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# Tocilizumab and corticosteroids for COVID-19 treatment in elderly patients

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**Background**. The mortality rate for coronavirus disease-19 (COVID-19) increases with age. Some anti-inflammatory drugs such as tocilizumab or steroids have been proposed for the treatment of severe disease; however, few data are available in the elderly.
**Methods**. A retrospective case-series of patients hospitalized between March 1st and June 15th, 2020 with confirmed COVID-19 by RT-PCR testing on throat/nasopharyngeal swabs and age ≥ 65 years was analysed. Patients were retrospectively divided into three groups according to the chosen treatment [standard of care (SOC), tocilizumab or corticosteroids] and patient characteristics and occurrence of adverse events were compared among groups.
**Results**. Overall, 206 patients were included, 148 treated with standard of care, 42 with steroids and 16 with tocilizumab. Patients treated with steroids or Tocilizumab presented more frequently with fever (p = .003), dyspnea (p < .001), bilateral opacities/infiltrates at chest X-ray (p =.026) or CT-scan (p = .020), and more frequently required non-invasive/invasive ventilation (p < .001). Crude mortality was 27%, without differences among groups (p = .074). No specific adverse events were observed during/after the administration of steroids or tocilizumab; however, a trend towards an increased risk of secondary infections was described compared to SOC (p = .097). At multivariate logistic regression, only tocilizumab administration was an independent predictor of secondary infections (aOR = 6.72, 95% CI = 1.43-31.39, p = .015).
**Conclusions**. Tocilizumab and corticosteroid could have a possible role for severe form of pneumonia in course of COVID-19 also in elderly patients, even if great attention to the monitoring of infectious complications should be paid in this special population.

**Key words**: COVID-19, tocilizumab, corticosteroids, elderly

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*The Authors declare no conflict of interest*

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19), initially described in Wuhan (China) in December 2019, is known to be caused by a novel beta-coronavirus, named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1].

On 11th March 2020, the World Health Organization (WHO) announced COVID-19 outbreak a pandemic, that counts until now more than 30.000.000 of cases and almost 950.000 of deaths [2].

COVID-19 includes a wide spectrum of clinical features and variable outcome due to many underlying conditions, such as age, cardiovascular or respiratory comorbidities, diabetes mellitus, obesity and others [1,3,4]. Older age, which was already reported as an independent predictor of mortality in SARS and MERS, is certainly one among the most important prognostic variables also for COVID-19 [3]. In fact, elderly patients are more susceptible in terms of severity of illness, percentage of admission to the intensive care unit (ICU), and mortality rate [5]. This could be explained by age-dependent defects of the immune system and an excess of type 2 cytokines production, which would lead to an increase in viral replication and a more prolonged pro-inflammatory response [3].

Indeed, it had been demonstrated that the inflammatory reaction is the main driver of pulmonary damage, with the recruitment of a wide spectrum of pro-inflammatory cytokines [6]. Therefore, in this scenario, a lot of therapeutic strategies had been studied to calm down the cytokine cascade. Due to the central role of IL-6 in the inflammatory reaction, a recombinant humanized anti-human IL-6 receptor monoclonal antibody called Tocilizumab has been one of the first explored options. Tocilizumab binds the soluble interleukin-6 receptor (sIL-6R) and inhibits signal transduction [6]. The effectiveness of this therapeutic strategy is still debated. In fact, an international study performed by Xu et al, in Shanghai [6] shows that Tocilizumab effectively improves clinical symptoms and represses the deterioration of severe COVID-19 patients. Similar results were obtained by Biran et al. [7], who demonstrated a reduction in mortality rate for patients with COVID-19 treated with Tocilizumab in ICU. In Brescia (Italy) the monoclonal antibody against sIL-6R was employed in 100 patients with COVID-19 pneumoniae with encouraging results [8]. However, other studies showed discordant results, such as that of Campochiaro et al., in which no difference in terms of outcome was found between patients who received tocilizumab and those treated with standard management. Moreover, in the first group, the occurrence of opportunistic infections like candidemia and pulmonary aspergillosis was reported [9].

Another therapeutic intervention proposed to mitigate inflammatory organ injury in SARS-CoV-2 infection is the use of glucocorticoids. The New England Journal of Medicine reported the preliminary results of the controlled, open-label Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial of dexamethasone in patients hospitalized with COVID-19 [10]. Dexamethasone is a synthetic adrenal corticosteroid that has both anti-inflammatory as well as immunosuppressive properties [11]. The mean age of the patients was 66.1 +/- 15.7. This study shows an improvement of clinical conditions in terms of a reduction of 28 days mortality in patients that were treated with oxygen support (invasive or non - invasive ventilation) [10]. Another study carried by Villar et al. on a sample of 277 patients showed that the early use of dexamethasone could increase ventilator-free days compared to patients who did not receive this treatment [12].

None of these studies, however, was focused on the elderly, and the efficacy and safety of tocilizumab and corticosteroids in these patients in the setting of COVID-19 is currently unknown.

Therefore, we aimed to describe the safety profile of these therapeutic strategies in a cohort of COVID-19 patients older than 65 years of age treated in five large Infectious Disease Centers in Southern Italy.

## PATIENTS AND METHODS

### Study design

A retrospective case-series of all consecutive patients with age ≥ 65 years, hospitalized between March 1st and June 15th 2020, with confirmed SARS-CoV-2 infection by PCR on nasopharyngeal swabs was analyzed across five COVID-19 hospitals in Southern Italy.

Patient demographics, clinical and microbiological characteristics were retrieved, by reviewing all available medical records.

Patients were retrospectively divided into three groups according to the chosen treatment [standard of care (SOC), tocilizumab or corticosteroids].

All medical supportive care and antivirals in use in Italy during the first months of COVID-19 pandemics in Italy (such as lopinavir/ritonavir and hydroxychloroquine) were defined as “standard of care”, including also the use of empiric antibiotic therapy.

Steroid therapy was prescribed according to treating physician; therefore, the dosage was not standardized. However, at least 10 mg/day of dexamethasone for 5 days were usually prescribed at that time.

Tocilizumab was administered at the dosage of 8 mg/kg as a single infusion. All patients treated with tocilizumab (excluding 2) were also under steroid therapy.

In general, steroid treatment were administered to patients considered affected by a moderate to severe COVID-19, while tocilizumab was prescribed to patients with severe or critical disease, after informed consent and as compassionate use.

### Laboratory diagnosis of COVID-19

Nasopharyngeal swabs were used to diagnose COVID-19 in all patients. Tests were performed at a central hub laboratory using real-time reverse transcriptase PCR [real-time PCR assay targeting E-gene, RdRP-gene and N-gene, performed with the protocol previously reported by the WHO (https://www.who.int/docs/default-source/coronaviruse/uscdcrt-pcr-panel-for-detection-instructions.pdf?sfvrsn=3aa07934_2)].

### Definitions of co-infections and secondary infections

Co-infections were defined as all other diseases caused by a pathogen different from SARS-CoV-2 at the time of COVID-19 diagnosis.

Secondary infections were defined as all other diseases caused by a pathogen different from SARS-CoV-2 occurring in course of COVID-19, which were not present at the moment of admission for COVID-19.

During analysis, five independent reviewers evaluated microbiology isolates to determine the clinical significance; pathogens identified but not warranting targeted therapy were defined as commensal and nonsignificant infective pathogens and were not reported in this study.

### Data analysis

All data were anonymized and collated on an electronical database.

Descriptive statistics were produced for demographic, clinical and laboratory characteristics of cases. Mean and standard deviation (SD) were obtained for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed variables, number and percentages for categorical variables.

The distribution between groups (according to treatment administered) of clinical conditions and laboratory findings was analyzed by univariable parametric or nonparametric tests, Kruskal Wallis or Mann Whitney Test (where appropriate) for continuous variables and with Pearson's $\chi 2$ test (Fisher's exact test where appropriate) for categorical variables, according to data distribution.

Survival analysis (Kaplan-Meier curves estimates) was performed to explore the impact of different therapies on patient overall survival probability.

Finally, univariate logistic regression was performed in order to assess predictors of secondary infections elderly; then a stepwise multivariate logistic regression model was applied to control for potential confounders and was adjusted for variables associated (p value < 0.1) at univariable analysis with endpoint at univariable analysis.

### Ethics

The research did not require a formal approval from the ethics committee according to the Italian law since it was performed as an observational retrospective study in the context of normal clinical routines (art. 1, leg. decree 211/2003). However, the study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. All patients provided informed consent for the use of their data for research purposes. In any case, data were previously anonymized, according to the requirements set by Italian Data protection Code (leg. Decree 196/2003).

## RESULTS

### General characteristics of the study population

A total of 206 patients with confirmed SARS-CoV-2 infection and age > 65 years [median (IQR) age 80 (72 – 86) years, males in 48% of cases] were included.

Overall, 148 (72%) subjects were treated only with supportive care, antivirals, and antibiotics according to the physician judgment. Conversely, 42 (20%) and 16 (8%) were treated with steroid therapy and Tocilizumab, respectively. In Table I, the general features of the study population according to the administered treatment are resumed.

One third of patients suffered from a severe respiratory failure: 83 (40%) required at least 10 lt/min of oxygen therapy, 58 (28%) non-invasive mechanical ventilation (NIV), and 14 (9%) invasive mechanical ventilation.

Notably, patients treated with steroid or Tocilizumab had a more severe disease presentation; in fact, they were more frequently affected by fever > 38°C ($p = .003$), cough ($p = .030$) and dyspnoea ($p < .001$) and prevalently presented bilateral opacities/infiltrates at chest X-Ray ($p = .026$) or chest computed tomography ($p = .020$), or a severe respiratory disease requiring high flux oxygen therapy (> 10 lt/min, NIV or invasive mechanical ventilation, $p < .001$ in all cases) if compared with those assigned to standard of care.

Crude in-hospital mortality was 27% (23%, 40% and 31% for standard of care, steroids and Tocilizumab group respectively, $p = 0.074$).

Kaplan-Meier curves estimated of survival probability of patients, according to therapy prescribed, was made. As shown in Figure 1, no significant difference in risk of death among patients affected by COVID-19 (log rank p-value = .195) was observed in our cohort, after stratification for standard of care, steroid therapy or tocilizumab ± steroids.

### Adverse events and secondary infections during or after steroid/tocilizumab administration

The 25% of patients in this cohort suffered from at least one secondary infection during hospitalization. No other adverse events except than secondary infections

**Table I.** General features of the study population according to the administered treatment.

| | Overall (n. 206) | Standard of care (n. 148) | Steroid therapy (n. 42) | Tocilizumab (n. 16) | P-value |
|---|---|---|---|---|---|
| Median Age (IQR), years | 80 (72-86) | 80 (72-86) | 81 (72-86) | 75 (70-85) | .543 |
| Male sex - n (%) | 98 (48) | 65 (44) | 22 (52) | 11 (69) | .131 |
| **Comorbidity - n (%)** | | | | | |
| Hypertension | 122 (60) | 82 (55) | 28 (68) | 12 (75) | .139 |
| Any heart disease | 92 (45) | 59 (40) | 24 (59) | 9 (56) | .066 |
| Diabetes (pts. 161) | 50 (24) | 31 (21) | 14 (34) | 5 (31) | .176 |
| Chronic obstructive lung disease | 46 (22) | 27 (18) | 12 (29) | 7 (44) | **.034** |
| Chronic kidney disease (KDOQI stage III or more) | 23 (11) | 16 (11) | 6 (15) | 1 (6) | .637 |
| Any neurologic disease | 48 (23) | 36 (24) | 10 (24) | 2 (12) | .562 |
| Concurrent cancer - n (%) | 27 (13) | 17 (11) | 9 (22) | 1 (6) | .149 |
| Immunocompromised state - n (%) (pts. 203) | 7 (3) | 3 (2) | 4 (10) | 0 | **.042** |
| Living in a health care facility - n (%) (pts. 197) | 96 (49) | 70 (48) | 22 (59) | 4 (27) | .098 |
| **Signs and symptoms around the time of hospitalization - n (%)** | | | | | |
| Fever (> 38°C) | 114 (55) | 71 (48) | 31 (74) | 12 (75) | **.003** |
| Cough | 82 (40) | 51 (34) | 21 (50) | 10 (62) | **.030** |
| Dyspnea | 126 (61) | 78 (53) | 35 (83) | 12 (81) | **< .001** |
| Chest X-ray positive for opacities on admission - n (%) (pts. 179) | | (n. 135) | (n. 34) | (n. 10) | |
| No opacities | 23 (13) | 23 (17) | 0 | 0 | **.026** |
| Monolateral opacities | 40 (22) | 32 (24) | 7 (21) | 1 (10) | |
| Bilateral opacities | 116 (65) | 80 (59) | 27 (79) | 9 (90) | |
| Chest CT-Scan positive for infiltrates/ consolidations on admission - n (%) (pts. 74) | | (n. 46) | (n. 17) | (n. 11) | |
| No infiltrates/consolidations | 13 (18) | 13 (28) | 0 | 0 | **.020** |
| Monolateral infiltrates/consolidations | 5 (7) | 2 (4) | 1 (6) | 2 (18) | |
| Bilateral infiltrates/consolidations | 56 (76) | 31 (67) | 16 (94) | 9 (82) | |
| **Antiviral treatment during hospitalization - n (%)** | | | | | |
| Lopinavir/r | 93 (46) | 60 (41) | 21 (51) | 12 (75) | **.026** |
| Hydroxychloroquine | 147 (72) | 101 (69) | 32 (76) | 14 (87) | .240 |
| Azithromycin (pts. 163) | 37 (23) | 24 (21) | 7 (19) | 6 (43) | .162 |
| > 10 L/min of O2 therapy during hospitalization - n (%) | 83 (40) | 49 (33) | 22 (52) | 12 (75) | **.001** |
| Non-invasive ventilation during hospitalization - n (%) | 58 (28) | 31 (21) | 17 (40) | 10 (62) | **< .001** |
| Invasive mechanical ventilation during hospitalization - n (%) (n. 150) | 14 (9) | 4 (4) | 5 (17) | 5 (36) | **< .001** |
| At least one secondary infection - n (%). | 52 (25) | 32 (21) | 13 (31) | 7 (43) | .097 |
| Median Hospitalization Days (IQR), days (pts. 190) | 22 (12 -39) | 22 (12-39) | 26 (7-41) | 20 (15-44) | .697 |
| In-Hospital Mortality- n (%) - | 56 (27) | 34 (23) | 17 (40) | 5 (31) | .074 |

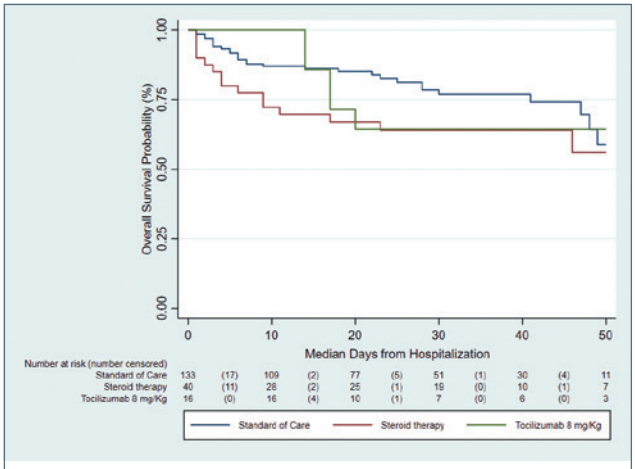
Boldface means statistically significant ($p < .05$)

were recorded in course of steroid therapy or after Tocilizumab administration.

In Table II, all secondary infections occurring during or after steroid/tocilizumab administration are shown.

A trend towards a higher incidence of infections in both the tocilizumab/corticosteroids group and in the only corticosteroid arm compared to SOC was noticed at univariable analysis ($p = .097$). By conducting a stepwise multivariable logistic regression model (Tab. III), adjusted for age, sex, comorbidity, clinical picture at admission, severity of respiratory failure, and treatment administered, only Tocilizumab treatment [adjusted Odds Ratio (aOR) = 6.72, 95% Confidence Interval (95%CI) = 1.43-31.39, $p = .015$] was associated with an increased risk of secondary infections during hospitalization.

"Invasive mechanical ventilation during hospitalization"




Fifteen patients in SOC group and two patients in Steroid Therapy group were excluded from the KM because data regarding time of hospitalization were unavailable.

**Figure 1.** Survival probability of patients, according to therapy prescribed.

was dropped in the final multivariable analysis due to the high number of missing cases. However, by performing the analysis after including this variable, the association between tocilizumab and secondary infections was confirmed (data not shown).

## DISCUSSION

The clinical spectrum of COVID-19 is wide and includes asymptomatic infection, fever without respiratory problems or even severe pneumonia with respiratory failure and necessity of non-invasive or invasive ventilation [3].
Many studies demonstrated that the mortality rate in patients over 60 years old is much higher than overall mortality [4] and it has been investigated a lot regarding the risk predictors of elderly patients. Several factors were related to poor outcomes in this population such as symptoms of dyspnea, comorbidities like cardiovascular disease, diabetes mellitus or obesity [13].
Despite gaps in understanding all pathogenic mechanisms causing COVID-19, it is now clear that immune system response plays a central role in development of pulmonary damage [1]. Some studies have shown a significant relationship between the disease severity and levels of pro-inflammatory cytokines and subsets of immune cells, suggesting that the immune dysregulation and the high level of pro-inflammatory cytokines could be the main cause of tissue injury [14].
Considering this background, we aimed to describe safety profile of two anti-inflammatory drugs like tocilizumab and steroids focusing on elderly patients infected with SARS-CoV-2 and treated using these strategies. Although previous studies investigated the role of these drugs in preventing the worsening of the disease, even with discordant results [6-8,10,14], none of them was focused on the elderly, and the efficacy and safety of tocilizumab and corticosteroids in these patients in the setting of COVID-19 is unknown.
It should be underlined that, due to its retrospective nature, this is not a study aiming to assess the efficacy of tocilizumab and steroids against COVID-19, as, of course, patients who underwent to these therapeutic strategies were more severe than those who were only treated with the standard of care; however, our results show no association between mortality rate and type of administered therapy.
Regarding the safety profile of these drugs, we did not observe the emergence of any specific adverse effect in patients treated with tocilizumab and steroids apart from infections, confirming what found in previously studies [6,10].
A quarter of patients (25%) suffered for secondary infections. According to the multivariable logistic regression model, tocilizumab treatment was associated with an increased risk of secondary infection during hospitalization. This in line with the paper of Toniati et al. [8], in which a similar rate of secondary infections was reported in a population with a median age of 62 (57-71) years.

**Table II.** Secondary infections recorded during hospitalization

| | Standard of care (n. 148) | Steroid therapy (n. 42) | Tocilizumab (n. 16) |
|---|---|---|---|
| **Type of infection, n (%)** | | | |
| No infections | 116 (78) | 29 (69) | 9 (56) |
| Bacterial Sepsis | 11 (8) | 4 (10) | 2 (13) |
| Fungal Sepsis (Candida spp.) | 0 | 2 (5) | 1 (6) |
| Bacterial Pneumonia | 3 (2) | 2 (5) | 3§ (19) |
| CA-UTI | 15 (10) | 3 (6) | 1 (6) |
| Other infections | 3* (2) | 2** (5) | 0 |

CA-UTI: catheter associated urinary tract infections; §: 1 case of pulmonary aspergillosis; *: 2 cases of C.difficile colitis and 1 skin and soft tissue infection; **: 1 case of C.difficile colitis and 1 case of dental abscess

**Table III.** Univariate and multivariate logistic regression for predictors of secondary infections.

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% C.I. | P-value | aOR | 95% C.I. | P-value |
| Age (per 1 year increase) | 1.00 | 0.97-1.04 | .672 | 0.98 | 0.94-1.03 | .608 |
| Male sex | 0.75 | 0.39-1.41 | .380 | 0.47 | 0.21-1.08 | .076 |
| Hypertension | 1.5 | 0.77-2.91 | .231 | 1.15 | 0.52-2.54 | .728 |
| Diabetes | 0.81 | 0.37-1.73 | .589 | 0.64 | 0.25-1.64 | .355 |
| Chronic kidney disease (KDOQI stage III or more) | 1.72 | 0.68-4.34 | .248 | 1.88 | 0.62-5.64 | .259 |
| Chronic obstructive lung disease | 2.15 | 1.06-4.37 | **.034** | 2.30 | 0.97-5.43 | .057 |
| Any neurologic disease | 1.16 | 0.55 - 2.42 | .686 | 1.23 | 0.49-3.09 | .658 |
| Any immunosuppressive condition | 0.51 | 0.06 - 4.37 | .542 | 0.41 | 0.42-4.12 | .454 |
| **Signs and symptoms around the time of hospitalization** | | | | | | |
| Fever (> 38°C) | 0.92 | 0.40-1.73 | .802 | 0.95 | 0.41-2.19 | .915 |
| Dyspnea | 1.80 | 0.91-3.55 | .090 | 1.37 | 0.58-3.21 | .467 |
| **Chest X-ray positive for opacities on admission - n (%)** | | | | | | |
| No opacities | 1 | | | 1 | | |
| Monolateral opacities | 0.66 | 0.22-1.95 | .460 | 0.44 | 0.13-1.50 | .195 |
| Bilateral opacities | 0.51 | 0.20 - 1.32 | .169 | 0.31 | 0.10-0.98 | **.046** |
| >10 L/min of O2 Therapy during hospitalization | 1.89 | 1.00 - 3.56 | **.050** | 1.61 | 0.71-3.64 | .247 |
| **Treatment administered** | | | | | | |
| Standard of care | 1 | | | 1 | | |
| Steroid therapy | 1.62 | 0.75 - 3.48 | .212 | 2.41 | 0.91 - 6.37 | .074 |
| Tocilizumab - 8 mg/kg - | 2.81 | 0.97 - 8.15 | .056 | 6.72 | 1.43 - 31.39 | **.015** |
| Invasive mechanical ventilation during hospitalization | 5.61 | 1.75 - 17.94 | **.004** | / | | |

OR: odds ratio; 95% C.I.: 95% confidence interval; aOR: adjusted odds ratio; Boldface means statistically significant ($p < .05$)

Conversely, in other studies regarding the use of Tocilizumab and steroids in COVID-19 patients younger than our population, no evidence of a higher frequency of secondary infections was reported compared to the standard of care [6,15].

The strengths of this study are represented by its quite large "real life" cohort focused on elderly, and its evaluation of possible adverse events during/after administration of anti-inflammatory treatment for COVID-19. However, it has also some limitations. First, its retrospective nature and all related biases; second, the inadequate design to evaluate the efficacy of anti-inflammatory treatment on mortality.

In conclusion, despite a likely increased risk of secondary infections after Tocilizumab administration, no other adverse events were recorded in this study. Therefore, tocilizumab and corticosteroid therapies could have a possible role for severe form of pneumonia in course of COVID-19 also in elderly patients, even if great attention to the monitoring of infectious complications should be paid in this special population.

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