Renal Dosing of Antiviral Agents for COVID-19 (Case)

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  • Gilead, Merck, Pfizer, ViiV
Case

• 68 yo male, HIV+ 1986, virally suppressed since 2004.
• Comorbidities include hepatitis B, seizure disorder, depression, CKD (eGFR ~27). Resides in assisted living home.
• Medications:
  • Bictegravir/emtricitabine/TAF, levetiracetam 500 mg BID, atorvastatin 10 mg, olanzapine 25 mg, sertraline 25 mg, calcitriol 0.25 ucg, acetaminophen prn

• Oct/2023 → Diagnosed with COVID
Renal Impairment & COVID-19

- Patients with renal impairment at increased risk for severe outcomes with COVID-19
- COVID-19 can cause renal issues (AKI, tubulopathy, glomerulopathy)

- Need to know how to dose COVID agents in people with renal impairment
  - However, limited PK/safety data in this population
  - Exclusion from clinical trials, monograph restrictions
COVID Antivirals in Renal Impairment

- Remdesivir
- Molnupiravir
- Nirmatrelvir/ritonavir

- Focus on experience in patients with advanced renal impairment (eGFR<30)
Remdesivir Pharmacokinetics

- **Dosing:** 200 mg IV day 1, then 100 mg IV daily
  - Mild-moderate: 3 days total
  - Hospitalized: 5 days total, can be extended to 10

- Remdesivir is rapidly converted to nucleoside core (GS-441524), activated intracellularly to TP analogue GS-443902
- GS-441524 primarily undergoes renal clearance
Remdesivir in renal dysfunction

- Not recommended in eGFR<30 (manufacturer)

Davoudi-Monfared et al. American Journal of Therapeutics (2022) 29(5)
RDV in renal dysfunction: concerns

Mitochondrial toxicity

Potential nephrotoxicity

• Observed after prolonged exposure
• Increased kidney injury not observed in RDV trials (Wang et al. 2020)

Accumulation of SBECED vehicle

Potential risk of kidney or hepatic toxicity

• Toxicity in animal models @ doses 50- to 100-fold ↑ than clinical
• Accumulates in renal impairment but is not resorbed

Limited PK

3-fold to 6-fold ↑ in RDV parent & metabolite in hemodialysis (n=1)

• New data and clinical experience available
RDV in COVID-19 patients with renal impairment: systematic review

Eligible studies (n=22) including:
  Cohort (n=8)
  Observational (n=8)
  Case series (n=3)
  Case report (n=3)

- No increase in adverse effects (hepatic, renal, GI) attributable to remdesivir vs. patients with normal renal function were reported

- eGFR <30 (n=327)
- ESRD on RRT (n=238)
- AKI (n=177)
- Kidney transplant (n=117)
Remdesivir Use in the Real-World Setting: An Overview of Available Evidence

- Included 4 additional publications of patients with renal impairment vs. previous systematic review
  - Kidney transplant (n=165)  Elec et al. 2022
  - Advanced kidney disease eGFR<30 (n=444)  Stancampiano et al. 2022

- “All real-world studies showed that remdesivir was relatively safe and well-tolerated in patients with severe renal disease”
REDPINE: Safety of RDV in hospitalized patients with moderate/severe renal insufficiency

- PopPK modeling:
  - Up to 5-fold ↑ AUC metabolite

- No significant different in all-cause death or IMV by day 29
- No new safety signals identified with increasing concentrations of the GS-441524 metabolite or the excipient SBECED

Humeniuk et al. CROI 2023, #514. Santos et al. ECCMID 2023, #P2635.
Remdesivir in eGFR<30 mL/min

- No dose adjustment required
- No dose adjustment required
- Do not use. Discontinue immediately if eGFR<30
Remdesivir in eGFR<30 mL/min

Research Letter | Infectious Diseases
Remdesivir in Patients With Severe Kidney Dysfunction
A Secondary Analysis of the CATCO Randomized Trial

Matthew Cheng, MD, CM; Rob Fowler, MDCM, MS(Epi); Srinivas Murthy, MD, CM, MHSc; Ruxandra Pinto, PhD; Nancy L. Sheehan, PharmD, MSc; Alice Tseng, PharmD

Discussion
In patients with eGFR less than 30 mL/min/1.73 m² at baseline who received remdesivir, there was no increased risk of transaminitis or toxic kidney effects at day 5.
Molnupiravir Pharmacokinetics

- Prodrug of NHC, rapidly converted to NHC-TP
- Minimal renal excretion

- EUA label:
  - Population PK analysis: no impact of mild/moderate RI on PK of NHC
  - PK not evaluated in eGFR<30
  - Severe RI, ESRD, dialysis not expected to have significant impact on NHC pk

- No dose adjustment required in any degree of renal impairment

Molnupiravir Safety in Severe Renal Impairment

- Phase III study in outpatients (MOVe-OUT) excluded eGFR<30 or dialysis patients
- Real-world experience:

<table>
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<tr>
<th>Study</th>
<th>Stage of CKD</th>
<th>Adverse effects</th>
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| Dufour et al. (2023) | • N=3 maintenance hemodialysis  
• N=1 stage 4: transplant (eGFR 18)  
• N=1 stage 5 (eGFR 11) | • None reported  
• Renal function remained stable |
| Cho et al. (2023) | • N=11 stage 4 (eGFR 15-30)  
• N=1 stage 5 (eGFR <15)  
• N=1 stage 5D (eGFR<15 on RRT) | • GI upset (n=3), leading to early drug d/c in 2  
• 1 patient with schizoaffective disorder hospitalized on day 3 due to worsening insomnia & visual hallucinations |
Nirmatrelvir is a CYP3A4 substrate but metabolic clearance is minimal when boosted with ritonavir.

**eGFR mL/min**  | **Recommendation (monograph)**
--- | ---
60 to <90 (mild) | Standard dose
30 to <60 (moderate) | ↓ to 150/100 mg BID
<30 (severe) | Not recommended

NMV/r in dialysis or eGFR<30: data

**Standard dosing/adjusted**

- NMV 300/100 BID (Dong Rong 2023)
  - N=8 critically ill patients on CCRT; 5 received standard NMVr dose
  - >10x higher NMV vs historical

- NMV 150 or 300 mg QD with rtv 100 mg BID (Lu 2023)
  - n=18 on dialysis: 132-238% ↑ Cmin
  - More AEs with higher NMV dose

- NMV 150 mg/rtv 100 mg BID
  - Lingscheid (2022): PK in hemodialysis (n=4); 4-fold ↑ Cmax but no accumulation
  - Real world experience (Wales): n=12, similar side effect profile as in pts with higher eGFR

**50% dose reduction (=moderate RI)**

- NMV 300 /100 mg x 1, then 150 mg/rtv 100 mg daily
  - Hiremath (2023): n=134 on dialysis. 96% completed treatment; well tolerated, no SAEs
  - Chan (2023): n=65 (59 dialysis, 6 eGFR<30): well tolerated, AEs similar as eGFR>30

**75% dose reduction**

Dosing NMV/r in kidney transplant patients

- Transplant immunosuppressives:
  - Up to 10-fold ↑ in CNI concentrations

- NMV/r + tacrolimus: significantly associated with AKI (41.13%), serum creatinine ↑ (14.18%), renal impairment & renal failure (@2.84%)

Dosing NMV/r with tacrolimus: initial

- **Low:** Resume at 25-75% dose
  - TAC TDM q2-4 days

- **Therapeutic:** Resume at 25-75% of dose
  - TAC TDM q2-4 days

- **High:** HOLD
  - TAC TDM q2-4 days

Start NMV/r 12-24h after last TAC dose

TAC TDM Day 7
Yes We Can (Use Nirmatrelvir/Ritonavir Even in High Immunological Risk Patients Treated with Immunosuppressive Drugs)!

Proposed algorithm (based on simulation model):

• Day 1 (start of NMV/r): 1/8\textsuperscript{th} TAC dose
• Days 2-5: hold TAC
• End of Day 6: 50% TAC dose
• Day 7: 75% TAC dose
• Day 8: 100% TAC dose
Simplified TAC dosing with NMV/r

Day 0: Hold TAC

Days 1-5: NMV/r treatment

Day 7: TAC TDM

- Subtherapeutic (<4 ug/L): Resume at 75% of dose, then 100% dose
- Therapeutic (4-6 ug/L): Resume at 50% of dose, then 100% dose
- Supratherapeutic (>6 ug/L): Resume at 33% of dose, repeat TDM at 2-4 days

Day 10:

TDM 1 week later (if needed)

- Similar proportion of patients within therapeutic range by 2nd TDM with simplified protocol (n=20) vs standard OST protocol (n=24)
- Low incidence of TAC toxicity, no episodes of acute rejection

Case

- 68 yo male, HIV+, hepatitis B, seizure disorder, CKD (eGFR 27), in assisted living home
  - Medications: B/F/TAF, levetiracetam, atorvastatin, olanzapine, sertraline, calcitriol, acetaminophen

- Remdesivir: not logistically feasible
- Molnupiravir: not available in Canada
Case

- COVID: prescribed NMV/r at modified dose

Special Dosing Considerations:

eGFR <30 mL/min:
Day 1: Nirmatrelvir 300 mg and ritonavir 100 mg
Days 2-5: Nirmatrelvir 150 mg and ritonavir 100 mg once daily.

- DDIs:
  - Held: atorvastatin
  - Continued other comedications including ARVs
Emerging data support use of COVID antivirals in patients with severe renal impairment

- Remdesivir & molnupiravir:
  - Standard dose in renal impairment
  - Potential access/logistical barriers

- Nirmatrelvir/ritonavir:
  - Dose reduction in eGFR<30
  - Simplified algorithm for dosing with transplant immunosuppressives