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ORIGINAL RESEARCH

Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study

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ABSTRACT

Background: Tocilizumab, an inhibitor of the interleukin-6 receptor, may decrease the inflammatory response and control the symptoms of severe coronavirus disease 2019 (COVID-19), but the evidence is scarce.

Methods: This retrospective study included patients with severe COVID-19 requiring oxygen therapy who received tocilizumab in seven centers across Poland. We assessed on-treatment changes in clinical status and inflammatory markers.

Results: Twenty-eight patients were included (19 male), with a mean age of 61.7 ± 12.4 years. The mean time from symptom onset to the first tocilizumab dose was 10.5 ± 5.7 days. Clinical status improved within 24 hours in 11 (39%) patients, within one week in 23 (82%) patients, and within two weeks in 25 (89%); one (4%) patient showed no change and two (7%) patients died. Sixteen patients (57%) no longer needed oxygen therapy within a week ($p < 0.001$). The serum concentrations of C-reactive protein, procalcitonin, and fibrinogen decreased significantly ($p \leq 0.001$). Lung changes improved in 21 (84%) patients within two weeks of treatment; 19 had minimal or no changes upon final examination.

Conclusions: Tocilizumab can control the symptoms of severe COVID-19 by reducing the inflammatory response and rapidly improves the clinical status in most patients.

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COVID-19; SARS-CoV-2; tocilizumab; interleukin-6; therapy

1. Introduction

Since the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, with three million confirmed cases and over 200,000 deaths as of April 29 2020 [1]. The disease caused by the virus, termed COVID-19, is asymptomatic or mild in about 80% of cases; however, but the remainder have a severe or critical illness, which can lead to acute respiratory distress syndrome and multi-organ failure [2,3]. The overall case fatality rate is about 2% but may be greater than 50% in critically-ill patients [3,4].

There are several risk factors for severe disease or death in patients infected with SARS-CoV-2, such as male sex, age above 65 years, and cardiovascular or respiratory diseases [5]. However, the mechanisms remain unknown. One hypothesis is that severe COVID-19 is caused by a rapid overproduction of proinflammatory cytokines (termed a cytokine storm), which damage vital organs and cause death [6]. Indeed, concentrations of several proinflammatory cytokines, including interleukin (IL)-6, are substantially increased in patients with severe COVID-19 [7]. However, standard anti-inflammatory treatments appear to be insufficient for controlling the cytokine storm in COVID-19. Therefore, tocilizumab, an inhibitor of the IL-6 receptor, has been used by several groups to treat patients with severe COVID-19.

Although preliminary reports show that tocilizumab may help control the symptoms of COVID-19 and reduce the levels of proinflammatory cytokines, more data are needed [8–12]. Pending the publication of controlled trials, here we report our experience with tocilizumab in patients with severe COVID-19.

2. Methods

2.1. Study design and setting

This was a retrospective study of patients with COVID-19 who received tocilizumab between March 15 and April 30 2020 across seven infectious disease wards in Poland. Tocilizumab was injected intravenously at a maximum single dose of 800 mg, and if there was no clinical improvement, the dose could be repeated after at least 8 hours. Tocilizumab was given off-label in accordance with the recommendations of the Polish Association of Epidemiologists and Infectiologists [13,14]. In each site, the local bioethics committees approved the treatment, and all patients provided informed consent.

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Article highlights

- The clinical status improved in 82% of patients with COVID-19 on continuous oxygen therapy within a week of the first tocilizumab dose.
- Oxygen saturation levels improved significantly in patients with COVID-19 following tocilizumab treatment.
- Following treatment, 84% of patients showed an improvement in lung changes upon imaging examination within ten weeks.
- C-reactive protein, procalcitonin, and fibrinogen levels decreased, while lymphocyte and platelet counts increased, after tocilizumab treatment.
- Good patient outcomes were associated with decreased interleukin-6 concentrations one week after tocilizumab treatment.
- There were no significant safety issues related to tocilizumab administration.

2.2. Patients

We included adult patients (aged ≥18 years) with COVID-19 who met the following criteria: cough, dyspnea, or fever (>38°C); positive result of a polymerase chain reaction (PCR) test for SARS-CoV-2 from a pharyngeal swab; typical lung changes on chest x-ray (ground glass opacities) or chest computerized tomography (CT; cobblestone road sign, atoll sign); need for continuous oxygen therapy; oxygen saturation ≤94% at any time after admission; and serum IL-6 concentration above the upper limit of normal (ULN).

2.3. Outcomes

The primary outcome was an overall change in the clinical status within a week of the first tocilizumab dose (improvement, no change, worsening) as judged by the attending physician. Radiological improvement, rated subjectively, and the need for oxygen therapy or mechanical ventilation were also assessed. Oxygen saturation and serum IL-6 concentrations were analyzed before the first tocilizumab dose and on subsequent days. We also implemented a semi-objective scale for assessing outcomes after treatment based on the baseline level of oxygen saturation (i.e., 90% vs. ≥ 90%). Following tocilizumab treatment, the outcomes included: mechanical ventilation and death, mechanical ventilation and survival, no mechanical ventilation and clinical improvement after 24 hours, and no mechanical ventilation and clinical improvement or within 24 hours. The IL-6 concentrations were measured with the Elecsys® IL-6 electrochemiluminescence kit (Roche Diagnostics, six sites) or the Beckman Coulter Unicell DXI 800 kit (Beckman Coulter, one site). Routine laboratory studies were done one to three days before the first tocilizumab dose, and one to three days after the last dose. The studies included complete blood count; serum biochemical studies, including C-reactive protein (CRP), procalcitonin, and fibrinogen; and coagulation studies. The routine studies were done at local hospital laboratories. Standard 12-lead electrocardiography was used to monitor for the prolongation of the corrected QT interval (QTc).

2.4. Statistical analysis

Data were presented as means ± standard deviations or medians (interquartile ranges), as appropriate. The McNemar test with continuity correction was used to compare frequencies of variables before and after treatment with tocilizumab. The Wilcoxon singed-rank test was used to compare median values of continuous variables before and after tocilizumab. A $p < 0.05$ was considered significant. The R software (version 3.6) was used for all calculations.

3. Results

3.1. Patients

In total, 28 patients (19 male) fulfilled the inclusion criteria, with a mean age of 60.7 ± 12.4 years. SARS-CoV-2 was detected by PCR in 27 patients. We included one patient with a negative PCR test because this patient had anti-SARS-CoV-2 IgA/IgM antibodies and met all other inclusion criteria. The median time from symptom onset to diagnosis was 4 (2–7) days. The median oxygen saturation at admission was 89% (88–93%). Oxygen saturation at any time between admission and the first tocilizumab dose was <90% in 24 (86%) patients, and ≤94% in all patients.

Fourteen (50%) patients had hypertension, six (21%) had diabetes, two (7%) had asthma, and two (7%) had chronic obstructive pulmonary disease. There were single instances of the following diseases: heart failure, stroke, chronic kidney disease, rheumatoid arthritis, chronic lymphocytic leukemia, schizophrenia, depression, and factor V Leiden mutation. Table 1 presents the frequency of COVID-19 symptoms and treatments used along with tocilizumab.

3.2. Effect of tocilizumab on clinical status

The mean time from symptom onset to the first tocilizumab dose was 10.5 ± 5.7 days. Twenty-four patients (86%) received a second dose (9–92 hours after the first dose). The doses ranged from 3.8 mg/kg to 12 mg/kg (first dose, 6.4 ± 1.9 mg/kg; second dose, 6.4 ± 2.1 mg/kg). Clinical status improved in 11 (39%) patients within 24 hours of the first tocilizumab dose; an improvement was seen within a week of treatment in 23 (82%) patients, and within two weeks in 25 (89%). One (4%) patient showed no change in clinical status within two weeks, and two (7%) patients died. Oxygen therapy was needed in all patients at baseline and in 12 (43%) patients within a week of the first tocilizumab dose ($p < 0.001$). Oxygen saturation improved from 89% (88–91%) before the first tocilizumab dose to 94% (92–97%) on the next day and to 97% (94–99%) at day 10 ($p \leq 0.001$ for all comparisons with baseline; Figure 1). Mechanical ventilation was needed in five (17%) patients before tocilizumab and in three (11%) more patients after the first tocilizumab dose. Following tocilizumab, the need for mechanical ventilation, resulting in either death or clinical improvement, was associated with a baseline oxygen saturation level of <90%; and a baseline oxygen saturation level of ≥90% was associated with no mechanical ventilation and frequent clinical improvement within/after 24 hours (Figure 2). As shown in Table 2, patients with a rapid

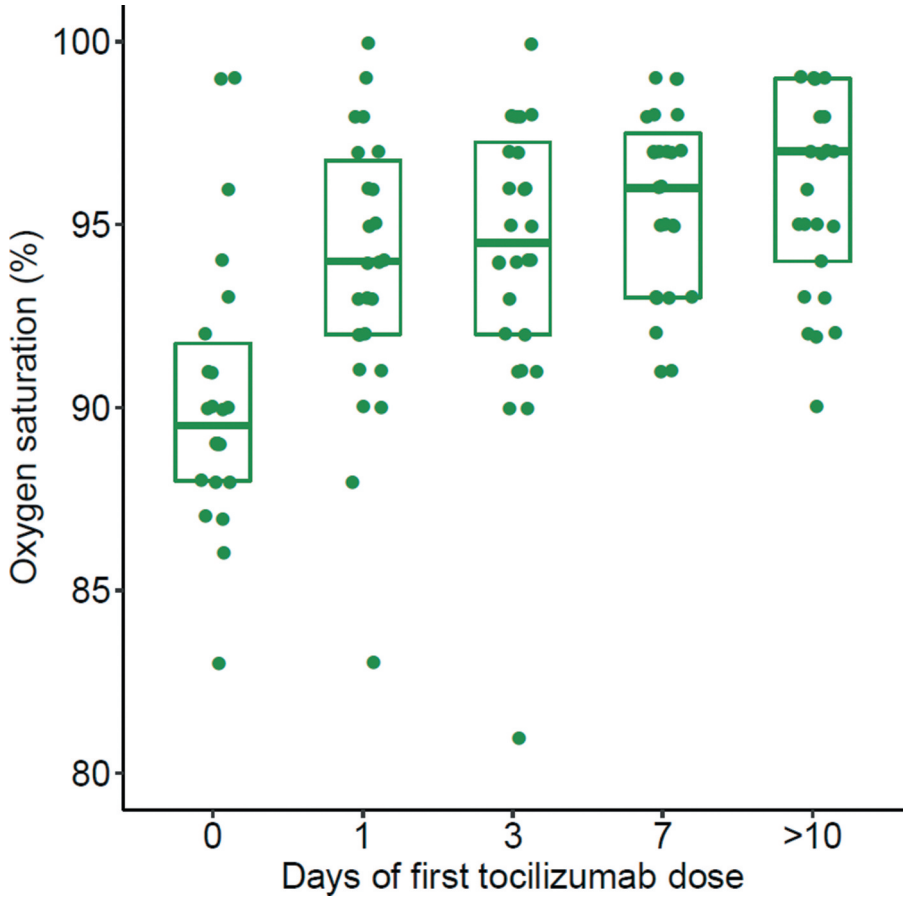

Figure 1. Oxygen saturation before and after the first tocilizumab dose in patients with severe COVID-19. Middle bar shows median; upper and lower bars show interquartile range.

clinical improvement received similar concomitant medications to those who had a slower response to treatment or died.

3.3. Effect of tocilizumab on imaging examinations

Twenty-five patients had repeated chest X-ray or chest CT during and/or after hospitalization. Among them, lung changes improved in 21 (84%) patients after at least two weeks (range 2–10 weeks) of treatment, with 19 showing minimal or no changes in the final examination. As shown in Figure 3, 59% of these 21 patients showed an improvement in lung changes within 2–8 weeks, and all 21 (100%) had improved after >8 weeks. For those patients who did not show improvement (n = 4), the repeated imaging was performed within six weeks of treatment; thus, an improvement in lung changes is still possible.

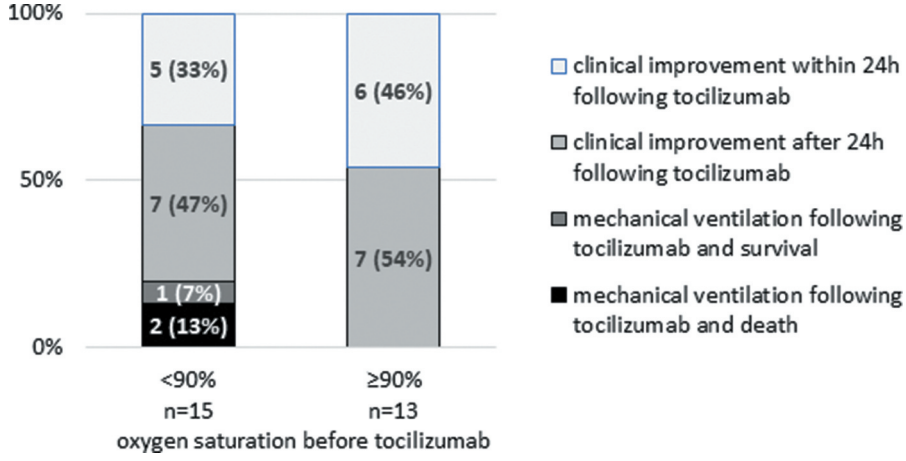

Figure 2. A semi-objective scale for assessing outcomes after treatment based on the baseline level of oxygen saturation (<90% vs. ? 90%). Following tocilizumab treatment, the outcomes included: mechanical ventilation and death, mechanical ventilation and survival, no mechanical ventilation and clinical improvement after 24 hours, and no mechanical ventilation and clinical improvement or within 24 hours.

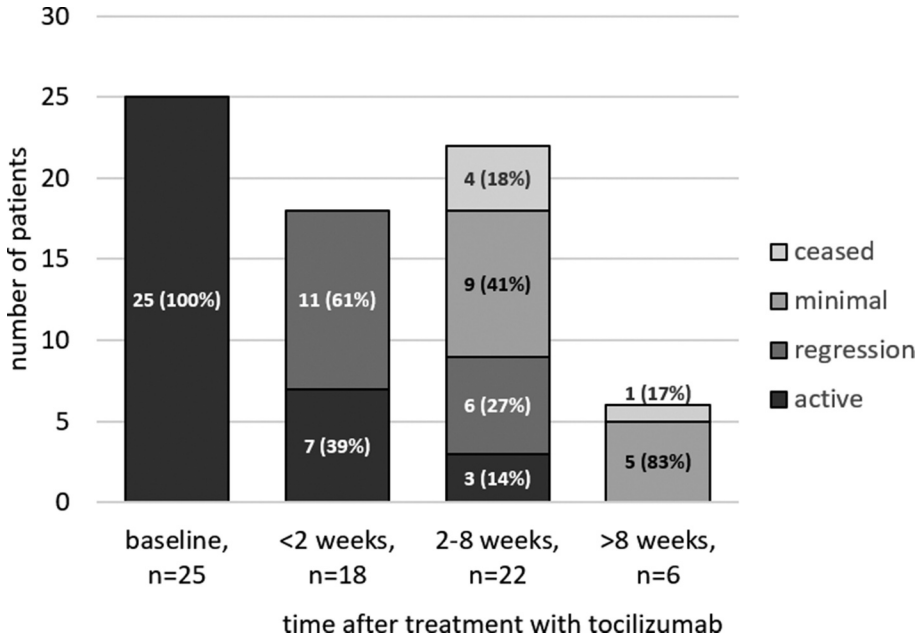

Figure 3. The proportion of patients showing varying degrees of lung changes (ceased, minimal, regression, or active) on repeated chest CT and/or X-ray images before (baseline) and after treatment with tocilizumab.

3.4. Effect of tocilizumab on laboratory results

CRP concentration was increased (≥5 mg/dL) in all patients before tocilizumab, and normalized (<5 mg/dL) in 13 (46%) patients after tocilizumab ($p < 0.001$). The median concentrations of procalcitonin and fibrinogen decreased significantly after treatment with tocilizumab ($p \leq 0.001$). Meanwhile, the concentration of IL-6 increased considerably after treatment

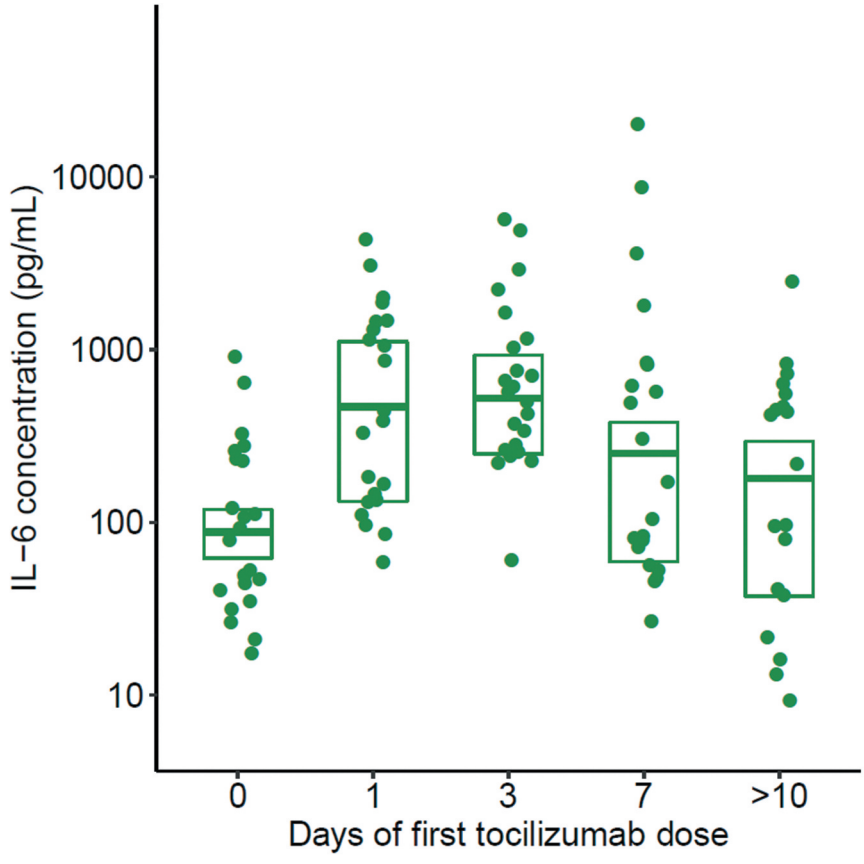

Figure 4. Serum IL-6 concentrations before and after the first tocilizumab dose in patients with COVID-19. Middle bar shows median; upper and lower bars show the interquartile range.

with tocilizumab until day three ($p < 0.001$), when it started to decrease (Figure 4).

Lymphopenia (<1.5 × 10^9/L) was observed in 24 (86%) patients before tocilizumab and in 15 (54%) patients after tocilizumab ($p = 0.041$). The median lymphocyte and platelet counts increased significantly after treatment with tocilizumab ($p \leq 0.003$). Table 3 presents the changes in laboratory variables during treatment with tocilizumab. The highest baseline IL-6 concentration of 1,041 pg/mL was noticed in a patient who later died, who also demonstrated extremely high IL-6 levels (19,770 pg/mL) seven days after tocilizumab administration. However, the baseline IL-6 concentration observed in the second patient who died was only 64 pg/mL. We found that patients with a high (>100 pg/mL) baseline concentration of IL-6 more frequently demonstrated delayed or no improvement compared to those with low IL-6 levels, although the difference was not significant (25% vs. 19%, respectively; $p > 0.05$).

3.5. Safety

The activity of alanine aminotransferase increased slightly after tocilizumab treatment ($p \leq 0.022$). The median QTc interval increased from 426 ms (402–450) before tocilizumab to 431 ms (412–449; $p = 0.012$) after tocilizumab. One patient had markedly increased systolic blood pressure (220 mg Hg) following tocilizumab treatment. Two patients died: a 67-year-old man with hypertension, diabetes, and chronic kidney disease; and an 84-year-old man with hypertension, heart failure, and diabetes. We found patients with at least two chronic diseases were more unlikely to improve within 24 hours of treatment and are at a higher risk of death (Figure 5). All adverse events were considered unrelated to tocilizumab.

4. Discussion

This retrospective study suggests that tocilizumab may improve the symptoms of COVID-19 in patients with severe disease. We found that tocilizumab increased blood oxygenation and reduced the need for oxygen therapy within a week of the first dose. The clinical improvement was paralleled by the regression of radiological lung changes and a reduction in the concentrations of inflammatory markers.

Our results are in line with two previous retrospective studies from China. Luo et al. [8] observed that tocilizumab stabilized or improved the clinical status in 10 of 15 patients with COVID-19 (moderate to critical illness). Similarly, Xu et al. [9] reported that tocilizumab reduced oxygen dependence and increased oxygen saturation among 21 patients with severe or critical COVID-19. We found that 25 patients (89%) no longer needed oxygen therapy, and oxygen saturation improved shortly after the first tocilizumab dose. Both Xu et al [9] and our group found that tocilizumab improved radiological lung changes in patients with severe COVID-19. However, the need for mechanical ventilation did not change significantly in our cohort, which suggests that tocilizumab may no longer be effective in patients with respiratory failure. Alternatively, these patients may have improved over a longer period than that observed in our study (i.e., one week).

Most patients (86%) in our cohort received a repeated tocilizumab dose, compared to 14% and 33% in previous studies [8,9]. Luo et al. [8] suggested that a repeated dose of tocilizumab might be more effective than a single dose. These investigators observed that three of four critically-ill patients who received a single dose of tocilizumab died. In contrast, in the study by Xu et al. [9], no patients died, even though most received only one tocilizumab dose. In our study, one patient died despite receiving two tocilizumab doses. Due to a lack of evidence, it is difficult to determine the optimal tocilizumab dose in patients with COVID-19; however, it seems justified to repeat the dose when no improvement is seen [13,14].

Treatment with tocilizumab in our patients decreased the concentrations of inflammatory markers, including CRP, procalcitonin, and fibrinogen. These results are in line with the two previous studies in China [8,9]. Other studies have shown that increased lactate dehydrogenase levels and lymphocytopenia are associated with an increased risk of death in COVID-19 [15]. We found that tocilizumab decreased the concentration of lactate dehydrogenase (non-significantly) and increased the lymphocyte count. Moreover, we observed that platelet counts increased after treatment with tocilizumab. This observation is important because low platelet counts are associated with a higher risk of death in COVID-19 [16]. The concentration of IL-6, already high at baseline in our

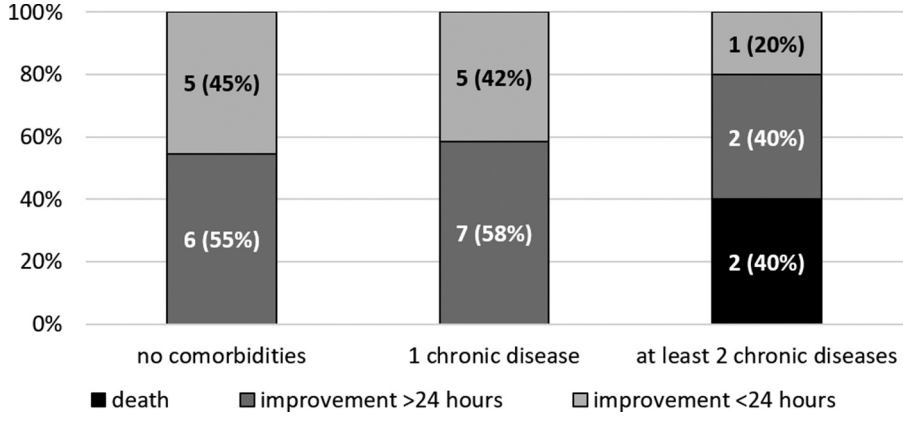

Figure 5. The proportion of patients who showed rapid (<24 hours) or slow (>24 hours) improvement or death following tocilizumab treatment depending on the number of comorbidities.

patients, increased further after tocilizumab injection for the next three days, and then it started to decrease. A similar pattern was observed in patients with rheumatoid arthritis, Castleman disease, and COVID-19 [8,17]. It is hypothesized that initially tocilizumab blocks the clearance of IL-6 through the IL-6 receptor, which increases the concentration of IL-6, and then the prolonged treatment reduces inflammation, leading to a decrease in IL-6 production [17]. Despite the critical role of IL-6 in the pathogenesis of severe COVID-19, there was no clear association between baseline IL-6 levels and clinical outcomes of the treatment.

Since the main indication of tocilizumab is rheumatoid arthritis, its safety profile has been widely assessed in several clinical trials in rheumatology. The most common adverse events were mild infections, which were observed in 34% of patients. Gastrointestinal disorders, neutropenia, and elevation in aminotransferase, bilirubin, and cholesterol levels were observed much less frequently [18]. Similar adverse events were observed in COVID-19 patients by Campochiaro et al. [10]. According to Morena et al. [11], the most frequent side effects were an increase of hepatic enzymes (29%), thrombocytopenia (14%), and serious bacterial and fungal infections (27%), and mortality was associated with mechanical ventilation at baseline.

In our study, treatment with tocilizumab appeared safe, with no adverse events attributable to this medication. The prolongation of QTc was likely due to concomitant chloroquine therapy.Similar to tocilizumab, the IL-1 receptor antagonist anakinra is used in the treatment of hyperinflammatory conditions. According to Cavalli et al. [19], inhibition of IL-1 with high-dose anakinra was associated with clinical improvement in 72% of patients. As anakinra is considered very safe, it has even been administered in patients with severe viral infections (e.g., Epstein Barr virus, influenza H1N1, and Ebola) [20]. There are a few reports of the use of anakinra in COVID-19, which have confirmed its good safety profile [21,22]. Still, its evaluation remains difficult due to the number of comedications used for both COVID-19 and coexistent conditions [21,22].

Viral pneumonia may result in long-term lung disability as a consequence of both the disease itself and from treatment-related organ damage. Indeed, in a number of SARS or influenza survivors, the lung function gradually improved over 15 years, with most patients never reaching their pre-infection status [23,24]. Therefore, long-term pulmonary consequences of COVID-19 are highly probable; although, their evolution is fairly predictable, as most patients are elderly and have a number of chronic conditions [25]. The optimal monitoring technique for these patients seems to be chest CT, which was performed in the majority of our patients [26]. To date, there are only a few post-recovery observations of the long-term impact of SARS-CoV-2 infection on lung tissue and pulmonary function, which have demonstrated significant pulmonary outcomes in some patients and complete recovery in others [25,27]. In contrast to these reports, we found an improvement in lung changes on chest CT/X-ray in 84% of patients in our study. Most of these patients demonstrated no (ceased) or minimal lung changes between two and eight weeks after treatment, which could be a result of the anti-inflammatory activity of tocilizumab.

Our study had limitations. First, the study cohort was a small and heterogeneous sample (i.e., patients with different comorbidities, different co-treatments). Second, the study was retrospective in nature, which could be associated, for example, with selection bias. Third, the clinical and radiological improvements were rated subjectively, and the raters were not blinded. Fourth, there was no comparative group due to no registered standard of care with confirmed effectiveness in COVID-19 at the moment of data collection. Despite of concomitant medication with chloroquine and lopinavir/ritonavir in large majority of patients, it does not seem to affect course of the disease according to recent research. Objective outcomes, such as the need for oxygen therapy and inflammatory markers, confirmed the effect of tocilizumab.

5. Conclusion

In conclusion, tocilizumab shows promise in the treatment of severe COVID-19. Tocilizumab may improve the clinical status in patients with COVID-19 by reducing the inflammatory response, which is reflected by the regression of lung changes and a reduced need for oxygen therapy or mechanical ventilation. The outcomes of current randomized, controlled trials should provide more evidence on the efficacy and safety of tocilizumab in patients with COVID-19.

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Author contributions

All authors had full access to all the data in the study and take responsibility for its integrity and the accuracy of the analysis. RF and KT were responsible for the study concept and design. KT, AP, JSR, SS, AG, MP, JNO, TWL, DZM, JDK, AH, and RF were responsible for the acquisition, analysis, or interpretation of data. RF was responsible for drafting the manuscript and the statistical analysis.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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