Episode 221 : Update on COVID drugs

Dear colleagues,

The main focus of the next few episodes will be to get an update on antiviral (and other anti-COVID) drugs. Today, I will discuss the latest on Molnupiravir and Paxlovid.

Ep 221-11 is a reassuring paper from California, confirming the reduced severity of omicron.

Molnupiravir (and Favipiravir)

Mechanism of action : The active 5'-triphosphate serves as a competitive substrate for SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), and once incorporated into nascent viral RNA, **induces an antiviral effect via accumulation of mutations** that increase with each viral replication cycle.

Ep 221-1: W Fisher Sc Transl Med Dec 2021: Important phase 2a study in 200 outpatients non-vaccinated and within 96 H of diagnosis.
Patients were randomized 3:1 to molnupiravir (400 or 800 mg) or placebo, orally 2 X daily for 5 days:

1) Primary endpoint = time to **viral RNA clearance** in the 800 mg molnupiravir group (median 14 days) compared to the placebo group (median 15 days) (log rank pvalue= 0.013).
   - By study end (4 weeks): 92.5% of participants receiving 800 mg molnupiravir achieved viral RNA clearance compared with 80.3% of placebo recipients
2) Secondary endpoint = recovery of **infectious virus**
   - At day 3: 1.9% of the 800 mg molnupiravir group had infectious virus compared with 16.7% of placebo group.
   - At day, infectious virus was not isolated from any participants receiving 400 or 800 mg molnupiravir compared with 11.1% of placebo recipients.

So clear antiviral effect

Ep 221-2: Bernal NEJM Dec 2021: Phase 3 in 1400 outpatients unvaccinated adults with mild-to-moderate, within 5 days of laboratory-confirmed Covid-19 and at least one risk factor for severe Covid-19 illness: 800 mg Molnupiravir or placebo during 5 days.

1) **Risk of hospitalization** or death in patients after randominsation through day 29 was lower with molnupiravir [6.9 3%] than with placebo [9.7 %].
1) One **death** was reported in the molnupiravir group and 9 were reported in the placebo group through day 29.

Clinical benefit, but only 30% relative risk reduction of COVID-19 related hospitalization, with rather wide 95% confidence intervals (relative risk [RR] 0.69; 95% CI: 0.49–1.00)

Ep 221-3: FDA votes 13 versus 10 for emergency use authorization *for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death*

Remarks:

- *Most Committee members expressed **concerns over the mutagenicity** of molnupiravir on the viral genome, particularly in the spike gene.*
- *There were specific concerns over prolonged viral replication in **immunocompromised** individuals.*

- *Some Committee members stated they would not recommend molnupiravir in **pregnant** individuals (risk of mutagenicity).*
- *Unclear efficacy against the Delta and omicron variant,*

*Committee members agreed there is a **need for additional safety data**, as well as <u>further studies in the vaccinated and immunocompromised.</u>*

<u>Episode 221-4</u>: FDA letter to MSD on indications and limitations

<u>Indications:</u>
Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults:

- With positive results of direct SARS-CoV-2 viral testing, and
- Who are at high-risk for progression to severe COVID, including hospitalization or death, and
- For whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

<u>Limitations on Authorized Use</u>

- Not in patients who are less than 18 years of age.
- Not for initiation of treatment in patients requiring hospitalization due to COVID. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- Not for use for longer than 5 consecutive days.
- Not for use as pre-exposure or as post-exposure prophylaxis of COVID-19.

<u>Ep 221-5</u>: Phase 2 a trial on **Favipiravir** in asymptomatic or uncomplicated patients with COVID-19 Within 72 hours with 1800 mg BID Day 1, 800mg BID Days 2-10
N**o difference in time to viral shedding cessation or time to symptom resolution** by treatment arm.

<u>Paxlovid</u>

<u>Mechanism</u>: **Paxlovid** is a combination of:

- PF-07,321,332, also called **Nirmatrelvir**, an oral covalent 3CL protease inhibitor of SARS-CoV-2
- **Ritonavir**, an inhibitor of HIV-1 and HIV-2 protease. Ritonavir is here as an inhibitor of liver enzymes cytochrome P450 3A and CYP2D6, thus inhibiting the metabolism of PF-07,321,332 and allowing the administration of a lower dose of the substance.

<u>Ep 221-6</u>: DR Owen: preclinical data on PF-07,331,332

1) Is a pan-corona inhibitor

Virus	Cell line	EC_{50} nM (95% CI)	EC_{90} nM (95% CI)	n
SARS-CoV-1	Vero E6 + 2 µM CP-100356	151 , n=12 (108 to 212)	317, n=12 (225 to 446)	12
229E	MRC-5	190, n=3 (58.3 to 621)	620, n=3 (166 to 2320)	3
MERS	Vero 81 + 1 µM CP-100356	166, n=16 (145 to 191)	351, n=16 (301 to 409)	16

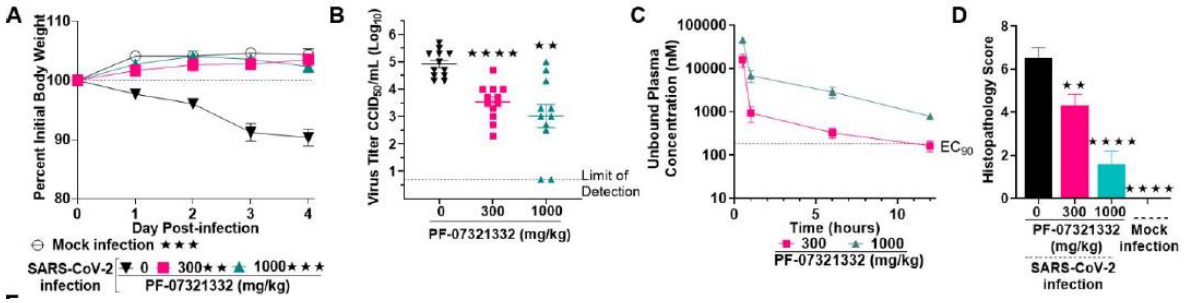
Table S4. PF-07321332 antiviral activity against SARS-CoV-1, 229E and MERS

2) Does not inhibit human proteases:

Protease	IC_{50} µM
Human Cathepsin B	>100
Bovine Chymotrypsin	>100
Human Thrombin	>100
Human Caspase 2	>100
Human Cathepsin D	>100
Human Cathepsin L	>100
Human Immunodeficiency Virus-1	>100
Human Elastase	>100

Table S3. Selectivity of PF-07321332 (6) against mammalian and HIV proteases

3) Active in a mouse model of SARS-CoV-2



4) Achieved oral plasma concentrations exceeding the in vitro antiviral cell potency and was safe, in a phase I clinical trial in healthy human participants.

Ep 221-7: Mahase comments in BMJ on phase 3 trial (not published):

1,219 high-risk patients who had recently been infected
Treated within 3 days

- 0.8% of Paxlovid were hospitalised, compared with 7% of placebo
- No deaths with Paxlovid vs 7 in placebo group

Treated within 5 days of symptoms appearing,

- 1% given Paxlovid vs 6.7 of pleco's in hospital
- No deaths with Paxlovid vs 10 in placebo.

Patients in the trial, which has not yet been published or verified, were elderly or had an underlying health condition which put them at higher risk of serious illness from Covid. They all had mild to moderate symptoms of coronavirus

Ep 221-8: FDA has authorized Paxlovid for use by adults and children over 12 years who have tested positive for SARS-CoV-2 and are at high risk of developing severe symptoms.

Pfizer is also continuing clinical trials for use

- on COVID-19 patients at standard risk of developing severe disease
- and, prophylactically, for people who had contact with infected individuals.

Ep 221-9: A warning by Joseph Heskin et al in Lancet that **Ritonavir**, the inhibitor of various drug metabolizing liver enzymes could enhance the activity (potentially lead to toxicity) by co-administered drugs such as statins, steroids, sedative hypnotics, anticoagulants, and antiarrhythmic therapies, many of which are prescribed in older populations at the greatest risk of complications from SARS-CoV-2 infection.

Ep 221-10: Ulrich in medRxiv 4 Jan shows that PF-07,321,332, also called **Nirmatrelvir,** maintains activity against 6 SARS-CoV-2 VOC, including omicron.

Note on omicron

Ep 221-11: During a period with mixed Delta and Omicron variant circulation in California, SARS-CoV-2 infections with presumed **Omicron** variant infection were associated with substantially **reduced risk of severe clinical endpoints and shorter durations of hospital stay**:

- Hospitalization risk = 0.48: 0.5 % of omicron versus 1.3 % of delta
- Hospital stay was 3.4 days shorter for omicron
- ICU admission = 0.26
- Death rate = 0.09