Katherine Elkort Abstract

Intravenous aviptadil and remdesivir for treatment of COVID-19-associated hypoxaemic respiratory failure in the USA (TESICO): a randomised, placebo-controlled trial

There is a clinical need for therapeutics for COVID-19 patients with acute hypoxemic respiratory failure whose 60-day mortality remains at 30-50%. Aviptadil, a lung-protective neuropeptide, and remdesivir, a nucleotide prodrug of an adenosine analog, were compared with placebo among patients with COVID-19 acute hypoxaemic respiratory failure. TESICO was a randomised trial of aviptadil and remdesivir versus placebo at 28 sites in the USA. Hospitalised adult patients were eligible for the study if they had acute hypoxaemic respiratory failure due to confirmed SARS-CoV-2 infection and were within 4 days of the onset of respiratory failure. Participants could be randomly assigned to both study treatments in a 2 × 2 factorial design or to just one of the agents. Participants were randomly assigned with a web-based application. For each site, randomisation was stratified by disease severity (high-flow nasal oxygen or non-invasive ventilation *vs* invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]), and four strata were defined by remdesivir and aviptadil eligibility, as follows: (1) eligible for randomisation to aviptadil and remdesivir in the 2 × 2 factorial design; participants were equally randomly assigned (1:1:1:1) to intravenous aviptadil plus remdesivir, aviptadil plus remdesivir matched placebo, aviptadil matched placebo plus remdesvir, or aviptadil placebo plus remdesivir placebo; (2) eligible for randomisation to aviptadil only because remdesivir was started before randomisation; (3) eligible for randomisation to aviptadil only because remdesivir was contraindicated; and (4) eligible for randomisation to remdesivir only because aviptadil was contraindicated. For participants in strata 2–4, randomisation was 1:1 to the active agent or matched placebo. Aviptadil was administered as a daily 12-h infusion for 3 days, targeting 600 pmol/kg on infusion day 1, 1200 pmol/kg on day 2, and 1800 pmol/kg on day 3. Remdesivir was administered as a 200 mg loading dose, followed by 100 mg daily maintenance doses for up to a 10-day total course. For participants assigned to placebo for either agent, matched saline placebo was administered in identical volumes. For both treatment comparisons, the primary outcome, assessed at day 90, was a six-category ordinal outcome: (1) at home (defined as the type of residence before hospitalisation) and off oxygen (recovered) for at least 77 days, (2) at home and off oxygen for 49–76 days, (3) at home and off oxygen for 1–48 days, (4) not hospitalised but either on supplemental oxygen or not at home, (5) hospitalised or in hospice care, or (6) dead. Mortality up to day 90 was a key secondary outcome. The independent data and safety monitoring board recommended stopping the aviptadil trial on May 25, 2022, for futility. On June 9, 2022, the sponsor stopped the trial of remdesivir due to slow enrolment. The trial is registered with ClinicalTrials.gov, NCT04843761. Between April 21, 2021, and May 24, 2022, we enrolled 473 participants in the study. For the aviptadil comparison, 471 participants were randomly assigned to aviptadil or matched placebo. The modified intention-to-treat population comprised 461 participants who received at least a partial infusion of aviptadil (231 participants) or aviptadil matched placebo (230 participants). For the remdesivir comparison, 87 participants were randomly assigned to remdesivir or matched placebo and all received some infusion of remdesivir (44 participants) or remdesivir matched placebo (43 participants). 85 participants were included in the modified intention-to-treat analyses for both agents (ie, those enrolled in the 2 x 2 factorial). For the aviptadil versus placebo comparison, the median age was 57 years (IQR 46–66), 178 (39%) of 461 participants were female, and 246 (53%) were Black, Hispanic, Asian or other (*vs* 215 [47%] White participants). 431 (94%) of 461 participants were in an intensive care unit at baseline, with 271 (59%) receiving high-flow nasal oxygen or non-invasive ventiliation, 185 (40%) receiving invasive mechanical ventilation, and five (1%)

receiving ECMO. The odds ratio (OR) for being in a better category of the primary efficacy endpoint for aviptadil versus placebo at day 90, from a model stratified by baseline disease severity, was 1·11 (95% CI 0·80–1·55; p=0·54). Up to day 90, 86 participants in the aviptadil group and 83 in the placebo group died. The cumulative percentage who died up to day 90 was 38% in the aviptadil group and 36% in the placebo group (hazard ratio 1·04, 95% CI 0·77–1·41; p=0·78). The primary safety outcome of death, serious adverse events, organ failure, serious infection, or grade 3 or 4 adverse events up to day 5 occurred in 146 (63%) of 231 patients in the aviptadil group compared with 129 (56%) of 230 participants in the placebo group (OR 1·40, 95% CI 0·94–2·08; p=0·10). Among patients with COVID-19-associated acute hypoxaemic respiratory failure, aviptadil did not significantly improve clinical outcomes up to day 90 when compared with placebo. The smaller than planned sample size for the remdesivir trial did not permit definitive conclusions regarding safety or efficacy.

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