Treatment of Severe Influenza A Infection with Celecoxib: a Double Blind Randomised Controlled Trial

Health Research Symposium, Hong Kong 2019

Ivan Hung, Kelvin To, KY Yuen

Division of Infectious Diseases

Department of Medicine

LKS Faculty of Medicine

The University of Hong Kong

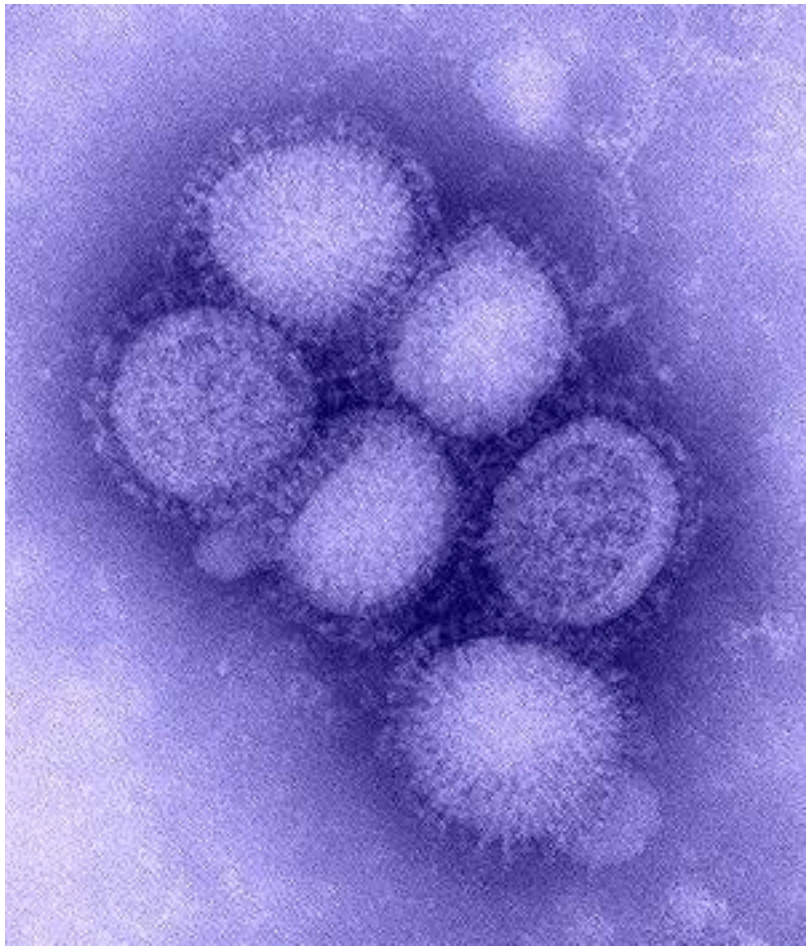
HKU Med

Disclosure

- Received honoraria from Pfizer, Roche, MSD, Abbvie, Ferring, Gilead and Chong Lap

Introduction

- Influenza poses a heavy burden to global health services
- WHO: 250,000 – 500,000 deaths worldwide; >500 deaths in Hong Kong in 2015
- At risk: elderly, young children, chronic illness
- Prevention by influenza vaccine is the best option
- Problems: poor vaccine uptake, vaccine mismatch, poor immunogenicity
- Neuraminidase inhibitor – oseltamivir- less effective for late presenters
- The new polymerase inhibitor – baloxavir; unknown effectiveness in hospitalized patients and late presenters

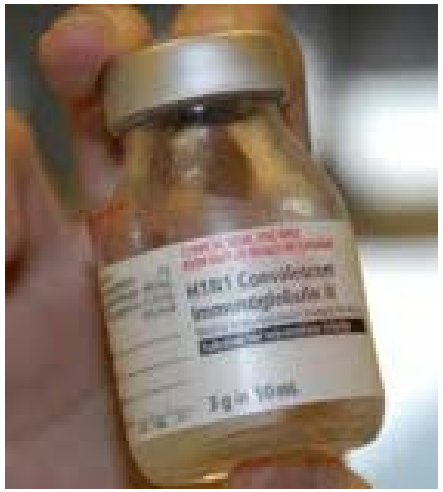


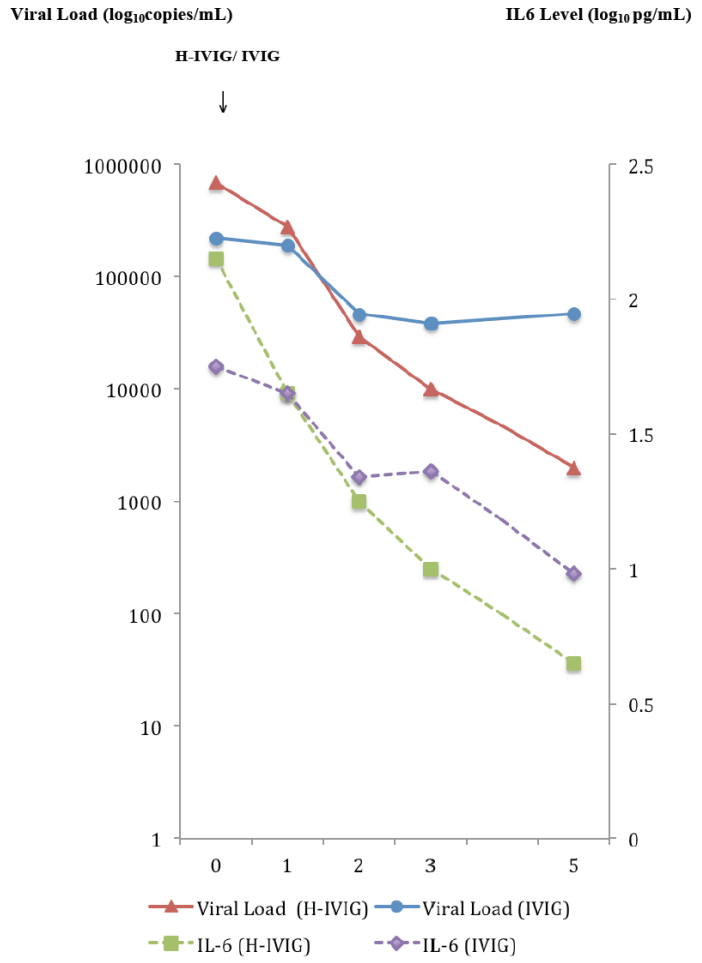
http:www.who.int/mediacentre/factsheets
http://emergency.cdc.gov/HAN

Adjuvant Therapy for Severe Influenza Infection

- Convalescent plasma/ hyperimmune IVIG reduced viral load/ cytokine/ mortality in severe H1N1 2009
- Very expensive and long preparation time

- Animal study using immunomodulators with COX-2 inhibitor celecoxib + zanamivir reduced mortality in mice infected with H5N1/ H7N9
- Combination therapy will be optimal for influenza treatment
- Investigate the effect of celecoxib + oseltamivir in severe influenza infection in human





Hung IF et al. Clinical Infect Dis 2011;52;447-56
Hung IF et al. Chest 2013;144:464-73
Beigel JH et al. Lancet Respir Med 2017;5:500-11

Zheng BJ, Yuen KY et al. PNAS 2008;105:8091-6
Li C, Zhang AJ et al. PLoS One 2014;18:9
Jin Y, Zhang G et al. J Gene Med 2011;13:243-9

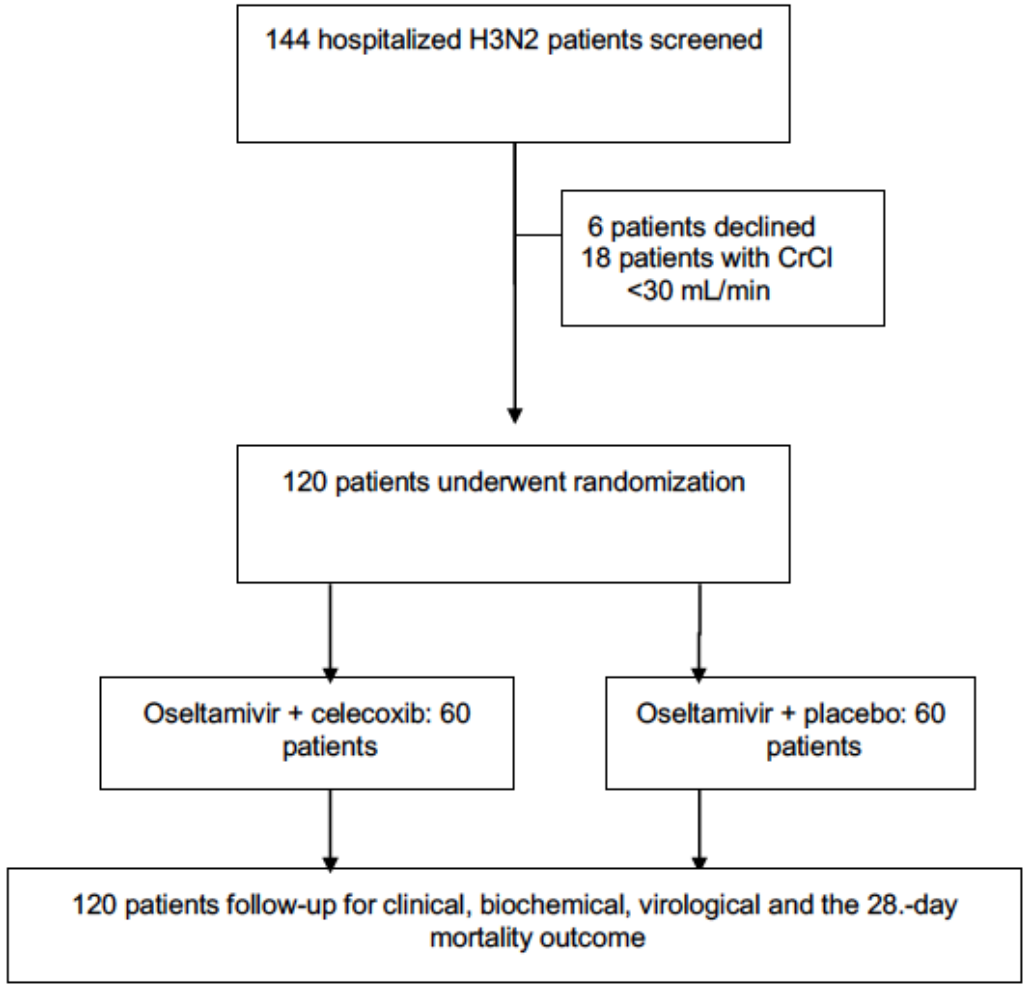
HKU Med

Method

- Prospective double blind randomised controlled trial (NCT02108366)
- Adult patients hospitalized for confirmed influenza A(H3N2) infection and on oxygen support
- December 2014 to March 2017
- Randomised to oseltamivir 75mg bd + celecoxib 200mg daily for 5 days vs. oseltamivir 75mg bd + placebo
- Antibiotics given to treat pneumonia/ concomitant infections
- Inclusion: symptom duration ≤72 hours, hospitalized A(H3N2) by NxTAG™, antiviral commenced within 24 hours after admission
- Exclusion: allergy to oseltamivir, NSAIDs, beta-lactam antibiotics, CrCl <30mL/min; hx of CHF
- Primary end point: 28 days mortality
- Secondary end point: NEWS, NPA viral load, cytokine, LOS

HKU Med

Recruitment Flow-chart



CrCl: creatinine clearance

HKU Med

Demographics, Clinical Features, Laboratory and CXR

	Oseltamivir + Celecoxib (n=60)	Oseltamivir (n=60)	*p* value
Demographics			
Median age in years (IQR)	70 (58.3-83.3)	73.5 (60.3-81.8)	0.85
Sex (male) (%)	31 (51.7)	39 (65)	0·18
Smoker (current or ex-smoker) no. (%)	31 (51.7)	27 (45)	0.47
Elderly home resident - no. (%)	26 (42.9)	29 (50)	0·58
Influenza vaccination (2014/5 season)	18 (30)	17 (28.3)	0·93
Past Medical History - no. (%)			
Cardiovascular disease	12 (20)	15 (25)	0.53
Pulmonary disease	32 (53.3)	31 (51.7)	0·86
Cerebrovascular disease	20 (33.3)	16 (26.7)	0·43
Liver disease	1 (1.6)	2 (3.3)	0.56
Renal disease	6 (10)	4 (6.7)	0·51
Malignancy	13 (21.7)	13 (21.7)	1.00
Presenting symptoms - no· (%)			
Fever	60 (100)	60 (100)	1.00
Cough	47 (78.3)	45 (75)	0.67
Sputum	40 (66.7)	42 (70)	0·70
Rhinorrhea	15 (25)	17 (28.3)	0.68
Sore throat	8 (13.3)	6 (10)	0.57

HKU Med

Demographics, Clinical Features, Laboratory and CXR

Chills	3 (5)	6 (10)	0·30
Wheezes	9 (15)	2 (3.3)	0·03
Headache	1 (1.6)	1 (1.6)	1.00
Dizziness	4 (6.7)	6 (10)	0.51
Dyspnea	21 (35)	30 (50)	0.10
Pleuritic chest pain	6 (10)	3 (5)	0.30
Vomiting	8 (13.3)	9 (15)	0·77
Diarrhea	4 (6.7)	3 (5)	0.70
Initial physical examination findings			
Median oxygen saturation· (%)	92 (90-94.5)	92 (90-96.8)	0·21
Median systolic blood pressure (IQR, mmHg)	100 (91-119.5)	100 (90-119.5)	0·80
Median pulse rate (IQR, /min)	80 (76-90)	82 (72-90)	0·80
Median respiratory rate (IQR, /min)	16 (16-18)	18 (16-20)	0.10
Median temperature (IQR.^{0}C)	38.2 (37.5-38.7)	38.1 (37.4-38.9)	0·58
Initial laboratory findings – median (IQR)			
Total white blood cell (x 10^9/L)	7.8 (5.8-11.3)	8.1 (6.6-11.5)	0·35
Neutrophil (x 10^9/L)	5.7 (4.4-8.8)	6.5 (5.1-9.2)	0·34
Lymphocyte (x 10^9/L),	0.9 (0.6-1.2)	0.9 (0.6-1.4)	0·52
Hemoglobin (g/dL)	11.9 (10.3-12.9)	12.8 (10.6-13.8)	0·11
Hematocrit	0.35 (0.32-0.39)	0.38 (0.32-0.4)	0·25
Alanine transaminase (IU/L)	21 (13-34)	19 (14-32)	0·35
Aspartate transaminase (IU/L)	18 (14-29)	21 (14.3-32)	0.39
Alkaline phosphatase (IU/L)	87.5 (75-104)	87.5 (60.3-110.3)	0·31
Sodium (mmol/L)	136 (132.3-138)	133.5 (132-139)	0·43
Creatinine (µmol/L)	66 (46.8-87.8)	74 (55.2-90.8)	0·26
Urea (mmol/L)	6.2 (4.5-7.9)	6.3 (4.2-10)	0·49
Glucose (mmol/L)	5.8 (5-8.2)	5.8 (5-6.7)	0·29
Creatine kinase (mmol/L)	183 (101-283)	163 (88-232)	0.26
Arterial pH	7.4 (7·3-7.5)	7.4 (7·4-7.5)	0·71
Arterial PO_2 (kPa)	11 (8.4-12.3)	12 (9-13.2)	0·21
Initial radiological findings – no· (%)			
Infiltrate	42 (70)	45 (75)	0·76
Consolidation	4 (6.7)	5 (8.3)	0.83
Baseline viral load (mean log_{10} copies/ml; 95% CI)	2.7 (1.2-4.1)	3.1 (2-4.3)	0·91
Baseline IL-6 (mean log_{10} pg/mL; 95% CI)	2.1 (1.8-2.4)	2 (1.2-2.9)	0.71
Baseline IL-10 (mean log_{10} pg/mL; 95% CI)	1.1 (0.9-1.2)	1.1 (0.9-1.4)	0.59
Baseline TNF-α (mean log_{10} pg/mL; 95% CI)	1.3 (1.1-1.4)	1.2 (1.1-1.3)	0.59
NEWS (mean, 95% CI)	4.9 (4.3-5.5)	5 (4.4-5.7)	0·77

*IQR: interquartile range; C.I·: confidence interval, NEWS: National Early Warning Score

HKU Med

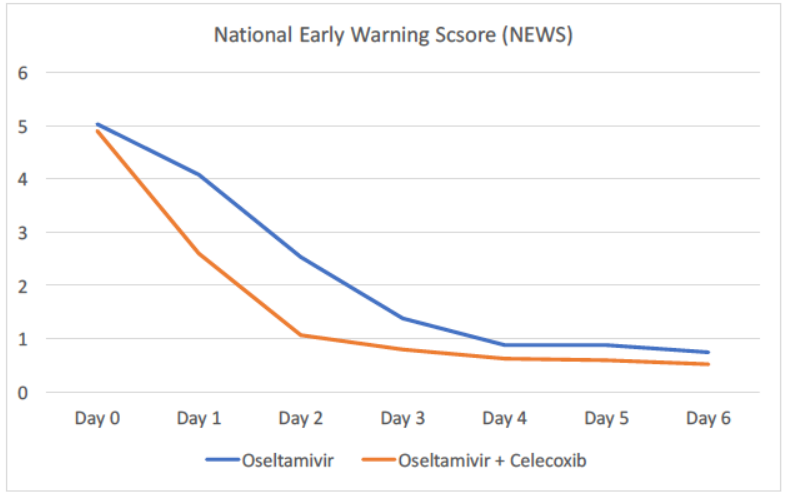
Treatment, Complications & Clinical Outcome

	Oseltamivir + Celecoxib (n=60)	Oseltamivir (n=60)	*p* value
Days of symptoms before starting antiviral treatment (median; IQR)	2 (1-3)	2 (1-3)	1.00
Respiratory support upon admission – no· (%)			
Oxygen	60 (100)	60 (100)	1.00
Mechanical ventilation	11 (18.3)	13 (21.7)	0·65
BiPAP	7 (11.7)	8 (13.3)	0·78
CPAP	34 (56.7)	35 (58.3)	0·85
ECMO	5 (8.3)	4 (6.7)	0.73
Complications – no· (%)			
Bacterial co-infection upon presentation	3 (5)	2 (3.3)	0·83
Ventilator associated pneumonia	4 (6.7)	8 (13.3)	0·04
Admission to ICU – no· (%)	12 (20)	13 (21.7)	0·82
Length of hospitalization (median; IQR)	9.5 (7-11.5)	9.5 (7-12)	0.64
Readmission ≤28 days from discharge - – no· (%)	8 (13.3)	10 (16.7)	0·61
Mortality – no· (%)			
28-day	7 (11.7)	16 (26.7)	0·037

*BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; IQR: interquartile range; ICU: intensive care unit;

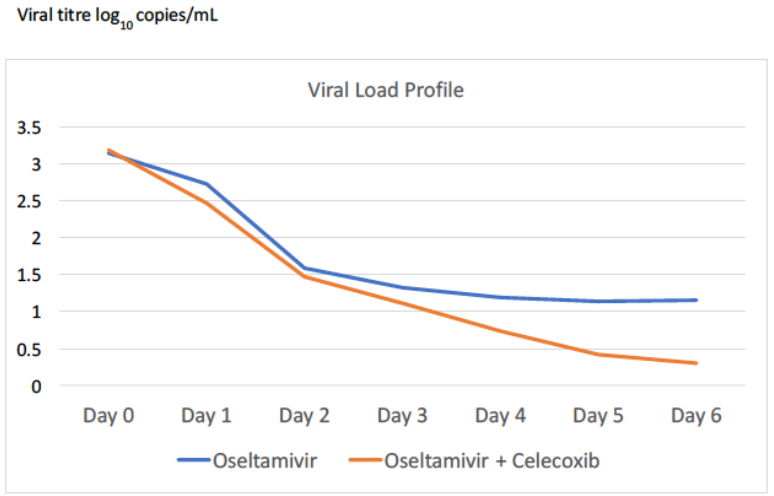
HKU Med

NEWS & Viral Load Profile



Days after first dose	0	1	2	3	4	5	6
Oseltamivir NEWS (95% CI)	5.03 (4.4-5.67)	4.08 (3.53-4.63)	2.53 (2.08-2.99)	1.38 (1.07-1.70)	0.88 (0.65-1.12)	0.88 (0.65-1.12)	0.75 (0.51-0.99)
Oseltamivir + Celecoxib NEWS (95% CI)	4.9 (4.28-5.52)	2.6 (2.15-3.05)	1.07 (0.79-1.34)	0.80 (0.57-1.03)	0.63 (0.45-0.82)	0.60 (0.41-0.79)	0.52 (0.36-0.67)
p-value	0·77	<0·0001	<0·0001	0·007	0.138	0.08	0.214

NEWS: National Early Warning Score

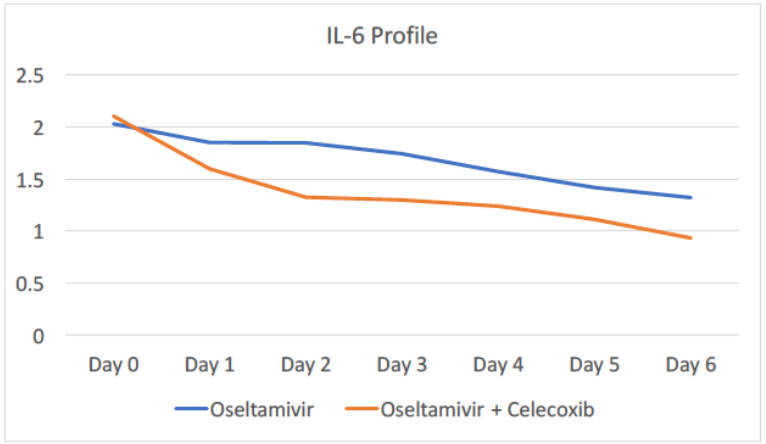


Days after first dose	0	1	2	3	4	5	6
Oseltamivir Viral titre log_{10} copies/mL (95% CI)	3.14 (2.01-4.28)	2.72 (1.40-4.04)	11.59 (0.18-30.0)	1.32 (0.01-2.63)	1.19 (0.19-2.57)	1.14 (0.18-2.45)	1.15 (0.19-2.50)
Oseltamivir + Celecoxib Viral titre log_{10} copies/mL (95% CI)	3.18 (1.64-4.72)	2.46 (1.34-3.58)	1.47 (0.64-2.29)	1.11 (0.36-1.86)	0.73 (0.11-1.36)	0.42 (0.07-0.91)	0.30 (0.14-0.75)
p-value	0·92	0·85	0·45	0.59	0.89	0.45	0·34

HKU Med

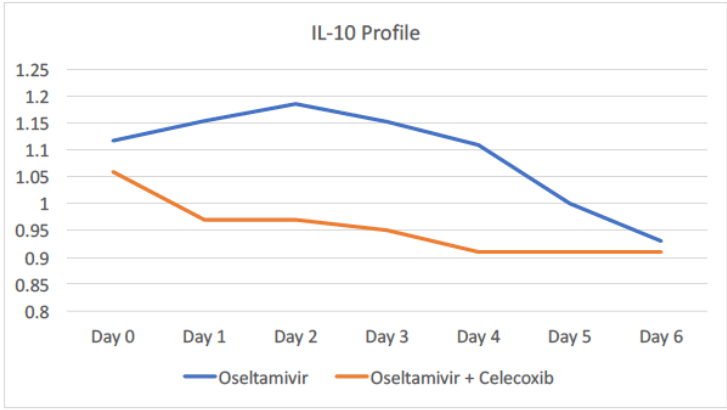
Cytokine Profile

log$_{10}$ pg/mL



Days after first dose	0	1	2	3	4	5	6
Oseltamivir IL-6 log$_{10}$ pg/mL (95% CI)	2.03 (1.18-2.87)	1.85 (1.16-2.54)	1.85 (1.15-2.54)	1.74 (1.10-2.39)	1.57 (1.03-2.11))	1.42 (0.98-1.86)	1.32 (0.91-1.72)
Oseltamivir + Celecoxib IL-6 log$_{10}$ pg/mL (95% CI)	2.11 (1.79-2.42)	1.60 (1.47-1.72)	1.33 (1.22-1.44)	1.29 (1.16-1.44)	1.24 (1.10-1.37)	1.11 (1.00-1.22)	0.93 (0.89-0.97)
p-value	0·71	0·036	0·001	0.027	0.020	0.005	0·016

log$_{10}$ pg/mL



Days after first dose	0	1	2	3	4	5	6
Oseltamivir IL-10 log$_{10}$ pg/mL (95% CI)	1.12 (0.86-1.38)	1.15 (0.85-1.46)	1.19 (0.84-1.52)	1.15 (0.85-1.45)	1.11 (0.74-1.48)	1.00 (0.80-1.20)	0.93 (0.85-1.01)
Oseltamivir + Celecoxib IL-10 log$_{10}$ pg/mL (95% CI)	1.06 (0.90-1.22)	0.97 (0.88-1.06)	0.97 (0.89-1.05)	0.95 (0.88-1.03)	0.91 (0.87-0.94)	0.91 (0.87-0.94)	0.91 (0.87-0.94)
p-value	·59	0.053	0.004	0.004	0.014	0.030	0·064

HKU Med

Results Summary

- Significantly lower 28-day mortality (p=0.037) in the oseltamivir-celecoxib combo group
- Significantly reduction in serial IL-6 and IL-10 from day 1 to day 5 ($p<0.05$) and NEWS from day 1 to day 3 ($p<0.01$)
- Kaplan-Meier analysis: combination treatment had lower 28 day mortality (HR:0.63; 95% CI 0.36-0.94; p=0.019)
- Adverse effects: no patients developed rise in creatinine, none developed cardiac/ GI side effects during study

HKU Med

Limitations

- Could not exclude beneficial effects of antibiotics
- All within 72 hours from symptom onset; none were late-presenters
- Validity and generalizability need to be tested in late presenters
- Unable to use in patients with renal impairment/ underlying CHF

HKU Med

Conclusions

- Combination of celecoxib-oseltamivir reduced mortality, serial NEWS and cytokine in hospitalized A(H3N2) patients without increased adverse effects

HKU Med

Acknowledgements

- The study is funded by the HMRF of the Food & Health Bureau of the Hong Kong SAR Government

Thank you!

HKU Med