

Safety and Efficacy of Multiple-Day Treatment with Intravenous Peramivir or Oral Oseltamivir in Hospitalized Adults with Acute Influenza

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BACKGROUND: Influenza is responsible for over 200,000 hospitalizations per year in the United States. Few studies have addressed the management of patients hospitalized with influenza.

METHODS: Eligible subjects were ≥ 18 yr old, had influenza symptoms for ≤ 72 hr, had a confirmed influenza A or B by RAT, were hospitalized, and met other criteria for enrollment during the 2007-2008 seasons in 6 countries. An exploratory composite endpoint (clinical stability) was the primary endpoint and required twice-daily measurements of temperature, oxygen saturation, heart rate, respiratory rate, and systolic blood pressure. This endpoint was met if 4 of the 5 measures attained normalization for at least 24 hours. Secondary endpoints included symptom severity, complications of influenza, and time to resumption of usual activities. Quantitative virologic assays were performed using nasopharyngeal specimens collected at enrollment and after 12, 24, 36, 48, 72 and 96 hours of treatment. Safety was assessed by reports of adverse events and clinical laboratory results.

RESULTS: 137 subjects were randomized to receive 5 days of treatment with either oral oseltamivir 75 mg twice daily (n = 46), intravenous (i.v.) peramivir 200 mg once daily (n = 45), or i.v. peramivir 400 mg once daily (n = 46). Predefined analyses focused on 122 subjects with PCR-confirmed influenza (mean age 59.4 yr; range 19-101 yr). Ninety-two subjects with influenza (75%) were either aged ≥ 60 years, had co-morbidities, had oxygen saturation $<94\%$ and/or had systolic hypotension at randomization. For the primary endpoint, there were no significant differences among treatments (Table). The exploratory composite endpoint (clinical stability) was found not suitable for the population studied (Cronbach's $\alpha = 0.434$). The mean days to resumption of usual activities were lower in subjects treated with peramivir (p=0.276). Decreases in viral titers after 48 hr were similar across the three treatments with a numerical trend suggesting a greater antiviral effect of peramivir compared to oseltamivir for influenza B viruses after 48 hours of treatment.

ENDPOINT	Oseltamivir 75 mg po bd, n=41	Peramivir 200 mg iv qd, n=41	Peramivir 400 mg iv qd, n=40	p value
Time to Clinical Stability (median hr) (95% CI)	28.1 (22.0, 37.0)	23.7 (16.0, 38.9)	37.0 (22.0, 48.7)	0.306
Time to Resumption of Usual Activities (mean days \pm SD)	13.2 (1.2)	8.2 (0.9)	9.2 (0.9)	0.276
Change in Viral Titer at 48 hours (mean \pm SD log ₁₀ TCID ₅₀ /mL)				
Influenza A and B (n = 94)	- 2.2 (1.4)	- 2.2 (1.0)	- 2.5 (1.0)	0.275
Influenza A (n = 66)	- 2.1 (1.1)	- 1.9 (1.1)	- 2.3 (1.0)	0.509
Influenza B (n = 28)	- 2.2 (2.1)	- 2.6 (0.6)	- 3.3 (0.9)	0.098

Among all subjects with confirmed influenza, 12 serious adverse events (SAEs) were reported with no mortality. Two other SAEs occurred in subjects who were not confirmed to have influenza; one of these was fatal with evidence of myocarditis on autopsy.

CONCLUSIONS: Peramivir and oseltamivir demonstrated generally similar efficacy and tolerability based on the clinical and virologic endpoints examined. These results are consistent with the hypothesis that early treatment of influenza with neuraminidase inhibitors may be beneficial in reducing morbidity in populations at risk.

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