


## ORIGINAL PAPER

## Infectious diseases

# Can treatment with teicoplanin improve the prognosis of COVID-19 patients?

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**Abstract**

**Aim:** In patients with COVID-19, no validated efficient treatment has been reported. Herein, we examine the effect of treatment with teicoplanin in hospitalised patients with COVID-19.

**Methods:** This retrospective study included 115 hospitalised patients in one medical centre. Fifty-four patients with laboratory-confirmed COVID-19 who received teicoplanin plus standard care were included in the Teicoplanin arm of this study, whereas 61 patients who were treated with standard care (SC) according to the Turkish Health Organization guidelines were included in the control arm. Patients' baseline characteristics, clinical presentation, treatment and outcomes were compared between the two groups.

**Results:** In this non-randomised control study, all baseline characteristics were comparable between the two arms and there were no significant differences in the presenting symptoms, comorbidities and clinical outcomes between the two groups. However, the mortality rate was significantly lower in the teicoplanin group than in the control group (1.9% vs 14.8%;  $P < .05$ ). In addition, no adverse reactions were found in the teicoplanin arm.

**Conclusions:** Teicoplanin administration is associated significantly with lower mortality in hospitalised patients with COVID-19 in our study. Further clinical investigations is required to verify the role of teicoplanin in COVID-19 patients.

## 1 | INTRODUCTION

The recent coronavirus disease 2019 (COVID-19) outbreak in China caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now spread worldwide because of the high transmission efficiency of the virus.<sup>1,2</sup> About 16%–21% of people with the virus become severely ill, and the mortality rate is 2%–2.5%.<sup>3</sup> However, few therapeutic agents have proven efficacious in human clinical trials. Several drugs, including remdesivir, ribavirin, interferon (IFN), favipiravir (FPV) and chloroquine/hydroxychloroquine have been used in SARS and Middle East respiratory syndrome (MERS) patients, although the efficacy of some drugs remains controversial.<sup>4</sup>

Teicoplanin, a glycopeptide antibiotic used to treat gram-positive bacterial infections, is relatively less toxic than other glycopeptides. Teicoplanin was shown to inhibit cellular invasion by Ebola virus, SARS-CoV and MERS-CoV by interfering with Cathepsin L activity.<sup>5</sup> It was recently demonstrated that the IC50 concentration of teicoplanin in vitro was 1.66  $\mu\text{M}$ , which is a much lower concentration than that reached in human blood (8.78  $\mu\text{M}$  for a daily 400 mg dose).<sup>6</sup> Zhou et al also reported that in coronaviruses, including SARS-Cov-2, teicoplanin acts at an early stage during the viral life cycle.<sup>5</sup> Zhang et al stated that given the mechanism of action, it is reasonable to recommend the use of teicoplanin in the early stages of COVID-19 infection.<sup>6</sup> In this study, we evaluated the clinical

outcomes of hospitalised COVID-19 patients receiving teicoplanin compared with a similar group of patients not receiving teicoplanin.

## 2 | MATERIALS AND METHODS

This retrospective and observational study enrolled a total of 115 patients with SARS-CoV 2 infection confirmed by polymerase chain reaction (PCR) of nasal swabs and thorax CT. The study group for this report was derived from an electronic database collected at Medistate Kavacak Hospital, Istanbul, from April to June 2020. Of these, the present study included COVID-19 patients free from any other serious pathological conditions: 54 received teicoplanin plus standard care (SC), whereas 61 received only SC. Teicoplanin was given once at a dose of 400 mg (following an 800 mg loading dose) within 24 hour after hospital admission. Patients were treated with an SC as suggested by the Turkish Health Organization Guidelines and included hydroxychloroquine 200 mg twice daily for a total duration of 5-10 d, Favipiravir 1.6 g twice daily on day 1, followed by 600 mg twice daily for a total duration of 5-10 d, azithromycin 500 mg once daily for 3 d, in necessary cases, tocilizumab 8 mg/kg twice with an interval of 12 h, antipyretics for fever and antibiotics to control secondary infection.

The two groups were compared in baseline demographics, pre-existing comorbidities, disease severity according to Turkish Health Organization Guidelines, biochemistry and haematology profile, treatment, adverse events, duration of hospital stays, the requirement for ventilation and mortality rate. Length of stay was calculated from the day of admission to either the day of discharge or the patient death. Demographical variables included age, sex and smoking status. Comorbidities included the history of pre-existing hypertension, diabetes mellitus, coronary artery disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease (CKD) or prior history of malignancy. Biochemistry and haematology profile included serum markers of disease severity including white blood cell count, lymphocyte count, eosinophil count, platelet count, serum ferritin, D-dimer, C-reactive protein (CRP) and procalcitonin. The main hospital admission indications according to Turkish Guidelines are: fever, muscle/joint pain, cough, sore throat symptoms, respiratory rate  $\geq 20$ /min, lymphopenia  $< 1000$ , ferritin  $> 500$  ng/ml, D-dimer  $> 1000$  ng/ml and Bilateral diffuse infiltration on chest X-ray or computed tomography. And also, respiratory rate  $\geq 30$ , dyspnoea and increased work of breathing [ $SpO_2 < 90\%$  or  $< 70$  mmHg (in room air)], oxygen requirement ( $\geq 5$  L/min with nasal cannula), lactate  $> 2$  mmol/L, hypotension [systolic blood pressure (SBP)]  $< 90$  mmHg,  $> 40$  mmHg drops from usual SBP, mean arterial pressure (MAP)  $< 65$  mmHg, skin hypoperfusion signs, organ dysfunction such as confusion, kidney and liver tests abnormalities, thrombocytopenia, elevated troponin level and arrhythmia were evaluated for the main intensive care unit (ICU) admission indications according to Turkish Health Organization Guidelines. All of these data were extracted from the electronic medical record.

### What's known

- There is the extensive knowledge that teicoplanin, a glycopeptide antibiotic used to treat the bacterial infection with low toxicity, previously showed to inhibit the invasion of cells by Ebola virüs, SARS-CoV and MERS-CoV, specifically effective on the activity of Cathepsin L. It has been reported that, in coronaviruses, teicoplanin acts on the early step of the viral life cycle by inhibiting the low pH cleavage of the viral spike protein by Cathepsin L.

### What's new

- Teicoplanin administration is associated significantly with lower mortality in hospitalised patients with COVID-19. Therefore, it is important to manage the COVID-19 patients with a safe, cheap and widely available drug, the present findings suggest that teicoplanin can be considered as a first-line treatment for SARS-CoV-2 to prevent disease progression and mortality.

Categorical variables were expressed as absolute frequency and percentage and compared with  $\chi^2$  test or Fisher's exact test. Continuous variables were expressed as median and interquartile range (IQR) and compared with Mann-Whitney *U* and Wilcoxon tests to analyse statistical differences. All the tests were two-sided and a *P* value  $< .05$  was considered statistically significant. The statistical analysis was carried out using SPSS.<sup>15</sup>

This study was approved by the Ethics Committee of Turkey Ministry of Health (2020-05-16T100919).

## 3 | RESULT

The patients enrolled in the study were aged with a mean of  $57.8 \pm 16.01$  and 78 were males (67.8%). At the time of admission, all patients had comparatively moderate/severe disease with cough, headache, sore throat, dispnea and pneumonia in different proportions. Some patients in both groups had underlying comorbidities such as hypertension, diabetes mellitus and lung diseases. About 43% of the patients were current smokers. Comparison of baseline characteristics, presenting symptoms, disease severity, comorbidities between COVID-19 patients treated with and without teicoplanin is shown in Table 1, although no statistically significant differences were observed between groups.

Of 115 patients in analyses, 54 (47%) received teicoplanin. In the teicoplanin group, 3 (5.6%) patients were treated with hydroxychloroquine, azithromycin; 30 (55.6%) with hydroxychloroquine, azithromycin and anticoagulant therapy; 21 (38.9%) with hydroxychloroquine, azithromycin, favipiravir and anticoagulant therapy. In 10 (18.5%) patients, quinolones or cephalosporins were added according to control secondary infection. Tocilizumab was required for

**TABLE 1** Comparison of baseline characteristics, clinical presentation, treatment and outcomes of COVID-19 patients treated with and without teicoplanin

Variables	Teicoplanin (n = 54)	No Teicoplanin (n = 61)	P value
<b>Characteristics of patients</b>			
Age, median (IQR)-y	61.20	54.85	.033
Sex			.515
Female-no. (%)	19 (35.2)	18 (29.5)	
Male-no. (%)	43 (70.5)	35 (64.8)	
<b>Pre-existing conditions</b>			
Hypertension-no. (%)	18 (33.3)	21(34.4)	.902
Diabetes mellitus-no. (%)	13 (24.1)	13 (21.3)	.724
Cardiac Disease-no. (%)	18 (33.3)	20 (32.8)	.950
Asthma-no. (%)	6 (11.1)	7(11.5)	.711
Currently smoking-no. (%)	24 (44.4)	26 (42.6)	.844
<b>Presenting symptoms*</b>			
Fever-no. (%)	39 (72.2)	42(68.9)	.693
Cough-no. (%)	47 (87.1)	51 (83.6)	.605
Shortness of breath-no. (%)	34 (63)	37(60.7)	.799
Heart rate, median (IQR)-beats/min	89 (85-94)	88 (86-94)	.937
Respiratory rate, median	16(14-16)	16 (14-18)	.196
Disease Severity-no. (%)	7 (12.9)	5 (8.19)	.219
<b>Severe disease</b>			
<b>Radiological pattern</b>			
Ground glass opacities	51 (94.4)	52 (85.2)	.107
Consolidation	17 (32.1)	27 (44.3)	.182
Halo Sign	3 (5.6)	9 (14.8)	.107

Abbreviation: IQR, interquartile range.

\*The values of presenting symptoms at hospital admission are shown based on available data.

2 (3.7%) patients. The median duration of teicoplanin therapy was 14 d (range 7-14). None of the patients had adverse effects related to teicoplanin administration.

In the SC group, 10 (16.4%) patients were treated with hydroxychloroquine, azithromycin; 41 (67.2%) with hydroxychloroquine, azithromycin and anticoagulant therapy; 10 (16.4%) with hydroxychloroquine, azithromycin, favipiravir and anticoagulant therapy. In 12 (19.6%) patients, quinolones or cephalosporins were added according to control secondary infection. Tocilizumab was required for 6 (9.8%) patients in the SC group. On follow-up day, three CRP and D-dimer showed a statistically significant decrease in the Teicoplanin group (CRP;  $P = .030$ , D-dimer;  $P < .001$ ). Comparison

of hemato-biochemical parameters, treatment between groups is shown in Table 2.

Thirty-five (64.8%) teicoplanin-treated patients required oxygen inhalation, 14 (25.9%) patients needed non-invasive mechanical ventilation and 16 (29.6%) required admission to an ICU. There were no statistically significant differences between the two groups. On the other hand, the mortality rate was statistically significantly lower in the teicoplanin group than SC (1.9% vs 14.8%;  $P < .05$ ) (Table 3).

## 4 | DISCUSSION

This retrospective study showed that it is safe to use teicoplanin in hospitalised patients with COVID-19 infection; moreover, its use was associated with a lower mortality rate. We also found a statistically significant decrease in CRP and D-dimer levels in the teicoplanin-treated group on follow-up day 3. We did not observe a significant difference in any other clinical outcomes, including the lengths of the hospital and ICU stays, despite the lower mortality.

After infection with SARS-CoV-2, the disease generally progresses within 1 wk of symptom onset because of uncontrolled viral replication in the upper respiratory tract<sup>8-11</sup>; this leads to immune anomalies and a cytokine storm.<sup>8,12,13</sup> Thus, an effective antiviral therapy capable of blocking viral replication during early infection may prevent disease progression and mortality. Zhou et al reported that teicoplanin acts in the early stage of the viral life cycle, inhibiting cleavage of the viral spike protein by cathepsin L at a low pH and thereby preventing the release of genomic viral RNA and attenuating virus replication. A recent study by the same authors also showed that the teicoplanin cleavage target sequence was conserved in the SARS-Cov-2 spike protein.<sup>5</sup> Moreover, Wang et al reported that in both mouse and rhesus macaque models, viral replication and histopathological injuries caused by SARS-CoV-2 infection were significantly inhibited by the lipoglycopeptide antibiotic, dalbavancin. Dalbavancin inhibits the interaction of the SARS-CoV-2 spike protein and ACE2 receptor by directly binding to ACE2 receptor and blocking the early stages of SARS-CoV-2 infection.<sup>13</sup> Ceccarelli et al investigated the use of teicoplanin in critically ill patients but found that it was not associated with a significant improvement in outcomes. They speculated that the antiviral activity of teicoplanin is likely more effective in the early clinical stages.<sup>14</sup>

Ceccarelli et al reported that the mortality and discharge rates of severe COVID-19 in three ICUs were 42.9% and 14.3%, respectively.<sup>7</sup> A recent study by the same authors showed that the crude in-hospital 30-d mortality rate was lower in the teicoplanin-treated group (35.2%) compared with the control group (42.8%), although the difference was not statistically significant.<sup>14</sup> In our study, all patients had moderate or severe disease and the mortality rate was significantly lower in the teicoplanin group. Unlike these two studies, the fact that our patient group consisted of moderate and severe patients may explain the lower mortality rates.

Variables	Teicoplanin (n = 54)	No Teicoplanin (n = 61)	P-value
<b>Baseline hemato-biochemical profiles</b>			
Lymphocyte count/mm <sup>3</sup> , median (IQR)	1305 (837-1792)	1400 (895-1895)	.799
CRP* (mg/L), median (IQR)	102 (31-139)	44 (13.9-111)	.091
D-dimer (µg/ml) median (IQR)	765 (412-1399)	540 (299-1044)	.328
Ferritin (U/L), median (IQR)	227 (115-393)	255(102-483)	.632
<b>Treatments approaches</b>			
Hydroxychloroquine-no. (%)	53 (98.1)	61 (100)	.470
Favipiravir no. (%)	24 (44.4)	25 (41)	.708
Anticoagulant therapy	51 (94.4)	50 (82)	.041
Anti IL-6 (tocilizumab)	2 (3.7)	6 (9.8)	.279
Required oxygen inhalation-no. (%)	7(13)	4 (6.6)	.244
Required NIMV-no. (%)	14 (25.9)	10 (16.4)	.209
Admission to ICU	16 (53.3)	14(46.7)	.416

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NIMV, non-invasive mechanical ventilation.

\*C-reactive protein.

**TABLE 2** Comparison of hemato-biochemical parameters and treatment of COVID-19 patients treated with and without teicoplanin

Variables	Teicoplanin (n = 54)	No Teicoplanin (n = 61)	P value
<b>Clinical outcomes</b>			
Duration of hospital stay, median (IQR)-day	8 (6-14)	7 (5-11)	.085
Duration of ICU stay, median (IQR)-day	10(5-15)	3(1-15)	.110
Death no. (%)	1 (1.9)	9 (14.8)	.018

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

**TABLE 3** Comparison of outcomes of COVID-19 patients treated with and without teicoplanin

Appropriate and rapid management of patients with mild to moderate symptoms is essential to prevent disease progression and mortality. It is important to investigate the utility of teicoplanin in the early stages of COVID-19. Glycopeptide antibiotics were used as antiviral agents for COVID-19, and for empiric treatment of possible superinfections. However, the role of teicoplanin in COVID-19 infection remains under investigation and the agent has not been approved by the FDA.

In a previous study, teicoplanin was administered at a dose of 600 mg/d, which usually results in a serum trough concentration >10 mg/L. This trough concentration is regarded as adequate for the treatment of bacterial infection.<sup>7</sup> A recent study reported that the IC50 concentration of teicoplanin in vitro was 1.66 µM, which is much lower than the concentration reached in human blood (8.78 µM for a daily dose of 400 mg).<sup>13</sup> In our study, teicoplanin was administered at a dose of 400 mg/d. Therefore, the routine dose used for COVID-19 patients can be considered to be 400 mg/d.

Ceccarelli et al reported that the peripheral lymphocyte count progressively and significantly improved after treatment. CRP and procalcitonin also showed statistically significant decreases in their study.<sup>7</sup> Similarly, we found that CRP and D-dimer levels

were significantly lower in the teicoplanin group on follow-up day 3. Also, we did not observe any adverse events related to teicoplanin administration.

This study had several limitations. Because of its retrospective, observational nature, potential differences between the groups might not have been detected because of the small sample size and lack of quantitative evaluation of the viral response. However, considering that the antiviral regimens of the groups were similar, no differences were expected. Another limitation was that disease status at baseline could not be confirmed by PCR in all patients. Nevertheless, all patients presented with symptoms, signs, blood test results and radiological findings compatible with COVID-19.

In conclusion, we found that teicoplanin administration was associated with lower mortality in hospitalised patients with COVID-19. It is important to manage COVID-19 patients with a safe, cheap and widely available drug. Our findings suggest that teicoplanin can be considered as a first-line treatment for SARS-CoV-2 to prevent disease progression and mortality. Appropriately designed randomised clinical trials are required to better elucidate the antiviral mechanism of teicoplanin, and its role in the management of COVID-19 patients.

## DISCLOSURE

The author declares no conflict of interest. The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: <http://www.textcheck.com/certificate/VdKouo>

## DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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