Use of Defibrotide in Patients with COVID-19 Pneumonia; Results of the DEFI-VID19 Phase 2 trial.

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Background: The clinical spectrum of COVID-19 ranges from pauci-symptomatic forms to severe disease characterized by respiratory failure requiring mechanical ventilation and intensive care unit (ICU) management, as well as multisystem involvement characterized by sepsis, organ dysfunction and death. Treatment of COVID-19 is not standardized, and respiratory failure from ARDS is the leading cause of mortality; in-hospital mortality at 28-days in our tertiary care center in Lombardia, northern Italy is currently 23% (Ciceri et al. 2020). Endothelial damage and thrombo-inflammation have been identified as common to both COVID-19 pathophysiology and veno-occlusive disease (VOD/SOS). Defibrotide (DF) has endothelial-protective properties, with pro-fibrinolytic, anti-thrombotic, anti-ischemic, anti-inflammatory, and anti-adhesive activity, but no significant systemic anticoagulant effects and is approved for the treatment of severe VOD/SOS .

Aim: A prospective, multicenter, phase II, single-arm, open label trial (DEFI-VID19, NCT04335201) was conducted in patients (pts) with COVID-19 ARDS to evaluate the efficacy of DF in addition to best available therapy per institutional guidelines. The primary endpoint was respiratory-failure rate (RFR) defined as progression of respiratory failure, i.e. severe gas transfer deficit (PaO2/FiO2<200 mmHg), need of ICU or death at day+14 from treatment start. Secondary endpoints included overall survival (OS) at 28 days, duration of hospitalization and safety.

A sample size of 50 pts was calculated to detect an absolute reduction of 20% in RFR at day+14, assuming a failure rate in non-treated pts of 70% (alpha=5%, power=90%, two-sided test). Pts received DF intravenously at 6.25 mg/kg/dose by 2-hour infusion repeated every 6 hours. Expected treatment duration was 14 days, with earlier discontinuation if clinical improvement occurred. LMWH at prophylactic dose was allowed. Approval was provided by the National IRB for COVID-19 trials at Institute Spallanzani (Rome) and by the Italian Agency for Drug (AIFA). All patients provided written informed consent.

Results: Overall, 52 pts were enrolled from September 2020 to April 2021; 48 were evaluated for efficacy and safety; 4 pts were excluded due to screen failure (n=2) or withdrawal of informed consent at day 2 after defibrotide was initiated (n=2). Median age was 60.5 years (range 53-71); 35 pts (73%) were male and 65% had comorbidities, with high blood pressure, obesity and COPD most common. Two pts had pre-existing diagnoses of non-Hodgkin lymphoma. Median time from onset of COVID-19 symptoms and from Sars-COV2 PCR by nasal swab to enrollment were 8 (range 7-10) and 3 days (range 1-6), respectively. All pts were hospitalized and scale 5 of 8-category ordinal scale by WHO criteria, requiring noninvasive ventilation with CPAP or high-flow oxygen, with a median P/F ratio of 211 (range 134-275) mmHg. At treatment start, the median and (range) lymphocyte counts, LDH, CRP, ferritin, D-dimer and IL-6 were 0.7 (0.5-0.9) x 10e9/L; 404 (291-491) U/L; 49 (22-97) mg/L; 823 (363-1088) ng/ml; 0.44 (0.28-1.29) µg/mL and 20 (11-32), respectively.

Median treatment duration was 8.5 days (range 6-11). Overall, 13/48 pts (27%) discontinued the treatment due to clinical worsening and/or need of further therapies: 9 pts experienced progressive respiratory failure and 6 of those were transferred to ICU for IOT (one pt required ECMO), and 4 required full anticoagulation due to pulmonary embolism (n=1), ischemic stroke (n=1), and femoral deep venous thrombosis (n=2). All pts who completed the treatment 35/48

(73%) were discharged with no need of oxygen support. Overall, 14 SAEs have been reported in a median time of 6 days (range 2-10): all unrelated to DF. No pts experienced hemorrhagic events. The incidence of RFR at day 14 was 25 (+/- 6)%, and at day 28, 27 (+/- 6) %. Probability of OS at day 28 was 89 (+/-4) %, at day 60 83 (+/- 5)%. Overall, 8 pts died from COVID-19 - related complications. No pts required re-admission after hospital discharge (median 14 days) or died after discharge.

Conclusion: Treatment with DF in pts with grade 5 WHO COVID 19 ARDS does not induce bleeding, and is associated with rapid restoration of respiratory function (73% of pts). Notably, no oxygen support was needed at discharge and a 1-month OS rate of 89% was observed, which is significantly higher than historical controls (77%; $p < 0.05$) treated in the same setting.

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