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REVIEW

Pharmaco-immunomodulatory interventions for averting cytokine storm-linked disease severity in SARS-CoV-2 infection

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Abstract

The year 2020 is characterised by the COVID-19 pandemic that has quelled more than half a million lives in recent months. We are still coping with the negative repercussions of COVID-19 pandemic in 2021, in which the 2nd wave in India resulted in a high fatality rate. Regardless of emergency vaccine approvals and subsequent meteoric global vaccination drives in some countries, hospitalisations for COVID-19 will continue to occur due to the propensity of mutation in SARS-CoV-2 virus. The immune response plays a vital role in the control and resolution of infectious diseases. However, an impaired immune response is responsible for the severity of the respiratory distress in many diseases. The severe COVID-19 infection persuaded cytokine storm that has been linked with acute respiratory distress syndrome (ARDS), culminates into vital organ failures and eventual death. Thus, safe and effective therapeutics to treat hospitalised patients remains a significant unmet clinical need. In that state, any clue of possible treatments, which save patients life, can be treasured for this time point. Many cohorts and clinical trial studies demonstrated that timely administration of immunomodulatory drugs on severe COVID-19 patients may mitigate the disease severity, hospital stay and mortality. This article addresses the severity and risk factors of hypercytokinemia in COVID-19 patients, with special emphasis on prospective immunomodulatory therapies.

Keywords COVID-19 · ARDS · Cytokines syndrome · Immune modulators · Therapeutics

Introduction

In March 2020, the World Health Organisation (WHO) declared the COVID-19 outbreak a global public health emergency. Consequently, COVID-19 waves further deteriorated situation causing persistent state of fear. This catastrophic situation created immediate need of therapeutics or vaccines resulting in emergency approval for prophylaxis and treatment of COVID-19. However, emergence of SARS-CoV-2 variants prompted concerns about the efficacy

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and sensitivity of approved medicines and vaccines, which are, regrettably, still hazy. In March–April, 2021, India faced a massive surge of COVID-19 cases and deaths, and was the world's leading country in terms of infection rate. Since inception of pandemic, many suggestions and speculations were made to spot possible cure for this disease. Various drug entities showed promising clinical results, but only a small percentage of these are approved and moved forward to phase trials (Rohilla 2020; Kumar et al., 2021). Majority of these drugs were targeted to counteract inflammatory aggravation during pathologic progression of COVID-19. Hypercytokinemia is an uncontrolled hyper-inflammatory reaction that occurs when a localised inflammatory response to a viral or bacterial infection spreads across the body. Endothelial dysfunction, vascular damage, and paracrine/metabolic dysregulation are all caused by dysregulated high cytokine levels, which eventually harm many vital organ systems (Leisman et al., 2020; Ye et al., 2020; Bhaskar et al., 2020; Fodor et al., 2021). The innate immune response is the first host anti-viral response against invading viruses, which triggers the release of type I/III interferon (IFNs), pro-inflammatory cytokines like TNF-α and interleukins like IL-1, IL-6, and IL-18. These cytokines and interleukins induce collective effect on the target cells and potentiate the adaptive immune response. However, dysregulated immune response is one of the cogent reasons of mortality associated with COVID-19, known as cytokines explosion or storm, which is represented by excessive secretion of cytokines such as, IL-2, IL-6, IL-7, IL-10, IP-10 (interferon-gamma-inducible protein), MCP-1 (monocyte chemoattractant protein), TNF-α and MIP-1α (macrophage-inflammatory protein), GM-CSF in human body and such patients are in strict need of ICUs (intensive care units) (Costela-Ruiz et al., 2020; Ragab et al., 2020; Khadke et al., 2020). Despite many critics raising concern about the excessive immune response or cytokine storm during the pathogenesis of COVID-19, there are several studies highlighting that lymphopenia and pneumonia are the critical immune dysregulation developed during the severe cases of COVID-19, which characterises the higher plasma levels of pro-inflammatory cytokines(Bhaskar et al., 2020; Ye et al., 2020; Fara et al., 2020). Two different autopsy reports demonstrated that the damage to vital organs was not associated with viral inclusion of the respective organs. It could be linked to severe immune injury, caused by cytokine storm, instead of direct viral damage (Xu et al., 2020a, b; Yao et al., 2021). In severe cases, cytokine storms harm healthy cells, first the lungs, and potentially spreading to other vital organs like the heart, brain, and kidney. Some studies highlighted that increased amount of pro-inflammatory cytokines in serum (e.g. IL-1, IL-6, IL-12, IFN-, IP-10, MCP-1, MIP-1, TNF-α, and GCSF), was correlated with pulmonary inflammation and acute respiratory distress syndrome in affected patients (Chen et al., 2020).

The extent of the severity of the disease is directly proportional to the cytokine storm (Cingolani et al., 2020), which often leads to multi-organ failure and death. Numerous retrospective studies of cytokine blockade such as IL-6, IL1-, JAK, NF-ƙB, GM-CSF inhibitors have shown promising results (Fara et al., 2020; Ragab et al., 2020; Ye et al., 2020). Several clinical trials are underway or recently completed, and the results are eagerly expected. Regardless of speedy vaccination drives and uptake in many countries, hospitalisations with clinical severity of COVID-19 are still being reported. It might be due to the propensity of mutation and virus evasion from protection that occurs through natural immunological selection (Thompson et al., 2021). Timely therapeutic intervention in patients with hyper-inflammation could prevent the illness from progressing to ARDS and eliminate the need for invasive ventilation. To our knowledge, there have not been any updated reviews shedding light on the effectiveness of immunomodulatory therapy to combat COVID-19 severity. This review enlightened the implications and risk factor of hypercytokinemia/cytokine storm for COVID-19 patients, with special emphasis on potential therapeutic strategies used to mitigate COVID-19 severity.

Risk factor associated with COVID-CSS (cytokine storm syndrome)

During a pandemic, COVID-19 disease is diagnosed through testing and most infections are self-limiting or mild forms, which can be recovered through standard operating procedures, but as the disease progresses and develops severe pneumonia, it becomes more difficult for clinicians to operate. Establishing ARDS during disease progression could be one of the leading causes of death. As estimated, 50 and 65% deaths were associated with ARDS and severe COVID-19 during early phase of the pandemic (Bhatraju et al., 2020). The probability of fatality or death with COVID-19 is greatly impacted by age and prior comorbidities. Older patients over 65, as well as those with chronic comorbidities such as cardiovascular disease, diabetes, hypertension, and respiratory illness, are far more vulnerable to severe or fatal disease outcomes. But, it is uncertain to determine the time of a patient's death in COVID-19, which is linked with pre-existing health conditions (Streeck et al., 2020; Bartlett et al., 2020). Low arterial oxygen concentrations, alveolar damage, and a dysregulated inflammatory response in the lungs are all symptoms of COVID-19 ARDS (Matthay et al., 2019). An earlier report stated that COVID-19 ARDS was caused by a "cytokine storm," which refers to severely ill COVID-19 patients having significantly higher levels of circulating inflammatory cytokine levels than those with mild disease or healthy controls (Mehta et al., 2020a, b; Blanco-Melo, 2020; Giamarellos-Bourboulis et al., 2020). Hypercytokinemia,

better described as a cytokine storm, massive release of many inflammatory cytokines in serum was determined in COVID-CSS (cytokine storm syndrome). Surprisingly, in many patients with severe COVID-19 disease, the serum IL-6 level was markedly elevated at around 100–1000 pg/ml (Blanco-Melo et al., 2020; Herold et al., 2020; Laing et al., 2020). This magnitude of elevated IL-6 levels in COVID-CSS is comparable to severe CART-cell CRS and higher than that of other hyper-IL-6 syndromes, including multicentric Castleman disease, where elevated IL-6 levels are noted beyond 100 pg/ml (England et al., 2021; van Rhee et al., 2014). In COVID-CSS, the foundation of immune dysregulation was correlated with the common terminal hyperinflammatory pathway that is characterised by markedly elevated IL-6, severe T-cell lymphopenia, and respiratory failure (Laing et al., 2020; Giamarellos-Bourboulis et al., 2020; Lucas et al., 2020; Coomes and Haghbayan, 2020). Among the elevated cytokines, IL-6 is primarily involved in pro-inflammatory activation during cytokine-mediated organ dysfunction and tissue damage (Crayne et al., 2019) and IL-6-directed therapy acts as the cornerstone of cytokine-based therapy (Hoiland et al., 2020; Kotch et al., 2019; Chen et al., 2019). Some studies demonstrated that IL-6 > 80 pg/m1 along with high C-reactive protein > 97 mg/l point towards probable respiratory failure and are specific in predicting death (Herold et al., 2020; Laguna-Goya et al., 2020). Stukas et al., 2020 reported IL-6 to be inversely proportional to the ratio of arterial oxygen tension and fraction of inspired oxygen (PaO2/FiO2) and static lung compliance (Stukas et al., 2020). IL-6 blockade with tocilizumab resulted in partial restoration of these immune defects (Giamarellos-Bourboulis et al., 2020; Mazzoni et al., 2020). In addition to IL-6, IL-12 (p40), MIP-1a, and MIP-1b are critical chemokines, accountable for the recruitment of activated immune cells to the site of infection (Schulz et al., 2016; Coper et al., 2007; Menten et al., 2002). The hematopoietic growth factor, GM-CSF (Granulocyte–macrophage colony-stimulating factor), is also a key immunological modulator. Upon receiving immunological stimuli, it is released by many cell types such as T cells, macrophages, endothelial cells, and fibroblasts, and it can control key cytokines that can drive both innate and adaptive immune responses (Hamilton, 2000). Other elevated inflammatory indicators such as C-reactive protein are substantially linked to IL-6 plasma levels in CSS with COVID-19 (Liu et al., 2020). Various studies have demonstrated high levels of high-sensitivity C-reactive protein (Hs-CRP) in the serum levels of severe COVID-19 patients. Persistently high levels of CRP are a sign of ongoing chronic inflammation and it is a key inflammatory indicator linked to increased risks of death and organ damage (Clyne & Olshaker, 1999; Schmidt-Arras & Rose-John, 2016; Sharifpour et al., 2020). Elevated CRP levels have been linked to disease severity and predictions in many viral respiratory infections such as SARS, MERS-CoV, and H1N1 (Ko et al., 2016; Vasileva & Badawi, 2019; Wang et al., 2004). CRP level assessment has recently been one of the major indicators for detecting COVID-19 disease severity. The major complication associated with COVID-19 disease is cytokine storm, and it is a leading cause of multiple organ failure and ARDS. As a result, effectively repressing the cytokine storm is critical for preventing severe COVID-19 consequences and lowering mortality (Fig. 1). Numerous efforts have been made throughout the world to assess the severity of the situation in real time and apply potential therapeutics to save patients' lives. Many immunomodulatory medicines have been used off-label as COVID-19 treatments in hospitalised patients based on preclinical results, but further evidence in the context of clinical practise is needed. Many repurposed drugs have been utilised and suggested for clinical studies, and a few drugs are showing promising outcomes.

Tocilizumab (IL-6 inhibitor)

Tocilizumab is a recombinant humanised monoclonal antibody that has been approved for use in the treatment of cytokine release syndrome. It is particularly effective in inhibiting IL-6 production. The dysregulated host immune response is reported in the severe case of COVID-19, which has a propensity to release excessive amounts of cytokines, resulting in a cytokine storm or pulmonary inflammation (Bhaskar et al. 2020; Ye et al., 2020). Among all the cytokines, IL-6 is predominately produced and can be an ideal target to circumvent COVID-CSS. Based on that, Tocilizumab, a monoclonal antibody inhibitor of IL-6, can be used to ameliorate the intense inflammatory response associated with severe COVID-19, and thus improve clinical outcomes. Various clinical studies have been showing promising results in COVID-19 treatment (Kumar et al., 2021) (Table 1). Xu et al. 2020a, b were the first to test tocilizumab's efficacy on 21 severe or critical COVID-19 patients. Clinical data indicated that symptoms, hypooxygenemia, and CT opacity changes improved quickly after tocilizumab treatment in the majority of patients, indicating that tocilizumab might be an effective COVID-19 treatment. This observation has prompted many clinical trial studies on tocilizumab. A few studies contradicted the efficacy of tocilizumab, and no significant clinical improvements were achieved through the administration of tocilizumab. But these trials have limitations like the inclusion of small numbers of patients, less severely ill patients, and the exclusion of critically ill patients (Stone et al., 2020; Hermine et al., 2021). The study by many research groups suggested that TCZ may lower the frequency of ICU hospitalisations and/or fatalities in patients with severe COVID-19 (Alattar et al., 2020; Commes and Haghbayan, 2020). Gupta et al., 2021, conducted a multicentre cohort study, enrolling 4485

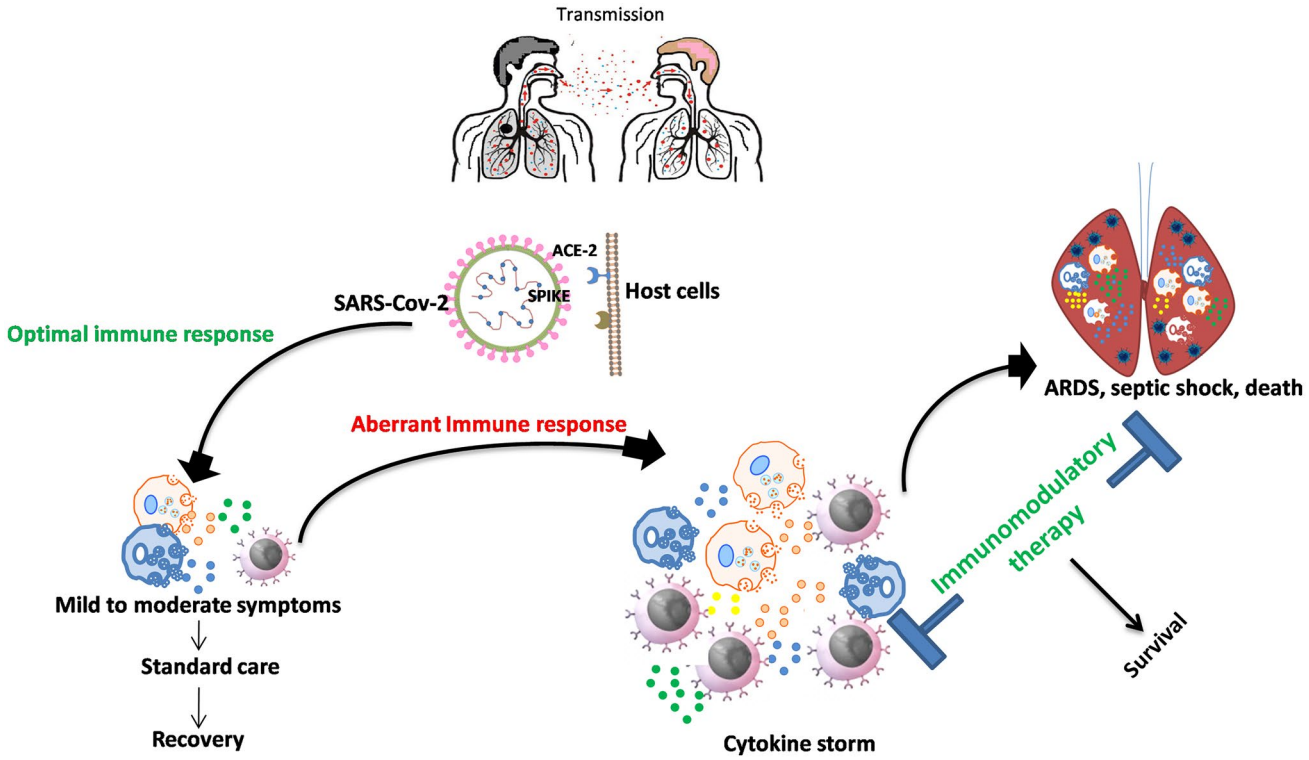

Fig.1 Schematic representation of the pathological progression of COVID-19 towards ARDS and possible reinforcement of immunomodulatory therapy to combat COVID-CSS

critically ill COVID-19 patients. After 27 days of therapy, individuals who received tocilizumab had a reduced risk of mortality than those who did not receive tocilizumab. The anticipated 30-day mortality was 27.5% in the tocilizumab-treated patients and 37.1% in the control groups (risk difference, 9.6%). In this investigation, patients who received tocilizumab in the first two days of ICU admission had a decreased risk of in-hospital mortality than patients who did not get tocilizumab in the first two days of ICU admission (Gupta et al., 2021). Gordon et al., 2021 conducted a large randomised, embedded, multifactorial adaptive platform trial for community acquired pneumonia (REMAP-CAP) and included a total of 803 patients. Among them, 353 patients were assigned to tocilizumab to examine the efficacy of tocilizumab on survival and organ support in critically ill patients with COVID-19, and the outcome showed a survival benefit over the current standard of care, which included corticosteroids (Gordon et al., 2021). Guillén et al., 2020 investigated the efficacy of tocilizumab in 64 hospitalised COVID-19 patients. After receiving tocilizumab, 49 patients (76.6%) demonstrated an early positive response. There were no deaths or recurrences of illness. There were no more bacterial infections as a result of the treatment during the hospitalisation. However, patients who responded well to TCZ were younger in age (Gullein et al., 2020).

Sarilumab

Sarilumab is completely a human MCA (monoclonal antibody) responsible for inhibiting the binding of IL-6 and its own α receptor. Sarilumab is approved by FDA (Food and drug administration) for its use against the treatment of ankylosing spondylitis and arthritis rheumatoid (severe and moderate) (Khiali et al., 2020). As it inhibits both membrane bound and soluble form of IL-6 and possibly suppresses the pro-inflammatory signalling by immune cells as well as pulmonary-epithelial cells; its use can be possibly predicted in reducing the pulmonary complications raised due to COVID-19, along with respiratory failure (Lescure et al., 2021). Sarilumab suppresses the growth of Calu3 (human lung cancer cell line) and binds with high affinity to epitope of IL-6R, thereby blocks both the activation (trans and cis) of IL-6 signalling (Yousefi et al., 2021). It is considered to be a safe and well-tolerated drug with recommended dosage not exceeding 200 mg every fortnight (Khiali et al., 2020; León López et al., 2020).

Various studies have been conducted by various researchers to check the efficacy and safety of sarilumab in patients suffering from rheumatoid arthritis (Table 2). A study done by (Bae and Lee, 2017) with four randomised controlled trials with 2667 patients suffering from rheumatoid arthritis

Table 1 Clinical studies evaluating the efficacy of tocilizumab for the treatment of SARS-CoV-2 infectious disease

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled for therapy, (M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l) IL-6 (> 7 pg/ml)		Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP IL-6		Adverse reaction	References
1	Single centre, Randomised, observational	21 (18 M/3F) Median Age:56.8	Fever, dry cough, chest tightness and nausea	75.06 ± 66.80	153.44 ± 296.63	4–8 mg/kg body weight (max 800 mg)	No mortality	16/19, 2.72 ± 3.60	–	No treatment-related adverse reaction	Xu et al., 2020a, b
2	Retrospective cohort	51(61/39) 28 were assigned for treatment; Median Age:65	Hypoxemia	16.1 (12.5–25.1)	14 (8 -59)	400 mg	21-day, mortality was 3 in treated and 5 in untreated group	–	–	No treatment-related adverse reaction	Kewana et al., 2020
3	Single centre, Prospective	100 (88 M, 12 F), Median age:62	Fever, cough, dyspnoea, Diarrhoea, severe pneumonia	113 (45–169)	41 (10 – 102)	8 mg/kg (max 800 mg) by 2 consecutive i.v. 12 h apart, 3rd infusion for non-responders	10-day mortality was 2% in treated group	2 (1–5)	–	3 patients showed septic shock, GI perforation	Toniati et al., 2020
4	Single centre retrospective, observational	15 (12 M, 3 F), Media age; 73	Moderate to critical	131.8 (10.7–257.9)	111 (16.4–627.1)	80–600 mg/time	7-day, mortality was 5% in treated group	< 5 mg/dl	–	No treatment-related adverse reaction	Luo et al., 2020
5	Single centre, retrospective, observational study	25 (23 M, 2 F) Media age; 58	Fever, cough, fatigue, dyspnoea, Diarrhoea	193 (121.6–302.4)	–	5.7 mg/kg	14-day, mortality was 12% in treated group	7.9 (6-11.3)	–	64%,Anaemia, 44% ALT rise and 20% QT interval prolongation	Alattar et al., 2020
6	Multicentre cohort	3924 (2464 M, 1460 F), 433 were assigned for treatment Median Age: 58	Fever, severe pneumonia	> 100	> 80		30-day, mortality was 27.5% in treated vs 37.1% in untreated	–	–	No treatment-related adverse events; Secondary infection, arrhythmia, and/or thrombotic event reported in few cases	Gupta et al., 2021

Table 1 (continued)

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled for therapy, (M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l) IL-6 (> 7 pg/ml)		Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP IL-6		Adverse reaction	References
7	REMAP-CAP's pragmatic, international design, randomised	353 (261 M, 92F) assigned for treatment, 402 untreated Median Age: 61.5	Severe pneumonia	150 (85–221) ($n = 207$)	–	8 mg/kg of body weight (maximum 800 mg, repeated after 12–24 h in non-responders)	21-day, mortality was 21.9% in treated and 30% in untreated			No treatment-related adverse events	Gordon et al., 2021
8	A retrospective observational study/Single centre	85, 62 were assigned for treatment (45 M, 17F) Median age: 63	Fever, pneumonia	–	–	324–800 mg 53% received 400 mg, 43,5% received 324 mg, 3.5% received 800 mg	14-day, mortality was 8% in treated and 47.1% in untreated	–	–	No treatment-related adverse events	Capra et al., 2020
9	Retrospective cohort	64, (47 M, 17 F) Median age: 62		50 (18–91)	85 (39–181)	600 mg TCZ administered for weight was ≥ 75 kg or 400 mg if the weight was < 75 kg. Non-respondent at 24 h subjected to a second dose of TCZ (400 mg) or intravenous corticosteroids	No death	22 (8–44)	–	No treatment-related adverse events	Guillén et al., 2020
10	Multicentric, open label, randomised	126, 60 were assigned for treatment (40 M, 20F) Median age: 61.5	Pneumonia	10.5 (5.0–14.6)	50.4 (28.3–93.20)	8 mg/kg up to a maximum 800 mg, 2nd dose repeated after 12 h	30-day, mortality was 3.3% in treated and 1.8% in untreated	–	–	Infection in 2 patients, GI bleeding in 1 patients	Salvarani et al., 2021

Table 1 (continued)

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled for therapy, (M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l) IL-6 (> 7 pg/ml)	Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP IL-6	Adverse reaction	References
11	Multicentric, open label, randomised	131, 63 were assigned for treatment	Moderate to severe pneumonia	119.5 (75.5–219.5)	8 mg/kg	30-day, mortality was 24% in treated and 36% in untreated	–	No treatment-related adverse events	Hermine et al., 2021

showed that Sarilumab at 150 mg and 200 mg is effective as well as tolerated among the patients. The adverse event rate of Sarilumab is very low, which is around 6.7–9.4 per 100 patients per year (Khiali et al., 2020).

In a study conducted by (Benucci et al., 2020) over 8 patients (6 males and 2 females, mean age 62 years) with confirmed positive PCR (polymerase chain reaction) reports, the patients were given sarilumab (400 mg) along with standard therapy of hydroxychloroquinone (400 mg), darunavir (800 mg), enoxaparin (100 U/kg), and azithromycin (500 mg). The study revealed that there was improvement of oxygenation and the oxygen requirement was reduced by 30%. Seven patients showed progressive and significant reduction in echo score and improvement of Horovitz index was observed significantly (Benucci et al., 2020). Within 14 days, 7 of the 8 patients were tested negative and discharged from the hospital, while an 83-year-old patient showed no improvement.

Another study done by (Benucci et al., 2020) on COVID-positive hospitalised patients (n = 8, t = 14 days), three doses were given viz. first dose (400 mg) after the first day of hospitalisation; second dose (200 mg) after 2 days and third dose (200 mg) after 4 days. Other standard treatments were also carried out alongside such as azithromycin, cobicistat, HCQ, darunavir and enoxaparin. The result showed significant improvement in the count of lymphocytes, CRP and echo score. Gremese et al., 2020 conducted open-label observational study on 53 patients suffering from COVID-19 with severe pneumonia. The patients were given 1–2 doses of sarilumab (400 mg) in 1–11-day intervals along with LPV/r, HCQ, DRV/r, GC and heparin azithromycin. The result showed significant improvement in 89.7% of the patients who were not admitted in ICU. After the treatment, oxygen therapy was not required by 85.7% of the patients, while 64.2% of the patients admitted in ICU no longer require the intensive care and was shifted to normal wards.

There are limited data available addressing the use of sarilumab in the case of COVID-19 and various clinical trials are still in progress. Overall, it can be concluded from the limited published evidences that sarilumab can be used in treatment of COVID-19 (moderate to severe cases). However, further research is still required to explore the efficacy and safety of Sarilumab in treatment of COVID-19 (Khiali et al., 2020). Della-Torre et al., in 2020, conducted an open-label cohort study and check the efficacy of sarilumab in severe COVID-19 pneumonia patients. Fifty-six patients (PaO2/FiO2 < 300 mm Hg with hyper-inflammation) were enrolled and given sarilumab therapy. Twenty-eight patients received 400 mg sarilumab intravenously in addition to standard of care, while rest 28 patients treated with standard of care alone. Sarilumab treatment resulted in clinical improvements in patients and they showed faster recovery. In patients with lung consolidation < 17 percent at CT scan, the

Table 2 Clinical studies evaluating the efficacy of sarilumab for the treatment of SARS-CoV-2 infectious disease

Sr. No	Types of Study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of Patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l) IL-6 (> 7 pg/ml)		Dosage and Duration with concomitant SOC	Day follow-up/ Mortality	Biomarkers level Post treatment CRP IL-6		Adverse reaction	References
1	Open label cohort	53 (47 M, 6F), 39 were assigned Median Age: 66	Fever, cough, Dyspnoea, severe pneumonia	142.7(68.3–86.1)	67.9(40.6 -131.2)	400 mg sarilumab, (66.7% with a single infusion; median PaO2/FiO2:146(IQR:120,212)] while 14(26.4%) in ICU [92.6% with a second infusion; median PaO2/FiO2: 112 (IQR:100,141.5)	14-day, mortality was 5.7%	–	–	Neutropenia, elevation of liver enzymes	Gremese et al., 2020
2	Open-label observational	56 (44 M, 22F) 28 (24 M, 24F) were assigned Median age: 56	Severe pneumonia	143 (101–224)	67.5 (37.5–127)	400 mg sarilumab	28-day, mortality was 7% in treated and 18% in untreated	< 6 mg/L (in 86% treated patients)		Neutropenia, elevation of liver enzymes	Della-Torre et al., 2020
3	Randomised, multifactorial, adaptive	865 (629 M, 236F), 48 (81.3%M) were assigned Median age: 63.4	Severe pneumonia	136 (105–204)	–	Single dose of 400 mg sarilumab	90-day, mortality was 22.2% in treated and 35.8% in untreated	1.62 (0.76–4.57)	–	No treatment-related serious	R.-C. Investigators et al., 2021
4	Randomised, double-blind, placebo-controlled, multinational	416, 332 were assigned Median age: 59	Fever, Cough, Dyspnoea	94·1 (44·6–176·8)	11·6 (5·1–26·5)	Single dose of sarilumab 200 mg (n = 159), or sarilumab 400 mg (n = 173)	60-day, mortality was 11% in treated and 11% in untreated	–	–	Neutropenia, elevation of liver enzymes	Lescure et al., 2021*
5	Single centre, retrospective	15 (12 M, 3F) Median age: 59	Respiratory insufficiency, pneumonia	15 (1.1–30.5)	61.9 (5.2–1000)	Single dose of 400 mg sarilumab/ 2nd dosage permitted after 24 h, if conditioned deteriorated	15-day, mortality was 5	–	–	No treatment-related adverse events	Montesarchio et al., 2020

Table 2 (continued)

Sr. No	Types of Study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of Patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6 (> 7 pg/ml)	Dosage and Duration with concomitant SOC	Day follow-up/ Mortality	Biomarkers level Post treatment CRP	IL-6	Adverse reaction	References
6	Randomised controlled trial cohort	255 (161 M, 94F), treatment categorised into two groups [stage IIB; ≤ 45%FiO2 (n = 149) Stage III; > 45%FiO2(n = 106)] Median age: 59	Fever	142 (132–153)	–	200 mg single dose sarilumab or 8 mg/kg tocilizumab	25-day, mortality was 2.7% in stage IIB and 22.6% death in stage III groups	–	–	No treatment-related adverse events	Sinha et al., 2020a, b
7	Randomised, placebo-controlled	201 99 (71 M, 28F) under treatment Median age: 60	Severe pneumonia	95.25 (48.9-142.8)	19.20 (6.00-46.00)	A single dose of 200 mg for patients < 75 kg body weight, or 400 mg for patients weighing ≥ 75 kg	15-day, mortality was 16.16% in the treated versus 15.69% in the control group	–	–	No treatment-related adverse events	Sancho-López et al., 2021

median time to clinical improvement following sarilumab was 10 days, compared to 24 days with standard therapy ($p = 0.01$). At day 28 of follow-up, the survival rate of sarilumab group was 93%, compared to 82% standard treatment; however, the difference was statistically not significant (HR 0.36; 95% CI 0.08–1.68; $p = 0.21$). But, patients with moderate pulmonary congestion healed quicker in the sarilumab therapy group (Della-Torre et al., 2020). In line with this study, Della-Torre et al., in 2021, conducted a study to assess the effectiveness of anti-cytokine therapies on COVID-19 patients with severe pneumonia and hyper-inflammation (PaO2/FiO2 ratio 300 mmHg with hyper-inflammation). The patients were given 5 mg/kg anakinra twice daily until clinical improvements were not obtained. A single dose of tocilizumab (400 mg) was administered and repeated every 24 h if the condition worsened. A single dose of 400 mg sarilumab was administered intravenously and the clinical outcomes were monitored and compared with standard care. The study included 107 patients treated with cytokine inhibitors and 103 patients treated with standard of care. Treatment resulted in a significantly greater survival rate compared to standard therapy in patients with PaO2/FiO2 ≥ 100 mmHg after a median of 106 days of follow-up (range 3–186) (p 0.001). Interestingly, anakinra also decreased mortality in patients with PaO2/FiO2 < 100 mmHg ($p = 0.04$) (Della-Torre et al., 2021). Studies suggested that the inhibition of IL-1 and Il-6 elevated response resulted in better survival rate, when treatment started early and before the establishment of ARDS.

Anakinra

Anakinra, a well-known IL-1 receptor antagonist, is used for the treatment of various hyper-inflammatory conditions like Still's disease, juvenile idiopathic arthritis, familial Mediterranean fever, etc. Anakinra is found to be super effective in treating cytokine storm syndrome including cytokine release syndrome as well as macrophage activation syndrome (Filocamo et al., 2020; Cavalli et al., 2020). It is approved by US-FDA (United States Food and Drug administration) for its use in the treatment of arthritis rheumatoid and multi-inflammatory diseases (Navarro et al., 2020). It is known to possess the ability to block the activity of pro-inflammatory cytokines (IL-1β and IL-1α). As previously discussed, patients with COVID-19 disease exhibit hyper-inflammatory symptoms similar to cytokine storm and the release of interferon, IL-18, IL-6 and IL-1β in patients with macrophage activation syndrome. These disorders can be prevented up to great extent using agents that block the cytokines. Anakinra is one such blocking agent that is found to be effective in the treatment of these diseases. The use of anakinra permits the prompt discontinuation due to its short half-life, and thus considered suitable to be used in the case of critical patients. Also, the anakinra is considered much safer as compared to other cytokine-blocking agents (Cavalli et al., 2020). Higher dosage of anakinra is recommended for patients suffering from heavy load of viral infection as in case of H1N1, Ebola and EBV (Filocamo et al., 2020). Anakinra tends to lower the death rate in patients having sepsis, liver dysfunction and disseminated-intravascular coagulation. Due to its short half-life and its property of inhibiting both the IL-1 subtypes, it could possibly be a promising treatment to cure severe COVID-19. A number of studies have been reported showing the beneficial effects of anakinra during initial treatment in patients suffering from COVID-19 disease (Aomar-Millán et al., 2021; Navarro-Millán et al., 2020) (Table 3).

A study was conducted by (Aomar-Millán et al., 2021) on 143 patients suffering from moderate hyper-inflammation and severe COVID pneumonia with the aim to depict the effect of anakinra on COVID patients. The patients were given standard therapy and were divided into 3 groups. Group 1 received pulses of methyl prednisolone, group 2 received tocilizumab in addition to methyl prednisolone and group 3 received anakinra as per the protocol. The first dose of anakinra was decided as per the weight of the patients. Patients with weight ranging from 50 to 60 kg were given dosage of 100 mg/12 h; 60 to 75 kg were given 100 mg/ 8 h and those above 75 kg were given 100 mg/ 6 h. All patients received a dosage of 100 mg/12 h from the second day onwards till day 6. The study lasted for 60 days. The results indicated that patients from group 3 who were receiving the dose of anakinra were associated with a lower risk of death rate. Also, the mean CD-4 count was reduced in group 3 after 3 days of the treatment. It was observed that none of the patients developed any complications after treatment with anakinra, and it was tolerated well among all the patients.

Another study conducted by (Navarro-Millán et al., 2020), on patients suffering from SARS CoV-2 with high fever and acute-hypoxemic respiratory failure (AHR failure). Out of 14 patients, 11 received anakinra treatment (100 mg every 6 h, subcutaneously) for maximum 19 days. Seven patients with AHR failure did not require mechanical ventilation anymore after anakinra treatment of ≤ 36 h and were discharged from the hospital. While the other 3 patients who did not received the anakinra treatment needed mechanical ventilation. The study suggested that the use of anakinra could prove to be beneficial for treating patients suffering from COVID-19 with cytokine storm syndrome. Various other studies are available and are still in queue to evaluate the efficacy and safety of anakinra in COVID-19 patients. (Cavalli et al., 2020), they have administrated high dose (5 mg/kg, twice daily, intravenously) and observed the positive outcome, which showed improved respiratory function among the patients. No adverse events were observed.

Table 3 Clinical studies evaluating the efficacy of Anakinra for the treatment of SARS-CoV-2 infectious disease

Sr. No	Types of Study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of Patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6 (> 7 pg/ml)	Dosage and Duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers Post treatment CRP	IL-6	Adverse reaction	References
1	Prospective, open label, interventional	69, 45 (35 M, 10F) were assigned for treatment Median Age:49.8	Severe pneumonia	150 (82–178)	55 (18–98)	100 mg twice daily for 3 days, followed by 100 mg daily for 7 days	14-day, mortality was 29% in the anakinra treated and 46% in controls	9 (4–59)	6.6 (2.8–6.6)	Neutropenia, Thrombocytopenia	Balkhair et al., 2021
2	Open label, single arm, non-randomised	309, 130 (81 M, 49F) were assigned for treatment Median Age:63	Fever, severe pneumonia	47.4 (14.3–105.5)	–	Single dose of 100 mg anakinra / 10 days	90-day, mortality was16.9% in treated and 30.8% in controls			Leukopenia, No treatment-related serious adverse event,	Kyriazopoulou et al., 2021
3	Retrospective, non-randomized	128, 63 were assigned for treatment (42 M, 21F); 30 patients received anakinra alone, whereas 33 received anakinra plus a glucocorticoid Median Age:59	Severe pneumonia	8.7 (4.4–13.5)	–	100 mg every 8 h for 3 days, followed by tapering (100 mg every 12 h for 1–3 days, followed by 100 mg every 24 h for 1–3 days) up to 9 days	10-day, mortality was 14% in treated and 43% in controls	< 5 mg/dl		No treatment-related serious adverse event	Pontali et al., 2021
4	Multicentre, open label, Bayesian randomised	116, 59 (43 M, 16F) were assigned for treatment Median Age:66	Mild-to-moderate pneumonia	121 (77–198)	–	200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5, If no improvement, treatment proceeded to 8 days	90-day, mortality was 27% in both treated and controls	–	–	ARDS, Bacterial sepsis, hepatic cytolysis	CORIMUNO-19 Collaborative group, 2021

Table 3 (continued)

Sr. No	Types of Study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of Patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l) IL-6 (> 7 pg/ml)	Dosage and Duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers Post treatment CRP IL-6	Adverse reaction	References
5	Retrospective, Observational	112, 56 were assigned for treatment (41 M, 15F) Median Age:65	ARDS	17.9 (11.8–30.7)	Anakinra was administered for 7 days at the dosage of 100 mg four times a day s.c., if managed in a regular ward, or 200 mg three times daily i.v., if managed in the intensive care unit	90-day, mortality was 37.9% in treated and 43.6% in controls	7.6 (7.6–10.5)	No treatment-related serious adverse event; Infection was observed in few cases	Franzetti et al., 2021
6	Retrospective cohort study	41, (28 M, 13F) Median Age:58.8	Fever, Dyspnoea	> 70 mg/L	100 mg daily for 5 days; 100 mg SQ every 6 h; or every 12 h for those with renal failure	30-day, mortality was 22% in anakinra treated and 46.2% in tocilizumab-treated group	–	No treatment-related serious adverse event	Langer-Gould et al., 2020
7	Prospective, observational cohort	120, 65 were assigned for treatment (52 M, 13F) Median Age:60	Severe pneumonia, hyperinflammation	14.8 (9.0–24.5)	200 mg every 8 h for 3 days, then 100 mg every 8 h up to day 14 with methylprednisolone	28-day, mortality was 13.9% in treated patients and 35.6% in controls	< 5 mg/dl	Anaemia, granulocytopenia, elevation of liver enzymes, infection	Bozzi et al., 2021
8	Monocentric retrospective case–control study	45, 29 were assigned for treatment Median Age:62	Moderate-to-severe ARDS, and hyperinflammation	143 ± 71	10 mg/kg per day (5 mg/kg twice daily, infused over 1 h)	21-day, mortality was 10% in treated and 44% in control groups	75% reduction	Bacteremia, elevation of liver enzyme	Cavalli et al., 2020

Table 3 (continued)

Sr. No	Types of Study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of Patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l) IL-6 (> 7 pg/ml)	Dosage and Duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers Post treatment CRP IL-6	Adverse reaction	References
9	Multicenter retrospective case–control study	22, 12 (6 M, 6F) were assigned for treatment Median Age:61	Bilateral pneumonia, hyper-inflammation	162 [122–212]	100 mg daily for 5 days tapered to 200 mg daily for 2 days and 100 mg for 1 day	20-day, no death in treated, while 10% death in control groups		No treatment-related adverse events	Cauchois et al, 2020
10	Single centre, retrospective, cohort	52 (36 M, 16F) Median Age: 71	Respiratory discomfort, sever form	173 –	100 mg twice daily for 3 days, and then tapered to 100 mg daily for 7 days	20-day, mortality was 25% in treated and 73% in the historical group	20 ± 20 –	No treatment-related adverse events, elevation of liver enzymes, thrombo-embolic events were observed in few cases	Huet et al., 2020

Baricitinib

Baricitinib (C16H17N7O2S), a reversible JAK inhibitor, i.e. Janus-associated-kinase inhibitor (JAK 1/ JAK 2) is approved in more than 65 countries to treat patients suffering from rheumatoid arthritis (moderate to severe) (Jorgensen et al., 2020). This small molecule not only inhibits the release of cytokines but also reduces the chances of viral entry, and thus seems to be an important drug possessing anti-inflammatory activity (Cantini et al., 2020). Using benevolent algorithms of artificial intelligence and due to the dual effective nature of baricitinib against viral entry and release of cytokines, its use can be predicted in COVID-19 infection. The anti-viral efficacy using baricitinib was demonstrated in liver spheroids of humans and showed a good safety profile when administered to patients suffering from COVID-19. Administration of baricitinib to patients reduced the mortality rate, their chances of admission to the intensive care unit, and a drop in the count of viral load was observed when detected through nasopharyngeal swabs (Petrone et al., 2021; Stebbing et al., 2020). Various adaptive treatment trials of COVID-19 showed that baricitinib when used in combination with remdesivir claimed better results in terms of reducing the recovery time and speeding up the status of improvement among COVID-19 patients (Table 4). Various in vitro studies and machine learning algorithms suggested that clathrin-mediated endocytosis in case of SARS CoV-2 can be inhibited using baricitinib due to its affinity towards AP2-associated protein AAK1, which is responsible for reducing the SARS-CoV-2 endocytosis (Cantini et al., 2020).

A study conducted by (Cantini et al., 2020) for duration of 14 days on 12 patients (2 females and 10 males) suffering from mild-to-moderate corona disease (CoV-19), the patients were given treatment of baricitinib (4 mg per day) along with ritonavir–lopinavir therapy. The treatment was tolerated normally without any adverse event. However, 1 patient was withdrawn from the study on 10th day due to elevation of transaminases (ALT: 298 U/L; AST: 267 U/L), which might be due to anti-viral therapy and not that of baricitinib treatment. Despite this, no other opportunistic or bacterial infection, haematologic toxicity or thrombophlebitis were observed. Significant improvement in parameters of respiratory function and all other clinical characteristic were observed in weeks 1 and 2 in comparison with baseline. The major depiction of the study involved the admission of 33% (i.e. 4 out of 12) of control group to ICU, which was 0 in case of baricitinib-treated group. Also, discharge rate of the patients in week 2 was 58% (i.e. 7 out of 12) in case of baricitinib-treated group, which was only 8% (i.e. 1 out of 12) in case of controls.

Another in vitro study was conducted by (Petrone et al., 2021) to evaluate the effect of baricitinib on the whole blood of 39 COVID-positive patients. Usually, low magnitude of cytokines (Th-2), predominance of Th-1 and high IFN- γ response are associated with immune response of COVID-19 patients. The result of the study depicts that there was significant drop in various immune factors such as IFN- γ; growth factors (FGF, GM-CSF); pro-inflammatory cytokines such as TNF- α, IL-6 and IL-1 β; Th-2 cytokines including IL-4 and 13, IL-10; chemokines (MIP-1 β, MCP-1 and IP-10) and other antigens upon baricitinib addition. All these factors are produced by innate immunity cells and by T and B cells and are considerably increased during the infection of COVID-19. The staphylococcal enterotoxin B-induced response was also dropped significantly upon baricitinib addition. Overall, the study concluded that baricitinib addition is responsible for lowering the SARS-CoV-2-specific response, including in patients suffering from mild or moderate coronavirus disease or in patients having a lymphocyte count of $\geq 1 \times 10^3/\mu l$.

Many other trials and studies have been done and are still in queue by various institutions in different countries to evaluate the effect of baricitinib on COVID-19 patients. Majority of the results confirms the safety of baricitinib therapy in number of clinical trials where no hematological or cardiovascular adverse event or infection took place after two weeks treatment (Cantini et al., 2020). This two-week duration is similar to that of duration in ongoing COVID-19 studies involving baricitinib therapy which lasts from 7 to 14 days (Jorgensen et al., 2020). Carpio-Orantes et al., in 2021 enrolled 30 patients, and 90% of them had moderate and 10% had severe ARDS. Patients receiving 4 mg/day baricitinib for 14 days demonstrated clinical improvement, with improved oxygen saturation and SAFI after 7 and 14 days of therapy. Ninety percent of patients healed, while ten percent died while undergoing therapy (Carpio-Orantes et al., in 2021). In 2021, Kalil et al. conducted a double-blind, randomised, placebo-controlled study in which they enrolled 1033 hospitalised COVID-19 patients and treated 515 of them with baricitinib in combination with remdesivir. When compared to remdesivir alone and the placebo group, treatment with combination medication resulted in better clinical results. Patients who received combo treatment healed more quickly than the control group (7 days vs. 8 days). Patients on mechanical ventilation respond better to combination treatment, recovering in 10 days compared to 18 days for placebo. The use of combination treatment resulted in fewer side effects (Kalil et al., 2021; Goletti and Cantini 2021). Marconi et al., 2021 conducted a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial, and 1525 participants were enrolled from 101 centres across 12 countries in Asia, Europe, North America, and South America. 764 of them received 4 mg/day baricitinib for 14 days with systemic corticosteroids or 761 patients assigned to placebo group who received only systemic corticosteroids. The baricitinib-treated group had a

Table 4 Clinical studies evaluating the efficacy of baricitinib for the treatment of SARS-CoV-2 infectious disease

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6(> 7 pg/ml)	Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP	IL-6	Serious adverse events	References
1	Single centre	12 (10 M/ 2F) Median Age: 63.5	Fever, Cough, Dyspnoea, Diarrhoea, moderate pneumonia	8.2 (5.8–14.5)	–	4 mg baricitinib for 7 days	No fatality, Discharge at week 2 occurred in 58% -treated patients vs 8% of controls	0.7–3.4	–	No treatment-related serious adverse event	Cantini et al., 2020
2	Cohort study	238 (159 M, 73F) Median age:59–63	Fever, dry cough, weakness, shortness of breath anosmia, diarrhoea, and sore throat, sever pneumonia	159 (44.5–231.4)	45 (10.5–75.7)	4:8 mg [usual dose (UD, n = 116):high dose (HD), n = 122] for 14 days along with standard treatment	30-day, mortality was 3.3% in HD vs. 6% UD groups	–	–	Thrombocytosis and mouth sore (2.4% HD vs 0.8% UD)	Hasan et al., 2021
3	Double blind, randomised allocation	1033 (652 M, 381 F) 507 sere assigned for treatment Median Age: 55	Pneumonia	–	–	4-mg baricitinib dose for 14 days plus 200 mg remdesivir for 1st day followed by 100 mg for 10 days	28-day all-cause mortality was 5.1% in the combination group and 7.8% in the control group	–	–	In 5% cases hyperglycemic, anaemia, decreased lymphocyte Count, and acute kidney injury are reported	Kalil et al., 2021
4	Single centre study	30 patients (73%M, 27%F) Median age: 58.5	Moderate to severe ARDS	10.0 (7.7 – 12.0	–	4 mg/day by 14 days	14-day all-cause mortality was 10% in treated groups	–	–	No treatment-related serious adverse event	Carpio-Orantes et al., 2021
5	Ncohort studyon-controlled, retrospective	15 (15 M)	Fever, cough, diarrhoea, confusion, shortness of breath	163 (79.8–240)	38.21 (2.49–130.0)	2–4 mg of baricitinib and hydroxychloroquine 200–400 mg daily	At day 30, 20% mortality was associated with the treatment	85.35 (12–240)	–	No treatment-related serious adverse event	Titanji et al., 2021

Table 4 (continued)

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6(> 7 pg/ml)	Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP	IL-6	Serious adverse events	References
6	Observational, longitudinal trial a	76, 20 (7 M, 13F) were assigned for treatment	Fever, Pneumonia	53.15 (43.08–77.63)	> 50	4 mg baricitinib twice daily for 2 days followed by 4 mg per day for the remaining 7 days	5% in treated and 45% in controls	9.7 (4.33–14.23)/Day 9	–	No treatment-related serious adverse event	Bronte et al., 2020
7	A case study	71-year-old male	Fever, cough and dyspnoea	106 mg/l	97.4 pg/ml	4 mg per day for 2 weeks	n/a	20 mg/l	14.3 pg/ml	No treatment-related serious adverse event	Cingolani et al., 2020
8	Double-blind, randomised, placebo-controlled trial	1525\ baricitinib assigned group [$n = 764$; (373 M, 219F)] Median age: 57.8	Fever, Pneumonia	65 mg/l	–	4 mg/day; however, 2 mg/day was given if the patient had a baseline eGFR of 30 to less than 60 mL/min/1·73 m^2 for 2 weeks	28-day all-cause mortality was 8.1% for treated and 13.1% for control group	–	–	No treatment-related serious adverse event	Marconi et al., 2021

38.2 percent lower death rate on day 28. On days 28 and 60, the estimated mortality rate of the baricitinib-treated group was 8% (n = 62) and 10% (n = 79), respectively, compared to placebo, which was 13% (n = 100) and 15% (n = 110). In comparison to the placebo, the baricitinib-treated group demonstrated fewer serious adverse reactions like serious infections and venous thromboembolic events (Marconi et al., 2021).

Ruxolitinib

Early hypercytokinemia causes an increase in IL-6 levels, which activates the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway, perpetuating the inflammatory processes. IL-6 forms a complex with either surface or soluble receptors (mIL-6R or sIL-6R) that activates gp130, which interacts with Janus kinases and regulates levels of cytokines. Blocking signalling events related to or at the level of cytokine production, such as JAK–STAT signalling in macrophages to alleviate IL-1 and IL-6 production, offers a promising therapeutic strategy for overcoming cytokine storm. Ruxolitinib is a JAK 1/2 inhibitor, licensed for use for the treatment of polycythemia vera and myelofibrosis (Ajayi et al., 2018). It has also been reported to be effective in the treatment of secondary hemophagocytic lymphohistiocytosis (Ahmed et al., 2019) by targeting the lethal effects of an aberrant host inflammatory response. Ruxolitinib alleviates the level of pro-inflammatory cytokines (IL-6, TNF-α, GM-CSF, MCP-1, and MIP-1α) and proliferation of cytotoxic T cells through the activation of regulatory T cells. Ruxolitinib can be effective against the consequences of the CSS in patients with COVID-19 (**Table 5**). Cao et al., in 2020 conducted a randomised, multicenter, placebo-controlled, single-blind phase II trial in hospitalised patients with severe COVID-19 to evaluate the efficacy and safety of ruxolitinib. In terms of clinical improvement, however, no significant differences were found, despite the fact that individuals treated with ruxolitinib had a numerically shorter median time to clinical improvement [IQR, 10–19] days vs 15 [IQR, 10–18] days, compared to placebo. In secondary outcomes, administration of ruxolitinib significantly mitigated the exuberant cytokine storm featured in severe COVID-19, alleviated the elevated levels of 48 cytokines, among which the levels of IL-6, NGF, IL-12 (p40), MIF, MIP-1a, MIP- 1b, and VEGF were significantly lower in the ruxolitinib group compared to control group. The finding depicts that ruxolitinib may exert its inhibitory impact on multiple critical cytokines rather than any particular cytokine, and these cytokines could be exploited as surrogate biomarkers in future ruxolitinib trials. Gozzetti et al., 2020 enrolled fourteen patients in their study to check the efficacy of ruxolitinib and administrated it at a dose of 7.5 mg/day for 14 days with a COVID-19 Inflammation Score (CIS) ≥ 10 out of 16 points. The authors reported that 12/14 patients achieved a significant reduction of CIS by ≥ 25% on day 7 with a sustained clinical improvement in 11/14 patients. D'Alessio et al., in 2021 conducted a non-randomised clinical study to assess the effect of ruxolitinib in patients with severe COVID-19 pneumonia, without mechanical ventilation. Five mg of ruxolitinib was given orally twice a day for 7 days and then tapered to a single dose per day for up to 10 days. In addition to ruxolitinib, all patients received methylprednisolone 1 mg/kg intravenously for three days followed by 0.5 mg/kg for five days and then oral prednisone, which was slowly tapered in the course of 2 weeks. The results depicted that the mortality rate of the treated patients was significantly reduced and there were no significant side effects compared to the control group. Secondary outcomes were decreased inflammatory response, defined as afebrile and 30% decreased CRP levels at the second clinical observation, i.e. 3–10 days after hospital admission (D'Alessio et al., 2021). In a study by Capochiani et al., 2020, 16 out of 18 enrolled patients exhibited a significant improvement in respiratory responsiveness during the first 48 h. After 7 days of ruxolitinib treatment, 11/18 patients had completely regained respiratory function (pO2 > 98 percent in spontaneous breathing), 4/18 patients had minimal oxygen requirements (2–4 L/m), 1/18 patients had stable disease, and 2/18 patients had advancing disease.16/18 patients had perfect respiratory function on day 14 of ruxolitinib therapy. 16/18 patients had perfect respiratory function on day 14 of ruxolitinib therapy. IL-6 levels dropped quickly in responsive patients (16/18). However, the non-responsive patients (2/18) showed a substantial rise in IL-6 plasma levels (Capochiani et al., 2020). In patients on ruxolitinib, anaemia is the most prevalent side effect. Long-term ruxolitinib treatment, on the other hand, was associated with a low rate of non-hematological side effects (Kiladjian et al., 2020).

Lenzilumab/mavrilimumab/otilimab (GM-CSF inhibitors)

GM-CSF is an immunoregulatory cytokine that plays an important role in the onset and progression of inflammatory disorders. GM-CSF levels have recently been found to be elevated in COVID-19 patients (Mehta et al., 2020a, b). Although GM-CSF is considered an appropriate response under some circumstances, in this case, the inflammatory response is observed to be disproportionate. The lung damage caused by COVID-19-induced hyper-inflammation can be improved by blocking the GM-CSF signalling, which can be done by opposition of the GM-CSF receptor or direct binding of circulating GM-CSF (Table 6). COVID-19 patients treated with a single dose of mavrilimumab, a

Table 5 Clinical studies evaluating the efficacy of Ruxolitinib for the treatment of SARS-CoV-2 infectious disease

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6 (> 7 pg/ml)	Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP	IL-6	Adverse reaction	References
1	Multicentre, retrospective, observational	18 (12 M, 6F) Median age: 62.5	Breathing difficulty, fever, nausea, Risk of Hyper inflammation	17.8 (4–82)	24.5 (4.5–111)	20 mg bids for first 48 h followed by two-step de-escalation at 10 mg bids, then reduced to 5 mg bids for a maximum of 14 days	No mortality was reported at day 14		< 7.8	No treatment-related adverse events	Capochiani et al., 2020
2	Non-randomised	32 (68.7/31.3) Median age: 67.5	Fever, severe pneumonia, breathing problem, dry cough, Risk of Hyper inflammation	14.6 (1.8–30)		5 mg rux twice daily for 7 days and then tapered to 5 mg daily up to 10-day	45-day mortality was 9% in treated and 30% in controls	1.33 (0.05–22)	–	No treatment-related adverse events	D'Alessio et al., 2021
3	Single centre retrospective	105 (58 M, 48F), 14 were assigned for rux treatment Median Age:65	Severe pneumonia	22.3 (1.6–67)	19 (3.1–282.1)	Median cumulative dose of 135 mg/ median 9 days	Only 1 mortality was reported at day 14	3.1 (0.3–48.7)/ Day 15	5.9 (2.1–11.2)/ Day 15	Mild anaemia and liver enzyme elevation	La Rosée et al., 2020
4	Multicenter, single-blind, randomised controlled trial	41, 20 were assigned for rux treatment (12 M, 8F) Median age:63	Severe pneumonia	≥ 25	≥ 50	5 mg twice a day	28-day, no mortality was in treatment group	≤ 10 mg/ml	≤ 7 pg/ml	Mild anaemia and liver enzyme elevation	Cao et al., 2020

Table 5 (continued)

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6 (> 7 pg/ml)	Dosage and duration with concomitant SOC	Day follow-up/ Mortality	Concentration of biomarkers post treatment CRP	IL-6	Adverse reaction	References
5	Prospective observational study	34 (18 M, 16F) Median age: 80.5	Severe pneumonia	73 (39–111)	–	Daily dose of 5 mg BID; increased to 10 mg BID after 24–48 h in case there was no improvement, further escalation to 25 mg daily was allowed after an additional 48 h	28-day mortality was 5.9%	12 (6–21)	–	Anaemia, urinary tract infection, creatinine and liver enzyme elevation	Vannucchi et al., 2021a
6	Single centre, Cohort	31 (18 M, 13 F) Median age: 70.5	Dyspnoea, severe pneumonia	79.1 ± 73.4	–	Dose of 5 mg b.i.d. for 15 days	15-day, no mortality was in treatment group	18.6 mg/dL ± 33.2 at day 15	–	No treatment-related adverse events	Mortara et al. 2021
7	Multicentre, cohort	218 (134 M, 84F) Median age: 70.5	Severe Pneumonia	~ 70 (22–125)	–	5 mg BID (median 10 days)	28-day, mortality was 12.8%	~ 20 ± 6 at day 14	–	Anaemia, liver enzyme elevation, thrombocytopenia	Vannucchi et al., 2021b

Table 6 Clinical studies evaluating the efficacy of lenzilumab/mavrilimumab for the treatment of SARS-CoV-2 infectious disease

Sr. No	Types of study (double-blind, a randomised allocation, an historical control, or simply a case study)	No. of patients enrolled, (% of M/F)	Symptoms	Biomarker level CRP(> 3.0 mg/l)	IL-6 (> 7 pg/ml)	Dosage and Duration with concomitant SOC	Days follow-up/ Mortality	Concentration of biomarkers Post treatment CRP	IL-6	Adverse reaction	References
1	Multicentre, double-blind, randomised	40, 21 were assigned for treatment (14 M, 7F) Median age: 54.8	Fever, nausea, breathing restriction, severe pneumonia	14 (9.9–18.8)	–	Mavrilimumab 6 mg/kg body weight single dosage	60-day, mortality was 5% in treated and 21% in controls	–	–	No treatment-related adverse events	Cremer et al., 2021
2	Single centre, prospective, cohort	39, 13 were assigned for the treatment (12 M, 1F) Median Age: 57	pneumonia	152 (100–177)	40 (28–60)	Single dose 6 mg/ kg Mavrilimumab	28-day, no mortality was in treated group, while 27% mortality in controls	Reduction up to ≥ 75%		No treatment-related adverse events	De luca et al., 2020
3	double-blind, randomised, placebo control	479, 236 (153 M, 83F) were assigned for treatment Median Age: 60.5	Breathing difficulty, fever, nausea, pneumonia	98.36 ± 75.57	–	Lenzilumab 600 mg via three intravenous infusions administered 8 h apart	28-day, mortality was 15.4% in treated group and 21.4% in controls	7.0 mg//ml	–	No	Temesgen et al., 2021
4	Randomised	12 (8 M/4F), Median Age: 65	Severe pneumonia	137	26.8	Lenzilumab 600 mg via three intravenous infusions	no mortality	51.2 (day 3)	16.1(day 3)	No treatment-related adverse events	Temesgen et al., 2020a
5	Case Cohort	39, 12 were assigned for treatment Median Age: 57	Breathing difficulty, fever, nausea, pneumonia	103.2 (52.7–159.9)	30.95 (24.18–34.05)	Lenzilumab 600 mg via three intravenous infusions	14-day, mortality was 8.3% in treated, and 18.5% in controls	–	–	No treatment-related adverse events	Temesgen et al., 2020b

monoclonal antibody which binds to the GM-CSF receptor, showed improvement in oxygenation and resulted in shorter hospitalisations (Bonaventura et al., 2020). Cremer et al., 2021, conducted multicentre, double-blind, randomised trial on 40 hospitalised COVID-19 patients with pneumonia, hypoxaemia and a C-reactive protein > 5 mg/dL. The primary efficacy outcome at day 14 for checking the patients free from mechanical ventilation was found to be 57% with mavrilimumab as compared to 47% with placebo; whereas, secondary outcome at day 28 to check the survival ratio was that 95% of the patients in mavrilimumab group were alive compared to 79% in untreated. However, the observation was not statistically significant, but this finding hypothesises the need for larger clinical trials to check their efficacy (Cremer et al., 2021).

Lenzilumab is a novel Humaneered® anti-human GM-CSF monoclonal antibody that binds directly to the GM-CSF and blocks further signalling through its receptor. It also showed strong binding affinity (25 pM) and a slow off-rate for glycosylated human GM-CSF (Padron et al., 2013). Temesgen et al., in 2020a, conducted the first clinical trial of Lenzilumab in neutralising the GM-CSF in patients with severe COVID-19-associated pneumonia. In their study, lenzilumab treatment resulted in clinical improvement in 11 out of 12 (92%), with a median time to discharge of 5 days. On day 3, mean CRP and IL-6 levels improved significantly (137.3 mg/l vs 51.2 mg/l, p = 0.040; 26.8 pg/ml vs 16.1 pg/ml, $p = 0.035$, respectively). After two days of lenzilumab therapy, cytokine analysis revealed a decrease in inflammatory myeloid cells. Temesgen et al., 2020b conducted a cohort study to evaluate the efficacy of lenzilumab in the treatment of patients hospitalised with COVID-19 pneumonia. Intravenous treatment with three doses of 600 mg of lenzilumab in 12 patients versus 27 patients comprising the matched control cohort (untreated), led to a significantly shorter time for clinical improvement in lenzilumab-treated patients, with a median of 5 days versus 11 days ($P = 0.006$). Compared to the untreated, the proportion of patients with acute respiratory distress syndrome (oxygen saturation/fraction of inspired oxygen < 315 mm Hg) was considerably reduced over time when given lenzilumab (P < 0.001). Inflammatory markers (C-reactive protein and interleukin 6) and disease severity markers (absolute lymphocyte count) improved significantly in lenzilumab-treated individuals compared to untreated patients. No treatment-emergent adverse events were associated with lenzilumab. Recently, Temesgen et al., 2021, conducted phase-3 randomised, double-blind, placebo-controlled study in 520 hospitalised severe COVID-19 patients across 29 sites in the United States and Brazil, and investigated the efficacy and safety of lenzilumab in improving the likelihood of ventilator-free survival without ventilation (SWOV). The likelihood of SWOV through day 28 was reduced by 54% in COVID-19 hospitalised patients with early treatment with lenzilumab. Although the patients were hypoxic, they did not require mechanical ventilation. The severity of COVID-19 disease is linked to a high level of CRP. In this trial, 77% of subjects with an evaluable CRP, had a baseline value < 150 mg/l and 74% had a baseline CRP value < 150 mg/l and age < 85. This study revealed that a CRP level of less than 150 mg/l was related with obtaining SWOV and distinguished developing hyper-inflammation from full-fledged CSS during the course of treatment. This study also demonstrated that early intervention with lenzilumab led to neutralisation of GM-CSF, which is a key factor responsible for initiation of CS in hypoxic patients. This also improved the probability of survival without the usage of mechanical ventilation and provided the greatest benefit over the usage of steroids and/or remdesivir.

Heparin

Heparin is a member of a family of polyanionic polysaccharides called glycosaminoglycans (Young, 2008). It is still one of the most commonly prescribed anticoagulants in clinical practice, for the prevention of thrombosis. Heparin has been shown to have various functions in inhibiting SARS-CoV-2 in the treatment of COVID-19 (Hippensteel et al., 2020). It is used as an anticoagulant in treating coagulopathy associated with severe SARS-CoV-2 infection. Tang et al., 2020 were the first to conduct a retrospective, cohort study, including 449 severe COVID-19 patients, 99 of whom had taken low-dose preventive doses of heparin for 7 days or longer. Those who received prophylactic heparin with sepsis-induced coagulopathy (SIC) score ≥ 4 had ~ 24.0 percent lowered mortality than non-users patients (40.0 percent vs 64.2 percent, $P = 0.029$) (Tang et al., 2020).

In 2020, Paranjpe et al., enrolled 2773 hospitalised patients with COVID-19 to evaluate the efficacy of anticoagulant therapy. In-hospital mortality was found to be 29.1% in patients receiving therapy and on mechanical ventilation support, with a median survival of 21 days, compared to 62.7% in non-users with a median survival of 9 days (Paranjpe et al 2020). Furthermore, heparin also displayed anti-viral characteristics, a study by Lang et al. 2011 demonstrated that heparinase or exogenous heparin blocked spike protein from attaching to hostile cells and prevented pseudovirus SARS infection. In 2020, using a surface plasmon resonance direct binding assay, Kim et al. demonstrated that the SARS-CoV-2 spike protein formed a highly strong (and nearly irreversible) bond with heparin sulphate, and has shown a greater affinity than either SRS-CoV or MERS-CoV spike protein (Kim et al., 2020). Despite this, few studies showed that the blocking of pro-inflammatory signalling pathways mediated by MAPK, NF-kB, and STAT-3 was also linked to heparin's protective

response in sepsis (Iba and Levy, 2017; Li et al., 2020). Heparin has been demonstrated to be easily coupled and absorbed into the cytosolic compartment, where it binds to the positively charged nuclear localisation sequence and prevents NF-kB from translocating to the nucleus (Letourneur et al., 1995; Akimoto et al., 1996; Dudas et al., 2000). The production of pro-inflammatory cytokines, chemokines, and adhesion molecules can be regulated by reducing inflammatory gene activation by blocking of NF-kB. Lower mortality was observed in COVID-19 patients who were treated with heparin, even after taking various parameters like age, gender, oxygen saturation < 90% and temperature > 37 °C (Ayerbe et al., 2020). Recently, a study in the US of COVID-19-hospitalised patients ($n = 786$) showed that patients who received anticoagulants had a reduced risk of mortality. Studies showed that early treatment with prophylactic anticoagulation resulted in reduced 30-day mortality, compared to no anticoagulation among hospitalised COVID-19 patients (Paranjpe et al., 2020). Amongst the 4297 COVID-19 patients admitted, 3627 (84.4%) who received prophylactic anticoagulation within 24 h of admission had a 27% reduced risk for 30-day mortality as compared to patients with no prophylactic administration (Rentsch et al., 2021). The treatments had no increased risk of serious bleeding events. Many more studies suggested that the inhaled unfractionated heparin (UFH) may provide therapeutic advantage over the course of the disease. UHF may prevent infection in upper respiratory tract, given by inhalations into the upper airways, a significant site of entrance for the virus (Haren et al., 2020; Braz-de-Melo et al., 2021).

Antifibrotics (tyrosine kinase inhibitors)

Nintedanib has been demonstrated to reduce IL-1 concentrations in bronchoalveolar lavage, and pirfenidone has been proven to diminish serum and lung IL-6 concentrations in murine models of pulmonary fibrosis, adding to the biological basis for Nintedanib and pirfenidone's usage in COVID-19. Umemura et al. (2021) conducted an interventional study for evaluation of the safety and efficacy of nintedanib for pulmonary fibrosis in COVID-19 patients with severe pneumonia. There was no significant difference in 28-day mortality in 30 patients that received nintedanib therapy in comparison to 30 control patients not receiving it (23.3% vs 20%, $P = 0.834$). However, the nintedanib group had considerably shorter periods of mechanical ventilation. It was hypothesised that the usage of nintedanib may offer potential benefits in minimising the COVID-19 induced lung injury (Umemura et al., 2021). Based on this observation, Nintedanib was referred for clinical trials to check its efficacy in the treatment of SARS-Cov-2 induced pulmonary fibrosis (NINTECOR) [ClinicalTrials.gov Identifier: NCT04541680]. A case report conducted by Ogata et al., in 2021, on a 78-year-old Japanese woman with no smoking history who suffered from a near-fatal COVID-19, required four-week invasive mechanical ventilation, with subsequent radiological features of pulmonary fibrosis. In parallel with systemic steroids, the patient was also given nintedanib therapy, which led to the patient being able to walk using a walking aid utilising oxygen at 4 L/min (Ogata et al., 2021). The current case suggests that nintedanib could be used to treat post COVID-19 fibrosis in a unique way. However, only one patient was examined in this study and more investigations are, thus, necessary.

Pirfenidone, also known as 5-methyl-1-phenyl-2-[1H]-pyridone, is a new anti-fibrotic agent with little side effects. Pirfenidone is licenced for the treatment of patients with mild-to-moderate Idiopathic Pulmonary Fibrosis (IPF). Pirfenidone has been shown to suppress apoptosis, downregulate ACE receptor expression, reduce inflammation through a variety of pathways, and alleviate oxidative stress and, thus, protect pneumocytes and other cells from COVID-19 invasion and cytokine storm concurrently. Based on known action mechanism and pathophysiology of pirfenidone for COVID-19 (Seifirad, 2020; Singh et al., 2021), the treatment with pirfenidone for severe COVID-19-related severe ARDS is referred for the clinical trials [Clinical trials NCT04653831].

Conclusion

Numerous initiatives have been undertaken to combat the SARS-CoV-2 epidemic. Many medicines and vaccines have received emergency approval from the WHO and FDA and are being used to treat the symptoms of this disease. Despite this, outbreaks continue to be diagnosed and spread in a number of countries. The emergence of SARS-CoV-2 variants raises concerns about the efficacy of authorised medicines and vaccines, and we still do not know what the SARS-CoV-2 virus and its variants may bring. CSS and ARDS are the most common clinical problems linked to severe instances of COVID-19 illness. The increased cytokine level causes typical organ damage in the more established CSS, although many clinical trials demonstrate that the cytokine-blocking yields in clinical benefit and survival. Numerous studies have shown that immunomodulatory treatments can help to reduce the severity of this disease and save lives. However, variability, limited sample sizes, and random recruitment raise concerns about the research that has been undertaken. A number of studies, both supporting and contradictory, have been published. We commended the efforts of all health authorities, supporting personnel, and scientists for identifying potential treatment options for severe instances of COVID-19 illness. Moreover, efforts on a global level are still needed, as demonstrated by the CSS phenotype

on the severe end of the illness spectrum in COVID-19 patients. Studies should be undertaken with a large sample size with a dysregulated immune response to determine the real effectiveness of immunomodulatory treatments.

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