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Original Research Article

Prospects of Monoclonal Antibodies in COVID-19 Treatment: A Systematic Review

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Abstract : ***Objectives:*** We reviewed the types of monoclonal antibodies being repurposed for COVID-19 therapeutics, the clinical outcomes and adverse effects so as to provide evidence the bedside physicians, the health policy-makers and the general public could employ in the COVID-19 management protocol. ***Data sources:*** We searched PUBMED, Google Scholar and SCOPUS. In addition, snow-balling of the selected articles were carried out to identify additional potentially relevant articles. All relevant articles up to 25 May 2020 were identified. Relevant preprints were also included. ***Study selection:*** Our search strategy identified 396 potentially relevant articles which decreased to 322 after duplicates were removed. 281 articles were screened out due to lack of relevance, using the Joanna Briggs Institute's critical appraisal checklists for evaluation of the quality of studies. The full text of the remaining 41 relevant papers were retrieved for full text evaluation after which only 19 studies from eight countries met our eligibility criteria and were included in the review. ***Data extraction:*** Three of the authors independently extracted data from the eligible journals using pre-designed MS tables. The results were compared and any conflict resolved by revisiting the journal in question. ***Data synthesis:*** A descriptive analysis of the data was performed. No formal meta-analysis was carried out due to the substantial heterogeneity between the studies. ***Conclusions:*** Monoclonal antibodies, especially tocilizumab and eculizumab hold some promise in the treatment of the disease but controlled clinical trials using them as monotherapy are needed to further evaluate this finding.

Keywords: Monoclonal antibodies, tocilizumab, eculizumab, COVID-19, treatment.

INTRODUCTION

The World Health Organisation has declared the coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, China in December 2019, a global pandemic (1). This evolving disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. As at 16th June 2020, there were over 7.9 million confirmed cases and well over 434 thousand deaths attributable to the disease across about 215 countries/areas/territories of the world [3].

It is known that coronaviruses (SARS-CoV, MERS-CoV and the novel SARS-CoV-2) cause severe lung pathology that result from induction of aberrant

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non-effective host immune response [4]. Available evidence [5-9] suggest the following chronology for the pathophysiology. SARS-CoV-2 enters the respiratory epithelium via respiratory droplets after contact with the infected person. The mean incubation period is about 4-5 days and the viral load peaks 5-6 days of onset of symptoms (the spectrum of symptoms include fever, dry cough, myalgia, difficulty in breathing, dizziness, headache, diarrhea, nausea, haemoptysis, acute respiratory distress syndrome and recently, anosmia and loss of taste).

The virus enters the host cell by the attachment of its spike proteins to the receptors called angiotensin converting enzyme 2 (ACE 2) and type II transmembrane serine protease (TMPRSS2). After invasion, the cell undergoes pyroptosis and releases damage-associated molecular patterns (DAMPs) which signal the neighboring epithelial and endothelial cells as well as the alveolar macrophages to produce pro-inflammatory cytokines and chemokines, particularly interleukin 6 (IL-6) [5, 8, 9]. These cytokines and chemokines then attract monocytes, macrophages and T cells which in turn amplify the inflammatory response which may lead to further accumulation of immune cells in the lungs culminating in pulmonary oedema, pneumonia, systemic cytokine storm and multiple organ damage. B cells also produce non-neutralising antibodies that may aid the infection by a mechanism called antibody-dependent-enhancement [5, 8].

Since COVID-19 pathophysiology is majorly predicated on cytokine storm otherwise called cytokine release syndrome, monoclonal antibodies could be used to mop-up some of the pro-inflammatory cytokines and chemokines driving the immune response haywire [9]. Monoclonal antibodies are being used in some inflammatory conditions with good outcomes [10, 11]. They are generally used therapeutically for inhibition of alloimmune and autoimmune reactivity, treatment of tumor and viral infections as well as antiplatelet therapy [11]. A recent work also points to the possibility of employing monoclonal antibodies prophylactically in COVID-19 management [12]. This would probably reduce the rate of COVID-19 infection. Recently, a human monoclonal antibody has been reported to neutralize SARS-CoV-2 and SARS-CoV in cell culture [13], supporting the potential effectiveness of monoclonal in COVID-19 treatment.

Some of the monoclonal antibodies approved for clinical use include tocilzumab (IL-6 inhibitor), eculizumab (complement C5 inhibitor), sarilumab (IL-6 inhibitor), siltuximab (IL-6 inhibitor), anakira (IL-1 inhibitor), muromonab (CD3 inhibitor), basiliximab (IL-2 inhibitor), daclizumab (IL-2 inhibitor), infliximab (TNF alpha inhibitor), rituzimab (CD20), trastuzumab (HER-2/neu inhibitor), palivizumab (respiratory syncytial virus) [10, 11, 14, 15].

The major drawbacks of monoclonal antibodies use in clinical practice are the comparative high cost [14] and the side effects associated with their use. These side effects include chills, pyrexia, headache, hypotension, arthralgia, infections (bacterial, fungal, viral), serum sickness and cancers [11, 16]. Cytokine release syndrome has also been reported with the use of tocilizumab [17].

Therefore, this systematic review was carried out to evaluate the types, clinical outcomes and the associated adverse effects of using monoclonal antibodies for COVID-19 therapeutics. This may provide supportive evidence not only for the bedside physicians but also the health policy-makers as well as the general public on the possibility of employing monoclonal antibodies in the COVID-19 management protocol as scientists/health professionals strive to find effective therapeutics and vaccine for the dreaded disease.

METHODS

This systematic review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18].

Search strategies

An electronic search of PUBMED, Google Scholar and SCOPUS was performed using the search terms: (COVID-19 OR SARS-CoV-2), AND (treatment, or therapy) AND monoclonal antibodies (including tocilzumab (IL-6 inhibitor), eculizumab (complement C5 inhibitor), sarilumab (IL-6 inhibitor), siltuximab (IL-6 inhibitor), anakira (IL-1 inhibitor), muromonab (CD3 inhibitor), basiliximab (IL-2 inhibitor), daclizumab (IL-2 inhibitor), infliximab (TNF alpha inhibitor), rituzimab (CD20 inhibitor), trastuzumab (HER-2/neu inhibitor), palivizumab) alone and in combinations. In addition, snow-balling of the selected articles were carried out to identify additional potentially relevant articles. All relevant articles up to 25 May 2020 were identified. In addition, preprints were also included because of paucity of published works on the topic.

Inclusion and exclusion criteria

The inclusion criteria were: being an adult over 18 years old, primary research articles (e.g., clinical trials, case reports/series, and prospective/retrospective studies), and journal articles in English language and publications between December 1 2019 and May 25 2020. Studies not reporting on therapeutic outcomes of monoclonal antibodies for COVID-19 were excluded.

Data extraction

Three of the author's independently extracted data from the eligible journals using MS tables pre-

designed for this purpose. The results were compared and any conflict resolved by revisiting the journal in question. The following information were extracted from the journal; author and year, study country, study design, number of patients, type of monoclonal antibody, key laboratory findings and final patient outcomes. The Joanna Briggs Institute's critical appraisal checklist [19] for the evaluation of the quality of studies on prevalence data was used to assess the quality of the studies included in the review.

DATA ANALYSIS

A descriptive analysis of the data was performed. Due to the substantial heterogeneity between the studies, no formal meta-analysis was carried out.

RESULTS

Description of selected studies

Our search strategy identified 396 potentially relevant articles which decreased to 322 after duplicates were removed. Screening of the titles and abstracts of the articles led to the removal of 281 articles due to lack of relevance. The full text of the remaining 41 relevant papers were retrieved for full text evaluation as shown (Figure 1). After detailed full text assessment, only 19 studies [17, 20-37] from eight countries (Italy, China, United States of America, Switzerland, France, Qatar, Turkey and Canada) met our eligibility criteria and were included in the review. Eight (42.1%) of the studies were from Italy. Table 1 represents the study type, candidate drugs and adjunct drugs deployed. A pie chart showing the distribution of the study locations of the included studies is depicted in Figure 2. Eighteen studies (94.7%) used tocilizumab, an anti-IL-6 monoclonal antibody, and one study used eculizumab, an anti- complement-5 monoclonal antibody. Fifteen (78.9%) of the studies used various adjunct drugs. Hydroxychloroquine (66.7%) and corticosteroids (66.7%) were most used adjunct drugs, followed by azithromycin (46.7%), and lopinavir/ritonavir (46.7%). Thalidomide was used in one of the studies. The study designs were variable. Only one (5.3%) was a prospective study comprising of 100 patients. Others were retrospective cohort studies (52.6%), case reports (31.6%) and case series (10.5%). None of these studies was a controlled clinical trial. Six studies retrospectively compared tocilizumab use in combination with standard therapy and standard therapy-only outcomes.

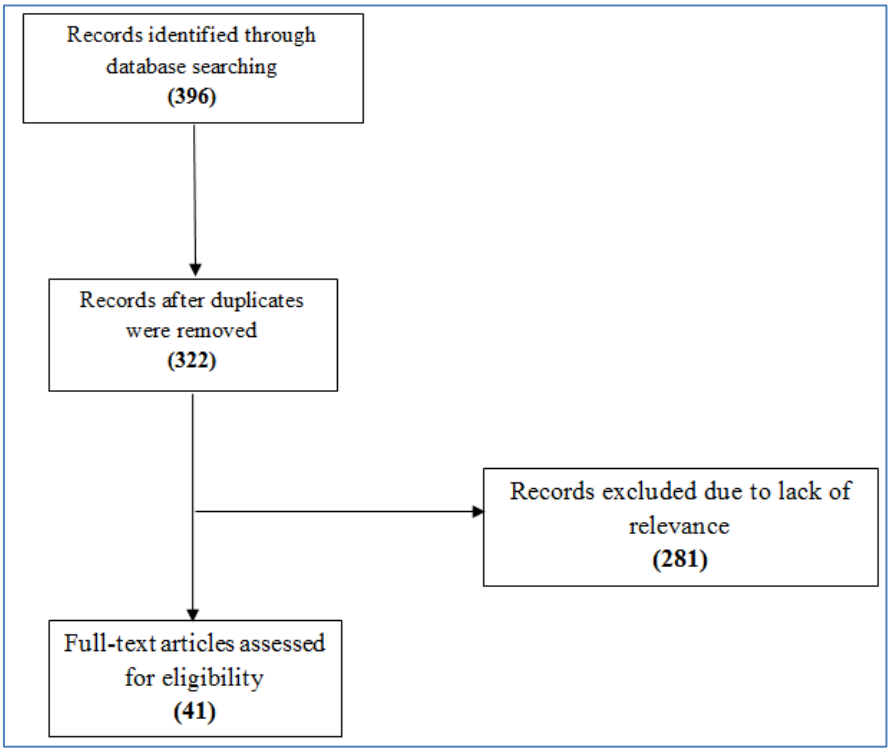

Fig-1: Flow diagram of for study selection

Table-1: Summary of authors, year of publication, types of study, candidate drug and adjunct drugs used

S/N	Author/year	Number of patients	Type of study	Candidate drug	Drug target	Adjunct drugs
1	Diurno *et al*, 2020	4	Case series	Eculizumab	Complecent C5.	Enoxaparin Lopinavir Hydroxychloroquine Ceftriazone Vitamin C
2	Zhang *et al*, 2020	1	Case report	Tocilizumab	IL-6	Moxifloxacin Bortezomib Thalidomide Dexamethasone
3	Cellina *et al* 2020	1	Case report	Tocilizumab	IL-6	Nil
4	Xu *et al*, 2020	21	Observational study	Tocilizumab	IL-6	Nil
5	Campochiaro *et al*, 2020	32	Retrospective cohort study	Tocilizumab	IL-6	Hydroxychloroquine, Lopinavir/ritonavir Ceftriazone Azithromycin
6	Mazzitelli *et al*, 2020	3	Case series	Tocilizumab	IL-6	Hydroxychloroquine, Lopinavir/ritonavir Azithromycin
7	Rimland *et al*, 2020	11	Retrospective cohort	Tocilizumab	IL-6	Azithromycin, Hydroxychloroquine, Ritonavir/Lopinavir, steroids
8	Toniati *et al*, 2020	100	Prospective cohort study	Tocilizumab	IL-6	Nil
9	Quartuccio *et al*, 2020	42	Single-centre retrospective study	Tocilizumab	IL-6	Antiviral Glucocorticoids
10	Colaneri *et al*, 2020	21	Retrospective study	Tocilizumab	IL-6	Hydroxychloroquine Azithromycin Heparin Methylprednisolone
11	Mihai *et al*, 2020	1	Case report	Tocilizumab	IL-6	Nil
12	Klopfenstein *et al*, 2020	45	Retrospective case control	Tocilizumab	IL-6	Hydroxychloroquine or lopinavir-ritonavir therapy and antibiotics, and less commonly corticosteroids
13	Michot *et al*, 2020	1	Case report	Tocilizumab	IL-6	lopinavir-ritonavir
14	Capra *et al*, 2020	85	Retrospective observational study	Tocilizumab	Il-6	Hydroxychloroquine Lopinavir Ritonavir
15	Alattar *et al*, 2020	25	Retrospective observational study	Tocilizumab	IL-6	Hydroxychloroquine, Azithromycin, Lopinavir/ritonavir, Ribavirin Interferon alpha 2a
16	Uslu *et al*, 2020	1	Case report	Tocilizumab	IL-6	Methylprednisolone
17	Wadud *et al*, 2020	44	Retrospective observational study.	Tocilizumab	IL-6	Hydroxychloroquine Azithromycin Hydrocortisone Methylprednisolone Dexamethasone
18	Luo *et al*, 2020	15	Retrospective	Tocilizumab	IL-6 IL-6	Methylprednisolone
19	Radbel *et al*, 2020	2	Case report	Tocilizumab	IL-6	Hydroxychloroquine, Azithromycin

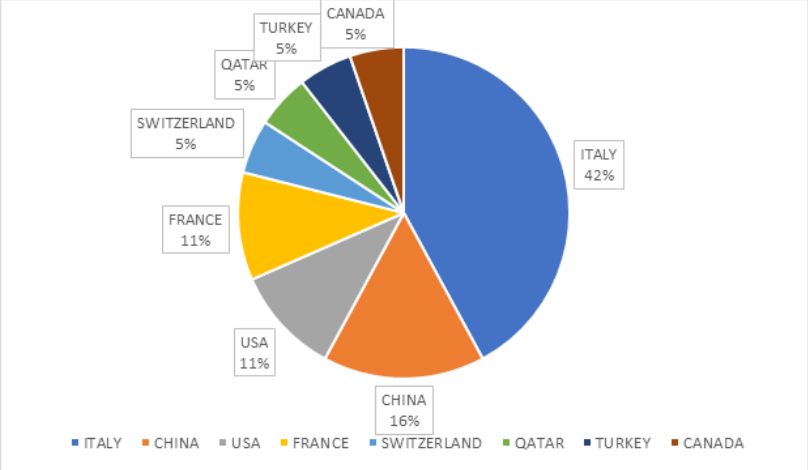

Fig-2: A pie chart depicting study locations of the studies included

Table-2: Summary of the clinical presentations and laboratory findings from the patients being reviewed

S/N	Author/year	Clinical presentations	Laboratory findings
1	Diurno *et al*, 2020	Fever Cough Dyspnoea, Respiratory failure.	Before therapy WBC = 11.500 x 10^9 cells/L CRP = 14.6mg/L After therapy WBC = 7.450 x10^9 cells/L CRP = 3.5mg/L
2	Zhang *et al*, 2020	Chest tightness Shortness of breath	Before therapy WBC = 4.41 x 10^9 cells/L CRP = 15.4mg/L IL-6 = 121.59pg/ml After therapy WBC = 4.26 x 10^9 cells/L CRP = 3.14mg/L IL-6 = 20.81pg/ml
3	Cellina *et al*, 2020	Syncope Dyspnea	Before therapy WBC = 10.9 x 10^9 cells/L CRP = 336mg/L IL-6 = 80ng/L After therapy WBC = 2.36 x 10^9 cells/L CRP = 96mg/L
4	Xu *et al*, 2020	Dry cough Fever Fatigue Nausea Rhinorrhea Chest pain	Before therapy WBC = 6.3±2.77 X 10^9/L CRP =75.06±66.80mg/L IL-6 = 153.44 ± 296.63pg/ml After therapy WBC =5.25±2.11 X 10^9/L CRP = 2.72±3.60mg/L IL-6 = 274.90 ± 414.08pg/ml
5	Campochiaro *et al*, 2020	Not stated	CRP: 156mg/dl Ferritin: 1400pmol/LL LDH: 469U/L
6	Mazzitelli *et al*, 2020	Cough Fever Shortness of breath Tachypnea	Case 1: Before therapy: IL-6 = 106.1pg/ml After therapy: IL-6 = 6.32pg/mL Case 2: Before therapy: IL-6 = 72.65pg/ml After therapy: IL-6 = 5.55pg/ml Case 3: Before therapy: IL-6 = 64.3pg/ml After therapy: IL-6 = 40.5pg/ml
7	Rimland *et al*, 2020	Not stated	Before therapy CRP = 211.6mg/L IL-6 =30.65pg/ml After therapy CRP = 19.7mg/L IL-6 = >400pg/ml
8	Toniati *et al*, 2020	Fever Dyspnoea Cough	Before therapy CRP = 113mg/L IL-6 = 41pg/ml

			D-dimer = 979mg/L Lymphocytes = 0.62 x10^9/L Ferritin = 1689pmol/L After therapy CRP = 2mg/L IL-6=1812pg/ml D-dimer = 2331mg/L Lymphocytes = 0.79 x 10^9/L Ferritin = 1352 pmol/L
9	Quartuccio *et al*, 2020	Not stated	Before therapy CRP = 70.1mg/L IL-6 = 63.5pg/ml LDH = 625U/L Creatinine kinase = 134U/L Neutrophils = 4.6 x 10^9/L Lymphocyte count = 6.9 x 10^9/L CD4+ T cells = 244.5/mm^3 CD8+ T cells = 77/ mm^3 After therapy CRP = 24.1mg/L IL-6 = 18.5pg/ml LDH = 442IU/L Creatinine kinase = 93IU/L Neutrophils = 3.7 x 10^9/L Lymphocyte count = 9.4 x 10^9/L CD4+ T cells = 370/mm^3 CD8+ T cells = 180 mm^3
10	Colaneri *et al*, 2020	Not stated	Lymphocytes: Day 0 = 0.6 x 10^9/L Day 7 = 0.96 x 10^9/L CRP: Day 0 = 21.4mg/L Day 7 = 0.63mg/L LDH: Day 0 = 445U/L Day 7 = 440U/L
11	Mihai *et al*, 2020	Cough Headache Malaise	Not stated.
12	Klopfenstein *et al*, 2020	Reduced oxygen saturation Confusion	CRP =158±70mg/L Lymphocytes 676±357 x 10^9/L
13	Michot *et al*., 2020	Fever Cough	CRP: Before therapy = 225mg/L After therapy = 33mg/L
14	Capra *et al.*, 2020	Fever	Not reported
15	Alattar *et al.*, 2020	Fever Cough Dyspnea	CRP = 95.2mg/L Lymphocyte = 0.9 x10^9/L Peripheral WBC count = 6.0 - 14.4 x 10^9/L and then to 4.9 x 10^9/L
16	Uslu *et al.*, 2020	Fever Cough Fatigue	Lymphocyte = 0.61-103 x10^9/L ESR = 77mm/hr CRP = 110mg/L D-dimers- 1657mg/L.
17	Wadud *et al.*, 2020	Not stated	Nil
18	Luo *et al.*, 2020	Not stated	Before therapy CRP = 126.9mg/L IL-6 = 16.4 – 627pg/ml After therapy CRP = 11.2mg/L IL-6 = 45.7 – 5000pg/ml
19	Radbel *et al.*, 2020	Fever Cough Dyspnea	Before therapy Ferritin = 1385ng/ml LDH = 368U/L IL-6 = 74.3pg/ml CRP = 9.0mg/L WBC = 7.0 x 10^9/L After therapy Ferritin = 38299ng/ml LDH = 5517U/L IL-6 = 345pg/ml CRP = 44.1mg/L WBC = 6.9 x 10^9/L

Critical appraisal/quality evaluation of selected studies

The Joanna Briggs Institute's critical appraisal checklist (19) for evaluation of the quality of studies was used to assess the quality of the different types of primary studies included in the review.

Overall, there were a total of 698 patients from the studies. There were 431 males and 222 females with a male/female ratio of 1.94:1. One study with 45 patients did not specify the gender prevalence in their study. Out of the 13 studies (68.4%) that stated the clinical presentations, 9(69.2%) had cough, followed by fever (61.5%) and dyspnoea (53.9%) (Table 2). Most of the studies (84.2%) stated the laboratory findings and all documented IL-6 and/or its surrogate marker, C-reactive protein (CRP). All, except one were consistently elevated prior to therapy. In those with repeat testing after commencement of therapy, there was remarkable decrease in the value of CRP in all the studies except that by Radbel *et al.* [17] where there was an elevated value after therapy. For IL-6, post-therapy values were varying with some showing reduction whilst others showed increase or remained minimally the same (Table 2). SARS-CoV-2 virus detection was by RT-PCR in all cases and some studies described CT scan findings of extensive bilateral ground glass opacities. Complete blood count was non-uniform in the studies. However, where present, lymphopenia was consistent. Other investigations findings varied according to patient's requirements and were not captured.

Table 3 shows comorbidities found in the patients, treatment outcome and adverse drug effects recorded in some studies. Fifteen studies (78.9%) stated co-morbidities found in the patients. Out of these, hypertension (80%) was the most frequent co-morbidity, followed by diabetes mellitus (73.3%), cardiovascular disease (53.3%) and obesity (26.7%). 75.9% of the patients from 17 of the studies with clearly reported clinical outcomes, recovered.

Sixty-four (15.9%) out of 403 patients that received tocilizumab died whilst 79 (27.1%) of 291 patients treated on standard regimen died. Other factors used to determine outcomes were resolution of chest CT scan findings, resolutions of symptoms, and reduction in pro-inflammatory markers (CRP and/or IL-6). All 4 patients treated with eculizumab survived. Treatment with monoclonal antibody was associated with reduced requirement for artificial mechanical ventilation in most studies. The adverse drug effects reported was infection including viral myocarditis, bacteraemia, candidaemia and invasive aspergillosis.

Table-3: Summary of the co-morbidities, outcome of treatment and adverse effects seen in studies under review

S/N	Author/year	Co-morbidities	Outcome of treatment.	Adverse effects
1	Diurno *et al*, 2020	Hypertension Chronic ischaemic heart disease Chronic obstructive bronchopathy Hypertension.	100% recovery.	Not reported.
2	Zhang *et al*, 2020	Multiple myeloma	100% recovery.	Not reported
3	Cellina *et al*, 2020	Not stated	100% recovery.	Not reported.
4	Xu *et al*, 2020	Not stated	90.5% full recovery. 9.5% were in stable clinical condition as at the time of report.	Neutropenia Elevated transaminases
5	Campochiaro *et al*, 2020	Not stated	69% recovery after 28-days. 15% died within the period.	Bacteremia Candidemia Invasive pulmonary aspergillosis Increased AST or ALT levels.
6	Mazzitelli *et al*, 2020	Hypercholesterolemia Hypertension Stroke Diabetes mellitus Hyperthyroidism Chronic kidney disease Fatty liver disease.	100% recovery.	Nil

7	Rimland *et al*, 2020	Hypertension Type 2 Diabetes Mellitus Lung Disease Cardiovascular Disease Liver Disease Renal Disease HIV Active Cancer Solid organ transplant	18.1% recovered. 45.5% remained in ICU 9.1% weaned from ICU to ward. 27.3% died after 17 days.	Ileus Bacterial pneumonia.
8	Toniati *et al*, 2020	Hypertension Obesity DM Cardiovascular disease.	77% recovered. 3% worsened clinically. 20% died after 10 days.	
9	Quartuccio *et al*, 2020	Hypertension Obesity Ischemic heart disease Diabetes	71.4% recovered.	Bacterial superinfection
10	Colaneri *et al*, 2020	Hypertension, Obesity Ischemic heart disease Diabetes Lung diseases Tumor	Not clearly stated.	Nil
11	Mihai *et al*, 2020	Systemic sclerosis Type 2 diabetes mellitus Obesity	100% recovery after 10 days.	Not stated.
12	Klopfenstein *et al*, 2020	Hypertension Cardiovascular diseases Diabetes mellitus COPD Immunosuppression Malignancy	75% recovery. 25% mortality.	Not stated.
13	Michot *et al*, 2020	Malignancy	100% recovery after 12 days.	None reported
14	Capra *et al*, 2020	Hypertension Diabetes Heart disease	92% recovered. 8% died after 20 days.	None detected
15	Alattar *et al*, 2020	Diabetes mellitus Chronic kidney disease Cardiovascular disease	36% recovered. 52% remained in ICU. 12% died after 14 days	Not clearly stated.
16	Uslu *et al*, 2020	Hypertension	100% recovery after 10 days.	None
17	Wadud *et al*, 2020	Not stated	61.4% survival after 17.9 days.	None stated
18	Luo *et al*,2020	Hypertension Diabetes Stroke. 4 had no comorbidities	Not clearly stated.	Not stated
19	Radbel *et al*, 2020	Type 2 diabetes Rheumatoid arthritis Aplastic anaemia	50% mortality. 50% clinical deterioration.	Viral myocarditis

DISCUSSION

In this review, most of the studies were retrospective cohort studies and the majority of the studies were carried out in Europe with fewer studies in China and USA. This represents the regions mostly affected by the COVID-19 pandemic ravaging the whole world. The review also showed that more males were affected by the disease than females. This may point to the fact that the disease probably has more predilections for males than females. The major monoclonal antibody used in the treatment of COVID-19 patients in this review was tocilizumab. Only one study featured eculizumab [25].

The main drugs used as adjuncts to the monoclonal antibodies in this review were hydroxychloroquine, moxifloxacin, lopinavir/ritonavir, ceftriaxone, azithromycin, dexamethasone, methlypredisolone, vitamin C and interferon 2α [22, 26, 33]. It is possible that these adjuncts might have influenced the overall outcome of the treatment with

monoclonal antibodies since some of the adjuncts like the corticosteroids also suppress inflammation just like the monoclonal antibodies [38]. Some of the adjuncts have antibacterial, antiviral or antioxidant properties which might have a possible positive effect on the outcome of the treatment. A huge source of concern is that the steroids used concurrently with the monoclonal antibodies in this review also have the capacity to delay the elimination of the virus and also increase the risk of secondary infections especially in patients with immunosuppression [37, 38]. Thalidomide, one of the adjunct drugs used in the articles reviewed also inhibits some cytokines (IL-6, IL-10, TNFα) important for plasma cell growth in the bone marrow environment [39, 40]. It also causes teratogenicity and sedation [41]. The effect of thalidomide may have influenced the clinical outcome and adverse effects manifested by some of the patients under review.

The major clinical features presented by the patients were cough, fever, breathlessness, fatigue, chest pain and syncope. These presentations were probably due to hypoxia and hypoxaemia occasioned by the infiltrative lesions in the lungs of the affected patients and their consequences [17, 29]. The laboratory parameters assessed included interleukin-6 (IL-6), C-reactive protein (CRP), white blood cells (WBC), ferritin, D-dimers, transaminases and lactate dehydrogenase (LDH). The levels of these laboratory parameters were consistently high before the treatment with the monoclonal antibodies. The level of CRP and IL-6 was significantly reduced following treatment with the monoclonal antibodies [24, 28, 31]. The level was however, increased in some other studies [17, 21, 27]. This may therefore suggest that certain individuals do not respond with lowered IL-6 despite the reduction in CRP which is a surrogate marker for the cytokine. It may also suggest that the consistently lowered CRP may be accounted for by other factors that may reduce the protein such as its related proteins or complexed ligands [29]. These other mediators may hold promise in understanding why individuals may not respond to therapy. The levels of IL-6, CRP and TNFα (tumour necrosis factor alpha) have been found to be elevated in COVID-19 patients and these are associated with acute respiratory distress syndrome, hypercoagulopathy, and disseminated intravascular coagulopathy in these patients [38].

In this review, the majority of the mortalities were suffered by COVID-19 patients with co-morbidities like diabetes mellitus, hypertension, multiple myeloma, malignancies, cardiovascular disease and chronic kidney diseases [22, 26, 32, 33]. Some patients however, showed full recovery in spite of the co-morbidities they had [25, 28, 30]. This suggests with that with good management, the effect of co-morbidity as a prognostic factor may be modulated positively.

The major adverse effects reported in this review were myocarditis, bacteremia, candidaemia, intestinal perforation, ileus, invasive pulmonary aspergillosis, elevated liver enzymes, and disseminated intravascular coagulopathy [17, 21, 32]. This underscores the need for a careful monitoring of these parameters in COVID-19 patients receiving tocilizumab or other monoclonal antibodies. Over all, patients that received tocilizumab and eculizumab had better outcome (more survival rates and less need for artificial ventilation) than those that did not receive the drugs [22, 26, 35]. It therefore shows that these drugs have some potential for the treatment of COVID-19.

LIMITATIONS

Owing to the paucity of studies on this theme, it was necessary to include all available studies including preprints which helped to capture as much patients as possible.

Also, none of the studies was a controlled clinical trial (most of the studies were case studies). This may limit the scope of applicability of these findings. Similar research may need to be done later when the results of controlled clinical trials using monoclonal antibodies in COVID-19 treatment are available.

More so, it is difficult to categorically state if the adverse drug effects observed in these studies were primarily due to the monoclonal antibodies or the adjunct medications given the patients' co-morbid state.

CONCLUSIONS

Monoclonal antibodies, especially tocilizumab and eculizumab hold some promise in the treatment of the disease but controlled clinical trials using them as monotherapy are needed to further evaluate this finding.

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