Questions

Q1 Paxlovid

Which *one* of the following statements about Paxlovid for treatment of COVID-19 infection is *false?*

- ❍ 1. It can reduce rate of hospitalization.
- ❍ 2. It can reduce the rate of death.
- ❍ 3. It is contraindicated for use with drugs that are highly dependent on CYP3A for clearance.
- ❍ 4. It can be started after 5 days of symptom onset.

Educational Point: On December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) for the investigational antiviral drug nirmatrelvir copackaged with the HIV-1 protease inhibitor ritonavir (Paxlovid) for oral treatment of mild to moderate COVID-19 in outpatients ≥12 years old who weigh at least 40 kg and are at high risk of progressing to severe disease, including hospitalization or death. Paxlovid was the first oral antiviral drug to be authorized in the US and Canada for treatment of COVID-19.

Nirmatrelvir inhibits the SARS-CoV-2 main protease (Mpro), preventing viral replication. Ritonavir does not have any activity against SARS-CoV-2, but it increases serum concentrations of nirmatrelvir by inhibiting its metabolism by CYP3A.

Issuance of the EUA for nirmatrelvir/ritonavir was based on the results of a randomized, double-blind, placebo-controlled trial (EPIC-HR) in 2246 nonhospitalized, unvaccinated adults with laboratory-confirmed SARS-CoV-2 infection, symptom onset within 5 days of randomization, and at least one risk factor associated with progression to severe disease. Nirmatrelvir 300 mg/ritonavir 100 mg twice daily for 5 days decreased COVID-19 related hospitalization or death through day 28 by 88% compared to placebo (0.8% vs 6.3%). There were 12 deaths in the placebo group versus none in the nirmatrelvir/ritonavir group. Delta was the primary SARS-CoV-2 variant in both groups.

The most common adverse effects of nirmatrelvir/ritonavir in EPIC-HR were dysgeusia, diarrhea, hypertension, and myalgia.

Both nirmatrelvir and ritonavir are CYP3A substrates; drugs that induce or inhibit CYP3A will affect serum concentrations of both drugs. Concurrent use of *Paxlovid* and strong CYP3A inducers, such as rifampin, carbamazepine, phenobarbital, phenytoin, or St. John's wort, can decrease serum concentrations of nirmatrelvir and ritonavir and is contraindicated.

Ritonavir is a strong inhibitor of CYP3A and may increase serum concentrations of drugs metabolized by CYP3A. ***Paxlovid* is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated serum concentrations are associated with serious or life-threatening events (e.g., amiodarone, midazolam).** Recommendations for concomitant use of other CYP3A substrates are listed in the FDA Fact Sheet. Ritonavir decreases serum concentrations of ethinyl estradiol and may reduce the efficacy of combination hormonal contraceptives.

There are no data on the use of nirmatrelvir in pregnant women. Observational data from the antiretroviral pregnancy registry did not show an increase in birth defects following use of ritonavir during pregnancies resulting in more than 6900 live births.

Ritonavir is secreted into human breast milk. No data are available on the presence of nirmatrelvir in human breast milk or the effects of either drug on the breastfed infant or milk production.