

Oral presentation 27

Effect of Efavirenz on bilirubin levels: Induction of UGT1A1 and bile efflux transporters

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Adding years of healthy life

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Background

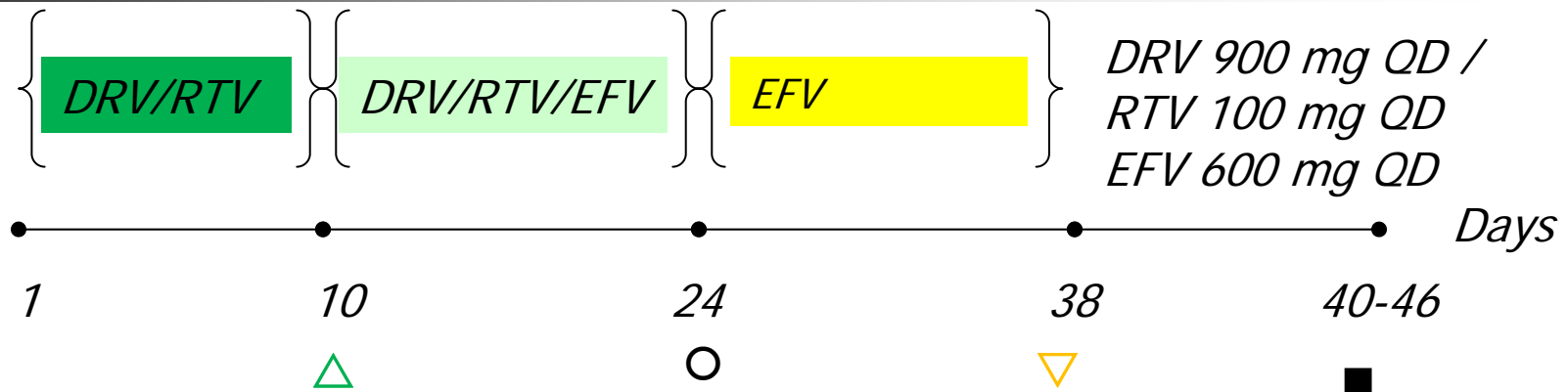
- Efavirenz is a general inducer of drug metabolic and transporter enzymes
- Ritonavir is a mixed inhibitor/inducer
- UDP-glucuronosyl transferase (UGT) isoform 1A1 is a phase 2 metabolic enzyme which metabolizes raltegravir
- Studies with raltegravir show that:
 - EFV reduces RAL AUC 36%, C_{min} 21% (ns)
 - RTV does not significantly reduce RAL



Background (2)

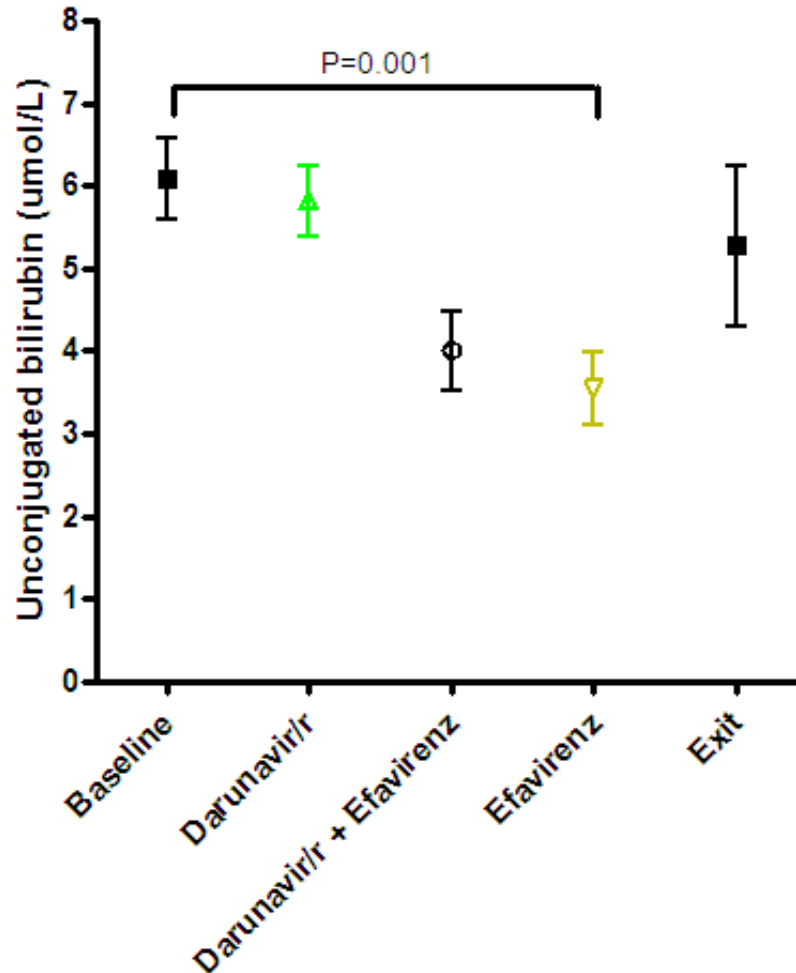
- Bilirubin is an endogenous substrate for UGT1A1 and bile efflux transporters
- UGT1A1 induction will reduce unconjugated bilirubin and increase conjugated bilirubin, while induction of bile efflux will reduce conj bilirubin
- This substudy aims to investigate the effect of efavirenz and darunavir /ritonavir on serum bilirubin levels

Methods and Subjects



- Single sequence 3-period interaction design between darunavir (DRV) / ritonavir (RTV) with efavirenz (EFV)
- 12 healthy volunteers - 7 males; 6 Chinese, 4 Malay, 2 Indians; ages 24 to 49 years old; weight 50 to 83 kg
- One Malay female subject developed grade 3 hepatitis lasting 150 days while on EFV – her data was excluded
- Fasting total / conjugated bilirubin measured at 5 points

Unconjugated bilirubin

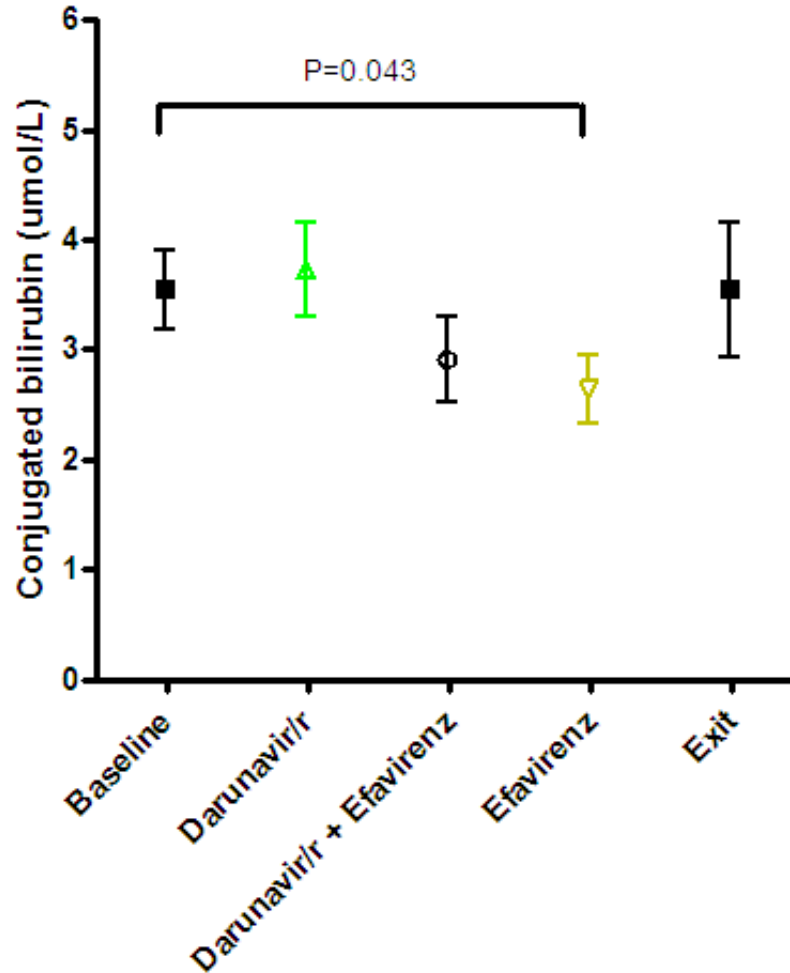




Unconjugated bilirubin

	Mean	SD	Difference vs baseline	90% CI of difference	P value
Baseline	6.09	1.64	Ref		
DRV/RTV	5.82	1.40	-0.27	-1.12 to 0.58	0.574
DRV/RTV with EFV	4.00	1.61	-2.09	-2.66 to -1.52	<0.001
EFV	3.55	1.44	-2.55	-3.53 to -1.56	0.001
Exit	5.27	3.23	-0.82	-2.26 to 0.62	0.328

Conjugated bilirubin





Conjugated bilirubin

	Mean	SD	Difference vs baseline	90% CI of difference	P value
Baseline	3.55	1.21	Ref		
DRV/RTV	3.73	1.42	0.18	-0.50 to 0.87	0.640
DRV/RTV with EFV	2.91	1.30	-0.64	-1.08 to -0.19	0.026
EFV	2.64	1.03	-0.91	-1.62 to -0.20	0.043
Exit	3.55	2.02	0.00	-0.88 to 0.88	1.000



Discussion

- Efavirenz reduced unconjugated bilirubin by 2.55 $\mu\text{mol/L}$ or 0.15 mg/dL (45%), suggesting induction of UGT1A1
- Efavirenz also unexpectedly reduced conjugated bilirubin by 0.91 $\mu\text{mol/L}$ (26%), suggesting concomitant induction of bile efflux pumps
- There was no significant effect of darunavir/ritonavir on bilirubin



Conclusions

- The general inducer efavirenz not only induces UGT1A1 but also bile efflux transporters eg BSEP(ABCB11), MRP2/3
- Efavirenz may reduce concentrations of substrates of these transporters
- An increasing number of drugs are being discovered to be cleared by these transporters eg statins, methotrexate, talinolol



Clinical Implications

- Monitoring treatment efficacy of co-administered drugs is essential when starting patients on EFV or other general inducers eg rifampin
- Look out for unexpected interactions involving non-cytochrome substrates
- More drug-drug interactions studies should be performed for suspected substrates of bile efflux transporters



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