B Cell depleted patients and Paxlovid

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Disclosures

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**PAXLOVID (Nirmatrelvir + Ritonavir)?**

**Nirmatrelvir + Ritonavir**
- Nirmatrelvir is a SARS-CoV-2 protease inhibitor
- Ritonavir is a CYP3A inhibitor used as a pharmacokinetic enhancer (‘booster’) to increase nirmatrelvir plasma levels
  - Ritonavir alone has no activity against SARS-CoV-2
  - Ritonavir at higher doses was previously used as an HIV-1 protease inhibitor
  - It is now used only as a pharmacokinetic enhancer in HIV and HCV

*Firas El Chaer, Jeffery J. Auletta, Roy F. Chemaly, Blood, 2022*
Drug Interactions

• Nirmatrelvir is a CYP3A4/P-gp substrate that undergoes renal excretion
• Ritonavir is a potent **inhibitor** of CYP3A4, CYP2D6 and P-gp inhibitor and is also metabolized by CYP3A4.
• Ritonavir is an **inducer** of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and UGT

**Inhibition** interactions by ritonavir can occur in 24-48 hours: **SIGNIFICANT** FOR PAXLOVID 5 DAYS

**Induction** interactions by ritonavir take up to 14 days: **NOT SIGNIFICANT** FOR PAXLOVID 5 DAYS

Other drugs affecting Paxlovid:

• Induction interactions *caused by inducing co-medications* such as carbamazepine are contraindicated as will significantly reduce concentrations and efficacy of Paxlovid. Stopping the inducing drug will not avoid these interactions.
What is a Clinically Significant Interaction?

In drug development phase drug interaction (DDI) studies concentrate on PK (ie plasma concentration changes).

The clinical need is to assess the risk of harm from a DDI in patients who often have complex comorbidities (including renal or hepatic impairment)

- In liver disease (cirrhosis) maybe altered enzyme/transporter expression, liver blood flow, protein binding.

Period of tx exposure
- HIV: Lifelong
- HCV: 8-12 weeks
- Covid-19: 5 days for paxlovid

Risk–benefit assessment
- Can DDIs be avoided?
- Can a drug be stopped?
- Is additional monitoring required?
Taking a drug history

Check ALL medicines:
- OTC
- Recreational drugs
- Hospital supplied such as:
  • SACT
  • OST
  • HCV/HIV/HBV treatment
  • Contraception
  • Steroid Injections
  • Depot antipsychotics

Multimorbidity
Polypharmacy (Inc non-prescription drugs/supplements etc)
‘Polydoctory’

DDIs

Reduced efficacy of agent?
Reduced efficacy of co-medication?*
Adverse effect?
Age-related Pharmacokinetic & Pharmacodynamic change

Perpetrator
Victim
DDI Resources – Apps and desktop versions

Top most searched comedications with nirmatrelvir/ritonavir globally

Drug-drug interaction queries from February 1, 2022 to August 15, 2023

- Pantoprazole: 144,081
- Losartan: 149,034
- Omeprazole: 170,052
- Metoprolol: 170,364
- Aspirin (Anti-platelet): 185,535
- Levothyroxine: 188,485
- Rosuvastatin: 188,942
- Metformin: 228,429
- Amlodipine: 306,720
- Atorvastatin: 384,095

Total number of queries: 10,515,177

www.covid19-druginteractions.org  google analytics
Managing drug interactions

Drugs contraindicated in the license due to CYP3A4 inhibition by ritonavir
- Do not co-administer

BUT
- Can the drug be safely stopped? 5 days vs 10 days +
B Cell depleted patients

Anti-CD20 antibody (aCD20)-based B cell-depleting strategies such as rituximab are widely used in B cell hematologic malignancies and across a variety of autoimmune disorders:

- B cell depletion occurs within 72 hours
- Normal B cells obtained 9-12 months after treatment
- Poor response to covid vaccination
- aCD20-related impairment of adaptive immunity means time to viral clearance significantly prolonged compared.
- Case series indicate PCR positivity over >80 days in some B Cell treated patients
- Longer courses of Nirmatrelvir/r +/- additional agents may be required
Case study patient 1

- 47 female treated with Rituximab-Bendamustine for Stage IVb follicular lymphoma
- May: Dry cough and ground glass changes on staging CT.
  - Nose and throat swabs PCR positive for SARS-CoV-2
- Treated with 10 days of remdesivir and dexamethasone.
- Readmitted 2 months later with fever and persistent SoB
- Remained PCR positive
- Stabilised and retreated with remdesivir and nirmatrelvir/r for 14 days as outpatient
<table>
<thead>
<tr>
<th>Date</th>
<th>Nose &amp; throat swab</th>
<th>Plasma</th>
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- **Viable virus cultured**

- **RDV & DEX**
- **RDV & DEX**
- **RDV & DEX**
- **RDV & PAX**
- **RDV + PAX**
- **RDV + PAX**
Managing longer term interactions with Paxlovid

Drug interactions when using Paxlovid for >5 days

Please check www.covid19-druginteractions.org for updates.

Data are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.

Differences in the drug interaction potential of Paxlovid when used for 5 days or for an extended duration

**Background**
- An extended treatment duration of Paxlovid (nirmatrelvir/ritonavir) may be used in a clinical trial setting or in patients with persistent SARS-CoV-2 viral shedding and relapsing COVID-19 pneumonia (for example, in immunocompromised patients)
- When Paxlovid is used for 10 days or more, its interaction profile differs from that of a 5 day treatment duration.

- Induction of CYPs (CYP 1A2, CYP 2BC, CYP2C9, CYP2C19) and UGTs by ritonavir may result in a clinically significant interaction
- Pausing medications for longer durations may have more risk of harm
What medications are affected?

<table>
<thead>
<tr>
<th>Examples of comediations with potentially clinically relevant interactions</th>
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<tr>
<td>The list below gives examples of drugs which may have a potentially significant interaction due to enzyme induction by ritonavir when Paxlovid is given for an extended duration.</td>
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<td>Artesunate (UGT)</td>
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<td>Asenapine (UGT1A1/CYP1A2)</td>
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<td>Acenocoumarol (CYP2C9/1A2/2C19)</td>
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<td>Agomelatine (CYP1A2)</td>
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<td>Artemether (UGT)</td>
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<td>Cyclophosphamide (CYP2B6&gt;2C9, 3A4)</td>
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<td>Dabigatran (P-gp)</td>
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<td>Dacarbazine (CYP1A2)</td>
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<td>Dipyridamole (UGT1A1)</td>
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<td>Dronabinol (CYP2C9&gt;3A4)</td>
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<td>Eltrombopag (UGT1A1/CYP1A2)</td>
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<td>Epirubicin (UGT2B7)</td>
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<td>Febuxostat (CYP1A2/UGT)</td>
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<td>Frovatriptan (CYP1A2)</td>
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<td>Gliclazide (CYP2C19)</td>
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<td>Glimepiride (CYP2C9)</td>
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<td>Glipizide (CYP2C9)</td>
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<td>Hydromorphone (UGT2B7)</td>
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<tr>
<td>Isavuconazole (CYP3A4/UGT)</td>
</tr>
</tbody>
</table>
Co-medications

- Olanzapine 10ng nocte
- Simvastatin 40mg nocte
- Omeprazole 20mg od

Other statins?

STOP
- Lovastatin
- Atorvastatin
- Rosuvastatin

CONTINUE
- Fluvastatin
- Pitavastatin
- Pravastatin
Managing DDIs – considering individual risk–benefits

No interaction expected

Potential weak interaction: no action required

Potential interaction: Dose adjustment or additional monitoring may be required

contraindicated / should not be co-administered

This is the problem- but made easier with short course!
Managing DDIs – considering individual risk–benefits

No interaction expected

Potential weak interaction: no action required

Potential interaction: Dose adjustment or additional monitoring may be required

contraindicated / should not be co-administered

This is the problem- but made easier with short course!
Case study patient 2- 57 year old male

2013 Follicular lymphoma- remission
2021: high BP and started on amlodipine 10mg and fluticasone nasal spray for allergies

30/4/22: Tested positive for SARS-CoV2 (omicron).
- Developed type 1 respiratory failure: high flow nasal oxygen and dexamethasone and remdesivir.
- Recovered and discharged home, although a nasal PCR for SARS-COV-2 remained positive.
Case study patient 2- 57 year old male

10/8/22: readmitted and deteriorated again with type 1 respiratory failure and subsequently remained in hospital for 3 months requiring 3 admissions to the High Dependency Unit for respiratory support.

- Continued positive test by nasopharyngeal swab for SARS-CoV-2 with low CT values and was treated with remdesivir and dexamethasone.
- Discharged home in December 2022.

In light of profound immunosuppression and multi-centre MDT discussion:
- 3 months of intravenous immunoglobulin (30mg every 3 weeks, Nov 2022 - Jan 2023) and paxlovid
- Remains PCR negative
Amlodipine: 2-fold increase in amlodipine exposure predicted
Consider reduction of amlodipine dose by 50% → may be difficult to do in practice

Options:
- Advise patient to be aware of symptoms of hypotension and pause treatment if symptomatic
- Consider withholding amlodipine for 8 days

- Half Amlodipine dose
- Monitor BP

Consider similar management strategies for other calcium channel blockers
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Fluticasone</th>
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<tr>
<td>Nirmatrelvir/ritonavir (5 days)</td>
<td>![Green Diamond]</td>
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<tr>
<td>Nirmatrelvir/ritonavir (extended administration; 10 days or longer)</td>
<td>![Yellow Triangle]</td>
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**Potential Weak Interaction**

Nirmatrelvir/ritonavir (extended administration; 10 days or longer) & Fluticasone

**Quality of Evidence:** Very Low

**Summary:**
Coadministration has not been studied. Fluticasone is metabolized by CYP3A4 and coadministration may therefore lead to elevated corticosteroid levels, Cushing's syndrome and adrenal axis suppression. The European product label for Paxlovid (5 day administration) does not recommend coadministration due to the risk of Cushing's syndrome and adrenal axis suppression; however, the American product label states this risk is low with short-term use of a strong CYP3A4 inhibitor. A retrospective review of published case reports of individuals developing a Cushing's syndrome while treated concurrently with a boosted HIV protease inhibitor and inhaled corticosteroids indicated that this adverse effect tended to occur after several months (and more rarely 2 weeks) of concurrent administration of these drugs. Therefore, the risk of developing a Cushing's syndrome is expected to be low when nirmatrelvir/ritonavir is used for an extended treatment duration (10 days or longer). However, prescribers should be aware of and to look out for signs of systemic corticosteroid side effects.
Conclusions

• Immunosuppression is a heterogeneous group with distinct immunopathology and clinical response

• As vaccine response remains suboptimal, particularly in those b cell depleted, these patients remain to be complex and difficult to treat

• Longer courses of nirmatrelvir/ritonavir can be considered but drug interaction propensity needs considered and can differ from 5 day licensed courses
With Thanks to:

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