

Virologic Analysis of Influenza Viruses after Therapy with a Single Intramuscular (IM) Dose of the Neuraminidase Inhibitor (NAI)

Peramivir (PVR) Versus Placebo (PBO) in Patients with Influenza in the Outpatient (OP) Setting

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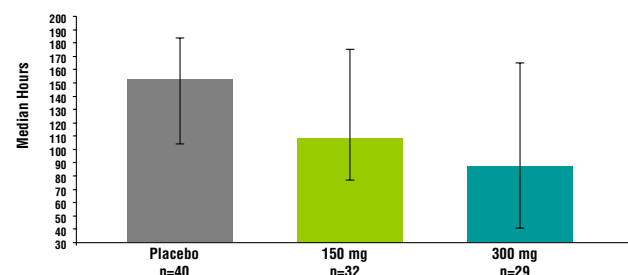
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INTRODUCTION

- Early treatment with NAIs is recommended for subjects hospitalized with influenza¹
- Concerns about emergence of resistance were raised after most seasonal H1N1 influenza A isolates in 2008 were found to be resistant to oseltamivir (OSE)², most with the H275Y mutation
- There are few reports of H275Y isolates after peramivir (PVR) treatment
- Peramivir is a neuraminidase inhibitor (NAI) approved in Japan and South Korea for treatment of influenza and in Phase 3 global trials for US approval
- Peramivir has in vitro activity superior to OSE and zanamivir (ZAN) against wild-type strains of influenza^{3,4}
- Resistance of seasonal H1N1 influenza A to PVR is only selected after multiple cycles of in vitro passage⁵
- In a completed randomized, placebo-controlled, double-blind Phase 2 trial (BCX1812-211), there were dose-related reductions in the median time to alleviation of symptoms of influenza in those patients given an adequate single intramuscular injection of PVR 150 mg or 300 mg⁶ as defined by a creatinine kinase (CK) elevation of at least 50 IU/L at 48 hours

Time to Alleviation of Influenza Symptoms: Post-Hoc Analysis –Subjects with Adequate Intramuscular Injection (by CK Increase)



Alexander et al., ISRV 2009
Error bars represent the 95% CI about the median hour value.

- With viral susceptibility data from BCX1812-211 now available, we assessed the potential development of resistance to peramivir in patients with influenza treated once with an intramuscular injection of peramivir or placebo

METHODS

Study Subjects

- ≥ 18 years old
- Symptoms consistent with diagnosis of uncomplicated acute influenza infection
- Positive RAT test for influenza A or B
- Presence of fever or history of fever within 24 hours
- Onset of illness within 48 hours

Study Design and Treatments

- Randomized, double-blind, study conducted at 151 sites in 7 countries from January to September 2007
- Eligible patients were randomly assigned to treatment with peramivir (PVR) 150 mg, PVR 300 mg, or placebo
- 4 mL PVR was administered, 2-mL intramuscular (IM) injection in each gluteal muscle
- Subjects were stratified according to current smoking behavior

Study Assessments

- Nasopharyngeal swabs were collected at baseline, Day 2, 3, 5, and 9
- Influenza A subtype and B infection was determined by RT-PCR, culture, or serology
- H275Y status was assessed by pyrosequencing in H1N1 specimens
- Seasonal A/H1N1 isolates without the H275Y mutation by pyrosequencing were considered wild type (WT)
- Quantitative viral burden was evaluated by determination of log₁₀ tissue culture infective dose₅₀ (TCID₅₀) at baseline and post treatment through Day 9
- Neuraminidase enzyme inhibition (NAI) assay was performed on virus MDCK culture supernatants by MUNANA technique to assess the IC₅₀ of PVR, oseltamivir (OSE) and zanamivir (ZAN) at baseline and post treatment
- Genotypic sequencing at baseline and post treatment was performed in 2 populations:
 - Paired isolates with change in IC₅₀ from baseline to last timepoint > mean + 2 SD
 - Subjects with viral shedding at Day 9

RESULTS

Study Subjects

- Demographic characteristics were similar at baseline among the 318 subjects enrolled to receive placebo, peramivir 150 mg and peramivir 300 mg IM
- Most subjects had influenza A infection and were non-smokers

Demographics: Subjects with Confirmed Influenza

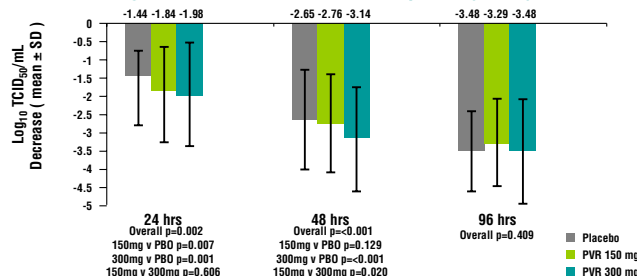
	Placebo N=109	Peramivir 150 mg N=104	Peramivir 300 mg N=105
Age (yr), mean (SD)	34.0 (12.2)	36.4 (15.5)	36.2 (12.6)
Male / Female (n / n)	57 / 52	42 / 62	49 / 56
Weight (kg), mean (SD)	77.4 (19.5)	77.1 (18.4)	79.8 (21.0)
BMI (kg/m ²), mean (SD)	26.5 (5.7)	27.4 (6.3)	27.4 (6.3)
Current Smokers, n (%)	25 (23%)	22 (21%)	22 (21%)
Onset of Symptoms, n (%)			
0 – 24 hours	35 (32%)	34 (33%)	25 (24%)
24 – 48 hours	74 (68%)	70 (67%)	80 (76%)
Influenza Infection*			
Influenza A	85 (78%)	85 (82%)	80 (76%)
Influenza B	23 (21%)	19 (18%)	23 (22%)
Influenza A and B	1 (1%)	0	2 (2%)
Composite Symptoms [†] , mean (SD)	14.5 (3.7)	14.3 (3.1)	14.1 (3.9)

*Confirmed by positive PCR result on nasopharyngeal specimen obtained at baseline.
[†]Composite score at baseline from 7 patient-rated symptoms of influenza

Virology Titers

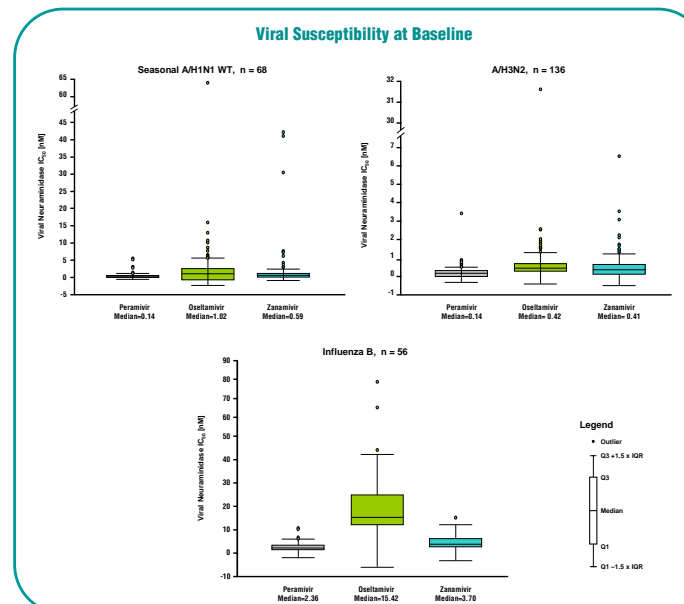
- Treatment with PVR was associated with greater decreases in influenza viral titers in nasopharyngeal secretions at 24 and 48 hours post-dose compared with placebo
- After 96 hours, there was no evidence of treatment group differences

Change From Baseline in Viral Titers: ITTI Population (n = 305)



Viral Susceptibility

- Mean and median IC₅₀ values for all influenza A and B viruses isolated at baseline were lowest for peramivir compared to the two other NAIs



- In pairs of influenza isolates obtained at baseline and up to 96 hr post therapy, there were no meaningful decreases in susceptibility in any treatment group

Viral Susceptibility, Median (Min, Max)

Influenza Virus Type	Treatment Group	NAI		
		Peramivir	Oseltamivir	Zanamivir
Influenza A (H1N1) Wild Type	PBO, n=27	IC ₅₀ of last positive culture 0.10 (0.01, 1.05)	1.13 (0.23, 13.02)	0.62 (0.06, 32.64)
	PVR 150, n=18	Fold change from baseline* 0.65 (0.04, 14.00)	1.04 (0.19, 7.92)	1.00 (0.12, 14.00)
		IC ₅₀ of last positive culture 0.22 (0.01, 2.34)	0.94 (0.10, 95.45)	0.62 (0.02, 10.39)
	PVR 300, n=19	Fold change from baseline* 1.97 (0.21, 69.50)	1.15 (0.12, 28.81)	0.73 (0.08, 14.60)
		IC ₅₀ of last positive culture 0.14 (0.01, 9.62)	1.72 (0.04, 24.37)	1.04 (0.21, 5.44)
	Influenza A (H3N2)	PBO, n=44	IC ₅₀ of last positive culture 0.18 (0.01, 2.63)	0.58 (0.06, 20.19)
PVR 150, n=37		Fold change from baseline* 1.12 (0.16, 18.00)	1.04 (0.16, 23.60)	1.19 (0.14, 25.38)
		IC ₅₀ of last positive culture 0.17 (0.02, 1.78)	0.41 (0.02, 3.99)	0.62 (0.05, 3.56)
PVR 300, n=40		Fold change from baseline* 1.18 (0.11, 53.00)	1.00 (0.07, 6.23)	1.28 (0.25, 5.98)
		IC ₅₀ of last positive culture 0.16 (0.04, 4.65)	0.51 (0.11, 13.09)	0.82 (0.04, 14.15)
Influenza A (Indeterminate)		PBO, n=2	IC ₅₀ of last positive culture 0.06 (0.01, 0.11)	0.67 (0.37, 0.96)
	PVR 150, n=3	Fold change from baseline* 5.67 (0.33, 11.00)	0.70 (0.23, 1.17)	1.03 (0.67, 1.39)
		IC ₅₀ of last positive culture 0.92 (0.69, 20.00)	17.47 (1.36, 42.75)	4.57 (0.67, 13.83)
	PVR 300, n=1	Fold change from baseline* 0.85 (0.69, 20.00)	1.73 (1.16, 2.52)	0.91 (0.51, 1.66)
		IC ₅₀ of last positive culture 0.98	15.65	2.37
	Influenza B	PBO, n=18	IC ₅₀ of last positive culture 2.53 (0.02, 6.30)	17.40 (0.06, 54.63)
PVR 150, n=14		Fold change from baseline* 1.12 (0.30, 3.04)	1.15 (0.24, 2.52)	1.02 (0.30, 2.41)
		IC ₅₀ of last positive culture 2.75 (1.02, 11.69)	17.87 (4.42, 32.95)	5.56 (3.16, 14.91)
PVR 300, n=19		Fold change from baseline* 1.03 (0.21, 2.08)	0.96 (0.24, 1.19)	1.12 (0.68, 2.71)
		IC ₅₀ of last positive culture 1.74 (0.29, 3.41)	14.80 (6.36, 32.57)	2.99 (1.07, 8.80)

*values = 1 indicate no change, values > 1 indicate a fold increase, and values < 1 indicate a fold decrease

- Genotypic analyses of the limited number of isolates from the 2 populations (paired isolates with change in IC₅₀ > mean + 2SD, n=20; subjects with viral shedding at day 9, n=18) found only 2 treatment-emergent H275Y mutations (1 at each PVR dose) in the subjects with paired isolates. No additional known resistance mutations were identified.

DISCUSSION

- The development of viral resistance is a matter of concern
- Results from this study conducted in 2007 suggest that IM peramivir treatment was associated with little development of viral resistance in these subjects with confirmed influenza based on the change from baseline in IC₅₀
- 2 PVR-treated subjects experienced a treatment-emergent H275Y mutation
- The H275Y mutation has been prevalent in OSE-resistant seasonal influenza A strains, although there have been few reports with peramivir treatment
- Currently, approx. 1% of 2009 H1N1 influenza A strains with oseltamivir resistance have been reported; however, one mutation (S247N) caused a small decrease in susceptibility to oseltamivir and zanamivir, but not to peramivir⁷
- Peramivir treatment reduced viral shedding in a dose-dependent manner compared with placebo
- There were some study limitations
 - Study treatment was limited to 1 day, so viral susceptibility after longer durations of treatment could not be assessed
 - Genotypes could not be obtained for all specimens in both subsets

CONCLUSIONS

- Baseline mean IC₅₀s for influenza A/H1N1 (wild type), A/H3N2, and B were as previously reported with the order being peramivir<zanamivir<oseltamivir
- Little change in IC₅₀ values was observed with treatment
- There was little evidence of resistance in influenza viruses up to 9 days after treatment with IM peramivir in patients with confirmed influenza
- 2 treatment-emergent mutations were observed
- Single-dose IM peramivir treatment significantly reduced viral shedding in a dose-dependent manner compared with placebo

ACKNOWLEDGMENTS

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