Drafting the article or revising it critically for valuable intellectual content: JC, SD, RK, PB, PS, SA, IJ, ARA, SI, TCH, NAAR, HL, MH; Final approval of the version to be published: JC, SD, RK, PB, PS, SA, IJ, ARA, SI, TCH, NAAR, HL, MH; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: JC, SD, RK, PB, PS, SA, IJ, ARA, SI, TCH, NAAR, HL, MH; Project administration: JC, SD, RK, PB, PS, SA, IJ, ARA, SI, TCH, NAAR, HL, MH.

Data sharing

The data that support the findings of this study are available from the corresponding author JC, upon reasonable request.

Funding

This paper was not funded.

Declaration of interest

The authors declare that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this article. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties. The authors are totally responsible for the views expressed in this paper, and they do not necessarily represent the decisions, policy or views of the World Health Organization.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Jaykaran Charan http://orcid.org/0000-0002-4857-6725
Siddhartha Dutta http://orcid.org/0000-0001-6525-5950
Praveen Sharma http://orcid.org/0000-0002-8324-737X
Iffat Jahan http://orcid.org/0000-0003-0551-3609
Salequl Islam http://orcid.org/0000-0001-6131-4132
Timothy Craig Hardcastle http://orcid.org/0000-0002-3967-0234
Nor Azlina A Rahman http://orcid.org/0000-0002-9046-6183
Mainul Haque http://orcid.org/0000-0002-6124-7993

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. Updated 9 July 2020. [cited 2020 Oct 20]. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions
2. World Health Organization. Rolling updates on coronavirus disease (COVID-19). Updated 31 Jul 2020. [cited 2020 Oct 20]. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
3. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Updated 20 Oct 2020. [cited 2020 Oct 20]. https://covid19.who.int
4. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20(6):355–362.
5. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620–2629.
6. Chen LD, Zhang ZY, Wei XJ, et al. Association between cytokine profiles and lung injury in COVID-19 pneumonia. Respir Res. 2020;21(1):201.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395 (10223):497–506.
8. Russano M, Citarella F, Napolitano A, et al. COVID-19 pneumonia and immune-related pneumonitis: critical issues on differential diagnosis, potential interactions, and management. Expert Opin Biol Ther. 2020;20(9): 959–964.
•• **This article points out that the role of IL-6 in the in inciting the inflammatory cytokine storm, which potentially damages the lungs and worsens the prognosis of the patient.**
9. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol. 2020 Jun;215:108427.
10. Zhou Y, Fu B, Zheng X, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl Sci Rev. 2020;7(6): 998–1002.
•• **This article points out that the role of IL-6 in the in inciting the inflammatory cytokine storm in COVID-19 patients.**
11. Sinha P, Mostaghim A, Bielick CG, et al. Early administration of interleukin-6 inhibitors for patients with severe COVID-19 disease is associated with decreased intubation, reduced mortality, and increased discharge. Int J Infect Dis. 2020;99:28–33.
•• **This article points out that the early administation of anti-IL-6 in COVID-19 may improve prognosis.**
12. The WHO Collaborating Centre for Drug Statistics Methodology. Updates included in ATC/DDD index. Updated 16 Dec 2019. [cited 2020 Oct 22]. https://www.whocc.no/atc_ddd_index/?code=L04AC&showdescription=no
13. Electronic Medicines Compendium (EMC). RoActemra 20mg/ml concentrate for solution for infusion. Updated 23 Jul 2020. [cited 2020 Oct 22]. https://www.medicines.org.uk/emc/product/6673/smpc#gref
14. Food and Drug Administration. ACTEMRA (tocilizumab) injection: prescribing INFORMATION. Updated 2017 Aug. [cited 2020 Oct 22]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf
15. Tocilizumab. Updated 29 Jul, 2015. [cited 2020 Oct 25]. https://www.pharmacodia.com/yaodu/html/v1/biologics/5f1d3986fae10ed2994d14ecd89892d7.html#:~:text=Tocilizumab%20was%20first%20approved%20by,)%20on%20March%2026%2C%202013
16. Antwi-Amoabeng D, Kanji Z, Ford B, et al. Clinical outcomes in COVID-19 patients treated with tocilizumab: an individual patient data systematic review. J Med Virol. 2020;92 (11):2516–2522.
17. De Rossi N, Scarpazza C, Filippini C, et al. Early use of low dose tocilizumab in patients with COVID-19: a retrospective cohort study with a complete follow-up. EClinicalMedicine. 2020 Aug;25:100459.
• **This article points out that there are no signigicant adverse events associated with administation of Tocilizumab in COVID-19.**
18. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020 Aug;2(8):e474–e484.
19. Keske Ş, Tekin S, Sait B, et al. Appropriate use of tocilizumab in COVID-19 infection. Int J Infect Dis. 2020 Oct;99:338–343.
20. Menzella F, Fontana M, Salvarani C, et al. Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation. Crit Care. 2020 Sep 29;24(1):589.
• **This article points out that the administation of anti-IL-6 in COVID-19 may be involved with higher incidences of secondary infections.**
21. 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.
22. 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.
23. Tomasiewicz K, Piekarska A, Stempkowska-Rejek J, et al. Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study. Expert Rev Anti Infect Ther. 2020 Aug 1;1–8. DOI:10.1080/14787210.2020.1800453.
24. Toniati P, Piva S, Cattalini M, et al. 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. Autoimmun Rev. 2020 Jul;19(7):102568.
• **This article points out that the adverse events associated with administation of Tocilizumab in COVID-19.**
25. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-center retrospective cohort study. Eur J Intern Med. 2020 Jun;76:43–49.
26. Lan SH, Lai CC, Huang HT, et al. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents.

2020 Sep;56(3):106103. Epub 2020 Jul 23. PMID: 32712333; PMCID: PMC7377685.
27. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med. 2020 Jun;76:36–42.
- **This article points out that the adverse events associated with administation of Tocilizumab in COVID-19.**
28. Tsai A, Diawara O, Nahass RG, et al. Impact of tocilizumab administration on mortality in severe COVID-19. Sci Rep. 2020;10(1):19131.
29. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020 May;5. DOI:10.1002/jmv.25964.
- **This article points out that the adverse events associated with administation of Tocilizumab in COVID-19.**
30. Quartuccio L, Sonaglia A, McGonagle D, et al. Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care. J Clin Virol. 2020 Aug;129:104444.
31. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Dec 10 ;383(24):2333–2344.
32. Uppsala Monitoring Centre: WHOProgramme for International Drug Monitoring. VigiBase. [cited 2020 Oct 27]. https://www.who-umc.org/vigibase/vigibase
33. Uppsala Monitoring Centre. VigiBase: signaling harm and pointing to safer use. [cited 2020 Oct 28]. https://www.who-umc.org/vigibase/vigibase/vigibase-signalling-harm-and-pointing-to-safer-use
34. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology. Updated 17 Aug 2020. [cited 2020 Oct 28]. https://www.whocc.no
35. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Medical Dictionary for Regulatory Activities(MedDRA). [cited 2020 Oct 28]. https://www.meddra.org/how-to-use/support-documentation/english/welcome
36. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999 Feb;20(2):109–117.
37. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA Hierarchy. [cited 2020 Oct 28]. https://www.meddra.org/how-to-use/basics/hierarchy
38. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020 Dec 3;383(23):2255–2273.
39. Zhu Z, Cai T, Fan L, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020 Jun;95:332–339.
40. Narasaraju T, Yang E, Samy RP, et al. Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol. 2011 Jul;179(1):199–210.
41. Wang J, Jiang M, Chen X, et al. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. 2020 Jul;108(1):17–41.
42. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. J Exp Med. 2020 Jun 1;217(6):e20200652.
43. Lefrançais E, Looney MR. Neutralizing extracellular histones in acute respiratory distress syndrome. A new role for an endogenous pathway. Am J Respir Crit Care Med. 2017 Jul 15;196 (2):122–124.
44. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. JCI Insight. 2020 Jun 4;5(11):e138999.
45. Bordon J, Aliberti S, Fernandez-Botran R, et al. Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. Int J Infect Dis. 2013 Feb;17(2):e76–83.
46. Miles K, Clarke DJ, Lu W, et al. Dying and necrotic neutrophils are anti-inflammatory secondary to the release of alpha-defensins. J Immunol. 2009 Aug 1;183(3):2122–2132.
47. Simon HU. Neutrophil apoptosis pathways and their modifications in inflammation. Immunol Rev. 2003 Jun;193(1):101–110.
48. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: a Randomized Clinical Trial. JAMA Intern Med. 2021 Jan 1;181(1):24–31.
49. Rimland CA, Morgan CE, Bell GJ, et al. Clinical characteristics and early outcomes in patients with COVID-19 treated with tocilizumab at a United States academic center. medRxiv. 2020. DOI:10.1101/2020.05.13.20100404.
50. Gatti M, Fusaroli M, Caraceni P, et al. Serious adverse events with tocilizumab: pharmacovigilance as an aid to prioritize monitoring in COVID-19. Br J Clin Pharmacol. 2021 Mar;87(3):1533–1540.
51. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-An observational study. PloS One. 2020;15(8):e0237693.
52. Gorgolas M, Cabello A, Prieto Perez L, et al. Compassionate use of tocilizumab in severe SARS-CoV2 pneumonia. When late administration is too late. medRxiv. 2020. DOI:10.1101/2020.06.13.20130088.
53. Kimmig LM, Wu D, Gold M, et al. IL6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. Front Med (Lausanne). 2020 Oct;7:583897.
54. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis. 2020 Jul 11;ciaa954. DOI:10.1093/cid/ciaa954.
55. Rose-John S, Winthrop K, Calabrese L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. Nat Rev Rheumatol. 2017 Jul;13(7):399–409.
56. Başaran S, Şimşek-Yavuz S, Meşe S, et al. The effect of tocilizumab, anakinra and prednisolone on antibody response to SARS-CoV-2 in patients with COVID-19: a prospective cohort study with multivariate analysis of factors affecting the antibody response. Int J Infect Dis. 2021 Apr;105:756–762.
57. Cassese G, Arce S, Hauser AE, et al. Plasma cell survival is mediated by synergistic effects of cytokines and adhesion-dependent signals. J Immunol. 2003 Aug 15;171(4):1684–1690.
58. Muraguchi A, Hirano T, Tang B, et al. The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. J Exp Med. 1988 Feb 1;167(2):332–344.
59. Masiá M, Fernández-González M, Padilla S, et al. Impact of interleukin-6 blockade with tocilizumab on SARS-CoV-2 viral kinetics and antibody responses in patients with COVID-19: a prospective cohort study. EBioMedicin. 2020 Oct;60:102999.
60. Cabanov A, Flood BA, Bloodworth J, et al. Abstract S04-02: treatment with tocilizumab does not inhibit induction of anti-COVID-19 antibodies in patients with severe SARS-CoV-2 infection. Clin Cancer Res. 2020 September 15;26(18 Supplement):S04–02.
61. Mori S, Ueki Y, Hirakata N, et al. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. Ann Rheum Dis. 2012 Dec;71(12):2006–2010.
62. Colaneri M, Bogliolo L, Valsecchi P, et al. Tocilizumab for treatment of severe COVID-19 Patients: preliminary results from SMAtteo COvid19 REgistry (SMACORE). Microorganisms. 2020 May 9;8(5):695.
63. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020 May-Jun;38(3):529–532.
64. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020 May 19;117(20):10970–10975.
- **This article points out that there are no signigicant adverse events associated with administation of Tocilizumab in COVID-19.**
65. Sanchez-Montalva A, Selares-Nadal J, Espinosa-Pereiro J, et al. Early outcomes of tocilizumab in adults hospitalized with severe COVID19. An initial report from the Vall dHebron COVID19 prospective cohort study. medRxiv. 2020. https://doi.org/10.1101/2020.05.07.20094599
- **This article points out that there are no signigicant adverse events associated with administation of Tocilizumab in COVID-19.**
66. Veiga VC, Prats JAGG, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. Br Med J. 2021;372:n84.