

**ANTIVIRAL DRUG
TREATMENTS FOR PATIENTS
WITH SEVERE SWINE-ORIGIN
INFLUENZA A (H1N1) (S-OIV)**

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OUTLINE

- Efficacy & safety of neuraminidase inhibitors (NI's)
- In vitro susceptibility of S-OIV to NI's
- Pharmacokinetic issues – drug delivery
- Therapeutic effects of oseltamivir in hospitalized patients
- In ferrets, some H5N1 clades required a larger dose
- Immunopathogenesis of severe influenza
 - Cytokine storm
- Conclusions

THE EFFICACY AND SAFETY OF OSELTAMIVIR & ZANAMIVIR FOR THE TREATMENT OF ADULTS (& CHILDREN) WITH UNCOMPLICATED INFLUENZA IS BEYOND QUESTION

- **Oseltamivir adult dose 75 mg p.o. BID x 5 days**
- **Zanamivir adult dose 10 mg inhaled BID p.o.**

Whitley et al 2001, Cooper et al 2003

SUSCEPTIBILITY OF S-OIV TO ANTIVIRAL DRUGS

- S-OIV is resistant to adamantanes
- S-OIV is susceptible to NI's

	Median IC ₅₀ (nM)		
	H1N1	H3N2	S-OIV
Oseltamivir	1.21	0.69	0.54
Zanamivir	0.39	2.02	0.50
Peramivir	0.67	0.58	0.08

DELIVERY OF ANTIVIRAL DRUG TO LUNGS OF PATIENTS WITH S-OIV PNEUMONIA WILL BE PROBLEMATIC

- Zanamivir

- 13% of drug inhaled by normal volunteers reaches bronchi & lung¹
- Has been administered as aerosol via endotracheal tube to 41 hospitalized patients²
- Intravenous doses up to 600 mg BID were well tolerated, efficacious against experimental influenza²

¹Cass et al 1999; ²Ison et al 2003; ³Calfee et al 1999

- **Oseltamivir**

- **77% oral bioavailability in uncomplicated influenza¹**
- **? Well absorbed in 3 patients with H5N1 respiratory & renal failure²**
- **Drug-drug interactions not reported**
- **IV formulation needed**

¹He et al 1999; ²Taylor et al 2008

- **Peramivir**

- **An intravenous dose of 600 mg once was well tolerated & efficacious compared to placebo**

EFFECTS OF OSELTAMIVIR TREATMENT OF ADULTS HOSPITALIZED WITH INFLUENZA

- **Six prospective observational studies:**

1. Toronto

- **Oseltamivir therapy of 103 patients was associated with a significant reduction in mortality (OR 0.21; 95% CI 0.06-0.80; p=0.03) compared to 403 not treated**
- **Oseltamivir 75 mg BID x 5 days**
- **72% started oseltamivir within 96 H of symptoms onset**

McGeer et al, 2007

2. Hong Kong

- Oseltamivir initiated at ≤ 96 H after symptom onset was associated with decreased mortality (OR 0.26; 95% CI 0.08-0.87; $p=0.03$)
- Presence of a major comorbidity (CHF, CVA, neoplasia, chronic hepatic or renal diseases) was associated with increased mortality (OR 9.3; 95% CI 2.4-36.3; $p=0.001$)
- Oseltamivir 75 mg BID x 5 days

3. Other studies in high-risk patients:

**Hematologic malignancies, and
Stem cell transplants**

**Oseltamivir reduced 1 or more of:
mortality, length of stay and
progression to pneumonia**

Bowles et al 2002, Nichols et al 2004, Chemaly et al 2006 & 2007

FERRETS INFECTED WITH A REPRESENTATIVE OF A CLADE OF H5N1 VIRUS WITH MARKED PATHOGENICITY REQUIRED A HIGHER OSELTAMIVIR TREATMENT DOSE

- Delayed treatment at 24 H post-infection required higher doses BID to be effective

Oseltamivir Dose (mg/kg/day)	Survived/Total	Mean Day to Death
0	0/3	6.7 \pm 0.4
10	0/3	7.3 \pm 0.3
25	3/3	>21

IMMUNOPATHOGENESIS OF SEVERE INFLUENZA?

Hypercytokinemia and Hyperactivation of Phospho-p38 Mitogen-Activated Protein Kinase in Severe Human Influenza A Virus Infection

“Demonstration of a positive correlation between nasopharyngeal virus load and hypercytokinemia suggests that early initiation of effective antiviral therapy may...attenuate these potentially harmful responses”

CONCLUSION

- **Confirm the good oral bioavailability of oseltamivir in seriously ill patients**
- **Unequivocally & rigorously establishing the efficacy of antiviral drug treatments for severe S-OIV disease by a controlled trial is now likely unethical**
- **Perhaps rational doses & durations can be determined by careful study of viral excretion and ? cytokines**

PERAMIVIR GENERALLY INHIBITS OSELTAMIVIR-RESISTANT H1N1 (non S-OIV) & H3N2 VIRUSES FROM OSELTAMIVIR TREATMENT FAILURE PATIENTS

Median (range) Fold-Increase in IC_{50} From Pre-Treatment Isolates (n=5)

Oseltamivir	Zanamivir	Peramivir
277 (130-463)	1 (1-3)	3.5 (1-100)