

# Tocilizumab and liver injury in patients with COVID-19

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## Abstract

Current mortality rate in patients with COVID-19 disease is about 2%, whereas 5% of patients require admission to the intensive care unit. It is assumed that interleukin (IL)-6 may be involved in the pathogenesis of severe COVID-19 infections; therefore, in the absence of a specific antiviral therapy, some authors have suggested that tocilizumab – a drug used to block the signal transduction pathway of IL-6 – could have beneficial effects in the management of severe COVID-19 disease. However, mild-to-moderate elevation in transaminases and drug-induced liver injury have been observed in patients treated with tocilizumab. We present seven cases of patients with elevated liver enzymes [up to five times the upper limit of normal (ULN)] at baseline who received tocilizumab for life-threatening COVID-19 disease. All patients had no history of liver or pulmonary disease and were admitted for acute hypoxemic respiratory failure, dyspnea and fever due to COVID-19 bilateral pneumonia. IL-6 was available in six patients, and was significantly increased particularly in those with severe impairment of lung function. All patients received tocilizumab (8 mg/kg/day) for two consecutive days because of lack of improvement after hydroxychloroquine, azithromycin and lopinavir/ritonavir treatment. After tocilizumab administration, clinical condition rapidly improved and liver function test normalized within 3 weeks of treatment. Tocilizumab may be effective for the treatment of severe COVID-19 disease, even in patients with elevated liver function tests. Further studies are needed to evaluate the impact of tocilizumab use on liver function tests in patients with pre-existing chronic liver disease.

**Keywords:** COVID-19, hepatotoxicity, IL-6, SARS-CoV-2, tocilizumab

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## Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by a novel coronavirus that is structurally related to the virus that causes severe acute respiratory syndrome (SARS). The currently reported mortality rate is approximately 2% and patients with preexisting respiratory or cardiovascular disease appear to be at the greatest risk for complications.<sup>1</sup>

About 5% of patients with COVID-19 disease require admission to the intensive care unit for acute respiratory distress syndrome or multiorgan failure.<sup>2</sup>

In the absence of a proven effective therapy, the management of these patients consists of invasive and noninvasive oxygen support and off-label or compassionate-use therapies.<sup>3</sup>

Even though mortality is particularly high in old people, several cases of severe COVID-19 have been observed in adults and young people, suggesting that a subgroups of patients might have a dramatic systemic disease due to the cytokine release syndrome (CRS) – a systemic inflammatory response caused by several factors such as viral infection and characterized by a rapid and significant increase in the serum level of pro-inflammatory cytokines.<sup>4,5</sup>

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The pathogenesis of CRS depends on several cytokine effects; however, interleukin (IL)-6 is considered to play a key role in the clinical manifestations of COVID-19 disease and to be a predictive marker of fatal outcome.<sup>6</sup>

Tocilizumab is a humanized recombinant monoclonal antibody used to block the signal transduction pathway of IL-6.<sup>5</sup> Tocilizumab is currently approved for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis but recently, in the absence of a specific antiviral therapy, some authors have proposed tocilizumab for the treatment of CRS in patients with COVID-19 infection.<sup>5,7</sup>

The most common side effects of tocilizumab include headache and hypertension but, rarely, hepatotoxicity ranging from mild transaminases elevation to severe drug-induced liver injury (DILI) can occur.<sup>8</sup> Currently, data on hepatotoxicity of tocilizumab in COVID-19 disease are limited and inconclusive.

In this article, we report seven cases of patients with elevated liver enzymes at baseline who received tocilizumab for severe COVID-19 disease with improvement of both hepatic and pulmonary function.

### Methods

We report seven cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) referred to the Emergency Room at Foggia Hospital.

All patients had no history of liver or pulmonary disease and were admitted for acute hypoxemic respiratory failure, dyspnea and fever due to COVID-19 bilateral pneumonia.

Table 1 summarizes the clinical characteristics of patients at baseline. Patients ranged from 44 to 73 years of age and were all male. All patients had PaO<sub>2</sub>:FiO<sub>2</sub> (arterial oxygen partial pressure: fraction of inspired oxygen) ratio <300 at baseline, and six out of seven required oxygen support with Venturi mask (40–60%). One patient showed a very low PaO<sub>2</sub>:FiO<sub>2</sub> ratio at first medical contact and needed non-invasive ventilation with continuous positive airway pressure (CPAP).

The patients were negative for influenza A and B virus, Adenovirus, and respiratory syncytial virus parainfluenza 1, 2 and 3. IL-6 was available in six patients and was significantly increased particularly

in those with severe reduction of PaO<sub>2</sub>:FiO<sub>2</sub>. All patients except one showed a severe lymphopenia at baseline, whereas all patients had increased D-dimer levels (Table 1).

### Results

Patients were treated with hydroxychloroquine (400 mg daily), azithromycin 500 mg daily for 3 days and lopinavir/ritonavir 400/100 daily; however, all showed a worsening in clinical conditions between 5 and 7 days after admission and needed mechanical ventilation support.

Therefore, after providing written informed consent, all patients received tocilizumab (8 mg/kg/day) for 2 consecutive days. Table 1 shows the temporal trend of liver function tests (at admission, before tocilizumab administration, 1 week and 3 weeks after treatment). Except for one, all patient had normal or only mildly elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at admission, whereas before tocilizumab administration all patients had increased transaminases [up to five times the upper limit of normal (ULN)].

Gamma-glutamyl transpeptidase (GGT) was normal in two patients at admission, whereas one patients had 4.5 times the ULN at baseline and a significant increase during the hospitalisation (up to 10 times the ULN).

Even if C-reactive protein (C-RP) and liver function test normalized within 3 weeks of treatment, most patients showed a significant improvement within 1 week. Liver biopsy was not performed because of critical respiratory conditions at admission and the prompt recovery after tocilizumab use.

All patients fully recovered and were discharged with outpatient follow up.

### Discussion

Infection with SARS-CoV-2 is associated with a broad spectrum of clinical respiratory syndromes, ranging from mild upper airway symptoms to life-threatening pneumonia.<sup>9</sup>

About 80% of cases are considered mild because patients have mild or no pneumonia, whereas 14% are classified as severe because of respiratory frequency  $\geq 30$ /min, reduced blood oxygen saturation

**Table 1.** Clinical characteristics of seven patients with alterations in liver function treated with tocilizumab.

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age-year	44	73	61	56	51	71	59
CRP-mg/dl	262	395	242	91	283	116	361
D-dimer-ng/ml	808	3581	1382	753	509	15169	710
IL-6 (pg/ml)	88,5	159,7	37,3	27,6	112,1	n.a.	270
Tocilizumab dosage (mg)	640	800	720	600	600	800	560
AST (UI/l)							
Admission	35	31	26	65	29	33	51
Before Tocilizumab (T0)	78	105	93	122	189	97	99
1 week later	37	50	55	53	36	29	26
3 weeks later	26	23	22	35	39	17	26
ALT (UI/l)							
Admission	47	43	30	118	30	36	36
Before Tocilizumab (T0)	128	49	100	199	118	120	49
1 week later	118	43	57	79	84	54	39
3 weeks later	51	38	30	40	35	28	54
GGT (UI/l)							
Admission	21	41	181	86	102	60	33
Before Tocilizumab	60	35	420	118	338	119	89
1 week later	23	58	50	72	167	89	81
3 weeks later	18	54	27	21	41	30	16
Reference ranges are as follows: AST 2–40 U/L, ALT 2–40 U/L, GGT 10–55 U/L, CRP 0.5–5 mg/dl, IL6 0,5–3 pg/ml, D-dimer 0–300 mg/dl. ALT, alanine aminotransferase; AST, ; aspartate aminotransferase CRP, C-reactive protein; GGT, Gamma-glutamyl transpeptidase; IL, interleukin.							

and PaO<sub>2</sub>:FiO<sub>2</sub> ratio <300. Finally, 5% have critical clinical conditions with more severe respiratory failure or multiple organ dysfunction.<sup>2</sup>

The global spread of COVID-19 infection has provided pivotal information on clinical and epidemiological characteristics of the disease. Particularly, a number of papers on the topic have reported that patients with COVID-19 may show varying levels of liver disease.<sup>10</sup> Cai *et al.* observed that about half of the COVID-19 patients showed abnormal liver test results at admission, most (90%) having mild liver test elevation; about 25% of them developed increased transaminase levels to more than 3× ULN during hospitalisation,<sup>10</sup> suggesting that

liver damage may be explained by viral infection *per se* or other causes such as drug use.

Other respiratory viruses produce similar elevations of liver function tests, which is thought to relate to hepatic damage from immune interaction involving intrahepatic cytotoxic T cells and Kupffer.<sup>11</sup>

Data on distribution of aminotransferases among patients with COVID-19 do not support hypoxic hepatitis being a common observation, and, recently, a new study found that SARS-CoV-2 virus may bind to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes causing cholangiocyte

dysfunction, inflammatory response and, finally, liver injury.<sup>12</sup>

A pathological study of post-mortem liver biopsy in a COVID-19 patient reported moderate steatosis and mild lobular and portal damage, commonly observed in sepsis.<sup>13</sup>

Clinical features and cytokine profile of critically ill patients with COVID-19 suggested that higher concentrations of some cytokines such as granulocyte-colony stimulating factor and tumour necrosis factor  $\alpha$  could be associated with the severity of illness.<sup>14</sup> More recently other authors have also observed an increased expression of IL-2R and IL-6 in the serum of severe COVID-19 infections.<sup>6</sup>

Interestingly, the incidence and time of occurrence of liver injury in patients with COVID-19 seems to be related to the disease severity. Data from a retrospective analysis including 131 patients showed a higher rate of liver injury in patients with respiratory failure requiring mechanical ventilation or shock (81.5%), in comparison with 51.9% of patients with mild, moderate or severe disease who did not require admission to the intensive care unit. The liver injury in patients on mechanical ventilation or with shock occurred earlier and recovered more slowly than patients with noncritical disease.<sup>15</sup>

Similarly, the largest study on COVID-19 by Guan *et al.* showed that the prevalence of elevated aminotransferases and bilirubin is 19% and 10%, respectively, in patients with non-severe disease, and 40% and 13%, respectively, in patients with severe COVID-19 disease.<sup>16</sup>

On the other hand, several authors reported data supporting the pivotal role of antiviral drugs in liver injury during COVID-19 infection. Jiang *et al.* found that in a multivariable analysis including COVID-19 patients with abnormal liver test results lopinavir/ritonavir use was related to liver injury, but only in patients with noncritical disease.<sup>15</sup> Similarly, Cai *et al.* observed a significant increase of transaminase levels during hospitalization: about 11% of patients developed ALT levels more than three times ULN, and 12% of patients increased GGT levels up to three times ULN. In this cohort, the use of lopinavir and ritonavir was the most important risk factor for liver damage because it increased the odds of liver injury by four-fold.<sup>10</sup>

In the absence of a proven effective antiviral therapy, and because of its approval in cytokine release syndrome, tocilizumab has been considered a promising drug for the treatment of severe COVID-19 infections.<sup>17</sup>

Clinical studies have shown very good effects of tocilizumab on clinical and biochemical parameters in patients with COVID-19. For this reason, tocilizumab, a humanized monoclonal antibody against the IL-6 receptor (IL-6R), has been recommended in severe COVID-19 disease by the National Health Commission of China.<sup>18</sup>

More recently, several authors have studied the potential benefits of tocilizumab in severe COVID-19 pneumonia and showed challenging but discordant results.

Morena *et al.* studied the efficacy and safety of tocilizumab in 45 Italian COVID-19 patients, showing a rapid and beneficial effect on inflammatory markers without a significant impact on the clinical outcomes.<sup>19</sup> Furthermore, Campochiaro *et al.* did not report a mortality reduction in a cohort of 32 COVID-19 pneumonia patients treated with tocilizumab, even if patients with a higher baseline PaO<sub>2</sub>:FiO<sub>2</sub> ratio experienced a clinical improvement.<sup>20</sup>

However, in a cohort of 78 patients with COVID-19 requiring mechanical ventilation support from the United States (US), tocilizumab was associated with a significant reduction in mortality rate, although superinfections occurred more frequently in treated patients.<sup>21</sup>

Probably, the interval time between admission and tocilizumab administration could play a pivotal role, and it could also explain the differences in clinical outcome reported by different authors.

Capra *et al.* treated 62 COVID-19 patients within 4 days from their hospital admission, and found that patients receiving tocilizumab showed a significantly greater survival rate as compared with control patients.<sup>22</sup> The authors concluded that tocilizumab use has a positive impact if used early during COVID-19 pneumonia because it increases survival and it is associated with a favourable clinical course.

Therefore, given the potential beneficial effect and the growing off-label use of tocilizumab for

the treatment of COVID-19 pneumonia, characterization of tocilizumab safety profile in this new setting has been addressed recently.

First, the side effects with tocilizumab use include potential hepatotoxicity. In registration trials, serum aminotransferase elevations occurred in a high proportion (10–40%) of patients receiving tocilizumab and, after its licensure, it has been linked to several instances of clinically apparent liver injury with jaundice.

Literature data showed that, in most cases, a severe hepatic injury was observed when tocilizumab was combined with other hepatotoxic drugs, and that liver failure and liver transplantation may occur in patient treated with tocilizumab.<sup>23</sup>

Recently, Gatti *et al.* analysed the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to study the serious adverse events after tocilizumab use.<sup>17</sup> The authors reported hepatic, pancreatic and pulmonary reactions after tocilizumab administration. Results showed that liver injury generally occurs after a median of 15 days, with potential overlap with clinical course of severe COVID-19 infections. A total of 2433 adverse events were found with tocilizumab use, and 91 patients developed a DILI. Liver injury occurred as unpredictable reaction, suggesting the need for a careful monitoring during and after treatment.

Data from real-life clinical practice about liver function in patients with COVID-19 treated with tocilizumab are limited. Di Giambenedetto *et al.* observed a resolution of respiratory symptoms and fever without adverse events in three patients treated with off-label use of tocilizumab.<sup>7</sup>

Mazzitelli *et al.* reported a case series including three patients with non-severe COVID-19 disease treated with a single dose of tocilizumab given subcutaneously. One out of three patients developed a mild and transient liver function test alteration 2 days after drug administration with rapid normalization, whereas another patient had a mild elevation of liver function test at baseline but no worsening in liver function were observed after tocilizumab therapy.<sup>24</sup> Campochiaro *et al.* observed a transitory increase in AST or ALT in 15% of patients between 9 and 13 days after tocilizumab administration, but no differences were found in comparison with the control group.<sup>20</sup>

On the other hand, Muhovic *et al.* recently reported the first case of drug-induced liver injury after tocilizumab administration in a 52-year-old patient who showed a 40-fold increase in transaminases. However, the transaminases normalized 10 days later and the authors speculated that the hepatotoxic effect could have been promoted by previous use of lopinavir/ritonavir.<sup>8</sup>

We reported our experience with seven patients admitted for severe COVID-19 pneumonia who developed a progressive worsening of clinical conditions. In our case, a mild liver injury appeared during COVID-19 pneumonia and worsened during hospitalization. All patients received hydroxychloroquine, azithromycin and lopinavir/ritonavir, and showed worsening of general clinical condition before tocilizumab administration.

Liver biopsy was not performed; however, in our opinion, both liver injury due to inflammatory response and antiviral drug use could have been involved in increasing transaminases before tocilizumab administration.

Our patients received off-label tocilizumab therapy and both respiratory failure and liver function impairment completely resolved.

In our experience, all patients had significantly increased but different IL-6 serum levels at baseline (from 27.6 pg/ml to 270 pg/ml; normal value 0.5–3 pg/ml). IL-6 is one of the main mediators of inflammatory and immune response and more than one-half of patients with COVID-19 have increased serum levels of IL-6.<sup>25</sup> A meta-analysis including nine studies with 1426 COVID-19 patients showed that IL-6 serum levels are associated with disease severity and high mortality risk.<sup>26</sup> Herold *et al.* found, in a cohort of 40 COVID-19 patients, that IL-6 levels  $\geq 35$  pg/ml at baseline had the strongest association with the need for mechanical ventilation support, and that the risk of respiratory failure was 22 times higher in patients with IL-6 levels  $\geq 80$  pg/ml than in patients with lower IL-6 serum levels.<sup>27</sup>

In our group, only one patient required mechanical ventilation at admission (patient seven); he had the highest values of IL-6 at baseline (270 pg/ml). However all the patients showed a worsening in clinical conditions during hospitalization (between 5 and 7 days after admission) irrespective of IL-6 serum level, and needed mechanical ventilation support.



Similarly, all the patients had a complete recovery of lung and liver function after tocilizumab administration irrespective of IL-6 values at baseline.

Our experience suggests that tocilizumab use may be effective in severe COVID-19 disease, even in patients with elevation of transaminase up to 5 times ULN and GGT up to 10 times ULN. The unavailability of liver biopsy is a limitation of our experience and we think it should be considered before tocilizumab treatment in patients with impaired liver function to exclude the impact of other antiviral drugs on liver injury during COVID-19 disease. Larger studies are necessary to validate the safety of tocilizumab therapy and to support its use in patients with chronic liver disease.

#### Author contributions

G Serviddio and R Villani: data interpretation and analysis, manuscript drafting, revision of the final draft; G Scioscia, D Lacedonia, MP Foschino-Barbaro, G Stallone: acquisition of data, design and revision of the final draft. All authors read and approved the manuscript

#### Conflict of interest statement

The authors declare that there is no conflict of interest.

#### Ethics approval and consent to participate

All patients provided written informed consent for the treatment and publication of their medical information. Ethics approval is not required for case reports or case series at our institution.

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