# Remdesivir

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**La FDA, en los USA, ha aprobado urgentemente el uso del antiviral remdesivir para el tratamiento de casos severos de Covid-19,**

**Only in English**

**AHFS Class:** Antiviral 8:18.32 *Observation:* Acronym definition. AHFS, American Hospital Formulary Service.

**Rationale**

Broad-spectrum antiviral (nucleotide analog prodrug) with activity against various viruses, including coronaviruses 24 In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells 1, 18 In Rhesus macaques infected with SARS-CoV-2, treatment with a 6-day regimen of IV remdesivir initiated 12 hours after virus inoculation was associated with some benefits (lower disease severity scores, fewer pulmonary infiltrates, lower virus titers in bronchoalveolar lavage samples) compared with vehicle control; remdesivir treatment did not reduce viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control 19 In vitro activity against SARS-CoV and MERS-CoV; active in animal models of SARS and MERS; prevented MERS in Rhesus macaques when given before infection and provided benefits when given after animal already infected 1-8. Pharmacokinetic data available from evaluations for Ebola

**Trials or Clinical Experience**

Note: Enrollment was terminated before the pre-specified number of pts was attained (lack of available pts); trial was insufficiently powered to detect assumed differences in clinical outcome. 21 Phase 3 randomized, open-label trial in hospitalized adults with severe COVID-19 (NCT04292899) sponsored by the manufacturer (Gilead): Initial study protocol designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg once daily for total of 5 or 10 days) in conjunction with standard of care in pts not receiving mechanical ventilation; 10 protocol subsequently modified to

add extension arms to evaluate safety and efficacy of 10-day regimen of remdesivir in conjunction with standard of care in pts who are or are not receiving mechanical ventilation. 10 Manufacturer announced that data available for the initial 397 pts not requiring mechanical ventilation at study entry (200 received a 5-day regimen and 197 received a 10-day regimen) indicate similar clinical improvement with both treatment durations. Time to clinical improvement for 50% of pts was 10 days in the 5-day treatment group vs 11 days in the 10-day treatment group. At day 14, 129/200 pts (64.5%) in the 5-day group and 106/197 pts (53.8%) in the 10-day group achieved clinical recovery. Pts who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms. 23 Note: Data regarding this initial pt population (e.g., disease severity and comorbidities at study enrollment, additional supportive treatment received) not provided to date. Phase 3 randomized, open-label trial in pts with moderate COVID-19 (NCT04292730) sponsored by the manufacturer (Gilead) is evaluating safety and antiviral activity of 5- and 10-day regimens of remdesivir in conjunction with standard of care compared with standard of care alone 11Phase 3 adaptive, randomized, placebocontrolled trial (NCT04280705; ACTT) in hospitalized adults sponsored by NIAID: Pts received remdesivir (200 mg IV on day 1, then 100 mg once daily for duration of hospitalization up to 10 days total) or placebo. 13 Sponsor announced that preliminary data analysis (total of 1063 pts) indicated shorter median time to recovery in remdesivir group (11 days) vs placebo group (15 days) and suggested that remdesivir treatment may have provided a survival benefit (mortality rate 8% in remdesivir group vs 11.6% in placebo group). 22 Note: Data regarding the pt population (e.g., disease severity and comorbidities at study enrollment, time to initiation of treatment after symptom onset, additional supportive treatment received) not provided to date. Expanded access IND protocol (NCT04323761): The manufacturer (Gilead) established a protocol for emergency access to remdesivir for the treatment of severe acute COVID-19 in hospitalized adults and children 12 years of age or older 17 Compassionate use access: The manufacturer (Gilead) is transitioning from individual compassionate use requests to an expanded access program for emergency access to the drug for severely ill pts with confirmed COVID-19. New individual compassionate use requests cannot be accepted, with the possible exception of requests for pregnant women and childrenother countries who were hospitalized with severe COVID-19 and received treatment with remdesivir; 40 pts received the full 10- day regimen (200 mg IV on day 1, then 100 mg IV on days

2-10), 10 pts received 5-9 days and 3 pts received less than 5 days of treatment with the drug. At baseline, 30 pts (57%) were receiving mechanical ventilation and 4 (18%) were receiving extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days after first dose, 36 pts (68%) showed clinical improvement based on oxygen-support status and 8 pts (15%) worsened. There were 7 deaths (13%), including 6 pts receiving invasive ventilation. Adverse effects (e.g., increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects. 16 Note: Data presented for this small cohort of pts offers only limited information regarding efficacy and safety of remdesivir for treatment of COVID-19. There was no control group and, although supportive therapy could be provided at the discretion of the clinician, it is unclear whether pts at any of the various study sites also received other therapeutic agents being used for treatment of COVID-19. In addition, data were not presented regarding the effects of remdesivir on viral load Adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib (ACTT2): This next iteration of NIAID's Adaptive COVID-19 Treatment Trial (ACTT) will evaluate possible benefits of using baricitinib (a Janus kinase [JAK] inhibitor) in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV -2 infection and evidence of lung involvement (abnormal chest x-rays, need for supplemental oxygen or mechanical ventilation). Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration of hospitalization or up to 10 days total) or the same remdesivir dosage given with oral baricitinib (4 mg once daily for the duration of hospitalization or up to 14 days total). 29

**Optimal dosage and duration of treatment**

Not known 25, 26 Phase 3 trial protocol (severe COVID19): 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2); 10 200 mg IV on day 1, then 100 mg IV daily on days 2 -10 (extension arms that include pts who are or are not receiving mechanical ventilation) 10 Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) 11 NIAID adaptive study protocol: 200 mg IV on day 1, then 100 mg IV

for duration of hospitalization up to 10 days total 13 Compassionate use access protocol: 200 mg IV on day 1, then 100 mg IV on days 2-10 16 Emergency use authorization (EUA) dosage recommended for adults and children weighing 40 kg or more: Loading dose of 200 mg by IV infusion on day 1, followed by 100 mg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 100 mg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts not requiring mechanical ventilation and/or ECMO).26 Emergency use authorization (EUA) dosage recommended for children weighing 3.5 to less than 40 kg: 5 mg/kg by IV infusion on day 1, followed by 2.5 mg/kg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 2.5 mg/kg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts not requiring mechanical ventilation and/or ECMO).

**Comments**

Not commercially available; most promising direct-acting antiviral (DAA) currently being investigated for COVID-19 Efficacy and safety of remdesivir for treatment of COVID-19 not established NIH COVID-19 Treatment Guidelines Panel recommends use of remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease; the NIH panel does not recommend remdesivir for the treatment of mild or moderate COVID-19 outside of clinical trials. 20 Emergency use authorization (EUA) for remdesivir: FDA issued an EUA on May 1, 2020 that permits use of the drug for the treatment of COVID-19 only in hospitalized adults and children with suspected or laboratory-confirmed COVID19 who have severe disease (defined as oxygen saturation [SpO2] 94% or lower on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO) and requires that the drug be administered by a healthcare provider in an inpatient hospital setting via IV infusion at dosages recommended in the EUA. 25, 26 Distribution of remdesivir under this EUA is controlled by the US government for use consistent with the terms and conditions of the EUA. 25, 26 The manufacturer (Gilead) donated remdesivir for use under the EUA; distribution to hospitals and other healthcare facilities is being directed by the HHSOffice of the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state health departments. To request remdesivir for use under the EUA, healthcare providers should contact their state health departments. 28 The EUA requires that healthcare facilities and healthcare

providers administering remdesivir comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch). 25, 26 Consult the EUA, 25 EUA fact sheet for healthcare providers, 26 and EUA fact sheet for patients and parent/ caregivers 27 for additional information

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