Poster 1081

Daclatasvir Pharmacokinetics in Healthy Subjects: No Clinically Relevant Drug–Drug Interaction With Either Cyclosporine or Tacrolimus

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1. BACKGROUND

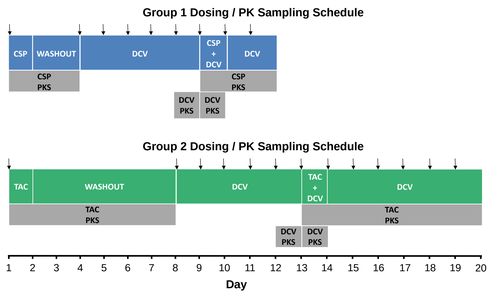
- Decompensated liver disease resulting from hepatitis C virus (HCV) infection is a leading indication for liver transplantation (LT)[1]
- Following LT, life-long therapy with immunosuppressants such as the calcineurin inhibitors cyclosporine (CSP) and tacrolimus (TAC) is required
  - CSP and TAC are substrates of both CYP3A4 and P-glycoprotein (P-gp)[2]
  - CSP is an inhibitor of both CYP3A4 and P-gp[3]
  - Both CSP and TAC have narrow therapeutic windows[2]
- HCV recurrence post-LT is common and characterized by:
  - High levels of HCV replication, and accelerated necroinflammation and fibrosis[4,5]
  - Significantly lower survival rates relative to non-HCV-infected LT recipients[4,5]
  - Limited treatment options
- Initiation and maintenance of therapy with peginterferon/ribavirin in LT recipients with recurrent HCV is complicated by:
  - Clinical characteristics that preclude full-dose therapy[6]
  - Dose reductions (30–70% of patients) and premature discontinuations (20–40% of patients) due to adverse events (AEs)[6]
  - Low rates of sustained viral response (SVR; ≈20%)[7]
  - Interferon-related immune-mediated allograft dysfunction[8]
- Direct-acting antivirals (DAAs) may provide new treatment options for patients infected with HCV, including LT recipients
- The use of currently available protease inhibitors (boceprevir and telaprevir) in LT recipients is complicated by potentially severe drug–drug interactions (DDIs) with calcineurin inhibitors[9,10]
- Daclatasvir (DCV) is a HCV NS5A replication complex inhibitor
  - Potent pan-genotypic (genotypes 1–6) antiviral activity *in vitro*[11]
  - Generally well tolerated with low potential for clinically significant DDIs[12–14]
  - Pharmacokinetic (PK) profile suitable for once-daily (QD) dosing with no food restrictions[15]
  - Studied in over 5500 patients in combinations with other DAAs, and peginterferon/ribavirin
  - Substrate of CYP3A4 and P-gp
  - Levels of unbound DCV are unaffected by moderate-to-severe hepatic impairment and dose adjustment is not required for this condition[16]
- DCV has been used successfully in combination with sofosbuvir as part of a DAA-only regimen without signs of a significant DDI with TAC in a LT recipient with severe recurrent cholestatic HCV[17]
- DCV has been used successfully in combination with peginterferon/ribavirin without signs of a significant DDI with CSP in a LT recipient[18]
- The aim of this study was to assess the effect of multiple doses of DCV on the single-dose pharmacokinetic (PK) profiles of CSP and TAC, and the effect of single doses of CSP and TAC on the PK profile of DCV

2. METHODS

- This was an open-label, single-sequence study in healthy male and female subjects aged 18–49 years with a BMI 18–32 kg/m^2
- Subjects were assigned to treatment with either DCV + CSP (Group 1; N = 14) or DCV + TAC (Group 2; N = 14), administered alone and in combination (**Figure 1**)
  - Group 1 received oral CSP 400 mg QD on Days 1 and 9 and oral DCV 60 mg QD on Days 4–11
  - Group 2 received oral TAC 5 mg QD on Days 1 and 13, and oral DCV 60 mg QD on Days 8–19
  - Group 1 serial PK sampling to determine CSP (measured pre-dose to 72 hours) and DCV (measured pre-dose to 24 hours post-dose) blood levels was initiated on Days 1 and 9, and 8 and 9, respectively
  - Group 2 serial PK sampling to determine TAC (measured pre-dose to 168 hours) and DCV (measured pre-dose to 24 hours post-dose) blood levels was initiated on Days 1 and 13, and 12 and 13, respectively
  - Subjects were required to fast prior to (10 hours) and after (4 hours) dosing on PK sampling days; standardized meals were provided
- Plasma levels of CSP, TAC, and DCV were determined by validated LC-MS/MS assays

2. METHODS (cont)

Figure 1. Study Design



Arrows represent a single dosing interval.
CSP, cyclosporine 400 mg once daily (QD); DCV, daclatasvir 60 mg QD; TAC, tacrolimus 5 mg QD; PKS, serial pharmacokinetic sampling period.
N = 14 in each treatment group.

- The PK profiles of CSP, TAC, and DCV were defined by standard PK parameters:
  - Maximal plasma concentration (C_{max})
  - Plasma concentration at the end of the dosing interval (C_{24}; DCV only)
  - Time of C_{max} (T_{max})
  - Plasma half-life ($T_{½}$; CSP and TAC only)
  - Area under the plasma concentration–time curve (AUC) from time zero to the last quantifiable concentration ($AUC_{0–T}$; CSP and TAC only); AUC from time zero extrapolated to infinity ($AUC_{0–\infty}$; CSP and TAC only); AUC during the dosing interval (AUC_{tau}; DCV only)
  - Apparent total body clearance (CLT/F; CSP and TAC only)
- Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were calculated to assess the effect of multiple doses of DCV on the measures of CSP and TAC single-dose exposure, and the effect of single doses of CSP and TAC on the measures of DCV multiple-dose exposure

3. RESULTS

- A total of 14 subjects were included in each treatment group
  - All subjects received treatment according to schedule
  - All subjects completed the study and were included in the PK analysis population
  - No subjects received non-study medication
- Subject demographic characteristics are presented in **Table 1**

Table 1. Demographic Characteristics

Parameter	Group 1 (N = 14) DCV 60 mg / CSP 400 mg	Group 2 (N = 14) DCV 60 mg / TAC 5 mg
Age, mean years (SD)	34.8 (7.1)	34.5 (8.7)
Male, n (%)	12 (85.7)	10 (71.4)
BMI, mean kg/m^2 (SD)	28.5 (2.7)	26.3 (3.7)
Race, n (%)		
White	6 (42.9)	10 (71.4)
Black / African American	7 (50.0)	4 (28.6)
Other	1 (7.1)	0 (0.0)

- The single-dose PK profile of CSP was unaffected by concomitant administration with multiple doses of DCV (**Figure 2a**)
  - The GMR 90% CIs for CSP $AUC_{0–\infty}$, $AUC_{0–T}$ and C_{max} were contained within the accepted boundary for no significant interaction (0.80–1.25) and included 1 (**Tables 2 and 3**)
  - CSP T_{max}, $T_{½}$, and CLT/F were comparable during both treatments

3. RESULTS (cont)

- Steady-state DCV geometric mean values for AUC_{tau} and C_{24} were increased by 40% and 56%, respectively, and the median T_{max} value was increased from 1.0 to 2.0 hours when DCV was co-administered with a single dose of CSP (**Figure 2b**)
  - The associated 90% CIs for the GMRs of DCV AUC_{tau} and C_{24} were entirely above 1.25 (**Tables 2 and 3**)
  - DCV C_{max} was unaffected and the 90% CI of the GMR was contained entirely within 0.8–1.25 and included 1

Figure 2. Group 1 Concentration vs Time Profiles

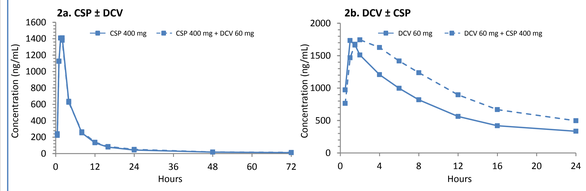


Figure 3. Group 2 Concentration vs Time Profiles

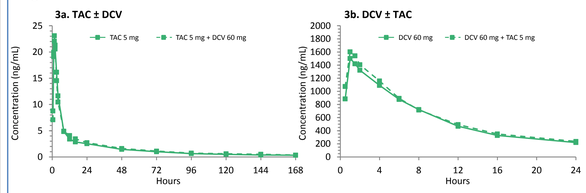


Table 2. Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	$AUC_{0–T}$ (ng·h/mL)	AUC_{tau} (ng·h/mL)	$AUC_{0–\infty}$ (ng·h/mL)	C_{24} (ng/mL)
Group 1					
CSP alone	1504 (20)	7825 (21)	ND	8198 (21)	ND
CSP + DCV	1447 (20)	7989 (24)	ND	8405 (24)	ND
DCV alone	1690 (31)	ND	16092 (32)	ND	306 (44)
DCV + CSP	1756 (25)	ND	22587 (24)	ND	475 (30)
Group 2					
TAC alone	22.8 (28)	225 (46)	ND	246 (44)	ND
TAC + DCV	24.0 (40)	224 (59)	ND	245 (56)	ND
DCV alone	1489 (20)	ND	13786 (28)	ND	205 (43)
DCV + TAC	1578 (27)	ND	14439 (30)	ND	226 (33)

N = 14 for all measurements; ND, not determined; underscore represents analyte of interest; all measurements are geometric means (CV %).

Table 3. Statistical Analyses

Comparison	C_{max}	$AUC_{0–T}$	AUC_{tau}	$AUC_{0–\infty}$	C_{24}
Group 1					
CSP + DCV vs CSP alone	0.96 (0.91, 1.02)	1.02 (0.96, 1.08)	ND	1.03 (0.97, 1.09)	ND
DCV + CSP vs DCV alone	1.04 (0.94, 1.15)	ND	1.40 (1.29, 1.53)	ND	1.56 (1.41, 1.71)
Group 2					
TAC + DCV vs TAC alone	1.05 (0.90, 1.23)	1.00 (0.87, 1.15)	ND	1.00 (0.88, 1.13)	ND
DCV + TAC vs DCV alone	1.07 (1.02, 1.12)	ND	1.05 (1.03, 1.07)	ND	1.10 (1.03, 1.19)

N = 14 for all measurements; ND, not determined; underscore represents analyte of interest; all measurements are geometric mean ratios (90% CIs).

- The single-dose PK profile of TAC was unaffected by concomitant administration with multiple doses of DCV (**Figure 3a**)
  - The GMR 90% CIs for TAC $AUC_{0–\infty}$, $AUC_{0–T}$ and C_{max} were contained within 0.80–1.25 and included 1 (**Tables 2 and 3**)
  - CSP T_{max}, $T_{½}$, and CLT/F were comparable during both treatments

3. RESULTS (cont)

- The steady-state PK parameters of DCV were unaffected by concomitant administration with a single dose of TAC (**Figure 3b**)
  - The GMR 90% CIs for DCV C_{max}, AUC_{tau}, and C_{24} were contained within 0.80–1.25 (**Tables 2 and 3**)
  - Median T_{max} was 1 hour during both treatments

Table 4. Treatment-Related AEs Occurring in ≥ 2 Subjects in Either Group

	Group 1 Treatment Phase			Group 2 Treatment Phase		
Preferred term, N (%)	**CSP**	**DCV**	**CSP + DCV**	**TAC**	**DCV**	**TAC + DCV**
Feeling hot	6 (42.9)	0	7 (50.0)	0	0	0
Headache	3 (21.4)	3 (21.4)	1 (7.1)	0	2 (14.3)	0
Diarrhea	3 (21.4)	1 (7.1)	2 (14.3)	0	0	0
Nausea	1 (7.1)	0	3 (21.4)	0	1 (7.1)	1 (7.1)
Sinus congestion	0	2 (14.3)	0	0	0	0
Constipation	0	0	0	2 (14.3)	0	0

N = 14 in all treatment groups and treatment group phases

- A summary of treatment-related AEs is presented in **Table 4**
- There were no deaths; serious AEs; AEs leading to discontinuation; or AEs relating to clinical laboratory results, vital signs, ECG abnormalities, or physical examinations
- A total of 21 of 28 subjects reported AEs
  - The majority of AEs (58 AEs in 20 subjects) were assessed as related to study treatment
- In both treatment groups, the number of AEs was similar during treatment phases

4. CONCLUSIONS

- No clinically relevant DDIs were observed when DCV was co-administered with either CSP or TAC
- Concomitant administration of CSP results in a modest but clinically insignificant increase in DCV exposure
- Co-administration of DCV with either CSP or TAC was well tolerated in healthy subjects
- These data suggest that dose adjustments may not be warranted during co-administration of DCV with CSP or TAC
- DCV-based regimens may provide new therapeutic modalities for the management of HCV infection in LT recipients who currently have limited treatment options

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6. DISCLOSURES

- This study was sponsored by Bristol-Myers Squibb
- M Bifano, R Adamczyk, C Hwang, H Kandoussi, and RJ Bertz are employees and may also be stockholders of Bristol-Myers Squibb
- A Marion is an employee and may also be a stockholder of ICON
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- This presentation includes discussion of investigational drugs not approved for use in humans