European Medicines Agency

Clinical evidence for viral load as surrogate endpoint for antivirals for Influenza

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COI Disclosures (Influenza) - FG Hayden

- Consulting:
  - U Alabama Antiviral Discovery and Development Consortium (personal honoraria)
  - Shionogi, Roche, ISIRV (meeting travel expenses)
  - Appili, Arcturus, Cidara, DIOSynvax, Eradivir, FujiFilm, Gilead, GSK, Janssen/JNJ, Leyden Labs, MedImmune, Merck, Ridgeback, Roche/Genentech, SAB Biotherapeutics, Shionogi, Versatope, Via Nova, Vir, (non-compensated)
- Trustee, International Society for Influenza and Other Respiratory Viruses (non-compensated)

Introduction: Virologic Endpoints in Influenza (1)

- Influenza Populations of Interest
  - Controlled human infection models (CHIM)
  - Uncomplicated illness in outpatient adults and children
  - Hospitalized patients
  - Critically ill patients receiving organ support
  - Immunocompromised hosts
- Trial endpoints for assessing clinical recovery are generally accepted for outpatients but vary across studies for hospitalized patients (normalization of vital signs, disease progression, ordinal scales, length of stay [LOS], mortality).

Introduction: Virologic Endpoints in Influenza (2)

- Most virologic studies focus on URT samples, but the sampling sites (nose, throat, NP), assay methods (culture, RT-PCR), and endpoints (Δ baseline, slope, AUC, duration) vary across studies.
- URT influenza A viral titers generally correlate with fever + Sx in outpatients.
- In addition to host factors and virus type/subtype, time from illness onset to initiating antiviral treatment is a key variable in magnitude of antiviral and clinical effects.
- Treatment-emergent antiviral resistance delays viral clearance and can impact clinical course, particularly in young children, critically ill patients, and IC hosts.

Phase 3 RCTs of NA Inhibitors in Uncomplicated Influenza

- Compared to placebo, oral oseltamivir[1,2] and single-dose IV peramivir[3] reduce virus titers by ~0.5-1.0 $log_{10}TCID_{50}$/ml at 1 day post dose and shorten the time to alleviation of illness (TTAS) by ~22-35 hrs.
- Significantly greater antiviral or TTAS reductions are not observed with 2-fold higher doses of either NAI.
- Despite much higher initial plasma levels, no greater antiviral or TTAS reductions are found with IV peramivir compared to oseltamivir.[4]

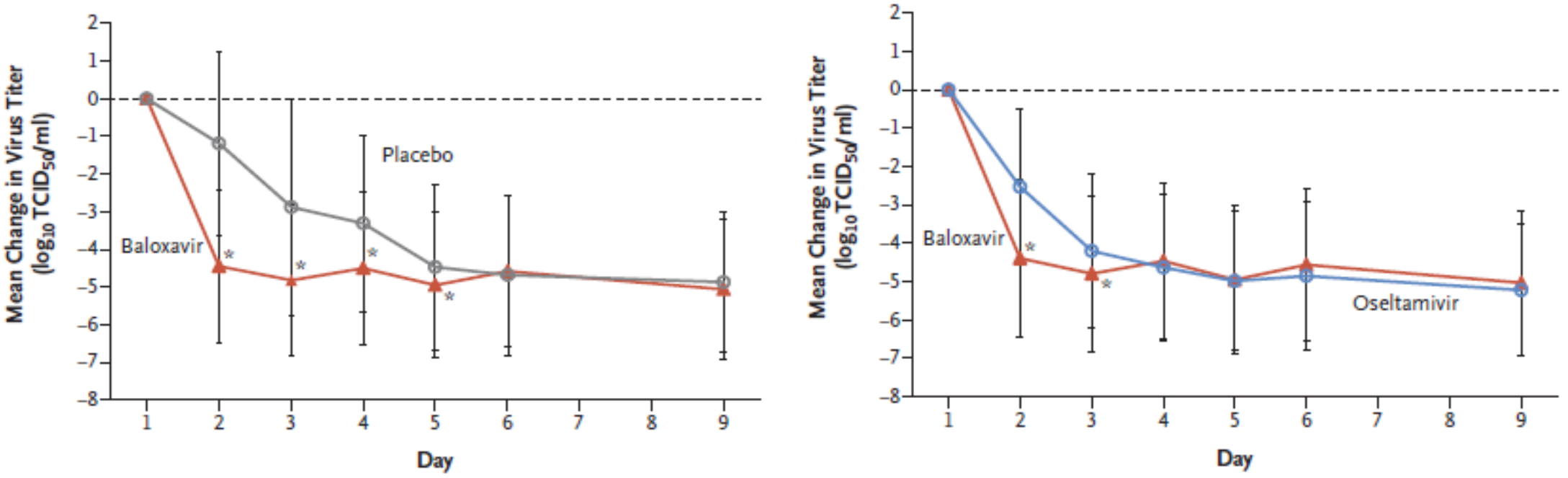
Table 5. Participants' Viral Titers*

	Study Group		
	Placebo (n = 71)	Oseltamivir, 75 mg (n = 67)	Oseltamivir, 150 mg (n = 73)
Baseline			
No. (%) shedding virus	71 (100)	67 (100)	73 (100)
Median titer (range)	3.5 (0.5-6.5)	3.5 (0.5-6.0)	3.3 (0.5-6.0)
Day 1			
No. (%) shedding virus	60 (85)	58 (87)	57 (78)
Median titer (range)	2.3 (0.0-5.5)	1.8 (0.0-6.0)	1.3 (0.0-5.3)
Day 3			
No. (%) shedding virus	20 (28)	19 (28)	20 (27)
Median titer (range)	0.0 (0.0-5.0)	0.0 (0.0-4.0)	0.0 (0.0-3.5)
Day 5			
No. (%) shedding virus	3 (4)	1 (1)	4 (5)
Median titer (range)	0.0 (0.0-2.3)	0.0 (0.0-0.5)	0.0 (0.0-0.5)

- Median time to illness alleviation: 71.5 hr (75 mg) vs 69.9 hr (150 mg) vs 103.3 hr (placebo)[1]

[1]Treanor et al., JAMA 283:1016, 2000; [2]Nicholson et al., [3]Kohno et al., AAC 54:4568, 2010; [4]Kohno et al., AAC 55:5267, 2011

CAPSTONE-1: Baloxavir Marboxil RCT in Uncomplicated Influenza

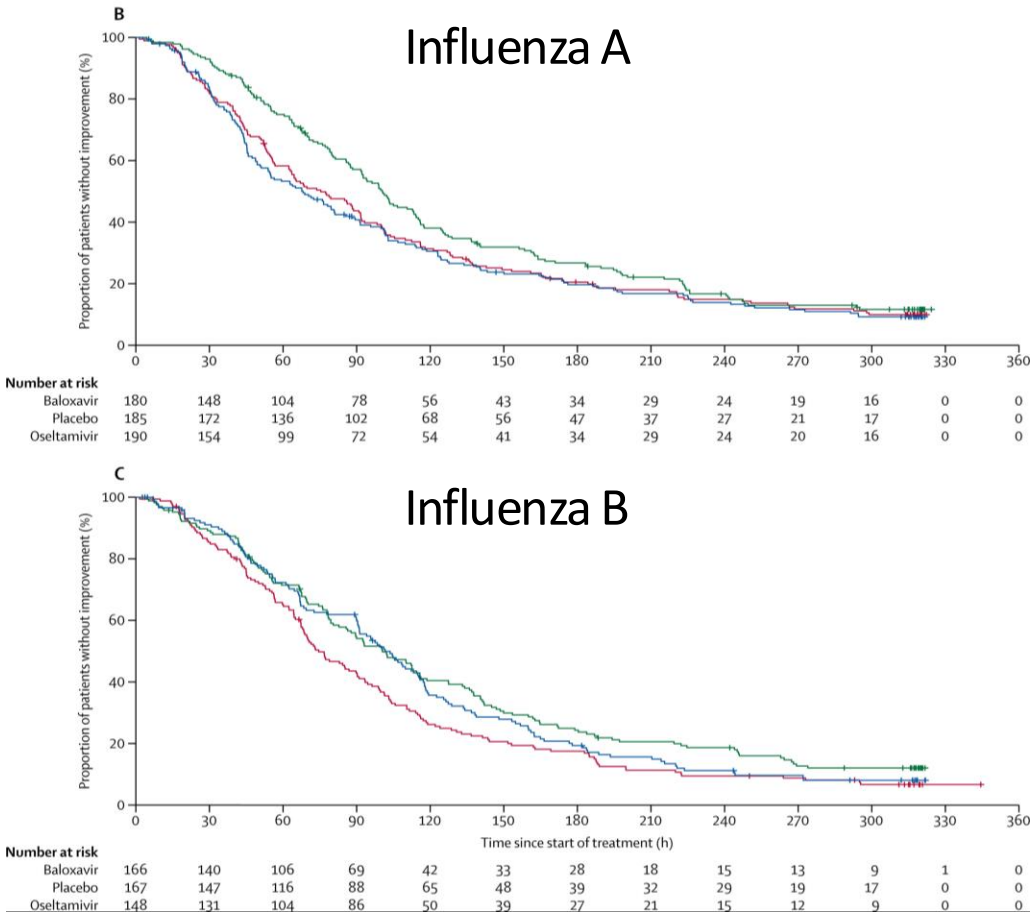


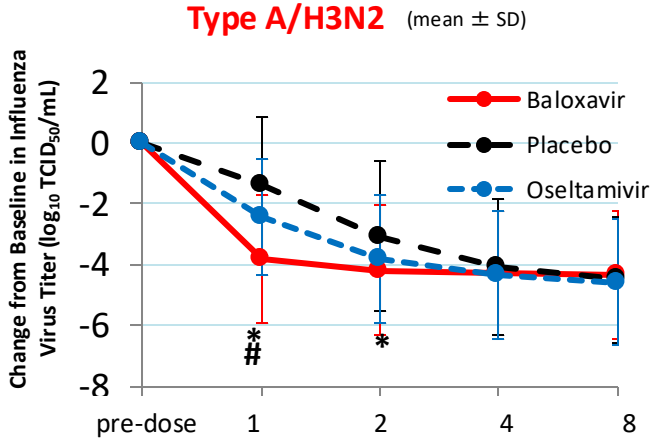
- Median $log_{10}TCID_{50}$/ml declines at Day 2: 4.8- baloxavir, 2.8- oseltamivir, and 1.3- placebo
- Median days to cessation of infectious virus detection: 1- baloxavir, 3- oseltamivir, 4- placebo
- Median time to symptom alleviation: 53.7 hr- baloxavir, 53.8 hr- oseltamivir, 80.2 hr- placebo

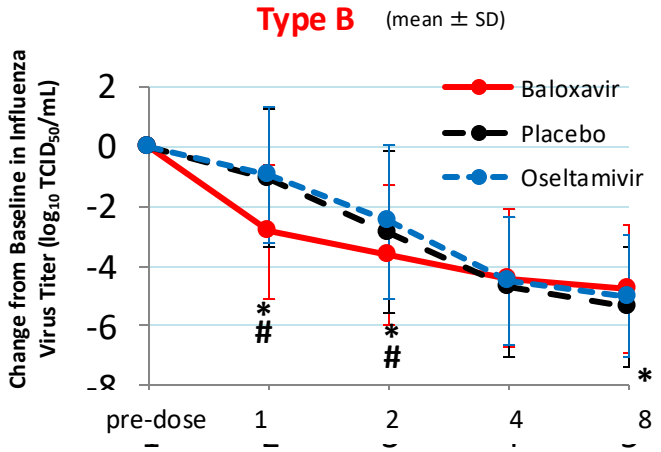
Hayden et al., N Engl J Med 379:913, 2018

CAPSTONE-2 RCT: Baloxavir Treatment RCT in High-Risk Outpatients

Time to improvement of influenza symptoms







Ison et al., Lancet Infect Dis 20:1204, 2020

Health Care Resource Utilization and Antiviral Rx in Outpatients

- 2018-2019 influenza season, US Truven MarketScan Research Databases
- Propensity-matched patients ≥12 years old
  - 56% aged 18-49 yr old (1% ≥65 yr); 15% comorbidity

	15-day follow-up			30-day follow-up		
	Baloxavir (n = 5080)	Oseltamivir (n = 10,160)	*P*	Baloxavir (n = 5080)	Oseltamivir (n = 10,160)	*P*
	All cause					
Patients with outcome, n (%)						
ED visits	72 (1.4%)	174 (1.7%)	.173	111 (2.2%)	264 (2.6%)	.121
Hospitalizations	11 (0.22%)	35 (0.34%)	.175	15 (0.30%)	55 (0.54%)	.041
Outpatient visits	1411 (27.8%)	2925 (28.8%)	.191	2168 (42.7%)	4299 (42.3%)	.668
Prescription fills	1641 (32.3%)	3197 (31.5%)	.296	2447 (48.2%)	4742 (46.7%)	.081

- Respiratory-related ED visits reduced from 1.2% to 0.6%, (P<.001) by day 30

Neuberger et al., Amer J Managed Care28(3):e88, 2022. https://doi.org/10.37765/ajmc.2022.88786

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

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

"Consequently, we outline the evidence to support the use of primary virological end points in studies of antiviral agents involving patients who are hospitalized with severe influenza or those who are at high risk of severe and life-threatening disease."

Ison et al., J Infect Dis 201(11):1654, 2010

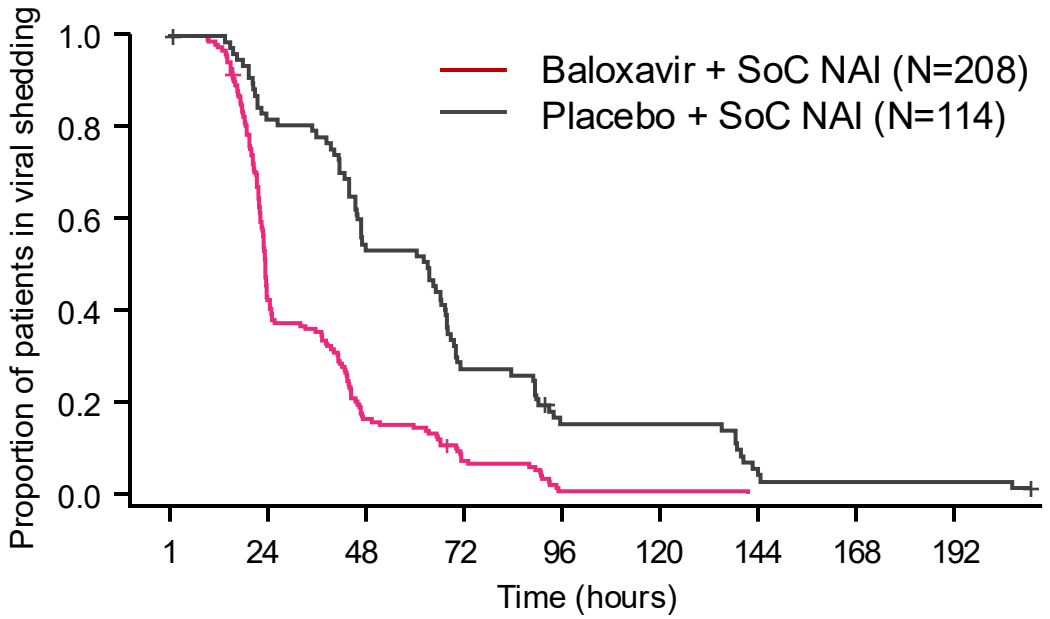
Viral RNA Measures in Hospitalized Influenza Patients

- URT influenza A viral RNA loads (VL) are higher in hospitalized influenza patients than outpatients and have been correlated with LOS.[1,2]
  - Older age, comorbidities, and systemic corticosteroid use associated with longer viral RNA detection.
- High URT VL (11% of 239 patients) has been associated with abnormal chest X-ray findings and lymphopenia but not prognosis.[3]
- In influenza-associated ARDS (n=59; 31% mortality) higher RNA loads in tracheal aspirates/BAL have been associated with mortality.[4]
- Higher influenza B viral loads have not been associated consistently with risk of hospitalization/ICU admission.[5,6]

[1]Lee et al., J Infect Dis 200:492, 2009; [2]Clark et al., J Infection 73: 598, 2016; [3]Lalueza et al., Eur J Clin Micro ID 38:667, 2019; [4]Pronier et al., J Clin Virol 136: 104761, 2021; [5]Granados et al., J Clin Virol 86:14, 2017; [6]Alves et al., J Med Virol 92:1350, 2020

Flagstone RCT: Combined Baloxavir or Placebo + SoC NAI in Hospitalized Influenza Patients

- Enrolment ≤ 96 hr of Sx onset
- Median duration of NPS infectious virus detection: 23.9 vs 63.7 hr (P<0.001)
- 1º outcome= median time to clinical improvement (TTCI): 97.5 vs 100.2 hr
- 28-day mortality numerically lower (2% vs 6%) with combination

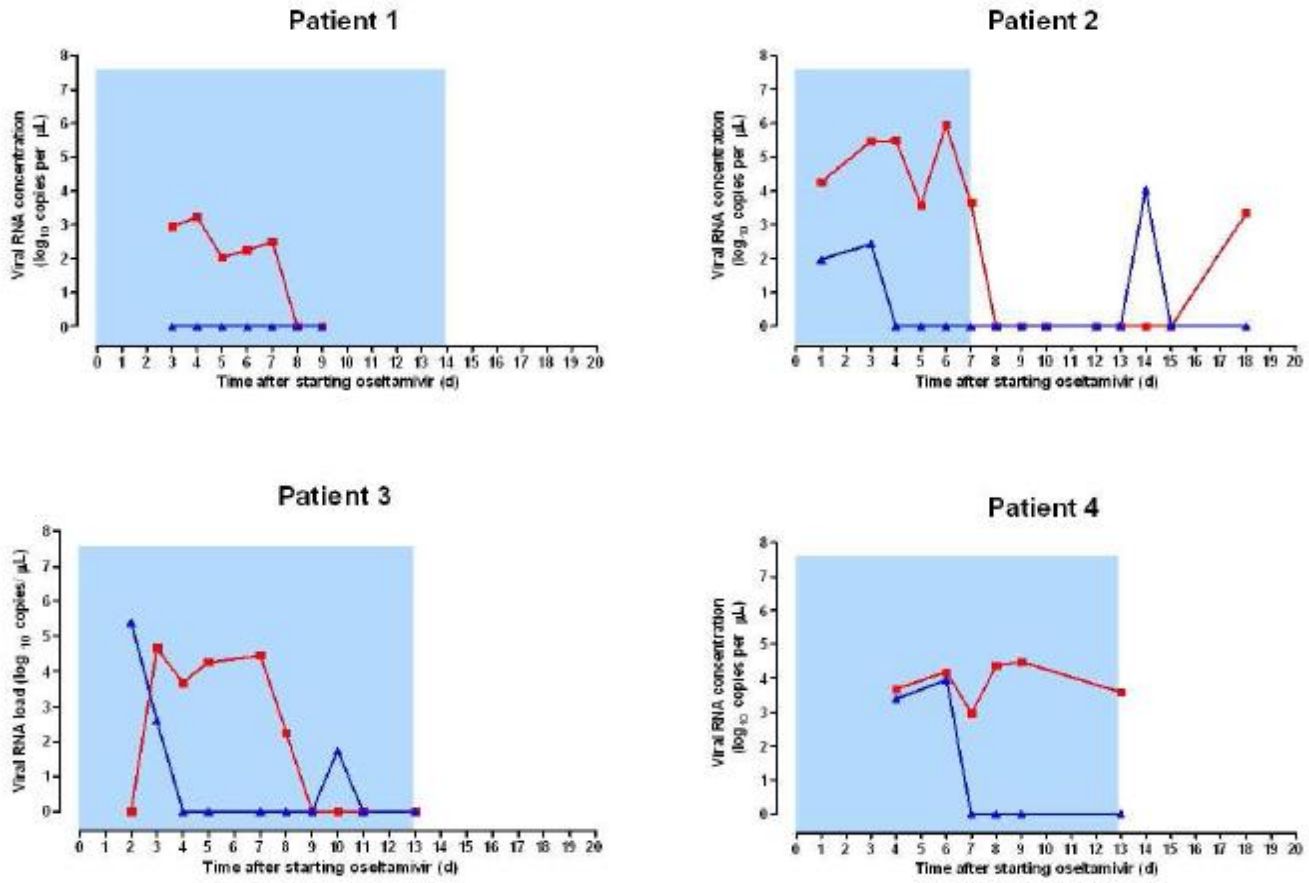


- PA/I38X substitutions in 1%
- NA/H275Y in 1% with combination vs 3% with NAI alone
- PA-I38T + NA-H275Y in 2 IC hosts

Kumar et al., Lancet Infect Dis 22(5):718, 2022

Pandemic H1N1 2009 Viral RNA Loads in Upper and Lower Respiratory Tract during Oseltamivir Therapy

- 28 patients with severe pneumonia (10 intubated)
- URT VL >1log$_{10}$ higher at entry than in 38 non-severe.
- Higher + more sustained VLs in tracheal aspirates than URT during oseltamivir
- Median time to negative VL 6 days (URT) vs 11 days (TA)
- No H275Y detected.



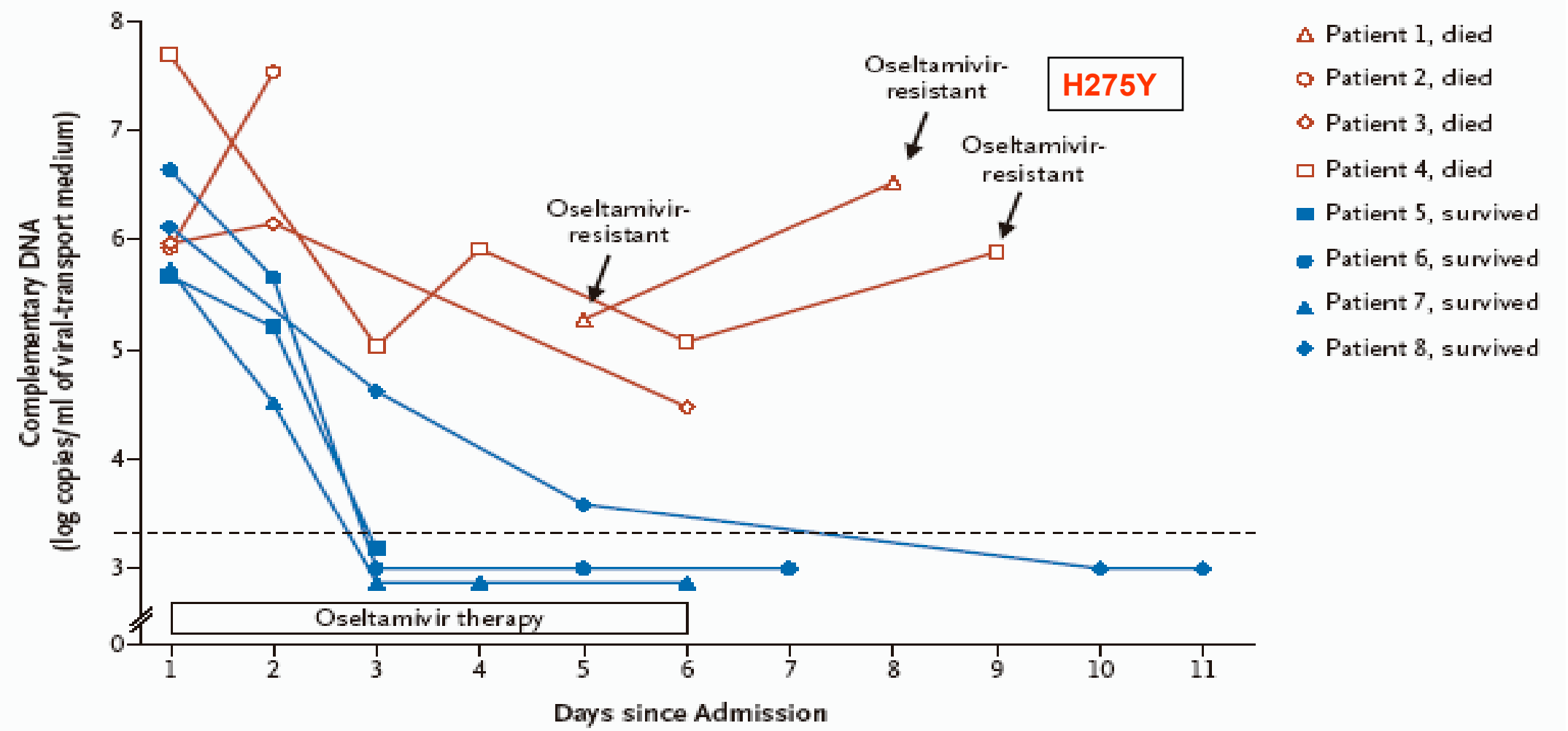
Lee et al., Antiviral Therapy 16:237, 2011

Treatment Emergent Oseltamivir Resistance in Severe Influenza A(H1N1)pdm09 Pneumonia

- Retrospective cohort study of 22 oseltamivir-treated patients with influenza A(H1N1)pdm09 infection + ARDS + persistent viral detection ≥5 days
- 5 (23%) had treatment-emergent detection of H275Y substitution in NA
  - 2nd sample at median of 8 days
  - More systemic corticosteroid use
- Patients with the H275Y-substituted virus had higher day-28 mortality than others (80% *vs* 12%; p=0.011)

Behillil et al., Clin Infect Dis 71(4):1089, 2020

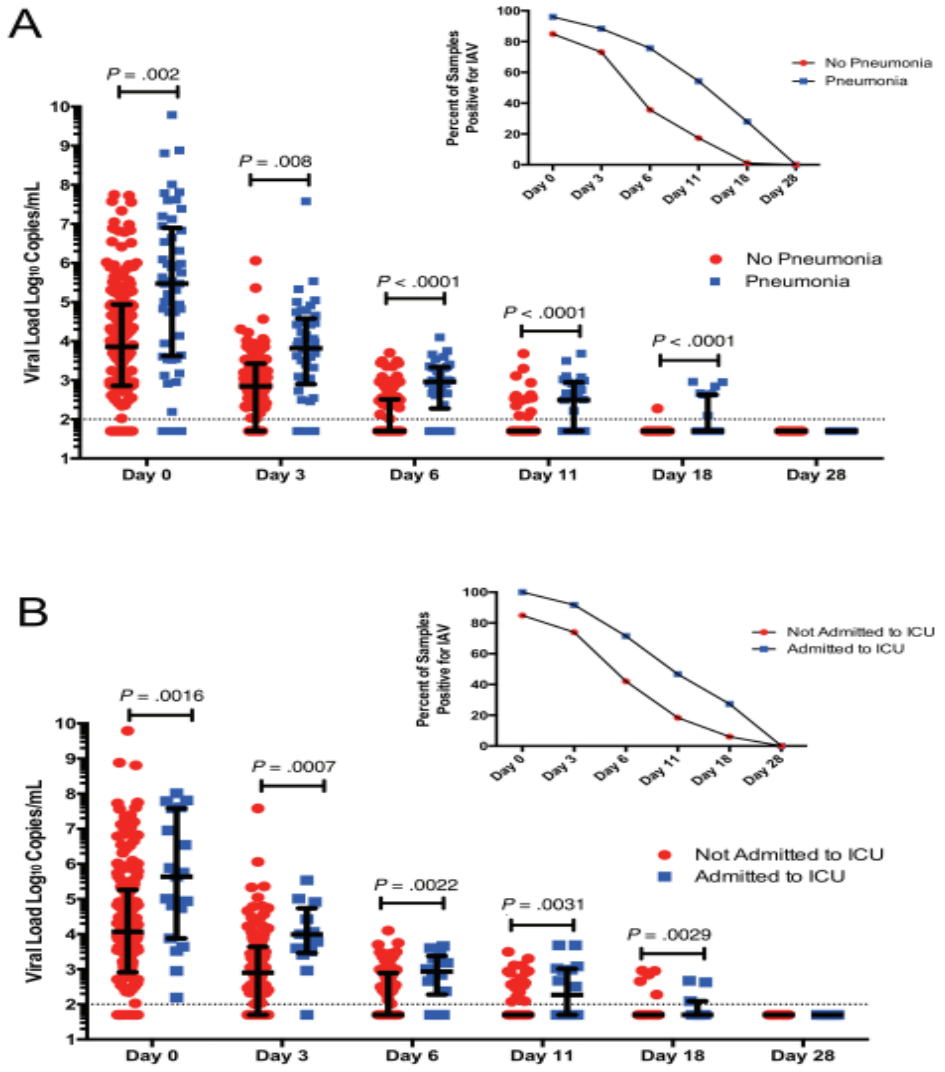
Pharyngeal Viral Loads and Resistance Emergence during Oseltamivir Treatment of H5N1



de Jong et al., NEJM 353:25, 2005

Influenza in Transplant Recipients: 5-Year Prospective Study

- 616 patients (477 SOT; 139 HSCT) at median 3.2 yr post Tx
- 66% hospitalized, 22% pneumonia at presentation, 11% ICU, 8% MV
- Higher URT VL at presentation in those with pneumonia, ICU admission, and no vaccine.
- Death ≤ 30 days in 2.9%
- 94% received oseltamivir for a median 5 days (range, 1–42 days)
- Antiviral Rx ≤48 hr of Sx onset → ↓ risk pneumonia



Kumar et al., Clin Infect Dis 67(9):1322, 2018

REMAP-CAP Trial in Hospitalized Influenza Patients

(Slide courtesy of Dr. Anthony Gordon, Imperial College, London)

▶Influenza antiviral domain

Inclusion criteria

- Hospitalised with moderate or severe influenza
- Laboratory-confirmed influenza
- Aged ≥28 days

Response Adaptive-Randomisation

▶ Other domains: corticosteroids vs not in those on suppl O_2; baricitinib vs tocilizumab vs neither in critically ill

▶ Primary endpoint:

- All-cause mortality at 90 days post-randomisation

▶ Secondary endpoints include:

- Hospital + ICU lengths of stay, ICU mortality at 90 days, ventilator-free days, organ failure-free days

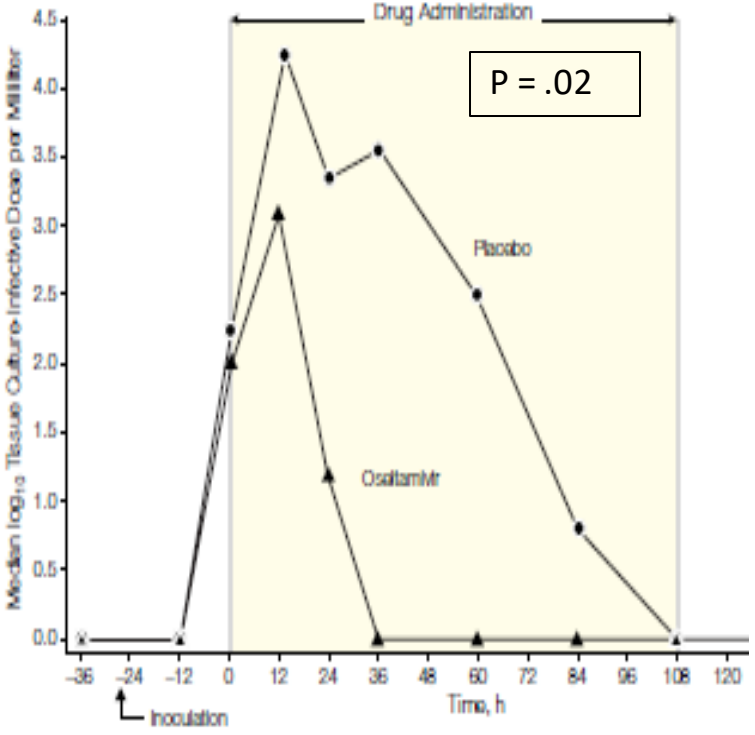
REMAP-CAP influenza antiviral domain protocol available at: https://www.remapcap.org/protocol-documents (Accessed June 2024)

Summary Points

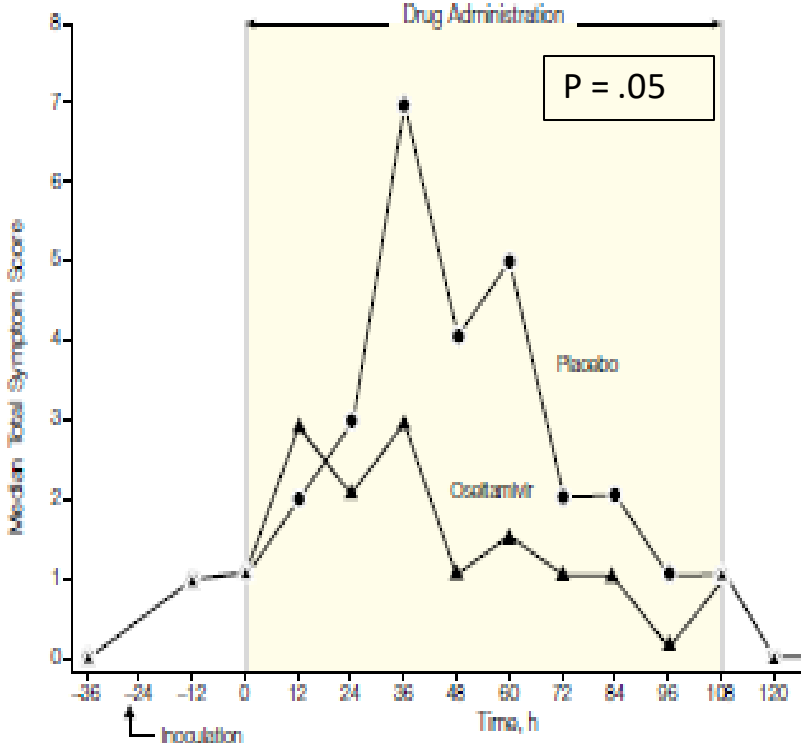
- In outpatients with uncomplicated influenza A illness, greater antiviral efficacy has not been proven to provide greater symptom relief but may further reduce the risk of influenza-associated complications.
- In serious influenza illness, failure to control replication is associated with poor outcomes and increased risk of resistance emergence.
  - Combining antivirals with differing MOA reduces the risk of treatment-emergent resistance.
- In hospitalized patients ongoing clinical trials (REMAP-CAP, Recovery, others) will provide key data regarding the efficacy of antiviral monotherapy/combinations, as well as usefulness of adding immunomodulatory interventions.

Thank You

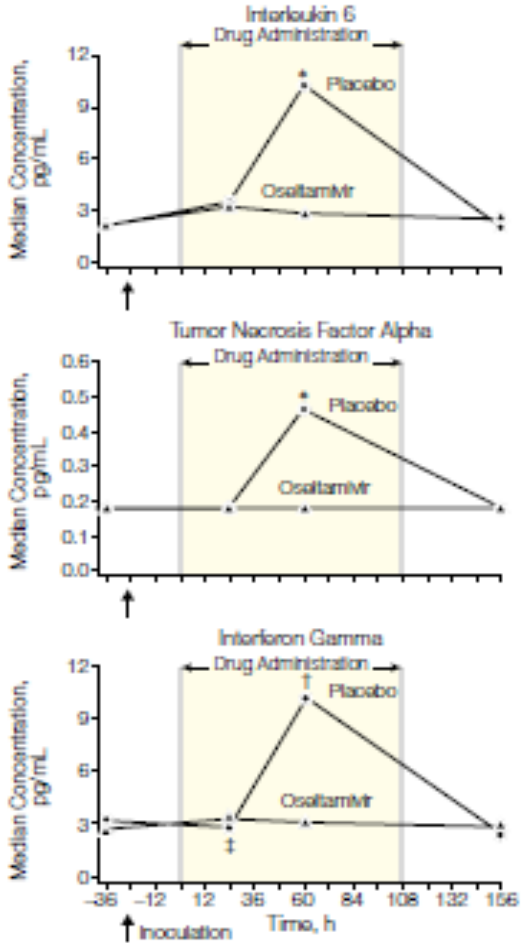
Oseltamivir Treatment in Experimental Influenza A(H1N1)



Nasal Lavage Virus Titers



Symptom Scores



Nasal Lavage Cytokines

- Treatment stated at 28 hr post inoculation
- Number infected = 56 oseltamivir, 13 placebo

Hayden et al., JAMA 282:1240, 1999

Antiviral Effects of IV Peramivir in Hospitalized Adults + Children

Table 8. Viral Shedding in Subjects With Positive Baseline and Postbaseline Viral Titer (ITTI Non-NAI SOC Population)

Titer Measurement	Placebo + SOC	Peramivir[a] + SOC	*P* Value
Measured by viral culture, $\log_{10}$ $TCID_{50}$/mL			
Baseline, median (range)	2.00 (0.75–4.50) (n = 15)	2.75 (0.75–4.50) (n = 23)	. . .
Change from baseline, median (95% CI)			
At 24 h	−1.13 (−1.75 to −.25) (n = 14)	−1.75 (−2.25 to −1.00) (n = 19)	.44
At 48 h	−1.38 (−1.75 to −.25) (n = 14)	−2.25 (−3.00 to −1.50) (n = 17)	.29
At 108 h	−1.75 (−2.75 to −.25) (n = 9)	−2.13 (3.50 to −.25) (n = 8)	.90
Measured by RT-PCR, $\log_{10}$ viral particles/mL			
Baseline, median (range)	5.84 (2.60–7.99) (n = 34)	5.43 (2.60–7.97) (n = 61)	. . .
Change from baseline, median (95% CI)			
At 24 h	−1.09 (−1.62 to −.80) (n = 34)	−1.49 (−1.84 to −1.22) (n = 57)	.56
At 48 h	−1.67 (−2.14 to −.87) (n = 33)	−2.02 (−2.49 to −1.46) (n = 55)	.17
At 108 h	−2.39 (−3.29 to −1.59) (n = 18)	−2.48 (−3.05 to −2.11) (n = 29)	.93

Abbreviations: CI, confidence interval; ITTI, intent-to-treat infected; NAI, neuraminidase inhibitor; RT-PCR, reverse-transcription polymerase chain reaction; SOC, standard of care; $TCID_{50}$, median tissue culture infective dose.

[a] Peramivir was given at a dosage of 600 mg once daily.

- No differences in time to clinical resolution (VS normalization), Sx alleviation, or resumption of usual activities in this subset (43 placebo, 73 peramivir).

de Jong et al., CID 59:e172, 2014