Feasibility and safety of angiotensin II administration in general ward patients during COVID-19 pandemic: a case series

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From December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic of coronavirus disease 2019 (COVID-19) that has frequently overwhelmed health care systems due to the high number of patients requiring admission to an intensive care unit (ICU).[1,2]

Angiotensin-converting enzyme 2 (ACE2) is a cellular membrane-bound vasopeptidase that has been identified as a functional receptor for SARS-CoV-2.[3]

Angiotensin II is an endogenous octapeptide with vasoconstrictor activity that has been recently suggested as a catecholamine-sparing agent for vasodilatory shock.[4] It has been hypothesised that angiotensin II may act as competitive inhibitor for ACE2 with SARS-CoV-2 and may therefore have antiviral activity.[5]

We have previously described our experience with the use of intravenous angiotensin II as compassionate therapy for patients with COVID-19 admitted to the ICU.[6,7] Early antiviral treatment may be associated with greater benefits. Therefore, we started administering intravenous angiotensin II as antiviral to patients with moderate COVID-19-related acute respiratory distress syndrome (ARDS) in the general ward, before invasive ventilation or shock requiring ICU admission. No published data are available on use of intravenous angiotensin II outside the controlled environment of the ICU. In this article, we provide our data on feasibility and safety of angiotensin II administration in a non-ICU setting.

We present a case series of seven COVID-19 patients with moderate ARDS who received intravenous angiotensin II in the general ward. Intravenous use of angiotensin II is not approved by the Italian Drug Administration Agency (*Agenzia Italiana del Farmaco* [AIFA]) or the European Medicines Agency (EMA). Accordingly, we obtained ethics approval for compassionate use of the drug and all patients provided a written informed consent. The data collection was part of the COVID-BioB study approved by the Hospital Ethics Committee (Protocol No. 34/int/2020) and registered on ClinicalTrials.gov (NCT04318366). Hospital organisation and clinical management of patients with COVID-19 at our centre have been previously published.[1,6]

We included patients who had confirmed SARS-CoV-2 infection with clinical or radiological signs of interstitial pneumonia and moderate ARDS.

Patients with cardiogenic shock, stage IV cancer, contraindications to deep venous thrombosis prophylaxis, hypertension requiring treatment, or receiving invasive ventilation at the moment of enrolment were excluded.

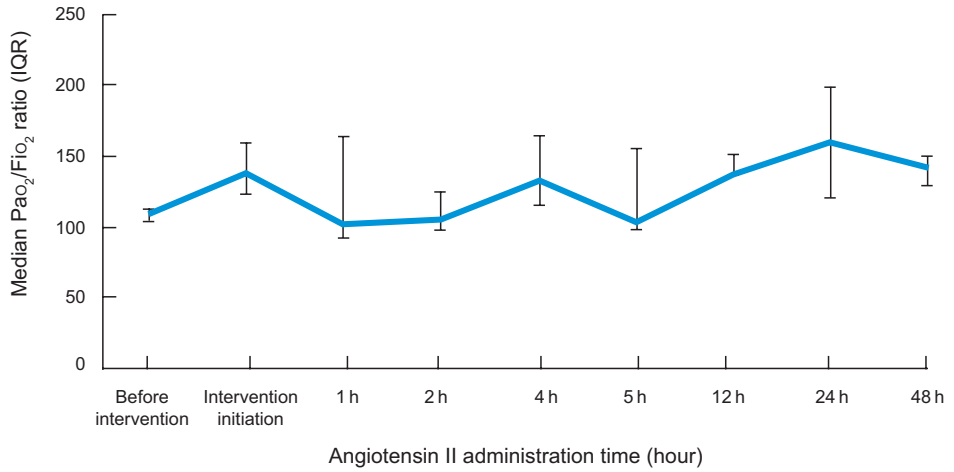
Details on patient monitoring, study drug preparation and administration, data collection, and study outcomes are presented in the Online Appendix. Angiotensin II (drug concentration 25 µg/mL) was infused in a dedicated vein at a starting dose of 5 ng/kg/min, aiming to achieve a mean arterial pressure greater than 65 mmHg unless clinical judgement suggested targeting higher values (eg, reduction in urinary output). If a dose of 10 ng/kg/min or over was reached, the patient was evaluated for vasopressor support and ICU admission.

Data were collected from medical records by trained investigators not involved in patient management. Haemodynamic and ventilatory variables were collected before angiotensin II administration and at 1, 2, 4, 6, 12, 24 and 48 hours after initiating treatment with angiotensin II. Patients were followed up until day 28.

The primary outcome was clinical improvement at day 28 — defined as an improvement of 2 points or more on a six-category ordinal scale compared with baseline.[8] Secondary outcomes included mortality, need for ICU admission and need for invasive mechanical ventilation. Safety outcomes were drug extravasation, limb or bowel ischaemia, arrhythmias, or uncontrolled hypertension during angiotensin II administration.

Baseline characteristics are presented in the Online Appendix (table 1). All patients had moderate ARDS at time of enrolment. Non-invasive ventilation was administered with 10 mmHg positive end-expiratory pressure in all patients, and PaO_2/FiO_2 (arterial partial pressure of oxygen/fraction of

Figure 1. Changes in PaO_2/FiO_2 ratio over time



FiO_2 = fraction of inspired oxygen; PaO_2 = arterial partial pressure of oxygen.

inspired oxygen) ratio was below 200. Haemodynamic data are presented in the Online Appendix (table 2), and changes in PaO_2/FiO_2 ratio and mean arterial pressure over time are shown in Figure 1 and in the Online Appendix (figure 1) respectively. At day 28, the median change in the six-category ordinary scale was +3, with clinically relevant improvement in four patients (57.1%) (Table 1) and one further patient improving after day 28 till hospital discharge.

During the follow-up period, three patients required invasive mechanical ventilation and admission to the ICU, two of whom died. In both cases, the main cause of death was barotrauma (pneumomediastinum). At day 28, one patient remained in the ICU, but was discharged after day 28, and all other patients were discharged from hospital (Table 1). No patient developed complications related to angiotensin II administration. In particular, there were no cases of drug extravasation, limb or bowel ischaemia, arrhythmias, or uncontrolled hypertension. After clinical improvement, a mild cutaneous hand rash was noted in a patient and angiotensin II was interrupted on a precautionary basis.

Table 1. Outcome data

Outcome	*N* = 7
Primary outcome	
Change in six-category ordinal scale value, median (IQR)	+3 (–1 to +3)
Clinically significant improvement	4 (57.1%)
Secondary outcomes	
Mortality at day 28	2 (28.6%)
ICU admission	3 (42.9%)
Need for invasive mechanical ventilation	3 (42.9%)
Status at day 28	
Died	2 (28.6%)
Alive, in ICU	1 (14.3%)
Alive, in hospital	0 (0.0%)
Discharged from hospital	4 (57.1%)

ICU = intensive care unit; IQR = interquartile range.

In this study, to our knowledge, we present for the first-time clinical data on the feasibility and safety of angiotensin II administration in hospital wards. Notably, our hospital already has longstanding experience in non-invasive ventilation and vasopressor administration outside the ICU.[2,9] In our published experience, we treated 129 patients with non-invasive ventilation on the ward over 7 months (about one new patient every 2 days). In our non-published recent experience, we have on average four hospitalised patients receiving vasopressors outside the ICU. Our study suggests that vasopressor administration outside the ICU is feasible, and may be considered in low resource settings such as during pandemics or major emergencies. Furthermore, our study is reassuring that low dose vasopressor on ward administration may be considered as a method to reduce the need for ICU beds and improve resource allocation.[10]

Nevertheless, larger studies are needed to ultimately confirm safety, efficacy and cost-effectiveness of angiotensin II administration in wards.

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Competing interests

None declared.

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