Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Is teicoplanin a complementary treatment option for COVID-19? The question remains

Sir,

We read with great interest the editorial by Baron et al. suggesting the potential use of teicoplanin as an alternative drug to treat patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Indeed, this glycopeptide antibiotic, commonly used to treat Gram-positive bacterial infections, also showed potential complementary antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and Ebola virus, as previously highlighted by Zhou et al.; moreover, influenza A and B viruses and feline infectious peritonitis virus (FIPV) were reported as potential targets of teicoplanin and its chemical derivatives [2–5]. Recently, additional studies have provided evidence that SARS-CoV-2, similarly to SARS-CoV, is a cathepsin L-dependent virus: in fact, these viruses require a multistep infection process including (i) receptor binding, (ii) change in spike (S) glycoprotein conformation, and finally (iii) cathepsin L proteolysis of the S protein, crucial for virus entry. Teicoplanin was found to specifically inhibit the activity of cathepsin L and potentially to play a critical role in blocking cell entry of the virus [2,6,7].

Based on the aforementioned, teicoplanin has been used either as a potential antiviral agent or as treatment of possible *Staphylococcus aureus* superinfection in our critical patients with severe SARS-CoV-2 pneumonia, since the latter may represent a major complication of respiratory viral infections [8].

We preliminary observed a cohort of 21 patients affected by severe COVID-19 (coronavirus disease 2019) lung involvement, hospitalised in three intensive care units (ICUs) of a large teaching hospital in Italy, Rome, and complementarily treated with teicoplanin.

Patients included in the analysis were Caucasian subjects (18 male and 3 female) admitted to the ICU for severe respiratory complications after a median of 7 days (range 3–9 days) from COVID-19 symptom onset. Baseline clinical characteristics of the cohort are shown in Table 1.

Patients were treated with an interim standard of care as suggested by the Italian Society of Infectious and Tropical Diseases (SIMIT) [9] of hydroxychloroquine 200 mg twice daily (b.i.d.) plus tocilizumab 8 mg/kg (up to a maximum of 800 mg/dose) twice with an interval of 12 h. All patients had previously discontinued lopinavir/ritonavir 200/50 mg (two tablets b.i.d.) without viral clearance. On ICU admission, the patients received teicoplanin 6 mg/kg every 24 h (loading dose every 12 h for three doses). The median duration of teicoplanin therapy was 10 days (range 7–12 days).

At follow-up after a 12-day course, the peripheral lymphocyte count, a marker of favourable prognosis, was progressively and significantly improved; C-reactive protein (CRP) and procalcitonin also showed a statistically significant decrease (Fig. 1). On the other hand, kidney and liver function did not significantly change and the PaO_2/FiO_2 was not significantly modified, although 5 patients (23.8%) were weaned from mechanical ventilation.

Table 1
Clinical characteristics of patients at baseline.

Parameter	Median	Range	IQR	%
Age (years)	72	48–82	64.25–76.75	–
CCI	3	0–5	–	–
SAPS II	41	19–55	33–50	–
WBC count ($\times 10^9$/L)	8.69	2.15–20.5	6.8–10.68	–
Creatinine (mg/dL)	1.54	0.48–3.39	1.09–1.83	–
BUN (mg/dL)	13.3	3.9–32	8.3–15.2	–
ALT (U/L)	27	5–88	19–42	–
AST (U/L)	37	14–201	27–76	–
PaO_2/FiO_2 ratio	152	51–262	114–190	
Orotracheal intubation	–	–	–	100
Previous NIV/CPAP	–	–	–	76.2

IQR, interquartile range; CCI, Charlson comorbidity index; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIV, non-invasive ventilation; CPAP, continuous positive airway pressure.

On Day 7 of treatment, 2 (9.5%) of the 21 patients observed achieved viral clearance; on Day 12, 1 patient (4.8%) was discharged from the ICU and 3 patients (14.3%) had died (on Days 6, 7 and11). Overall on Day 21, the ICU mortality rate, ICU discharge rate and viral clearance rate were 42.9% (9/21 patients), 14.3% (3/21 patients) and 40.0% (4/10 patients tested), respectively. No Gram-positive superinfections were observed; however, as a complementary observation, methicillin-resistant/teicoplanin-susceptible *S. aureus* was isolated from respiratory secretions in 4 patients (19.0%) with severe SARS-CoV-2 pneumonia, not being considered an agent of new infection in any case. None of the patients had adverse effects related to teicoplanin administration.

Therapeutic drug monitoring (TDM) was not available in our patients. However, teicoplanin was administered at a dosage of 600 mg/day, which corresponds to 6–8 mg/kg/day (following a 600 mg loading dose every 12 h for three doses), that usually results in a serum trough concentration of >10 mg/L, regarded as adequate for treatment of bacterial infections [10]. Moreover, a recent study showed that teicoplanin potently prevents the entrance of SARS-CoV-2 into the cytoplasm with an IC_{50} of only 1.66 μM, which is much lower than the routine trough serum drug concentration (~7–8 μM) [7]. Therefore, the routinely used teicoplanin doses adopted in our series might be considered as potentially adequate for the treatment of patients with SARS-CoV-2 infection.

This study has many obvious limitations, including its non-comparative retrospective observational nature, small simple size, short follow-up, lack of TDM and the impossibility of discriminat-

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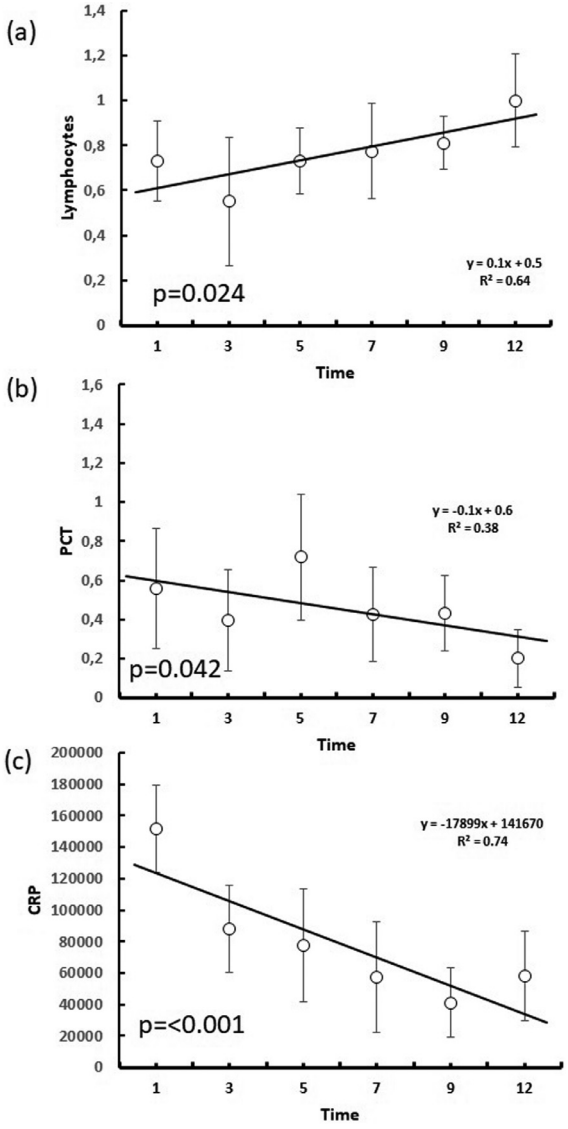

Fig. 1. Follow-up trends of (a) lymphocytes, (b) procalcitonin (PCT) and (c) C-reactive protein (CRP). Data are expressed as the mean ± standard deviation. Time is expressed in days. Student's *t*-test and linear regression analysis using Pearson's linear correlation coefficient (*R*) were performed to investigate the difference and correlation between the follow-up analysis [standard error (SE) associated with the data correlation were also reported].

ing specific effects of the different drugs used. Equally important, our observations were limited to critically ill patients requiring mechanical ventilation. Nevertheless, this is the first real-life report on the use of teicoplanin in vivo in subjects affected by COVID-19 and the results appear fairly acceptable when compared with a previous report from the same geographical area [11]. In conclusion, further clinical investigation is required to verify the definite role of teicoplanin, if any, as adjunctive therapy of COVID-19, at least in critically patients.

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