Drug-Drug Interactions with Grazoprevir/Elbasvir: Practical Considerations for the Care of HIV/HCV Co-Infected Patients

Reported by Jules Levin
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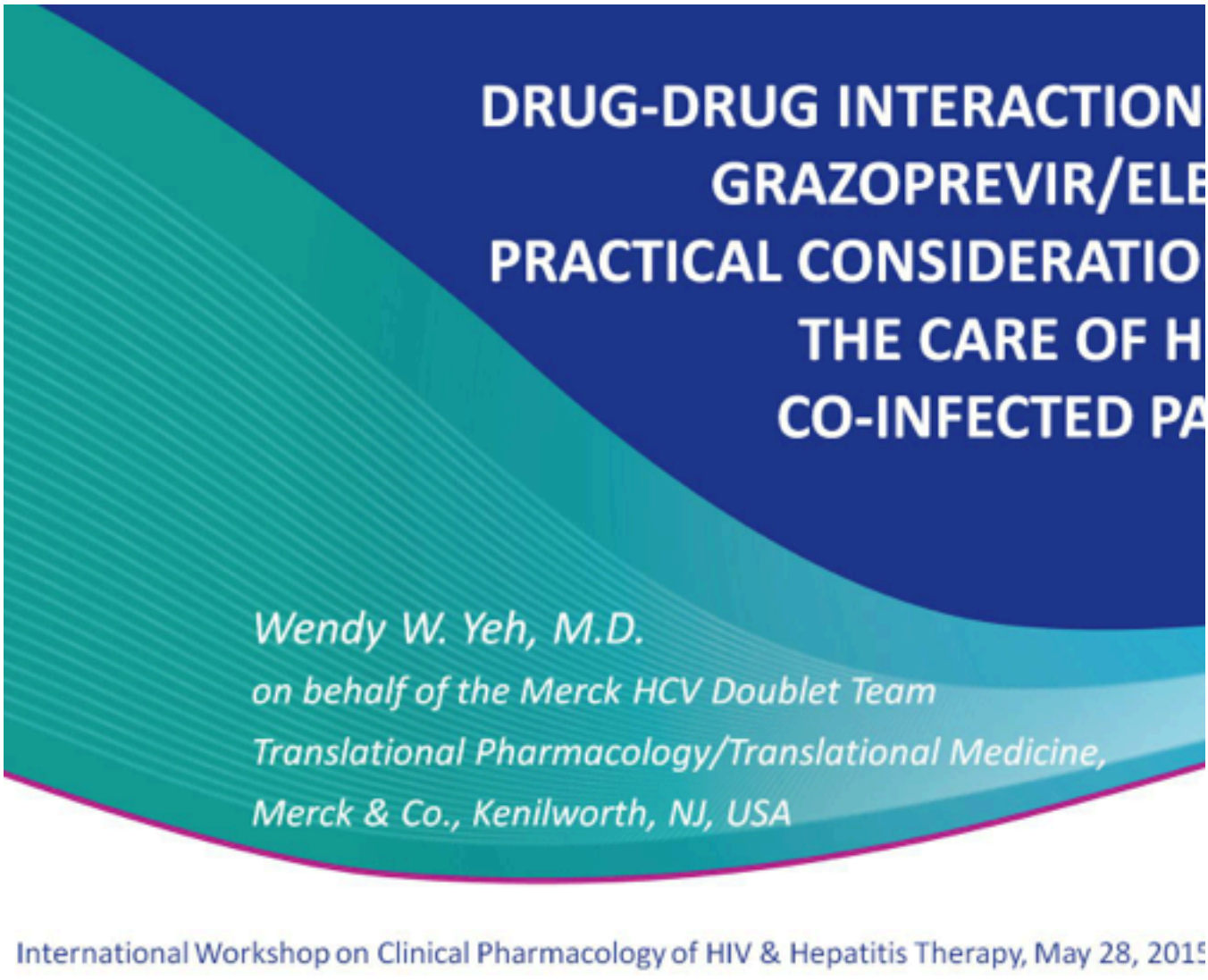
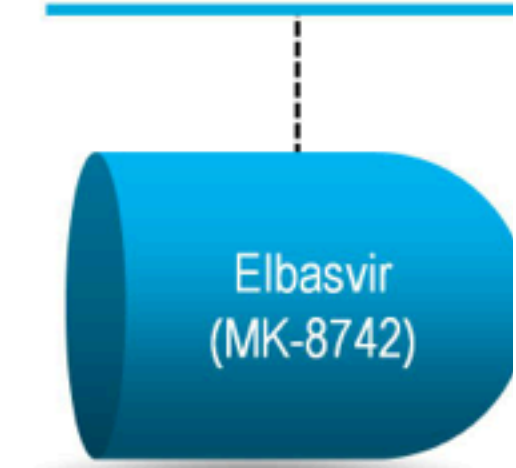


BACKGROUND

- HCV NS3/4A inhibitor
- 100 mg once daily, oral

- HCV NS5A inhibitor
- 50 mg once daily, oral



- Broad *in vitro* activity against most HCV genotypes [1-3]
- Retains *in vitro* activity against many clinically relevant resistance associated v
- All-oral, once-daily, one tablet, fixed-dose combination regimen

1. Summa V, et al. *Antimicrobial Agent Chemother* 2012:56;4161-67
2. Coburn CA, et al. *ChemMedChem* 2013; 8: 1930–40
3. Harper S, et al. *ACS Med Chem* Lett. 2012 Mar 2;3(4):332-6.

GRAZOPREVIR/ELBASVIR: RELEVANT METABOLISM AND TRANSPORTER PROPER

- **GRAZOPREVIR (GZR)**
  - **Metabolism**
    - CYP3A/P-gp substrate
    - Weak CYP3A inhibitor (34% ↑ in midazolam)
  - **Transporters**
    - Substrate of Organic Anion-Transporting Polypeptides
    - Inhibitor of intestinal Breast Cancer Resistance Protein (oral abstract #17)
- **ELBASVIR (EBR)**
  - **Metabolism**
    - CYP3A/P-gp substrate
  - **Transporters**
    - Inhibitor of intestinal BCRP (oral abstract #17)
    - Minimal P-gp inhibition

Petry et al., AASLD 2010; Talaty et al., AASLD 2013; Caro et al., AASLD 2013; Caro et al., AASLD 2013; Yeh et al., CROI 2014 ; Yeh et al., IWCPHHT 2014; Yeh et al., CROI 2015; Yeh et al., IWCPHHT 2015; Caro et al., IWCPHHT 2015

BACKGROUND

- HCV infection is a leading cause of morbidity and mortality among patients with HIV-1[1-3]
  - rapid progression of liver disease
  - increased risk of cirrhosis, end-stage liver disease, and
  - Treatment of HCV infection in the coinfected populatio represents an important unmet medical need
- Since medications to treat HIV/HCV concurrently may give to clinically significant drug-drug interactions, it is importa evaluate the potential for these interactions to inform coadministration of HIV ART with HCV DAA in co-infected patients

1. Monga HK, et al. *Clin Infect Dis* 2001;33(2):240-247. 2. Konerman MA, et al. *Hepatology* 2014;59(3):767-775
3. Pinchoff J, et al. *Clin Infect Dis* 2014;58(8):1047-1054. 4. Lo Re V, III, et al. *Ann Intern Med* 2014;160(6):369-379.
5. Rockstroh JK, et al. *J Hepatol* 2013;59(2):213-220.

GZR/EBR DDI RESULTS WITH COMMONLY USED HIV ART

HIV ARV	Effect on GZR AUC	Effect on EBR AUC	Effect on Interacting Drug AUC	Re
tenofovir disoproxil fumarate	↔ 0.9x	↔ 0.9x	↑1.2x with GZR ↑1.3x with EBR	
raltegravir	↔ 0.9x	↔ 1.0x	↑1.4x with GZR ↔1.0x with EBR	
dolutegravir	↔ 1.0x	↔ 1.0x	↑1.2x with GZR+EBR	
#63 rilpivirine	↔ 0.9x	↔ 1.1x	↔ 1.1x with GZR+EBR	
efavirenz	↓ 0.2x	↓ 0.5x	↔ 1.0x with GZR ↓0.8x with EBR	
darunavir/ritonavir	↑ 7.5x	↑ 1.7x	↔1.1x with GZR ↔1.0x with EBR	
atazanavir/ritonavir	↑ 10.6x	↑ 4.8x	↑1.4x with GZR ↔1.1x with EBR	
lopinavir/ritonavir	↑ 12.9x	↑ 3.7x	↔1.0x with GZR ↔1.0x with EBR	

Talaty et al., AASLD 2013; Caro et al., AASLD 2013; Yeh et al., CROI 2014 ; Yeh et al., CROI 2014; Yeh et al., CROI 2015; Yeh et al., IWCPHH

COMMONLY USED HIV ART THAT ARE EXPECTED TO HAVE NO DDI WITH GZR/EBR

- No DDI study with abacavir, lamivudine, emtricitabine, but r expected DDI= no dose adjustments
  - ABC, 3TC, FTC not expected to inhibit or induce any relevant metabolic enzymes or transporters of GZR and EBR
  - GZR and EBR are unlikely to alter the PK of ABC, 3TC, FTC sinc are renally cleared
- No DDI study with etravirine (moderate CYP3A inducer), bu etravirine is expected to decrease GZR and EBR exposures b on efavirenz DDI results= not recommended
- No DDI study with other HIV PIs, but unboosted atazanavir, saquinavir/r, tipranavir/r are expected to significantly increa exposures via OATP1B inhibition= not recommended

C-EDGE CO-INFECTED: PHA
STUDY OF GRAZOPRE
ELBASVIR IN PATIENTS V
HCV

Jürgen K. Rockstroh, Mark Nelson, Christine Katlama, Jay L
Josep Mallolas, Mark Bloch, Gail Matthews, Michael
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Stephanie Klopfer, Janice Wahl, Bach-Yen Nguyen, Eli
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MERCK

Presented at EASL 2015, *J Hepatol* 2015;62 (supp. 2): S675

C·E
CO-IN

STUDY DESIGN

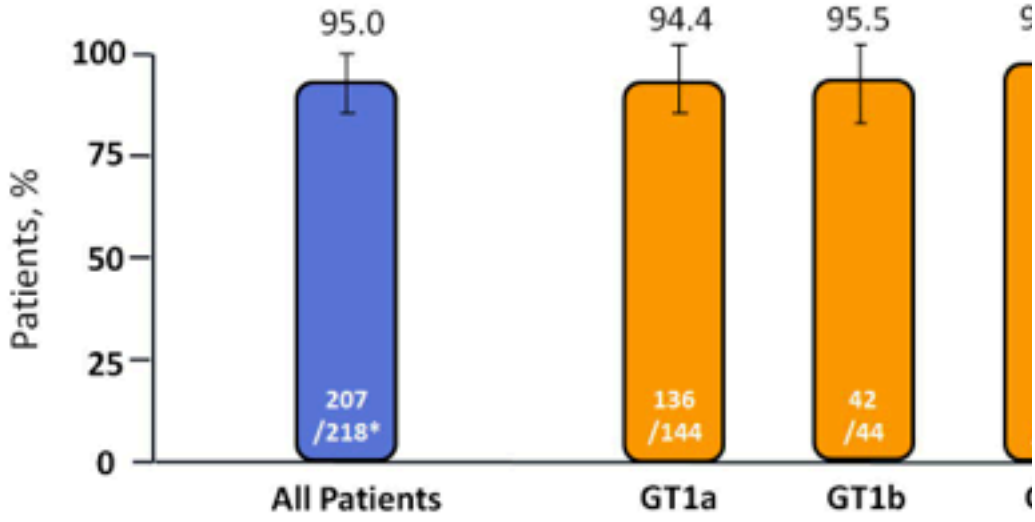
- An open-label, single-arm, multicenter study across Europe, US and Aust
- Primary endpoint: SVR12 (HCV RNA <15 IU/mL*)
- HCV treatment-naive patients with HCV GT1, 4 or 6 infection with or wit cirrhosis
- Co-infected with HIV-1:
  - Naive to ART with CD4+ >500 cells/mm^3 and HIV RNA <50,000 copies/mL
  - On stable on ART for ≥8 weeks and CD4+ >200 cells/mm^3 and undetectable
  - Stable antiretroviral therapy (ART) included TDF or abacavir, and either 3TC plus raltegravir, dolutegravir, or rilpivirine

*COBAS TaqMan v2.0 [LLoQ <15 IU/mL]

DEMOGRAPHICS: HIV DISEASE

	All Patients N = 218
Antiretroviral therapy, n (%)	
Receiving ART with undetectable HIV RNA	211 (96.8)
Naïve to ART	7 (3.2)
Baseline CD4 count (cells/µL)	
Mean (SD)	613 (0.57)
Median (1st quartile – 3rd quartile)	568 (424-766)
Antiretroviral therapy, n (%)	
Abacavir containing regimen	47 (21.6)
Tenofovir containing regimen	164 (75.2)
Raltegravir	113 (51.8)
Dolutegravir	59 (27.1)
Rilpivirine	38 (17.4)

SVR12 – FULL ANALYSIS SET



LTFU or discontinued unrelated to VF	4	3	1
Breakthrough	0	0	0
Relapse	6	4	1
Reinfection	1	1	0

*1 patient with GT6 infection and 1 patient with GT1 not-otherwise subtyped were also included; both patients achieved SVR12.

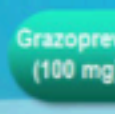
GT = genotype; LTFU = lost to follow-up

ADVERSE EVENTS

Patients with:	All Patients N = 218
Serious AE, n (%)	6* (2.8)
Serious drug-related AE, n (%)	0 (0)
Discontinuation due to AE, n (%)	0 (0)
Deaths, n (%)	0 (0)
Any adverse event†, n (%)	167 (76.6)
Fatigue	29 (13.3)
Headache	27 (12.4)
Nausea	20 (9.2)
Late ALT or AST >5.0 x ULN‡, n (%)	2 (0.9)
Lowest hemoglobin on treatment, n (%)	
≥8.5 to <10 g/dL	1 (0.5)
Elevation of total bilirubin¶, n (%)	
>2.5 – 5.0 × baseline	8 (3.7)
>5.0 × baseline	1 (0.5)
Creatinine >2.5 x baseline, n (%)	0 (0)

*2 SAEs were reported during the treatment period (convulsion and pneumonia) and 4 SAEs were reported during follov
acute psychosis and urinary retention; ulnar fracture; and spontaneous bacterial peritonitis)
†All AEs, regardless of relationship to study drug reported in >5% of patients.
‡ALT/AST >5× ULN after TW4 with an ALT/AST ≤ ULN between TW2 and TW4
¶ Bilirubin elevations were not associated with simultaneous ALT increases

SUMMARY OF GRAZOPREVIR AND ELBASVIR METABOLISM



- Other drugs may affect pharmacokinetics of grazoprevir (a substrate of CYP3A/P-gp and OATP1B) and elbasvir (CYP3A/ substrate)
  - CYP3A/P-gp inhibitors may be coadministered with GZR/
  - Coadministration with CYP3A/P-gp inducers with GZR/EB not recommended
  - Coadministration of OATP1B inhibitors with GZR is not recommended
- GZR and EBR are intestinal BCRP inhibitors*
  - Dosing recommendations for specific statins that are BC substrates when coadministered with GZR/EBR

*Caro et al., IWCPHHT 2015, oral abstract #17

SUMMARY OF GRAZOPREVIR AND ELBASVIR IN HIV/HCV CO-INFECTED PATIENTS

- High rates of SVR were achieved with excellent safety profile in patie
  HCV GT1, 4 and 6 and HIV co-infection receiving the all-oral FDC of G
- Current DDI guidance for treatment of HIV/HCV co-infection:
  - HIV NRTI (TDF, 3TC, FTC, ABC) may be coadministered with GZR/E
    without dose adjustment
  - HIV Integrase Inhibitors (raltegravir, dolutegravir) may be coadmi
    with GZR/EBR without dose adjustment
  - HIV NNRTI rilpivirine may be coadministered with GZR/EBR witho
    adjustment
  - Moderate/strong CYP3A/P-gp inducers (including efavirenz and
    etravirine) are not recommended for coadministration, since they
    decrease or is expected to decrease GZR and EBR concentrations
  - HIV protease inhibitors are not recommended for coadministratio
    they increase or are expected to increase GZR and EBR concentra