

Long Term Safety in HCV/HBV Co-infected HIV ART Naïve Adults Treated with Fosamprenavir/ Ritonavir

Edwin DeJesus¹, Andrzej Gladysz², Jose Vera³, Federico Pulido⁴, Giampiero Carosi⁵, Cindy Garris⁶, Naomi Givens⁷, Jane Yeo⁷, Mark Felton⁷

¹Orlando Immunology Center, Orlando, Florida, USA; ²Wroclaw University School of Medicine, Wroclaw, Poland; ³Centro Hospitalar de Cascais, Cascais, Portugal; ⁴Hospital Universitario Doce de Octubre, Madrid, Spain; ⁵Clinica di Malattie Infettive e Tropicali, Brescia, Italy; GlaxoSmithKline R&D, ⁶RTP, USA; ⁷Greenford, UK

Introduction

The interactions between hepatitis viruses and HIV are complex and clinically important. Co-infection with HIV has been associated with accelerated HCV-related liver damage and progression to end stage liver disease. Similarly, HBV DNA levels are higher in HIV-infected patients and HIV increases the risk of HBV-associated morbidity and mortality. Although antiretroviral therapy (ART) is beneficial for HBV and/or HCV co-infected subjects, active hepatitis increases their risk for ART-associated hepatotoxicity. Consequently, there is a need to understand how individual ARTs perform in co-infected patients.

Fosamprenavir (FPV) is a protease inhibitor approved in the US (Lexiva[®]), Europe (Telzir[®]), and other countries. FPV has been studied in clinical trials as once daily (QD) dosing boosted with ritonavir (RTV), or twice daily (BID) dosing with or without RTV. The efficacy and tolerability of FPV have been previously demonstrated in ART-naïve subjects (1,2). The objective of the analyses described here was to assess liver enzyme changes over 120 weeks of treatment with ritonavir boosted FPV (FPV/r) QD in HIV-1 infected ART naïve adults with HBV and/or HCV co-infection.

Methods

- 322 HIV-1 infected therapy-naïve adults received FPV/r 1400mg/200mg QD and ABC+3TC BID in study APV30002 (The SOLO Study). Of those, 211 subjects completed ≥ 48 weeks and continued the regimen in rollover study APV30005.
- Subjects with co-infection were allowed to enroll in SOLO if their HBV/ HCV infection was not clinically relevant within the last 6 months. Additionally, all patients must have had ALT and AST levels below Grade 3 ($< 5 \times$ ULN) within 28 days prior to FPV/r administration.
- To assess liver enzyme changes in subjects with or without HBV (HBS Ag positive) and/or HCV co-infection (anti-HCV positive), a review of ALT/ AST laboratory values and AEs from Baseline to Week 120 in SOLO/APV30005 was conducted.
- Toxicity grading for males [females] in U/L:
 - ALT: Normal range: 6-43 [6-34]; Grade 1: 54-108 [43-85]; Grade 2: 109-215 [86-170]; Grade 3: 216-430 [171-340]; Grade 4: > 430 [> 340]
 - AST: Normal range: 11-36 [9-34]; Grade 1: 45-90 [43-85]; Grade 2: 91-180 [86-170]; Grade 3: 181-360 [171-340]; Grade 4: > 360 [> 340]

Results

Table 1. Baseline Hepatitis Status

	SOLO FPV/r QD N=322 n (%)	APV30005 FPV/r QD N=211 n (%)
No Hepatitis	240 (75)	164 (78)
HBV and/or HCV positive	80 (25)	45 (21)
HBV positive	26 (8)	20 (9)
HCV positive	57 (18)	26 (12)
HBV and HCV positive	3 (<1)	1 (<1)
Unknown status	2 (<1)	2 (<1)

Table 2. Median [IQR] Baseline ALT and AST Values

	SOLO N=322 Baseline		APV30005 N=211 Baseline	
	No HBV and/or HCV N=240	HBV and/or HCV N=80	No HBV and/or HCV N=161	HBV and/or HCV N=43
ALT (u/L)	26 [19, 41]	41 [26, 73]	26 [19, 37]	41 [25, 60]
AST (u/L)	30 [24, 41]	42 [32, 60]	30 [24, 38]	40 [31, 57]

- As expected, median Baseline ALT and AST levels were higher in co-infected subjects than in those without co-infection (*Table 2*). Of the co-infected subjects, 18/43 (42%) and 12/43 (28%), respectively, had a Grade 1/2 ALT or AST toxicity at baseline. Of the non co-infected subjects, 32/161 (20%) and 25/161 (16%), respectively, had a Grade 1/2 ALT or AST toxicity at Baseline. Additionally, one non co-infected subject had a Grade 3 AST at Baseline.

Table 3. Median Change from Baseline [IQR] in ALT and AST (U/L)

	SOLO N=322 Week 48		APV30005 N=211			
			Week 48		Week 120	
	No HBV and/or HCV n=150	HBV and/or HCV n=43 ALT N=40 AST	No HBV and/or HCV n=161	HBV and/or HCV n=43 ALT n=42 AST	No HBV and/or HCV n=134	HBV and/or HCV n=35
ALT (u/L)	-9 [-22, -1]	-3 [-14, 21]	-8 [-17, -1]	-4 [-12, 18]	-8 [-19, 0]	-5 [-23, 0]
AST (u/L)	-8 [-17, -1]	-6 [-15, 7]	-7 [-17, 2]	-7 [-18, 0]	-8 [-17, -2]	-9 [-23, -2]
Note: The number of subjects differs between time points because subjects must have values at both Baseline and Week 48, or both Baseline and Week 120, to be included in the table.						

- Subjects in both the co-infected and non co-infected groups who completed at least 120 weeks had a median decrease in ALT and AST (Table 3).
- Median change from baseline [IQR] results at Week 120 were similar using a Last Observation Carried Forward (LOCF) analysis:
 - ALT: -7 [-19, 0] U/L for non co-infected (n=164); -4 [-20, 5] U/L for co-infected (n=45).
 - AST: -8 [-17, -3] U/L for non co-infected (n=164); -9 [-23, -2] U/L for co-infected (n=45).

Table 4. Treatment Emergent Grade 3/4 ALT/AST

	SOLO N=322 Week 48		APV30005 N=211			
			Week 48		Week 120	
	No HBV and/or HCV N=235	HBV and/or HCV N=78	No HBV and/or HCV N=164	HBV and/or HCV N=45	No HBV and/or HCV N=164	HBV and/or HCV N=45
ALT	6 (3%)	19 (24%)	2 (1%)	10 (22%)	5 (3%) [3 new cases]	13 (29%) [3 new cases]
AST	7 (3%)	12 (15%)	2 (1%)	6 (13%)	4 (2%) [2 new cases]	6 (13%) (0 new cases)

- The number of co-infected subjects with Grade 3/4 ALT or AST elevations did not markedly increase after Week 48 (*Table 4*):
 - Three co-infected subjects experienced a new treatment-emergent Grade 3/4 ALT elevation after Week 48.
 - No co-infected subjects experienced a new treatment-emergent Grade 3/4 AST elevation after Week 48.

Table 5. Adverse Events

	SOLO N=322 Week 48		APV30005 N=211 Week 120	
	No HBC and/or HCV N=240 n (%)	HBV and/or HCV N=80 n (%)	No HBV and/or HCV N=164 n (%)	HBV and/or HCV N=45 n (%)
Drug-related Grade 2-4 AE	98 (41%)	34 (43%)	71 (43%)	20 (44%)
Drug-related Serious AE	24 (10%)	8 (10%)	16 (10%)	5 (11%)

- Over 48 and 120 weeks, similar proportions of co-infected subjects and non co-infected subjects reported a drug related Grade 2-4 AE or drug related Serious AE (*Table 5*).
- The most common drug-related Grade 2-4 AEs in APV30005, excluding hypersensitivity to abacavir, were diarrhea (18/164, 11%), increased triglycerides (13/164, 8%), and nausea (10/164, 6%) in non co-infected subjects and nausea (6/45 13%), increased ALT (4/45, 9%), diarrhea (4/45, 9%), and vomiting (4/45, 9%) in co-infected subjects.
- One subject who was HBV and HCV negative at baseline prematurely discontinued FPV/RTV QD (approx. Week 68) due to a Grade 3 ALT which was considered by the investigator to be related to study drug.

Discussion

The prevalence of HBV and/or HCV co-infection with HIV is significant, estimated to be several million people worldwide (3). Treatment with effective HAART has been associated with slower progression to fibrosis for hepatitis co-infected patients (4). Therefore, long term safety data, especially with regard to hepatic toxicity of PI-containing HAART in HIV and HBV/HCV co-infected patients, is particularly pertinent.

An earlier analysis through Week 48 of the randomised phase of SOLO (5) had demonstrated that both FPV and NFV containing HAART had a favourable effect with a modest reduction in median ALT and AST levels in both HBV/HCV co-infected and non co-infected patients. By Week 48 approximately 20-25% of co-infected subjects in both the FPV and NFV arms experienced grade 3/4 elevations in ALT and AST (mostly ALT). It was suggested that some of these elevations might be due to the natural history of hepatitis infection or to immune reconstitution leading to HBV immune mediated response with ALT flares.

The present analysis through 120 weeks shows that the favourable median change from baseline in ALT and AST observed at Week 48 was maintained. New Grade 3/4 ALT and AST elevations after Week 48 were relatively rare, being observed in less than 7% (3/45) of co-infected subjects compared to 3% (5/164) in non co-infected subjects. There were no differences in the incidence of reported drug-related Grade 2-4 AEs or SAEs between the co-infected and non co-infected subjects through Week 120.

This long-term analysis shows that FPV/r is well tolerated in patients with hepatitis B/C co-infection with a similar median reduction in AST/ALT and a similar rate of drug-related Grade 2-4 AEs and SAEs compared to non co-infected subjects. Not surprisingly, Grade 3/4 increases in AST/ALT were more common in co-infected subjects but the majority of these occurred within the first 48 weeks with relatively few occurring between Week 48 and Week 120.

Conclusion

- **Subjects in both the co-infected and non co-infected groups who completed at least 120 weeks had a median decrease in ALT and AST.**
- **Few co-infected subjects experienced new treatment-emergent Grade 3/4 ALT or AST toxicities between Week 48 and Week 120.**
- **Incidence of AEs was comparable between co-infected subjects and those without co-infection.**
- **In co-infected subjects, minimal additional liver toxicity was observed with longer term FPV/r QD therapy.**

References

1. Rodriguez-French A, Boghossian J, Gray GE, Nadler NP, Quinones AR, Sepulveda GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr*. 2004; 35:22-32.
2. Gathe JC Jr, Ive P, Wood R, Schurmann D, Bellow NC, DeJesus E, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naïve HIV-1-infected patients. *AIDS*. 2004; 18:1529-1537.
3. Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palu G, et al. Short Statement of the First European Consensus Conference on the Treatment of Chronic Hepatitis B and C in Co-infected Patients. *J Hepatology*. 2005; 42: 615-624.
4. Pineda JA, Macias J. Progression of liver fibrosis in patients co-infected with hepatitis C virus and human immunodeficiency virus undergoing antiretroviral therapy. *J Antimicrob Chemother*, 2005; 55: 417-419.
5. Clumeck N, Fatkenheuer, Halota, Vera, Flamm, Stark, Sexton. ALT and AST Changes Over 48 Weeks in HIV-Infected Therapy-Naïve Adults with Hepatitis B (HBV) and/or C (HCV) Coinfection Treated with 908/r QD. 9th European AIDS Conference (EACS), October 25-29, 2003, Warsaw, Poland. Poster 9.6/5.

Acknowledgements

We would like to thank the patients who volunteered to participate in this study and the investigators and coordinators for their support in conducting the study.