Influenza Antivirals: Challenges and Future Directions

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Antivirals for Influenza: *Outline*

- Pandemic H1N1 observations
  - Effectiveness for treatment in severe illness
  - Resistance (H275Y in N1 viruses)
- Investigational agents + future directions
  - IV neuraminidase inhibitors
  - Antibody preparations
  - Antiviral combinations

Conflict of Interest Declarations- FG Hayden

- No personal honoraria from industry since 2006
- No grants to UVA from industry since 2006
- Member of NISN with honoraria to UVA since 2008
- Unpaid adviser (sometimes with access to confidential information) for Abbott, Adamas, Alios, Biocryst, Boehringer-Ingelheim, Crucell, GSK, Inhibikase, Kirin, Liquidia, Nexbio, Respivert, Roche, Theraclone, Toyama, 3V Biosciences, Vaxinnate since 2008

Current Neuraminidase Inhibitors in Pandemic H1N1 Influenza

Retrospective Studies of Early Oseltamivir Treatment in Pandemic H1N1

- Early (≤ 48 hrs) treatment associated with
  - ↓ duration of viral detection, fever, Sx
  - ↓ risk of pneumonia (OR 0.12, 95% CI 0.08- 0.18)
  - ↓ risks of death in severely ill (OR 24.2, 95% CI 12 -49) or ICU admit/death in hospitalized
  - ↓ risks of ICU admission (6% *vs* 31.5%) and mortality (0.5% *vs* 14.5%) in pregnant women
  - ↓ risks of hospitalization, ICU admit (8% *vs* 22%), and death (1% *vs* 6%) in SOT recipients

Cao et al., NEJM 9 Dec 09; Li et al., Chest 137:759, 2010; Yu et al., Options abst P-208; Kumar et al., Lancet ID 9 July 2010; Siston et al., JAMA 303:1517, 2010; Yang et al., J Infect 2010; Jain et al., NEJM 8 Oct 09

Delayed NAI Therapy in Severe Pandemic H1N1

Country	Patient type	No. patients	% oseltamivir pre-hospital* or ≤48 hr
USA	Hospital ICU	272 611 adults	9%* 8%*
UK	Hospital/ICU	226 children 405 adults	9%* 15%*
Argentina	Hospital/ICU	271 children	12-13%
USA	ICU Fatal	115 pregnant 30 pregnant	16% 4%
Mulitple	ICU	35 SOT	20%

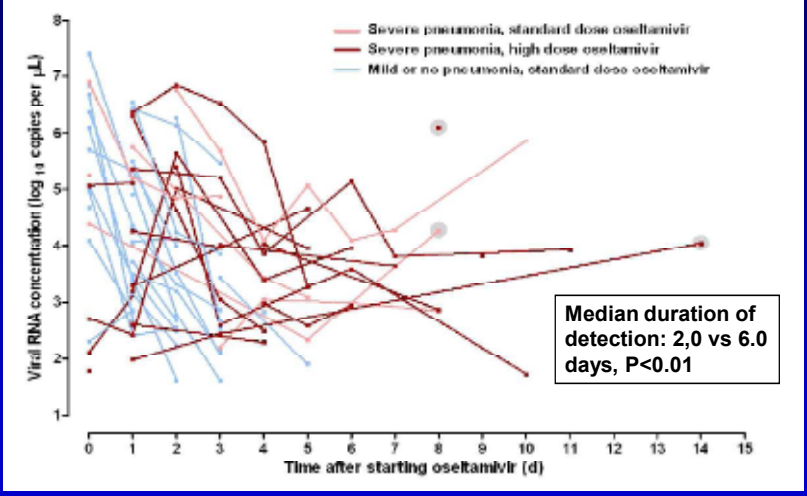
Jain et al., NEJM 361, 8 Oct 09; Nguyen-Van-Tam et al., Thorax 65:645, 2010; Thompson, ATS 2010; Siston et al., JAMA 303:1517, 2010; Libster et al., NEJM 2010; Kumar et al., Lancet ID 9 July 2010

Observational Reports on Delayed Oseltamivir Treatment in Pandemic H1N1 Influenza

Location	No. treated	Outcomes
USA (Siston et al., 2010)	115 pregnant women	↓ ICU (18 vs 46%) and death (5 vs 25%) risks if treated on day 3-4 vs >4
Mexico City (Domınguez-Cherit et al., 2009)	44 ICU	↑ survival with Rx (OR 7.4; 95% CI, 1.8-31.0)*
Argentina (Farias et al., 2010)	147 pediatric ICU	↓ mortality if Rx ≤1 day after hospital admit (OR 0.20; 95% CI, 0.07-0.54)

*After excluding pts dying within 72 hrs of illness onset

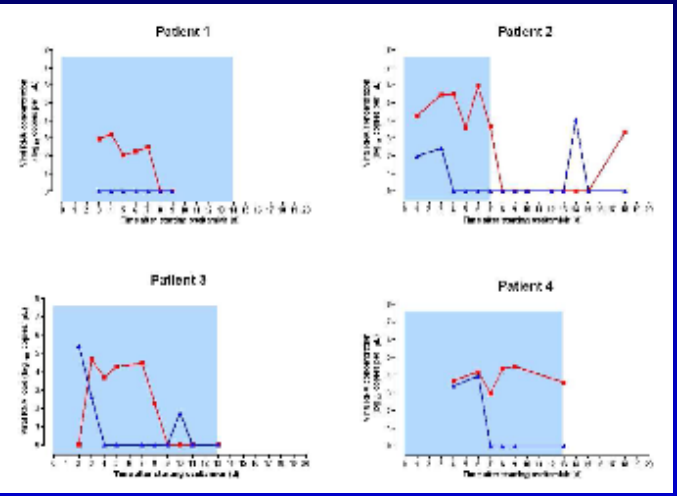
Nasopharyngeal Pandemic H1N1 RNA Levels in Hospitalized Patients Given Oseltamivir



Lee et al., Antiviral Therapy, in press and Options abst O-828, 2010

Pandemic H1N1 Viral RNA Loads in Upper and Lower Respiratory Tract during Oseltamivir

- Divergent responses common - higher + more sustained loads in LRT → prolonged treatment
- No H255Y detected



Lee et al., Antiviral Therapy, in press and Options abst O-828, 2010

Other NAI Findings in Severe Pandemic H1N1

- Oral oseltamivir
  - Adequate NG absorption in most critically ill patients
  - No dose alteration for obesity (< 200 kg)
  - Altered dosing regimens for premature infants, neonates, renal replacement therapies
- Nebulized zanamivir
  - Reports of bronchospasm in serious pH1N1 illness
  - Virologic failure with inhaled zanamivir in IC hosts
  - Risk for obstruction of ventilator filters (lactose carrier in commercial formulation)

Ariano et al., CMAJ 16 February 2010; Englund et al., MMWR 14 August 09; Kiatboonsri et al., CID 50:620, 2010; Kidd et al., Lancet 4 Sept 09; Acosta et al., JID 15 August 2010

Antiviral-Resistant Human Influenza Viruses with Global or Regional Circulation

Feature	Seasonal A(H3N2)	Seasonal A(H1N1)*	Pandemic A(H1N1)	Seasonal A(H1N1)+
Resistance (mutation)	M2I (S31N)	M2I (S31N)	M2I (S31N)	Oseltamivir (H275Y)
Recognition	2003	2005	2009	2007
Virulence	Yes	Yes	Yes	Yes
Genetic stability	Yes	Yes	Yes	Yes
Circulate in absence of drug	Yes	Yes	Yes	Yes

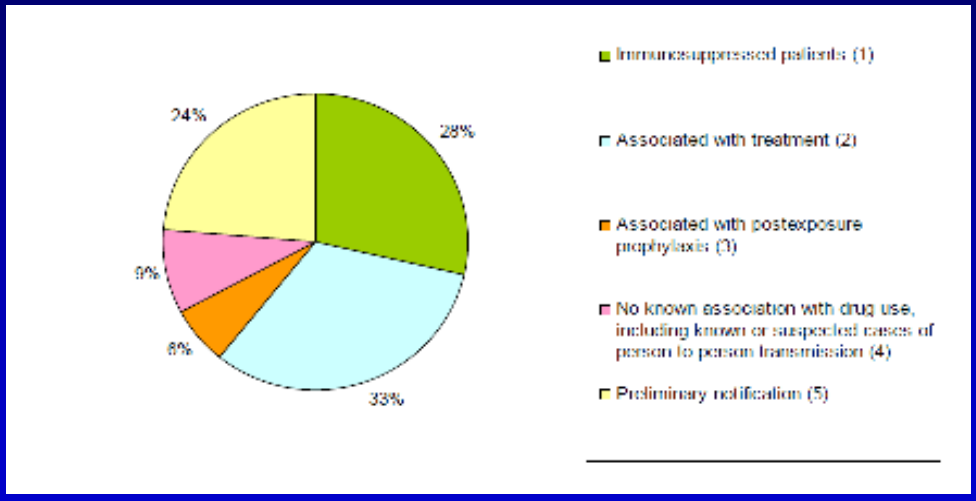
*Clade 2C viruses +Clade 2B viruses

Resistance Profiles of N1 from Clinical Isolates

NA change	Virus	Fold Δ in NA inhibition assay vs WT			
		Oselt	Zanam	Peram	Laninam
H275Y	Seasonal H1	>300	1-2	50->300	2
H275Y	Pandemic H1	227->300	1-2	58->300	2
I223R	Pandemic H1	25-45	10	7	NA
N295S	H5N1	57-138	2-27	3-130	NA

Mishin et al., AAC 49:4516, 2005; Wetherall et al., AAC 41:742, 2003; Yamashita et al., AAC 53:186, 2009; Baz et al., JID March 2010; Memoli et al.. CID 50; 1 May 2010; Hamelin et al., PLoS Path 6:e1001015, 2010; Duan et al., PLoS Path 6:e1001022, 2010; Earhart et al., JIPH 2:74, 2009; van der Vries et al., Options P-194, 2010; Takashita et al., Options P-175, 2010; Kiso et al., PLoS Path 6:e1001079, 2010 ; Rousset et al., Options P-198, 2010

Oseltamivir Resistance in Pandemic H1N1, WHO Reports to 18 August 2010 (N = 304)



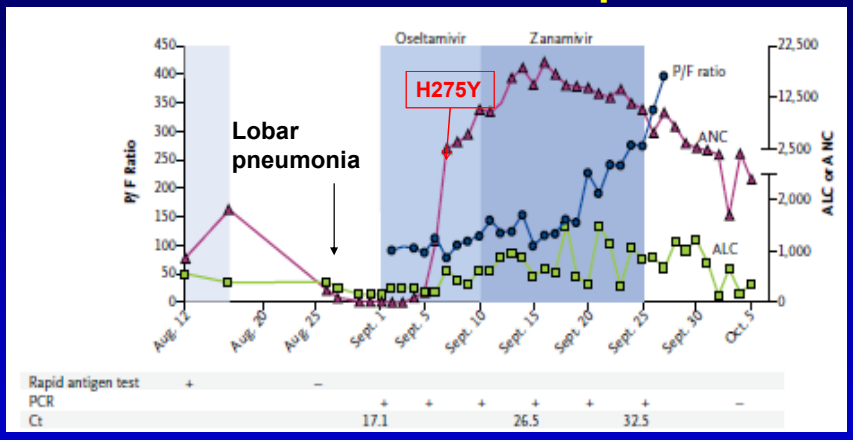
http://www.who.int/csr/disease/swineflu/oseltamivirresistant20100820.pdf

Emergence of Oseltamivir Resistance (H275Y) in Pandemic H1N1 Virus Post Therapy

Location	Patient group	No. patients	No. (%) resistant
Vietnam (Hien et al., 2010)	Mild-moderate illness, RT-PCR + >day 5	33	0*
Hong Kong (To et al., 2010)	Mild illness	35	0
	Hospitalized	34	1 (3%)
Scotland (Harvala et al., 2010)	Hospitalized, non-IC	22	0
	Hospitalized, IC host	10	5 (50%)
Australia (Wang et al., 2010)	Hospitalized, intensive care	25	3 (12%) 2 IC hosts

*Resistance detected in 3 hospitalized cases with RT-PCR positive > 5 days

IV Zanamivir for Oseltamivir-Resistant Pandemic H1N1 in Immunocompromised Host



- 10 yo girl with ALL and pH1N1 positive URI → diffuse pneumonia and mechanical ventilation → recovery

Gaur et al. NEJM, published online 23 December 2009

Oseltamivir Resistance (H275Y) in Pandemic H1N1

- Replication + illness like wild-type in mice + ferrets
- Transmissible by contact and respiratory routes in ferrets (varies with isolate) + guinea pigs
- Emergence as early as day 2-4 of treatment
- Associated with severe + fatal illness
  - Prolonged shedding (weeks) of resistant virus in IC hosts irrespective of continued oseltamivir
- Recovery from persons with no known drug exposure
- Clusters in community and healthcare settings

Tramonta et al., EID 16:1068, 2010; Harvala et al., Eurosurveillance 8 April 2010; Memoli et al., CID 1 May 2010; Mai et al., NEJM 362:86, 2009; Hamelin et al., PLoS Path 6:e1001015, 2010; Seibert et al., J Virol 25 Aug 2010; Kiso et al., PLoS Path 6:e1001079, 2010; Duan et al., PLoS Path 6:e1001022, 2010; Moore et al., Options abst P-190, 2010

Newer Influenza Antivirals

Investigational Anti-Influenza Agents

- NA inhibitors (NAIs)
  - Peramivir, zanamivir (IV)
  - A-315675 (oral)
- Long-acting NAIs (LANIs)
  - Laninamivir (topical)
  - ZNV dimers (topical)
- Conjugated sialidase
  - DAS181 (topical)
- Protease inhibitors
- HA inhibitors
  - Cyanovirin-N, FP
  - Arbidol (oral)
- Polymerase inhibitors
  - Ribavirin (oral, IV, inhaled)
  - Favipiravir/T-705 (oral)
  - Viramidine (oral)
  - siRNA (IV, topical)
- NP inhibitors (nucleozin)
- Interferons
  - IFN inducers
  - RIG-I activator (5'PPP-RNA)
- Antibodies (anti-HA, NA, M2)
- Cationic airway lining modulators (iCALM- topical)

Selected Anti-Influenza Agents in Clinical Development- September 2010

Agent	Target	Sponsor	Route	Development phase
Zanamivir	NA	GSK	IV	Phase 2 → 3
Peramivir	NA	Biocryst, Shionogi	IV	Phase 3*
Laninamivir (CS-8958)	NA	Biota, Daiichi-Sankyo	Inhaled	Phase 3
Favipiravir (T-705)	Polymerase	Toyama	Oral	Phase 2 → 3
DAS181	HA receptor	Nexbio	Inhaled	Phase 1→ 2

Note: IV formulation of oseltamivir under study *Licensed in Japan, S Korea

Comparative Plasma Levels of Neuraminidase Inhibitors in Adults

Drug	Route	Dose	Cmax (ng/ml)	Cmin (ng/ml)	Plasma T1/2 (hrs)
Oseltamivir	PO	150 mg q 12 hr	~380-560	~280	6-9
Zanamivir	IV	600 mg q 12 hr	32-39,700	340-490	1.8-2.1
Peramivir	IV	600 mg Q 24 hr	~43,800	~70	8-21

Adapted from Supplemental Table 5, Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. N Engl J Med 362:1708, 2010

Summary of Recent NAI Clinical Trials

- Uncomplicated influenza
  - Peramivir: single IV dose (300 or 600 mg) superior to placebo and comparable to 5 days of oseltamivir in adults (NB: not superior for resistant H1N1 (H275Y))
  - Laninamivir (CS-8958): single inhaled doses of 20 mg or 40 mg comparable to 5 days of oseltamivir in adults + children (NB: superior for resistant H1N1 in children)
- Hospitalized adults
  - Peramivir: multiple IV doses (200 or 400 mg) comparable to oseltamivir in hospitalized adults

Kohno et al., AAC 16 Aug 2010 and ICAAC 2009, abst V537a; Sugaya and Ohashi., AAC 54:2575, 2010; Ison et al., XIth ISRVI, Feb 2009

P-160

Interim Virological Analysis of a Prospective Single Arm Phase II Study of Intravenous Zanamivir for the Treatment of Hospitalised Patients with Influenza A/H1N1 2009 Infection

PJ Yates[1], CY Man[2], H Zhao[2], FM Marty[3], D Garot[4], V Thamlikitkul[5], AF Peppercorn[2]
[1]GlaxoSmithKline, Stevenage, UK; [2]GlaxoSmithKline, RTP, NC, US; [3]Brigham and Women's Hospital, Boston, USA; [4]Hôpital Bretonneau, Tours, France; [5]Siriraj Hospital, Mahidol University, Thailand

- 43 hospitalized pts (20-78 yrs); 79% co-morbidities
  - 86% prior oseltamivir Rx; 40% mechanical vent
  - Median of 5 days (range, 1-7 days) after illness onset
- Nasopharyngeal swab viral loads:

Assessment Day	n	Median change from Baseline, $\log_{10}$ copies/mL (range)
Baseline/Day 1	30	5.39 (2.86, 7.91)
Day 2	29	-1.17 (-2.53, 1.22)
Day 3	28	-1.69 (-3.11, 0.27)
Day 4	28	-1.91 (-5.06, 1.38)
Day 5	27	-1.85 (-5.06, 2.05)

Effect of Clinical and Virological Parameters on the Level of Neutralizing Antibody against Pandemic Influenza A Virus H1N1 2009

Ivan F. N. Hung,[1] Kelvin K. W. To,[1] Cheuk-Kwong Lee,[2] Chi-Kit Lin,[2] Jasper F. W. Chan,[1] Herman Tse,[1] Vincent C. C. Cheng,[1] Honglin Chen,[1] Pak-Leung Ho,[1] Cindy W. S. Tse,[2] Tak-Keung Ng,[4] Tak-Lun Que,[5] Kwok-Hung Chan,[1] and Kwok-Yung Yuen[1]

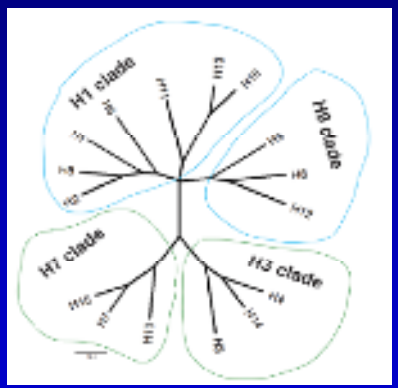
- 90% of the 881 convalescent donors had serum neutralizing antibody titer (NAT) ≥ 1:40.
  - Predictors of higher NAT: pneumonia, sputum production, higher nasopharyngeal viral load
- Convalescent plasma used for treatment in 20 severe pH1N1 patients- "effective treatment"
  - Randomized trial of hyperimmune globulin in progress

Hung et al. CID 51:274, 2010; Hong Kong Morning Post 1 July 2010

OPEN ACCESS Freely available online PLoS one

Heterosubtypic Neutralizing Monoclonal Antibodies Cross-Protective against H5N1 and H1N1 Recovered from Human IgM$^+$ Memory B Cells

- Monoclonals that inhibit group 1 subtype (H1 and H9 clades) membrane fusion by binding to region in the HA stalk
- Findings of neutralizing MoAbs to different epitope in group 2 (H7 and H3 clades) (Goudsmit. Options abst O-866, 2010)



Throsby et al., PLoS ONE 12:e3942, 2008
Eikiert et al., Science 324:246, 2009

Antiviral Combinations

Antivirals Combinations: *Preclinical Findings*

- If virus is adamantane-susceptible, synergistic interactions in vitro and ↑ survival in mice when combined with NAI or ribavirin.
  - If virus adamantane-resistant, no benefit to use in dual combination with oseltamivir or ribavirin.
- Ribavirin and oseltamivir show primarily additive interactions in vitro and in murine models of H5N1.
- Favipiravir and several NAIs show dose-related additive to synergistic effects for influenza A viruses in vitro and on survival in mice.

Smee et al. AAC 51:2010, 2009 and AAC 54:126, 2010; Ilyushina et al. Antiviral Ther 12:363, 2007 and AAC 52:3889, 2008; Tarbet et al. ICAR 2010

Combination Antiviral Therapies in Influenza

Combinations Tested in Humans for PK Interactions	Combinations Tested or Under Evaluation in Humans for Efficacy	Future Considerations for Use in Combinations
PO oseltamivir + amantadine	PO rimantadine + nebulized zanamivir	Polymerase inhibitor (favipiravir/T-705)
PO oseltamivir + favipiravir	PO oseltamivir + inhaled zanamivir	Sialidase inhibitor (DAS181)
IV peramivir + PO rimantadine	PO amantadine + ribavirin + oseltamivir	Antibody therapies
IV peramivir + PO oseltamivir		Other NAI (peramivir, laninamivir
IV zanamivir + PO oseltamivir		Interferons
		Immunomodulators

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Triple Combination of Amantadine, Ribavirin, and Oseltamivir Is Highly Active and Synergistic against Drug Resistant Influenza Virus Strains *In Vitro*

Jack T. Nguyen[1]*, Justin D. Hoopes[2], Minh H. Le[1], Donald F. Smee[2], Amy K. Patick[1], Dennis J. Faix[3], Patrick J. Blair[3], Menno D. de Jong[4], Mark N. Prichard[5], Gregory T. Went[1]*

- Triple regimen was highly synergistic against amantadine- and oseltamivir-resistant influenza A viruses in MDCK cells.
  - Synergy of the triple combination was significantly greater than that of any double combination tested.
- Dual NAI combos showed additivity to antagonism.

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Combined Oseltamivir and Inhaled Zanamivir in Seasonal Influenza

	O + Z n=157	O n=141	Z n=149	P value O+Z/O	P value O+Z /Z
Mean (SD) viral load Δ day 0 to 2 (log10 cgeq/µL)	2.14 (1.54)	2.49 (1.52)	1.68 (1.68)	0.060	0.016
Day 2 influenza RT-PCR < 200 cgeq/µL (%)	46%	59%	34%	0.025	0.028
Duration of symptoms in days (median, IQR)	4 [2.5-14]	3 [2-7]	4 [2.5-14]	0.018	0.96

Duval et al., PLoS Med, in press 2010

End Points for Testing Influenza Antiviral Treatments for Patients at High Risk of Severe and Life-Threatening Disease

1654 • JID 2010:201 (1 June) • PERSPECTIVE

Michael G. Ison,[1] Menno D. de Jong,[6] Kevin J. Gilligan,[2] Elizabeth S. Higgs,[2] Andrew T. Pavia,[4] Jerome Pierson,[3] and Frederick G. Hayden[5,7]

- Perspectives on use of primary virological end points in studies of antiviral agents involving patients hospitalized with severe influenza or IC hosts and others at high risk of severe and life-threatening disease.
- Need for large, systematic studies in target populations to assess correlations between virologic, biomarker, and clinical endpoints.

Antivirals for Severe Influenza: *Comments*

- Medical needs exist for more effective therapy of severe influenza.
  - Evaluate antiviral combinations in immunocompromised hosts and seriously ill patients.
  - Explore role of immunomodulatory interventions.
- Antiviral drug choices and clinical use increasingly complicated by antiviral resistance issues
  - Therapeutic monitoring in seriously ill and especially immunocompromised hosts
- Progress in development of intravenous NAIs and novel antivirals, including therapeutic antibodies.

Antiviral Resistance in Pandemic H1N1 Virus