P1101: PHASEI/II STUDY OF RALTEGRAVIR CONTAINING REGIMEN IN HIV/TB CO-TREATED CHILDREN AGED 6 to <12 YEARS

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Abstract (as submitted)

Background: Current antiretroviral (ARV) treatment options for HIV-infected children with TB disease are limited. Rifampicin (RIF) induces UDP-glucuronosyltransferase activity, accelerating the clearance of raltegravir (RAL). In adults, doubling the RAL dose partially overcame this pharmacokinetic (PK) interaction without safety concerns. We sought to establish the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

Methods: P1101 is a dose finding study of RAL in HIV-infected children from 4 sites in South Africa receiving RIF-containing TB therapy for at least one week, with three age cohorts: Cohort 1: 2 to <6 years (closed), Cohort 2: 6 to <12 years of age (closed) and Cohort 3: 4 weeks to <2 years, aiming to enroll 12 evaluable participants for PK and safety in each cohort. At enrollment participants start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose) and 2 nucleoside reverse transcriptase inhibitors. Intensive RAL PK sampling is conducted 5-8 days after ARV therapy is initiated, and then a 4th ARV is added. Clinical and laboratory assessments are routinely completed. RAL is stopped at TB treatment completion and participants are followed for another 3 months. PK targets are a geometric mean (GM) AUC12h of 14-45 μMxh and GM C12h ≥75 nM. Here we report the results from Cohort 2.

Results: Among 14 participants who received RAL, 7 (50%) were male, median age 8 years (IQR: 7-9), median baseline log_{10} RNA copies/mL 4.55 (IQR: 4.21-5.09), median CD4 count/μL 575 (IQR: 142-704), median CD4 percent 21% (IQR: 7-25). PK for all 14 children at Week 1 showed GM AUC_{12h} (%CV) of 38.8 μMxh (38%); the GM C12h was 227.6 nM (78%). 1/14 (7%; 95% exact confidence interval (CI) [0%, 34%] developed a Grade 4 AST and ALT, and Grade 3 Total Bilirubin, deemed possibly treatment-related, although consistent with an IRIS event and possibly due to concomitant medication; RAL was permanently discontinued. No other significant adverse events related to RAL were reported. 12/14 had evaluable efficacy data at week 8 (2/14 discontinued RAL prior to the week 8 visit, but after PK collection).

11/12 (92%; 95% CI [62%, 100%]) were virologically suppressed by Week 8. 1/12 had virologic failure with documented non-adherence, requiring discontinuation of RAL at 15 weeks. At Week 8, median changes from baseline were: log_{10}RNA copies/mL -2.78 (IQR: -3.41 to -2.09), CD4 count 162.5 cells/μL (IQR: 29-351.5], and CD4 percent 5% (IQR: 0.7-7.65). RAL was permanently discontinued in 4/14 participants because: 2/14 had AUC_{12h} >63 μMxh, meeting the PK end point despite being asymptomatic, 1 was non-adherent and 1 developed liver toxicity as mentioned above.

Conclusions: A 12mg/kg dose twice daily of the oral chewable formulation of RAL appears to achieve PK targets safely in HIV-infected children 6 to <12 years with TB disease who are also receiving rifampicin.

Background

- The burden of tuberculosis (TB) among HIV-infected adults and children is high in many resource-limited settings (RLS).
- Antiviral options for children co-infected with TB are limited because of drug interactions, especially with rifampicin-containing (RIF) TB regimens.
- Pediatric clinical trials for new drugs usually exclude TB co-infected children making it difficult to determine drug efficacy and safety in these co-infected children.
- RIF induces UDP-glucuronosyltransferase activity accelerating the clearance of raltegravir (RAL).
- In adults, doubling the RAL dose partially overcame this PK interaction with no safety concerns.[1]
- We obtained similar data in children 2 to 6 years of age in Cohort 1 of P1101[2], which seeks to determine the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

Methods

- IMPAACT P1101 is a Phase I/II dose finding study for RAL for HIV-infected children receiving RIF-containing TB therapy for at least one week.
- The 3 age cohorts include: Cohort 1: 2 to <6 years (closed), Cohort 2: 6 to <12 years of age (closed) and Cohort 3: 4 weeks to <2 years (enrolling). Results from Cohort 2 are presented here.
- Each cohort requires n=12 evaluable participants for pharmacokinetics and safety assessments.
- At enrollment, participants start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose).
- Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV (standard of care with TB treatment) is added, usually efavirenz (EFV) or lopinavir/ritonavir (LPV/r)
- Clinical and laboratory assessments are routinely completed.
- RAL is stopped at TB treatment completion and participants are followed for an additional 3 months.
- PK targets are geometric mean (GM) AUC_{12h} of 6-20 mgxh/L (14-45 μMxh) and GM C_{12h} ≥33 ng/mL (≥75 nM). (CV = Standard deviation/mean) are calculated.
- Virologic Success is defined as achieving at least 1- log_{10} copies/mL drop from baseline, or HIV RNA ≤ 400 copies/mL at Week 8

Objectives

- To determine the pharmacokinetics and appropriate dose of RAL when administered with RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.
- To determine safety and tolerance of RAL-containing ART when administered with RIF-containing anti-TB therapy in HIV/TB co-infected infants and children.

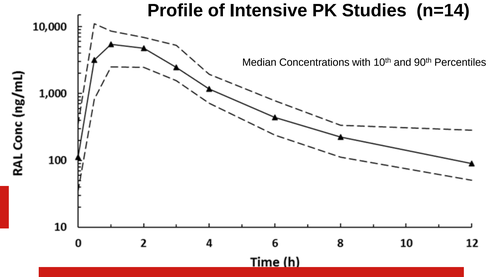
Baseline Characteristics of Cohort 2

	Median	25th Percentile	75th Percentile
AGE (years)	8	7	9
CD4 (%)	21	7	25
CD4 (cells/μL)	575	142	704
HIV RNA (log_{10}copies/ml)	4.55	4.21	5.09

- N=14
- Male: 7 (50%)
- Race: Black=14 (100%)
- Study Follow-up: 28 weeks (IQR: 17,36)
- All 14 participants began efavirenz after completion of intensive pharmacokinetic study for RAL

Intensive Pharmacokinetic Study Results

Profile of Intensive PK Studies (n=14)



PK Targets
- GM AUC_{12h} 6-20 mgxh/L (14-45 μMxh)
- GM C_{12h} ≥ 33 ng/mL (≥ 75 nM)

PK Results
- GM AUC_{12h} was 17.2 mgxh/L (38.8 μMxh; CV=38%)
- GM C_{12h} was 101 ng/mL (228 nM; CV=78%)

CD4 Results

Week 8: Change from Baseline in Median CD4% and CD4

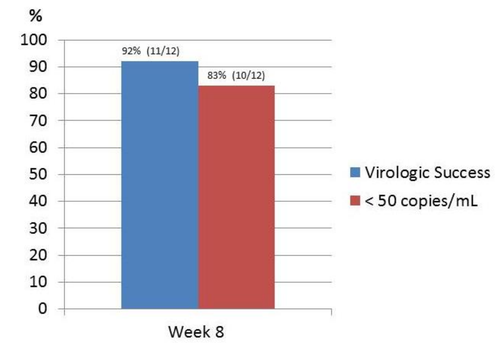
	Median	Q1, Q3
CD4 Count (μL^{-1})	162.5	29, 351.5
CD4%	5	0.7, 7.65

Safety Results

One 1 of 14 had an adverse event (AE) deemed possibly related to RAL by study team:
- Grade 4 AST/ALT , Grade 3 bilirubin elevations and Grade 2 rash.
- Child was receiving ARVs (abacavir, 3TC, efavirenz, and RAL), anti-tuberculous therapy, and cotrimoxazole.
- RAL stopped permanently; IRIS or reaction to concomitant medication deemed to be possible alternative explanations.

HIV-1 RNA Results

Virologic Responses (As Treated Analysis)



Note: Week 8 Log_{10}HIV-RNA Change from Baseline: Median: -2.78, IQR (-3.41,-2.09).

All 11 participants with virologic success achieved both HIV RNA reduction of >1 log10 and absolute level of <400 copies/mL."

1/12 had virologic failure with documented non-adherence, requiring discontinuation of RAL at 15 weeks.

Conclusions

- Doubling the dose of RAL for TB-HIV co-infected children 6 to ≤12 years of age while taking rifampicin achieved adequate PK levels.
- A dose of 12 mg/kg of RAL appears to safely achieve viral suppression as part of combination antiretroviral treatment for TB-HIV co-infected children taking rifampicin in this age group.
- Expanding options for treating co-infected children is possible.
- Further data from Cohort 3 (≥4 weeks to < 2 years) are required before considering the doubled dose for all TB-HIV co-infected infants and children who are treated with rifampicin.

The study team would like to thank the P1101 participants and families for their participation.

References

[1]Wenning LA, Hanley WD, Brainard DM, Petry AS, Ghosh K, Jin B, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrobial agents and chemotherapy. 2009;53(7):2852-6.

[2]Meyers T, Krogstad P, Samson P, Acosta E, Moye J, Townley E, Bradford S, Marillo L, Hovind L, Sise T, Teppler H, Dittmer S, Fairlie L, Hesseling A, and Cottom M for the IMPAACT P1101 Team. P1101: Phase I/II study of r raltegravir containing regimen in HIV-TB cotreated children. Abstract #845. 25th Conference on Retroviruses and Opportunistic Infections. Boston MA , March, 2018.

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