Evaluation of Pharmacokinetic-Pharmacodynamic Relationships for Efficacy Amongst Oseltamivir-Treated Paediatric Patients

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INTRODUCTION

- Oseltamivir is converted into oseltamivir carboxylate (OC), a selective influenza neuraminidase inhibitor, and is indicated for the treatment and prophylaxis of influenza.
- Results of a previous study demonstrated pharmacokinetic-pharmacodynamic (PK-PD) exposure-response relationships for oseltamivir efficacy in paediatric patients [Bulik CC et al., ICAAC 2014. A-010/A-011].
- A Phase 4 observational study, the Influenza Resistance Information Study (IRIS) was conducted with the goals of assisting in the detection of resistance and describing the clinical outcome of influenza infected patients.
- These data, in combination with demographic data and a previously-developed population pharmacokinetic (PPK) model [Kamal MA et al., AAC 2013;57:3470-7], provided the opportunity to evaluate PK-PD relationships for efficacy.

METHODS

Data

- Data from Years 1-3 of the IRIS study were used.

Analysis Population

- Paediatric patients (≤12 years) in the All Laboratory Confirmed Influenza Patients (ALCIP) population who had RT-PCR confirmed influenza and who received treatment with oseltamivir or no treatment.

Efficacy Endpoints

- Continuous efficacy endpoints included AUC over 12 days for total symptom score, individual symptom score (e.g., cough, fatigue, feeling feverish, headache, myalgia, nasal congestion, sore throat, and temperature), and viral load.
- Time-to-event efficacy endpoints included time to alleviation of total symptom score and individual symptom scores, and time to eradication of virus.

PK-PD Analyses for Efficacy

- Univariable relationships for efficacy were examined as follows:
  - ANOVA or non-parametric tests were used to evaluate relationships between continuous or categorical independent variables and continuous efficacy endpoints.
  - For time-to-event efficacy endpoints, log-rank tests were used to evaluate relationships for categorical independent variables and the likelihood ratio test from Cox proportional hazard regression was used to evaluate relationships for continuous independent variables.
- Independent variables included OC exposure measures (e.g., AUC, AUC:IC_{50}, daily dose, daily dose:IC_{50}), age, comorbidities, time from symptom onset to 1st dose, vaccination status, IC_{50}, mutation present at baseline, Day 1 viral load, influenza type and subtype.
  - Population predictions of OC AUC were estimated using demographic data and a previously-developed PPK model in which creatinine clearance (CLcr), age, and weight were covariates.

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METHODS

- As serum creatinine (SCr), an input for CLcr, was not collected, CLcr was calculated using the following formula [Johnson TN et al., ClinPharmacokinet;45:931-56]:
  - CLcr =((-6.1604 x BSA^2)+(99.054 x BSA)-17.74) x1.73/BSA
- OC exposure measures were evaluated as continuous variables and as two- and three-group categorical variables to account for potential non-linearity and/or non-monotonicity.
  - Two-group exposure measures were constructed using the split of a regression tree for a continuous efficacy endpoint or a cutoff value that maximized the log rank test derived from a univariable Cox proportional hazard regression model for a time-to-event efficacy endpoint.
  - Three-group independent variables were constructed by determining a pair of cutoff values that minimized the likelihood ratio P-value using linear regression for a continuous efficacy endpoint or the log rank P-value derived from the Cox proportional hazard regression.
- Multivariable analyses were carried out for each efficacy endpoint with separate models for each OC exposure measure and form of OC exposure measure.
- Final multivariable models were constructed using stepwise selection of non-exposure covariates with inclusion or exclusion at each step based on improvement in Akaike's information criterion.
- For each final multivariable model, interactions between the OC exposure measure and each of the independent variables retained in the model were evaluated to determine the consistency of the presence and degree of the exposure-response relationships among subgroups defined by a given independent variable.

RESULTS

- A total of 875 patients were in the ALCIP population, were evaluable for at least one efficacy endpoint, and received oseltamivir or no treatment.
- Males represented 52.7% of the patients. The mean (min-max) age was 6.2 (1-12) years.
- Viral type and subtype information was available for all 875 patients.
  - A total of 575 patients were infected with Influenza A and 300 with Influenza B.
  - Of those patients infected with Influenza A, 451 were infected with the subtype H1 Pandemic, 5 with subtype A-H1, and 119 with subtype A-H3.

Table 1. Summary statistics for OC exposure measures and IC_{50}

Independent variable	Number of patients	Median (Range)
IC_{50} (nM)	831	0.41 (0.02 to 176)
AUC (μg/L•h)	868	3,413.1 (0 to 12,245.9)
AUC:IC_{50}	824	959.0 (0 to 315,363.3)
Daily dose (mg)	875	60.0 (0 to 150.0)
Daily dose:IC_{50}	831	12.7 (0 to 4,500.0)

- Univariable PK-PD analyses for efficacy demonstrated that higher OC exposures were associated with lower symptom scores and faster times to alleviation of symptoms.

RESULTS

- The results of the multivariable PK-PD analyses for efficacy demonstrated relationships for continuous and time-to-event efficacy endpoints and one or more OC exposure measure in the presence of other independent variables.
  - Higher OC exposures were associated with lower symptom score AUC values, faster times to symptom alleviation, and/or faster times to viral resolution.
- Multivariable models demonstrating the most informative exposure-response relationships are summarized in **Table 2**.
  - Independent variables retained in these models were influenza type and subtype, age, vaccination status, and time from symptom onset to 1st dose.
  - Paediatric patients who were infected with Influenza B or who were previously vaccinated had poorer outcomes.

Table 2. Multivariable models for influenza symptom time-to-event and continuous endpoints[a]

Influenza symptom or quality of life endpoint	OC exposure: Variable definition	OC exposure: Hazard ratio (95% CI) or parameter estimate (SE)	OC exposure: Likelihood P-value[b]	OC exposure: Wald P-value[b]	Impact of OC exposure: Time to 25, 50, and 75% of the population achieving the time-to-event endpoint (days) or Mean (95% CI) predicted value[c]	Other independent variables retained in the model (P-value)[b]
Multivariable models for time-to-event efficacy endpoints						
Time to alleviation of total symptom score (N=673)	AUC < 7,404	1.0	0.011	N/A	8, >11, >11	Vaccination status (0.06), and time from symptom onset to 1st dose (<0.001)
	AUC ≥ 7,404	1.62 (1.14 to 2.30)			7, 9, >11	
Time to alleviation of feeling feverish (N=808)	AUC < 2,902	1.0	0.013	N/A	Influenza A 2, 2, 4	Mutation present at baseline (0.023), age (0.06), and IC_{50} value (0.04)
	AUC ≥ 2,902	1.20 (0.104 to 1.38)			Influenza B 2, 3, 5 Influenza A 0, 2, 3 Influenza B 2, 3, 4	
Time to alleviation of cough (N=812)	AUC < 5,021	1	<0.001	0.12	H1-Pandemic 6, 9, >11 Influenza A-H1 4, 6, 9 Influenza A-H3 7, >11, >11 Influenza B 6, 9, >11	Vaccination status (0.05) and time from symptom onset to 1st dose (<0.001)
	5,021 ≤ AUC < 7,305	1.18 (0.955 to 1.47)			H1-Pandemic 6, 9, >11 Influenza A-H1 4, 6, 8 Influenza A-H3 7, >11, >11 Influenza B 5, 8, >11	
	AUC ≥ 7,305	1.86 (1.40 to 2.46)		<0.001[d]	H1-Pandemic 5, 7, >11 Influenza A-H1 3, 5, 6 Influenza A-H3 5, 8, >11 Influenza B 4, 6, 9	
	5,021 ≤ AUC < 7,305 vs. AUC ≥ 7,305	1.57 (1.17 to 2.10)		0.003	N/A	
Time to alleviation of fatigue (N=804)	AUC < 7,404	1.0	<0.001	N/A	3, 5, 7	Viral load on Day 1 (0.1)
	AUC ≥ 7,404	1.53 (1.21 to 1.94)			2, 4, 5	
Time to eradication of virus (N=875)	AUC < 4,761	1.0	0.003	N/A	4, 8, 9	Viral load on Day 1 (0.001), age (0.001, and time from symptom onset to 1st dose (0.026)
	AUC ≥ 4,761	1.28 (1.09 to 1.50)			4, 6, 9	
Multivariable models for continuous efficacy endpoints						
Headache AUC (N=724)	AUC:IC_{50} < 2,086	0	0.024	N/A	14.3 (13.8-14.7)	Vaccination status (0.14), age (<0.001), and time from symptom onset to 1st dose (0.009)
	AUC:IC_{50} ≥ 2,086	-0.821 (0.362)			13.4 (12.8-14.0)	
Nasal congestion AUC (N=803)	AUC = 0	0	0.001	0.19	Influenza A 23.0 (22.2-23.8) Influenza B 24.9 (24.0-25.9)	Age (<0.001) and viral load on Day 1 (0.09)
	1,755 ≤ AUC < 7,328	-0.688 (0.527)			Influenza A 22.3 (21.5-23.1) Influenza B 24.3 (23.2-25.3)	
	AUC ≥ 7,328	-2.98 (0.799)		<0.001[d]	Influenza A 20.0 (18.5-21.5) Influenza B 22.0 (20.5-23.5)	
	1,755 ≤ AUC < 7,328 vs. AUC ≥ 7,328	-2.29 (0.817)		0.005	N/A	
Sore throat AUC (N=740)	AUC:IC_{50} < 2,036	0	0.049	N/A	15.0 (14.5-15.5)	Age (<0.001) and time from symptom onset to 1st dose (0.011)
	AUC:IC_{50} ≥ 2,036	-0.773 (0.392)			14.2 (13.6-14.8)	
Temperature AUC (N=619)	AUC:IC_{50} < 956	0	<0.001	N/A	334.3 (333.9-334.7)	Age (0.001) and time from symptom onset to 1st dose (0.042)
	AUC:IC_{50} ≥ 956	-1.22 (0.275)			333.1 (332.7-333.5)	

a. For each efficacy endpoint, the model considered the most informative is shown.
b. Likelihood ratio and Wald chi-square tests were used to assess statistical significance at α=0.05.
c. Evaluated at mean values of other continuous independent variables in the model.
d. Represents Wald p-value for pairwise comparison between lowest and highest exposure groups.

CONCLUSIONS

- The results of the univariable and multivariable analyses demonstrated that higher OC exposures were associated with improved outcomes.
- The impact of the independent variables was such that those patients who were infected with Influenza A or who were previously vaccinated had better outcomes.
- Due to the observational nature of the study, all PK data was predicted using demographic data and a previously-developed PPK model. As such, only 40% of the variance on clearance was explained by patient covariates.
- The multivariable models derived based on these analyses will be useful to investigators involved in the development of clinical trials designed to evaluate new antiviral agents in paediatric patients.
  - These models can be used to help investigators determine which influenza symptoms are the most sensitive to the impact of OC exposure, and in turn, which to monitor during an efficacy study; and
  - Results of individual models can be used to identify patients who could benefit the most from increased OC exposure and those, based on the independent variables evaluated, who would be at higher risk of a poor response.