Remdesivir (GS-5734) Pharmacology

Remdesivir is an **adenosine nucleotide analog prodrug** with **broad-spectrum antiviral activity** demonstrated both *in vitro* and *in vivo* in animal models. It has shown efficacy against **Ebola virus** , **Marburg virus** , **SARS-CoV** , and **MERS-CoV** .

The drug is manufactured by **Gilead Sciences** .

Mechanism of Action

Remdesivir is a **prodrug** of **GS-441524** , which must undergo intracellular metabolism to its active triphosphate form. As an **adenosine analog** , it mimics natural adenosine but is structurally distinct.

Once inside infected cells:

- The active metabolite **GS-443902 (triphosphate form)** competes with adenosine triphosphate (ATP) for incorporation into viral RNA by **viral RNA-dependent RNA polymerase (RdRp)** .
- This results in **premature termination of RNA transcription** —specifically, the polymerase halts RNA synthesis at **i + 3** nucleotides after remdesivir is incorporated.
- Importantly, the drug **evades viral proofreading** by **3?–5? exoribonuclease (ExoN)** , leading to defective viral genomes and inhibition of viral replication.

Antiviral Spectrum

- **Previously tested against** : Ebola, Marburg virus, SARS-CoV, and MERS-CoV.
- **Current relevance** : Demonstrated significant *in vitro* inhibition of **SARS-CoV-2** , the virus responsible for COVID-19.

Uses and Indications

- **Ebola virus disease** : Trialed but did not show adequate efficacy.
- **Marburg virus** : Investigated for therapeutic use.
- **COVID-19** : Authorized under Emergency Use Authorization (EUA) for hospitalized patients with **moderate to severe** disease. Multiple **Phase III clinical trials** are ongoing to determine its optimal use.

Administration

- **Route** : Intravenous (IV) infusion.
- **Dosing durations** :
    - 5-day regimen for most patients.
    - 10-day regimen considered for patients requiring invasive mechanical ventilation or

ECMO.

Pharmacokinetics

- **Metabolism** : Hepatic metabolism via **esterase hydrolysis** followed by conversion to GS-441524.
- **Enzymatic involvement** : Partially metabolized by **CYP2C8, CYP2D6, and CYP3A4** .
- **Excretion** : Primarily renal.

Adverse Effects

- **Common** :
  - Nausea
  - Vomiting
  - Transaminitis (elevation of liver transaminases)
- **Less common but significant** :
  - Respiratory failure
  - Hypokalemia
  - Hypoalbuminemia
  - Anemia
  - Thrombocytopenia
  - Jaundice

Viral Resistance

The **3?–5? exoribonuclease (ExoN)** enzyme in coronaviruses can **recognize and remove erroneous nucleotides** , potentially **reducing remdesivir's efficacy** . Mutations in the **ExoN gene** may **increase resistance** to the drug by enhancing proofreading or reducing incorporation of the analog.

Drug Interactions

- **CYP450 inducers** such as **rifampicin** , **carbamazepine** , **phenytoin** , and **phenobarbital** can **lower plasma concentrations** of remdesivir, possibly reducing its therapeutic effect.
- Use with caution when co-administered with these agents.

Molecular Background and Replication Cycle of SARS-CoV-2

- The **S (Spike) protein** of SARS-CoV-2 binds to **ACE2 receptors** on host cells.
- After entry, the virus releases RNA, forms an **RNA replicase-transcriptase complex** , and uses **host ribosomes** to translate viral proteins.
- The **RNA-dependent RNA polymerase (RdRp)** synthesizes new viral RNA strands, which combine with structural proteins to form new virions that are released by **exocytosis** .
- Remdesivir interrupts this cycle by interfering with the **RdRp** , inhibiting viral RNA synthesis.

Current Research and Status

- **Emergency Use Authorization** granted for treatment of hospitalized patients with COVID-19.
- Ongoing clinical trials aim to determine:
    - Optimal dosing duration
    - Efficacy across different severity levels
    - Long-term outcomes