The role of immunomodulating agents for treatment of severe influenza

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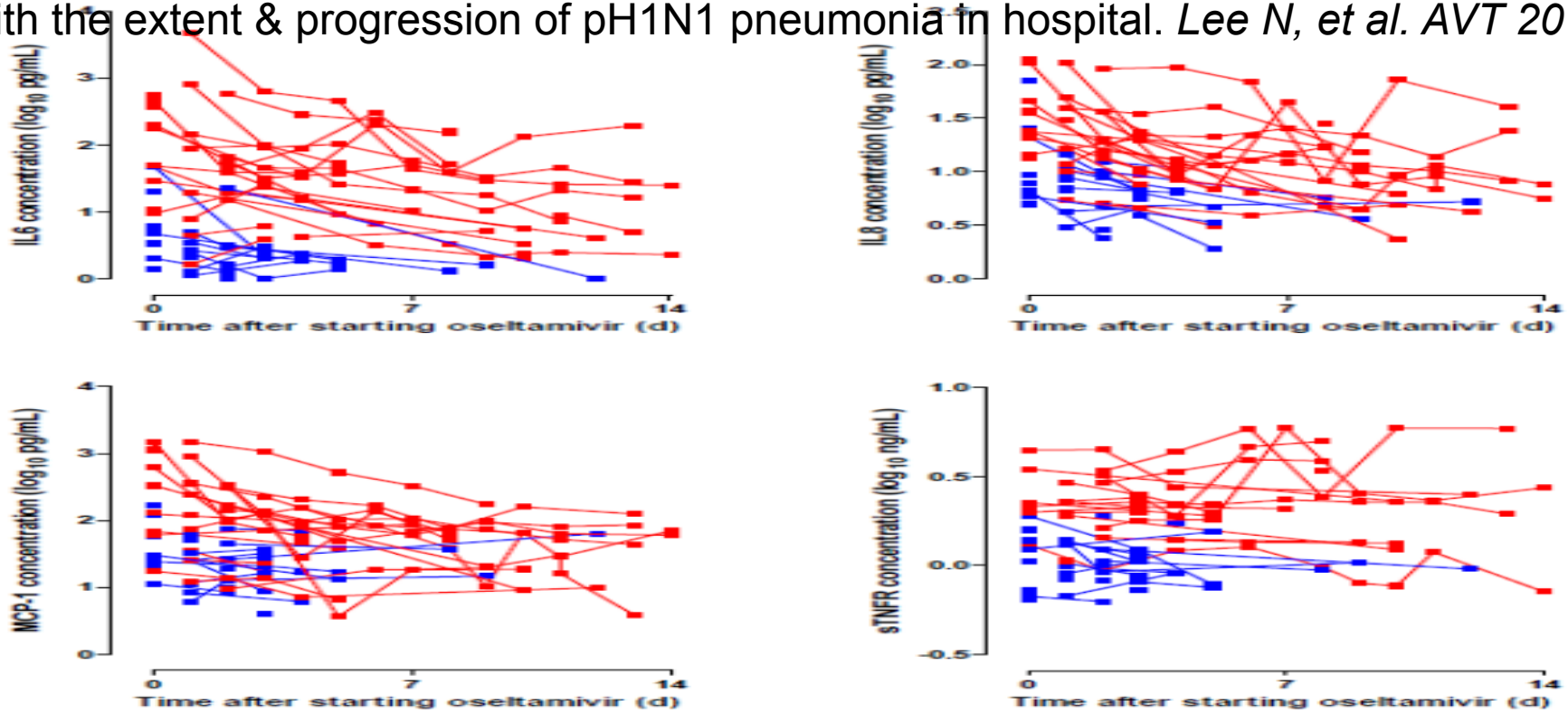
I have no financial relationships with commercial interests to disclose

Adjunctive immuno-modulatory agents for severe influenza

- Systemic corticosteroids
- Passive immunotherapy- Convalescent plasma, hyper-immune IVIg, IVIg.
- Other agents (eg macrolide, NSAID, sirolimus, nitazoxanide, statins, NAC, herbal medicine, chloroquine, pamidronate, peroxisome proliferator-activated receptor-agonists, celecoxib, melasazine, mycophenolic acid, anti C5a antibody, ARB, human mesenchymal stromal cells, endosomal NOX2 inhibitor)

Figure 4. Serial plasma concentrations of IL-6, CXCL-8(IL-8), CCL2(MCP-1) and sTNFR-1 in patients with severe H1N1 pneumonia, shown according to day after treatment commencement

High plasma levels of IL-6, IL-8, MCP-1 & sTNFR-1 were observed, which correlated with the extent & progression of pH1N1 pneumonia in hospital. *Lee N, et al. AVT 2011.*



'Red' line indicates patients with severe pneumonia. 'Blue' line indicates patients with milder illnesses.

N=2649 adults hospitalized with influenza in HK, Singapore & Beijing in 2008-11
Flu A/H3N2 (>45.8%), Flu B (11.1%), A(H1N1)pdm09 (36.3%)

- Pneumonia (40.8%), resp failure (48.6%) , assisted ventilation(11.5%)
- Bacterial super-infections (10.8%) - *S. pneumoniae, S. aureus, H influenzae*
- 73.8% received oseltamivir (44.5% ≤2 days & 65.5% ≤5 days after illness onset);
- 23.1% given systemic corticosteroids.
- Bacterial super-infections ↑ risk of death (adj HR 2.2, 95%CI 1.5–3.1)
- Systemic corticosteroids ↑ risks of super-infections (2.7% → 9.7%) & deaths (adj HR 1.7, 95% CI 1.1–2.6) when controlled for indications.

Lee N, Leo YS, Cao B, et al. ERJ 2015

Corticosteroids as adjunctive therapy in the treatment of influenza (Review)

Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS
Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD010406.

On meta-analysis, corticosteroid Rx was associated with ↑ in mortality (OR 3.06, 95%CI 1.58 to 5.92). Pooled subgroup analysis of adjusted estimates of mortality from 4 studies found OR 2.82, 95% CI 1.61 to 4.92.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Corticosteroid therapy			
Mortality	141 per 1000	334 per 1000 (206 to 493)	OR 3.06 (1.58 to 5.92)	1915 (13 studies)	⊕◯◯◯ very low[a]
Hospital-acquired infection	See comment	See comment	Not estimable	619 (3 studies)	⊕◯◯◯ very low[b]
Critical illness (composite outcome including death and intensive care unit admission)	See comment	See comment	Not estimable	322 (2 studies)	⊕◯◯◯ very low[c]
Mechanical ventilation	See comment	See comment	Not estimable	377 (2 studies)	⊕◯◯◯ very low[d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

High-dose corticosteroids associated with increased mortality & longer viral shedding in pts with influenza A (H7N9) viral pneumonia.

TABLE 5. Outcomes From 65 Propensity Score–Matched Patient Pairs

Outcome	All			Low-to-Moderate Corticosteroid Dose			High Corticosteroid Dose		
	Corticosteroid, *n* = 65	Control, *n* = 65	*p*	Corticosteroid, *n* = 39	Control, *n* = 39	*p*	Corticosteroid, *n* = 26	Control, *n* = 26	*p*
Mortality,[a] *n* (%)				(25–150mg/d methylpred)			(> 150 mg/d methylpred eqv)		
30-d mortality	19 (29.2)	8 (12.3)	0.019	9 (23.1)	6 (15.4)	0.508	10 (38.5)	2 (7.7)	0.021
60-d mortality	27 (41.5)	10 (15.3)	0.002	14 (35.9)	6 (15.4)	0.057	13 (50.0)	4 (15.4)	0.022
Nosocomial infections,[a] *n* (%)									
HAP	17 (26.2)	18 (27.7)	1.000	10 (25.6)	12 (30.8)	0.804	7 (26.9)	6 (23.1)	1.000
HAP complicated by bacteremia, *n* (%)	7 (10.8)	3 (4.6)	0.289	3 (7.7)	1 (2.6)	0.625	4 (15.4)	2 (7.7)	0.625
Nosocomial bacteremia or candidemia, *n* (%)	4 (6.2)	2 (3.1)	0.625	0 (0.0)	1 (2.6)	1.000	4 (15.4)	1 (3.8)	0.250
Invasive pulmonary aspergillosis or mucormycosis, *n* (%)	4 (6.2)	4 (6.2)	1.000	2 (5.1)	1 (2.6)	1.000	2 (7.7)	3 (11.5)	1.000
Viral shedding (d)[b]	14 (12–17)	12 (11–15)	0.027	13 (10.3–16)	12 (10.5–15)	0.252	15 (13.5–20)	13 (10.8–15.3)	0.039

Cao B, et al. Crit Care Med 2016

Systemic Corticosteroids

We suggest against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day.

(Weak recommendation; low quality of evidence)

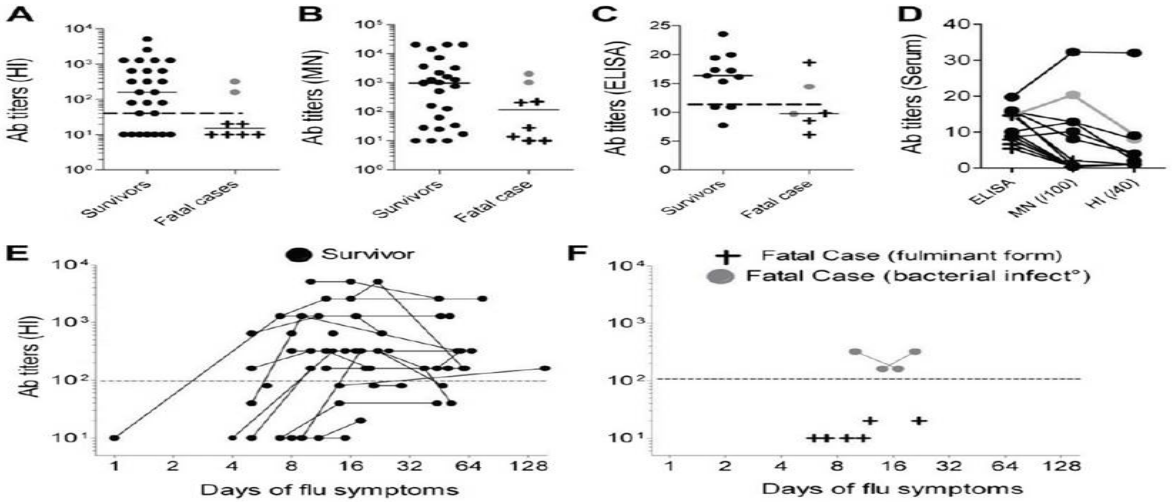
Survival Sepsis Campaign. ESICM 2016

What may be useful?

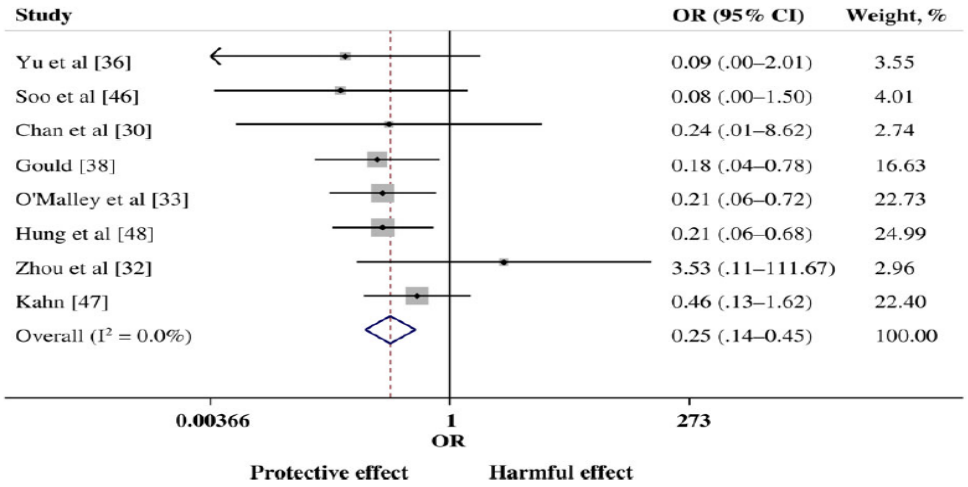
- Convalescent plasma
- Hyperimmune IVIg
- IVIg

Guihot, Luyt, Parrot, *et al.*: Low Titers of Anti-H1N1 Antibodies Predict Fatal Influenza Infection

Am J Respir Crit Care Med Vol 189, Iss 10, pp 1240–1249, May 15, 2014



Fatal cases of pH1N1 unable to mount Ab response vs survivors



Exploratory post-hoc meta-analysis of studies of SARS & severe influenza showed a significant ↓ in the pooled odds of mortality following convalescent plasma vs placebo or no Rx (OR 0·25; 95%CI 0·14 to 0·45). Mair-Jenkins J. JID 2015

Resp rate ≤20/min for adults or age-defined thresholds of 20-38/min for children) & a room air SaO2≥ 93%.

Pts with severe flu A or B (hypoxia or tachypnoea) randomly assigned to either 2U (or paed eqv) of anti-influenza plasma (HI Ab at least 1:80) + std care vs std care alone, & FU for 28 days. Beigel JH, et al. Lancet Respir Med 2017

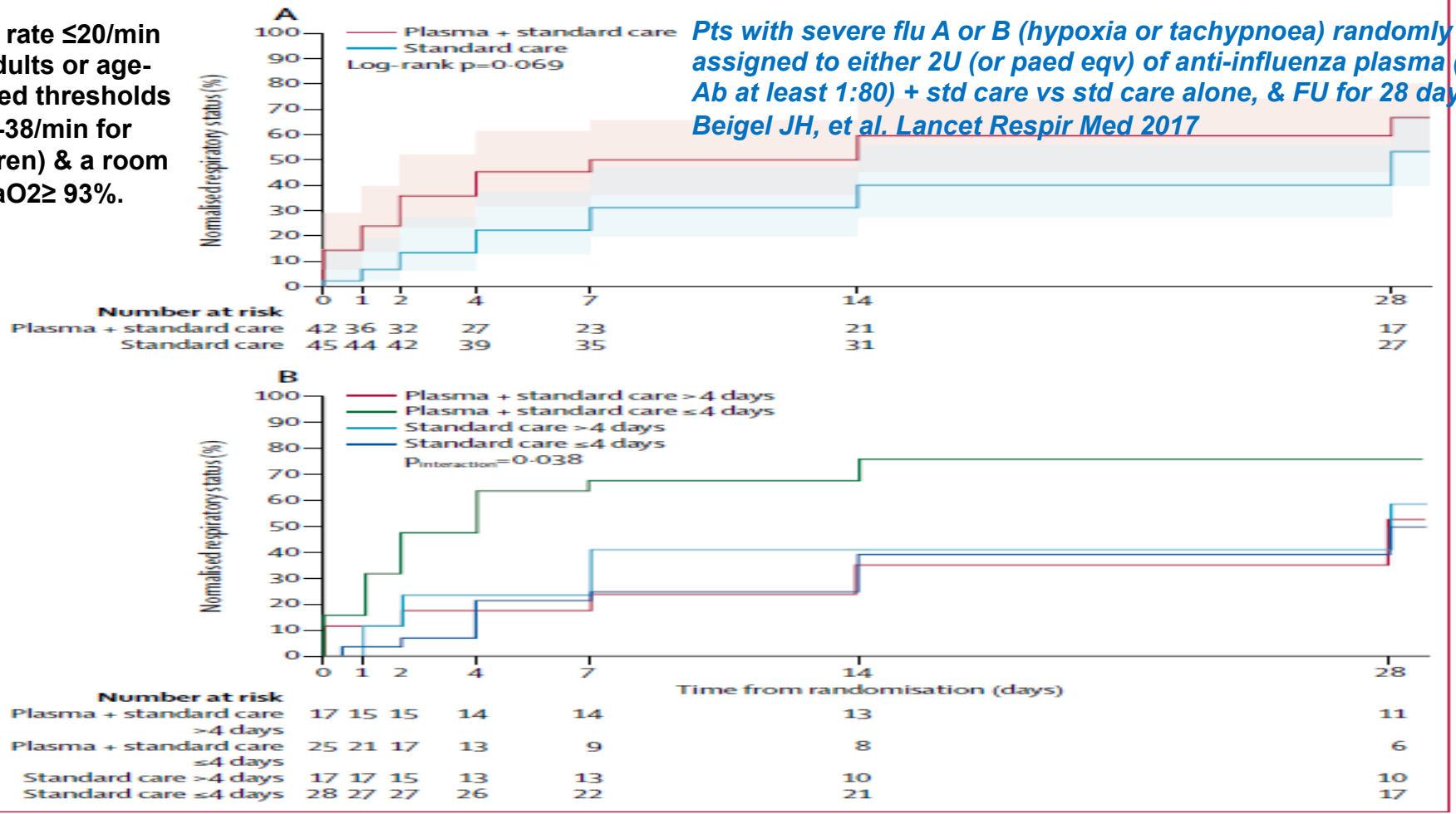


***Figure 2*: Kaplan-Meier curves of normalised respiratory status over time with intention-to-treat analyses in the primary efficacy population**
Shaded areas denote 95% CIs. Normalised respiratory status over time, by randomised treatment (A) and by randomised treatment and days from symptoms onset to randomisation.

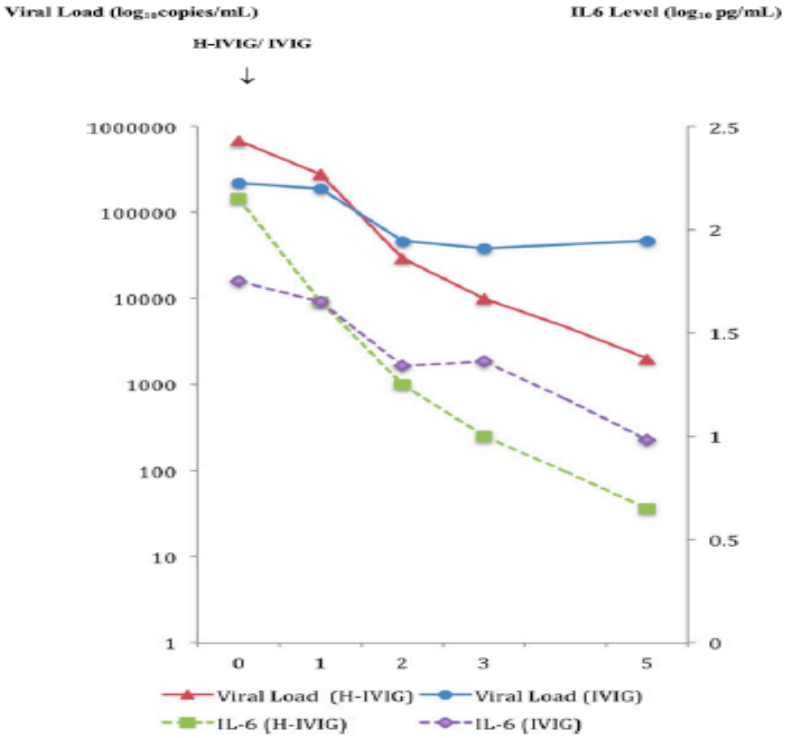
Hyperimmune IV Immunoglobulin Treatment

A Multicenter Double-Blind Randomized Controlled Trial for Patients With Severe 2009 Influenza A(H1N1) Infection

- Pts on standard antiviral therapy & ICU support randomized to receive H-IVIG (n = 17) or IVIG (n = 18).
- The H-IVIG group had lower D5 & 7 viral load vs the control.
- H-IVIG treatment was the only factor which independently reduced mortality (OR: 0.14, 95% CI, 0.02-0.92; p=0.04) among those (n=22) who received either H-IVIG or IVIG < 5 days of symptom onset .

Hung IF. Chest 2013

5 hospitals in HK comparing H-IVIG prepared from plasma of persons who had recovered from A(H1N1)pdm09 vs normal IVIG made before 2009 .



Days after ICU admission
Treatment: H-IVIG; Control: IVIG
H-IVIG/ IVIG infused on day 0 of ICU admission.
Viral load: lowest detection limit 2.95 $\log_{10}$copies/mL; IL-6 lowest detection limit 0.2 $\log_{10}$pg/mL

FIGURE 3. Temporal changes of viral load and IL-6 level in treatment and control groups. See Figure 1 legend for expansion of abbreviations.

Prepandemic IVIG & sera from Kawasaki disease pts treated with this IVIG found to have A(H1N1)pdm09-specific micro-neutralization & hemagglutination inhibition Abs. *Hong DK, et al. Pediatr Infect Dis. 2011*

Significant neutralizing Abs vs A(H2N2) viruses in human IVIg lots made from 1993 to 2010 in Japan. *Kubota-Koketsu R, et al. Biologics. 2012; 6:245-7.*

IVIG manufactured from 1999 to 2014 exhibited significant HI & MN titers vs all investigated strains (A/H1N1, A/H3N2, & B). *Onodera H. Biologics. 2017; 11: 23–30.*

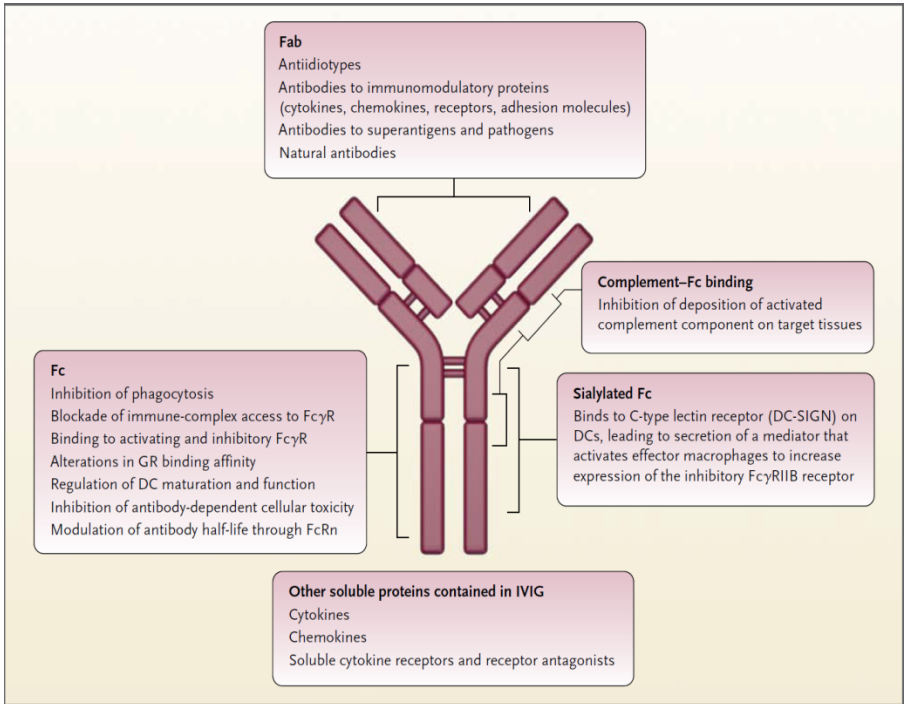
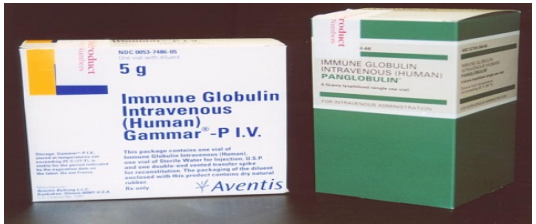


Figure 1. Structure of IgG Molecule in Relation to Various Antiinflammatory and Immunomodulatory Activities.
Intravenous immune globulin (IVIG) also contains numerous soluble proteins with biologic activity. DC denotes dendritic cells, FcγR receptor for the Fc portion of IgG, FcRn neonatal Fc receptor, and GR glucocorticoid receptor.

N Engl J Med 2012;367:2015-25.



Malaysia

A case of acute respiratory distress syndrome associated with novel H1N1 treated with intravenous immunoglobulin G

Chong JL, et al.

Journal of Microbiology, Immunology and Infection (2011) 44, 319–322

59yr old M, 4 days of fever & 2 days of SOB. Rx oseltamivir 150mg bd, ceftriaxone & azithromycin on D7 illness (D1 hosp adm)

IVIg given at D14-18 of illness

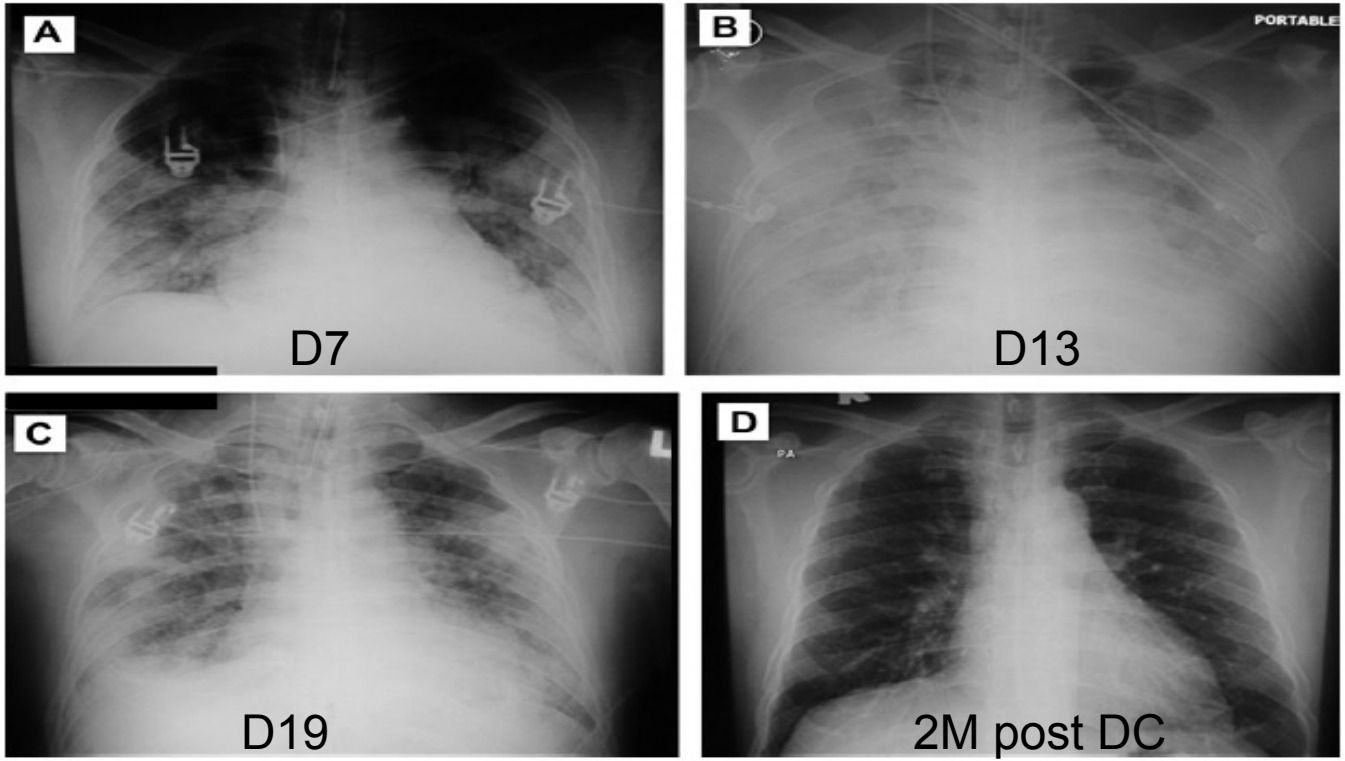


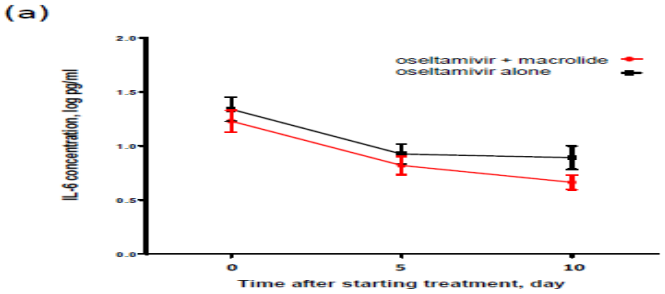
Figure 1. Chest radiographs show (A) bibasal pathy opacity on Day 7 of illness (Day 1 of admission); (B) worsening opacity up to upper zone on Day 13 of illness (Day 6 of oseltamivir 150 mg bd, pre–IV IgG); (C) improvement of chest radiograph on Day 19 of illness (1 day after completion of IV IgG for 5 days); and (D) minimal pulmonary fibrosis 2 months after discharge.

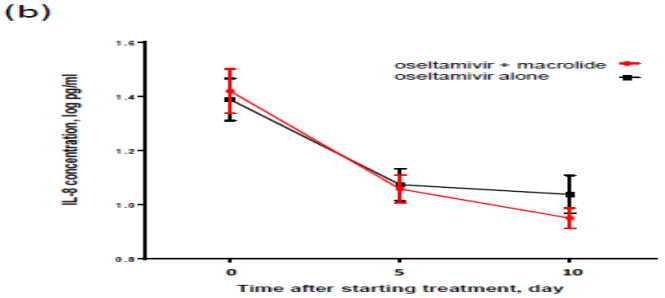
Agents with some positive human data but need more studies

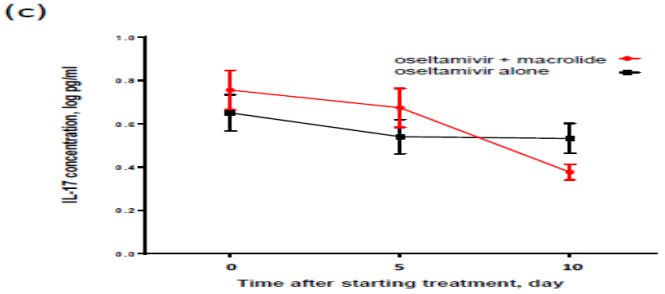
- Macrolide ± NSAID
- Sirolimus
- NAC
- Nitazoxanide (NTX)

Anti-inflammatory effects of macrolide treatment in influenza infections – results of a randomized controlled trial

Oseltamivir & azithromycin (500mg/d) (n=25) vs oseltamivir alone (n=25) for 5 days.







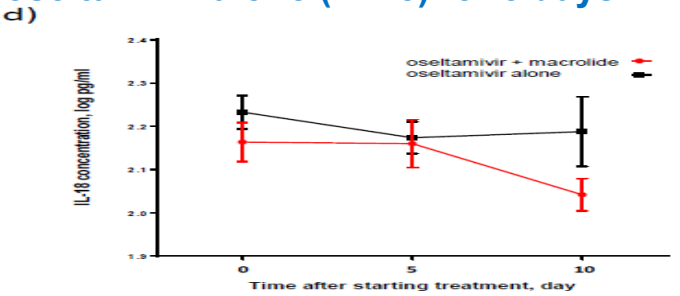
Faster ↓ in pro-inflammatory cytokines IL-6, IL-8, IL-17 & CXCL9/ MIG in the oseltamivir-azithromycin gp;

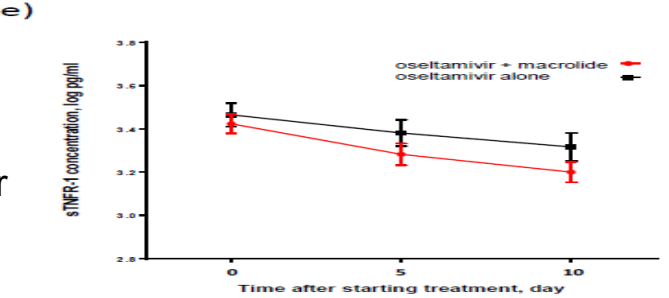
Trends of ↓ shown for sTNFR-1, IL-18, & CRP.

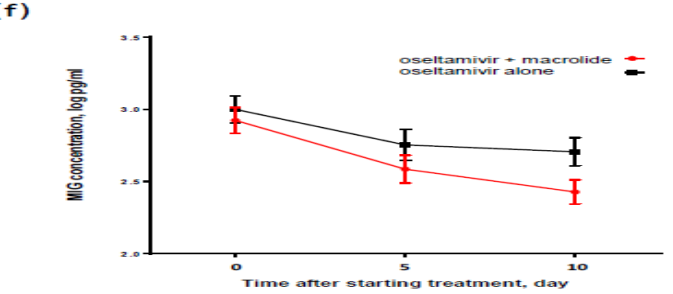
No significant difference in viral RNA decline (P=0.78) or culture-negativity rate.

An insignificant trend in ↓symptom-score (β -0.463, 95%CI-1.297,0.371, P=0.28; -79.0% *vs* -70.4%).

Lee N, et al. Antiviral Res 2017

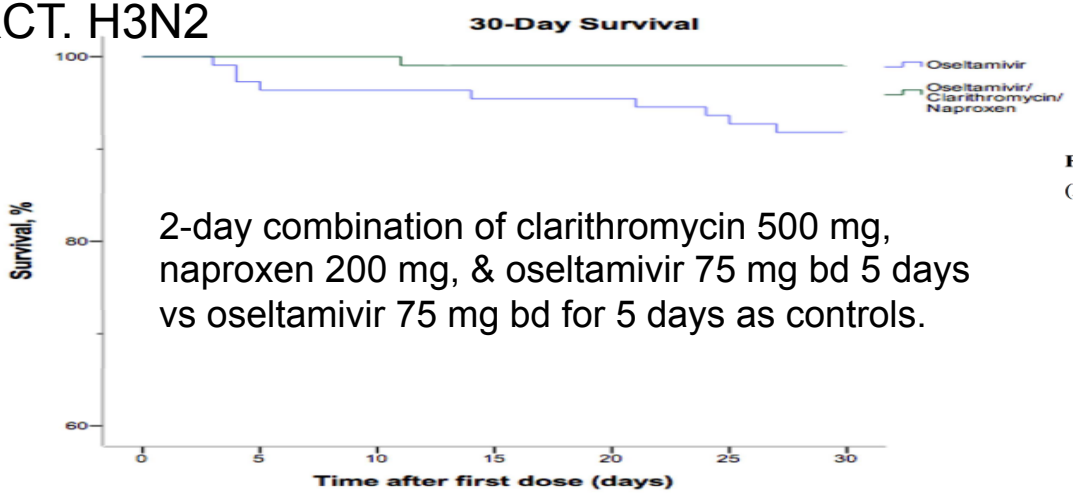






RCT. H3N2

Figure 2. 30-day Survival in Patients Treated With Oseltamivir/ Clarithromycin/ Naproxen Combination and With Oseltamivir alone



Days after first dose/ Number survived	0	5	10	15	20	25	30
Oseltamivir group (n)	110	106	106	105	105	102	101
Oseltamivir/ Clarithromycin/ Naproxen group (n)	107	107	107	106	106	106	106

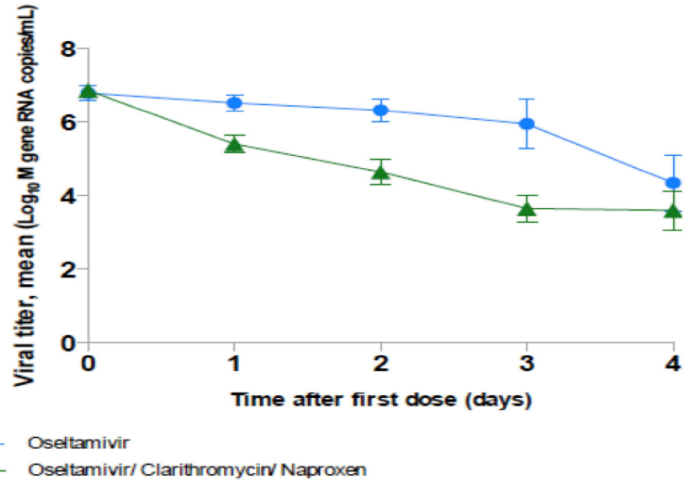
Log-rank test: *P*=0.01

2-day combination of clarithromycin 500 mg, naproxen 200 mg, & oseltamivir 75 mg bd 5 days vs oseltamivir 75 mg bd for 5 days as controls.

Triple therapy was associated with lower 30-D mortality (P=0.01), less frequent ICU/HDU adm (P<0.001), & shorter LOS (P<0.0001) vs oseltamivir alone.

Figure 3. Profile Of Viral Titer After Treatment

(Error-bars represent standard error of mean)



NPA virus titer, PSI (day 1-3;P<0.01), & NPA specimens with NAI resistant H3N2 quasispecies ≥5% (day 1-2;P<0.01) were significantly lower in the combination Rx group. Combination Rx was the only independent factor associated with lower 30-D mortality (OR: 0.06; 95%CI, 0.004-0.94; P=0.04). *Hung IF, et al. Chest 2017*

Adjuvant Treatment With a Mammalian Target of Rapamycin Inhibitor, Sirolimus, and Steroids Improves Outcomes in Patients With Severe H1N1 Pneumonia and Acute Respiratory Failure*

In cell culture, H5N1 infection caused autophagic cell death through mTOR signaling. Inhibition of the mTOR could potentially inhibit autophagic cell death & may have +ve impact in preventing ARDS.

All pts received oseltamivir 75mg bd for 10 days & prednisolone 20mg/ D for 14days! Sirolimus gp received 2mg/d for 14 days.

TABLE 2. ICU Outcomes Comparison Between the Sirolimus and Nonsirolimus Groups

Variables	Sirolimus ($n = 19$)	Nonsirolimus ($n = 19$)	p
Worse creatine, mg/mL	2.2±2.4	2.9±2.4	0.09
Renal failure	8 (42.1)	12 (63.2)	0.33
Onset of hypotension	1 (5.3)	6 (31.6)	0.09
Liberation of mechanical ventilator within 3 mo[a]	16 (84.2)	9 (47.4)	0.04
Duration of ventilatory support in survivors, d[a,b]	13.8±22.3	33.0±44.8	0.03
Extracorporeal membrane oxygenation support	2 (10.5)	8 (42.1)	0.06
ICU mortality	3 (15.8)	8 (42.1)	0.15

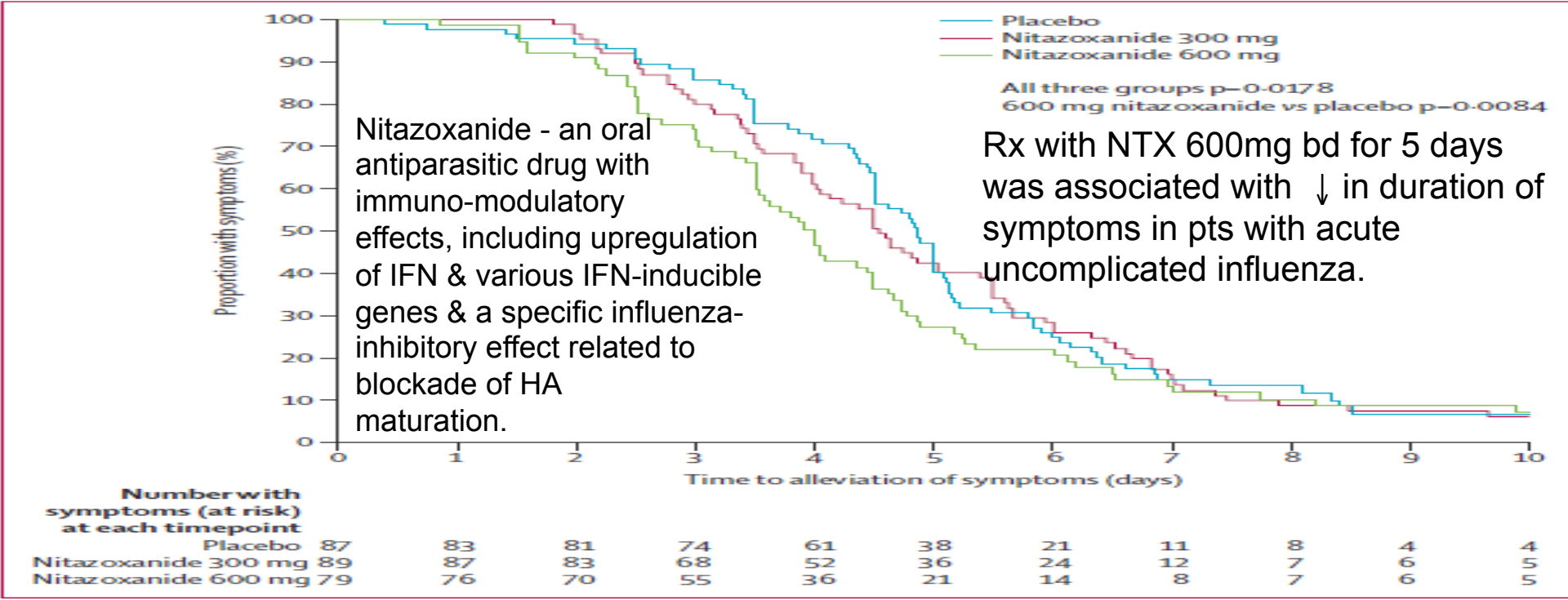
[a]$p < 0.05$.

[b]Of survivors of H1N1 infection, 16 received sirolimus and 11 was in the nonsirolimus group.

Data expressed as number (%) or mean ± SD.

LRT viral RNA negativity D7= 75% vs 33%, p<0.05.

Wang CH, et al. Crit Care Med 2014; 42:313-21



Nitazoxanide - an oral antiparasitic drug with immuno-modulatory effects, including upregulation of IFN & various IFN-inducible genes & a specific influenza-inhibitory effect related to blockade of HA maturation.

Rx with NTX 600mg bd for 5 days was associated with ↓ in duration of symptoms in pts with acute uncomplicated influenza.

Figure 2: **Kaplan-Meier plot of time from first dose to alleviation of symptoms for patients with confirmed influenza**

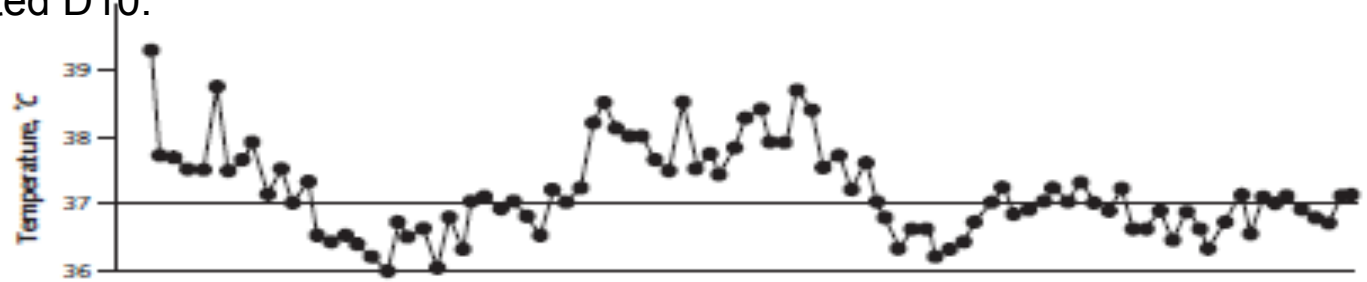
N=624, randomly assigned to placebo bd, NTX 300 mg bd, & NTX 600 mg bd.
The median duration of symptoms for participants receiving placebo was **116·7** h (95% CI 108·1–122·1) vs **95·5** h (84·0–108·0; p=0·0084) for those receiving 600 mg NTX & **109·1** h (96·1–129·5, p=0·52) for those on 300 mg NTX.

Haffizulla J, et al. Lancet ID 2014

High-Dose *N*-Acetylcysteine Therapy for Novel H1N1 Influenza Pneumonia

Lai KY, et al. Annals Intern Med 2010; 152:687-8

48 yr old lady with severe pneumonia & septic shock. **Rx NG oseltamivir, 75 mg bd, & IV antibiotics on D1. Oseltamivir ↑ to 150 mg bd from D2 & started high-dose *NAC* D3** at 100 mg/kg continuous IV infusion daily for 3 days & then oral NAC 600mg bd but worse. High dose NAC restarted D10.



Home on D20

	7/15	7/16	7/17	7/18	7/19	7/20	7/21	7/22	7/23	7/24	7/25	7/26	7/27	7/28	7/29	7/30
CRP	183			38.8		11.7	11.3	11.5	132		101		27.4	20.0	16.5	15.0
H1	+							+	+	+	+	−	±	±	−	−
Mx	+							+	−	−	+	−	−	−	−	−
M	PCV	PCV	PCV	VC	VC	CPAP	CPAP	CPAP	PCV	PCV	PCV	VC	CPAP	CPAP	CPAP	NC
FiO_2	1.0	0.7	0.6	0.4	0.4	0.35	0.4	0.5	0.85	0.5	0.4	0.35	0.35	0.35	0.35	4L
PEEP	18	18	18	15	12	10	10	13	16	15	13	10	8	8	8	0
NO	20	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0

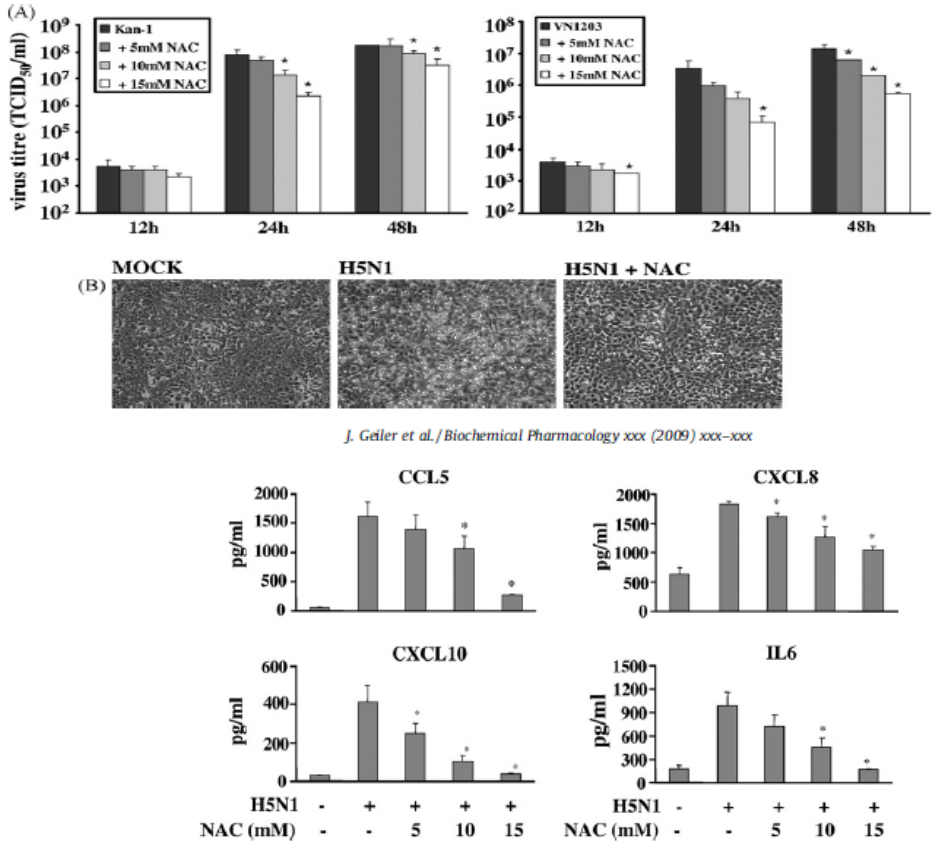
HDNAC — *Oral NAC* — HDNAC

Both CRP & FiO2 ↓ whenever HDNAC infused

CPAP = continuous positive airway pressure; CRP = C-reactive protein (mg/L); H1 = polymerase chain reaction for human swine influenza A H1 gene; HDNAC = high-dose *N*-acetylcysteine (100 mg/kg per day); M = ventilator mode; Mx = polymerase chain reaction for influenza A virus matrix gene; NC = nasal cannula (O_2 L/min); NO = nitric oxide (ppm); PEEP = positive end-expiratory pressure; PCV = pressure-controlled ventilation; VC = volume-cycled ventilation.

N-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus

Geiler J, et al. Biochem Pharmacol 2010



NAC at [ ] 5-15mM ↓ H5N1-induced cytopathogenic effects, virus-induced apoptosis & viral loads 24 hrs post infection. NAC ↓ production of pro-inflam molecules in H5N1-infected lung epithelial (A549) cells.

Antiviral & anti-inflam mechanisms of NAC: inhibition of activation of oxidant sensitive pathways including transcription factor NFKB & mitogen activated protein kinase p38.

Mata M, et al. NAC inhibits mucin synthesis & pro-inflammatory mediators in alveolar type II epithelial cells infected with flu virus A & B & with RSV. Biochem Pharmacol. 2011.
Garozzo A, et al. NAC synergizes with oseltamivir in protecting mice from lethal influenza infection. Int J Immunopathol Pharmacol.2007.

Fig. 4. Influence of N-acetyl-L-cysteine (NAC) treatment on production of cytokines/chemokines in H5N1-infected A549. A549 cells were infected with A/Thailand/1(Kan-1)/04 (H5N1) at a MOI of 0.01. NAC treatment was performed continuously starting 24 h prior to infection. Twenty four hours post-infection supernatants were analysed for CCL5, CXCL8, CXCL10, or IL-6 using ELISA. Data represent the mean ± SD of three separate experiments. *$P < 0.05$ relative to untreated virus control.

Agents with uncertainty

- Statins
- Herbal Medicine

Confronting the next influenza pandemic with anti-inflammatory and immunomodulatory agents: why they are needed and how they might work

David S. Fedson

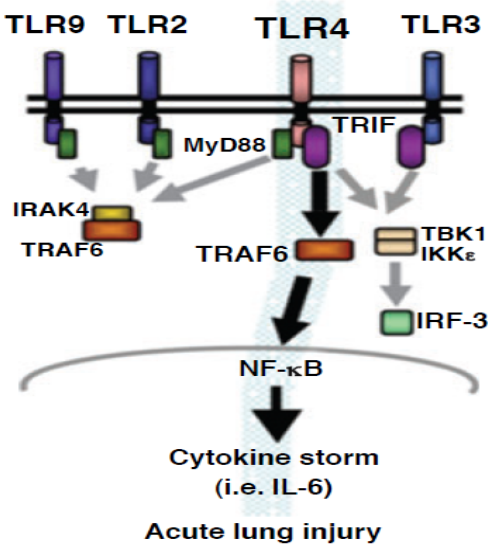


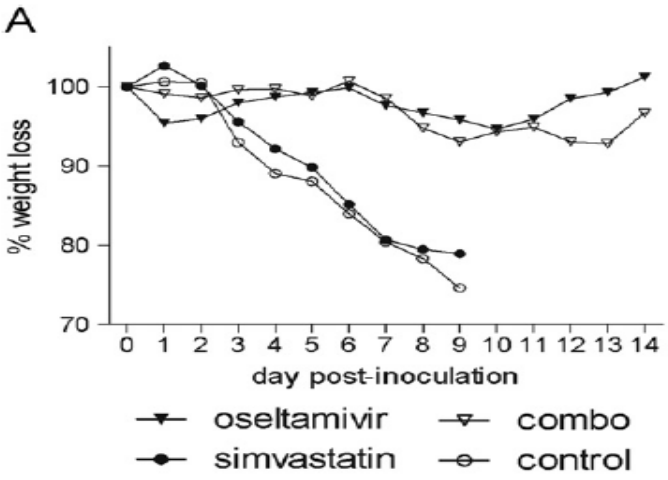
Figure 2. Schematic diagram of the signaling cascade that leads from Toll-like receptor 4 (TLR4) through TIR-domain-containing adaptor-inducing IFN-b (TRIF), tumor necrosis factor-receptor associated factor (TRAF6), and NF-kappaB to the up-regulation of pro-inflammatory cytokines and resultant acute lung injury [from figure 2(J) in Ref. (42)].

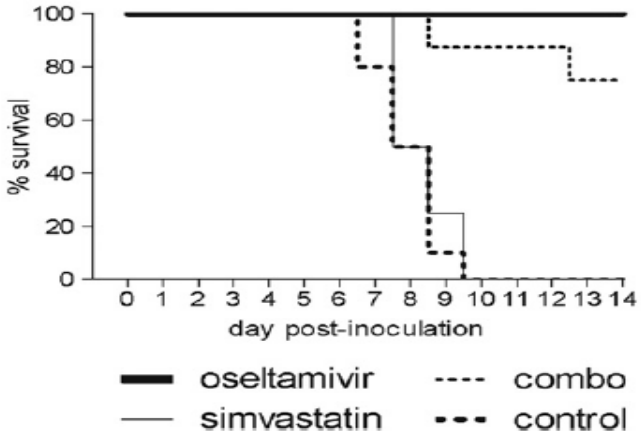
Table 1. Cell signaling in acute lung injury and the opposing effects of statins, fibrates and glitazones*

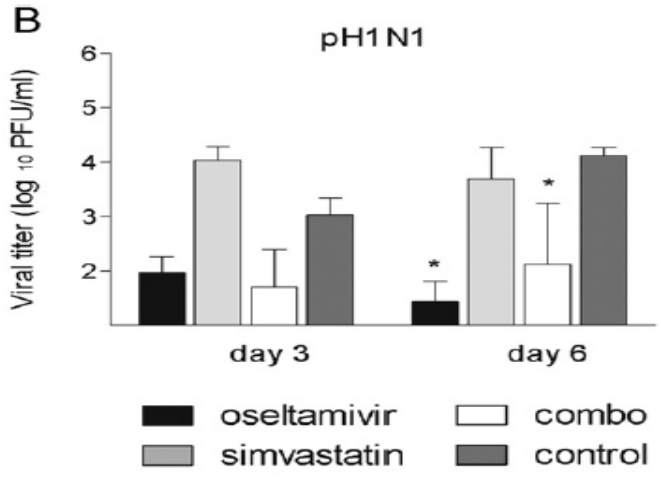
Cell signaling molecules	Acute lung injury	Statins	PPARα fibrates	PPARγ glitazones
ROS	>	fl	fl	fl
TLR4	>	fl	fl	fl
NFjB >	>	fl	fl	fl
IL-6	>	fl	fl	fl
HO-1	—	>	>	>

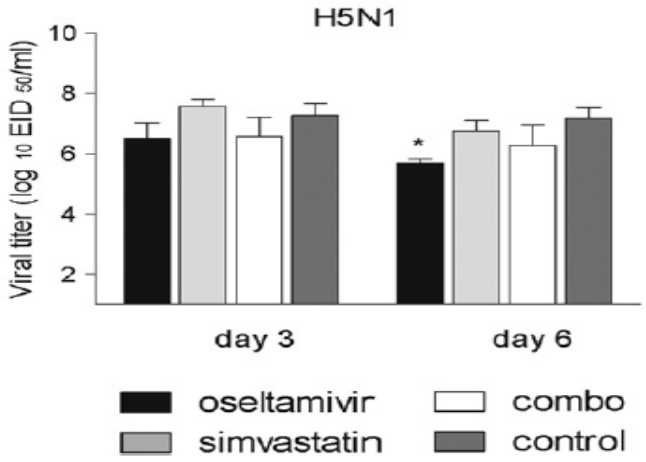
*The cell signaling molecules and their activities in acute lung injury are based on findings reported in Ref. (42). The activities of statins, fibrates, and glitazones are based on the author's unpublished data. ROS, reactive oxygen species; TLR4, Toll-like receptor 4; NFjB, nuclear factor-kappaB; IL-6, interleukin-6; HO-1, heme-oxygenase-1.

J.A. Belser et al. / Virology 439 (2013) 42–46









Unlike oseltamivir, simvastatin did not ↓morbidity, mortality, or viral load of mice infected with H1N1 or H5N1 viruses.

No added benefit when mice were treated with Oseltamivir + simvastatin.

Simvastatin Rx ↓ the production of IFNɣ, IL-10, & TNFα in the lungs of H5N1 virus-infected mice on day 3p.i ($p<0.05$)

Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome

N Engl J Med 2014;370:2191-200.

A multicenter trial in which pts with sepsis-assoc ARDS randomly assigned to receive either enteral rosuvastatin or placebo in a double-blind manner. Rosuvastatin did not improve clinical outcomes in pts with sepsis-assoc ARDS & may have contributed to hepatic & renal organ dysfunction.

Table 2. Main Outcome Variables.*

Variable	Rosuvastatin (N=379)	Placebo (N=366)	Difference (95% CI)	P Value
Death in health care facility to day 60 — no. (%)†	108 (28.5)	91 (24.9)	4.0 (–2.3 to 10.2)‡	0.21
Ventilator-free days to day 28 — no.§	15.1±10.8	15.1±11.0	0.0 (–1.6 to 1.5)	0.96
ICU-free days to day 28 — no.	14.3±10.1	14.4±10.3	–0.2 (–1.6 to 1.3)	0.84
Organ-failure–free days to day 14 — no.¶				
Free of cardiovascular failure	8.5±4.8	8.7±4.9	–0.2 (–0.9 to 0.5)	0.59
Free of coagulation abnormality	10.7±5.1	11.1±4.8	–0.3 (–1.1 to 0.4)	0.34
Free of hepatic failure	10.8±5.0	11.8±4.3	–1.0 (–1.7 to –0.4)	0.003
Free of renal failure	10.1±5.3	11.0±4.7	–0.9 (–1.7 to –0.2)	0.01

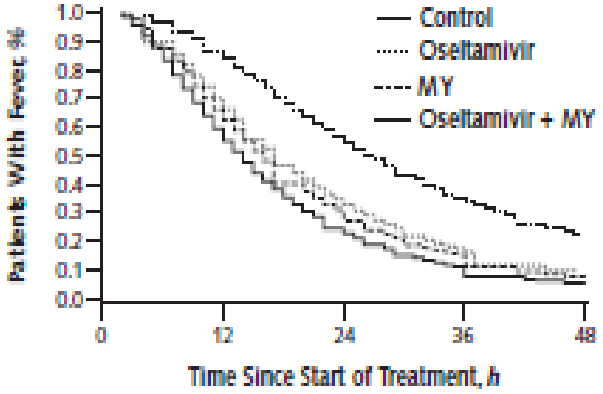
Oseltamivir Compared With the Chinese Traditional Therapy Maxingshigan–Yinqiaosan in the Treatment of H1N1 Influenza

A Randomized Trial

Mildly ill hosp pts without lung infiltrates. Age 15-59yrs.

Wang C, et al. Ann Intern Med 2011.

Appendix Figure 1. Fitted curves from accelerated failure time models for median time to fever resolution.



Patients, *n*					
Control	103	90	55	34	17
Oseltamivir	102	68	37	10	6
MY	103	66	31	20	14
Oseltamivir + MY	102	58	24	6	2

MY = maxingshigan–yinqiaosan.

2 pts who received MY had nausea & vomiting.
No viral kinetics data!

English Translation	Chinese Simplified Script	Traditional Script
Maxingshigan decocotion	麻杏石甘汤	麻杏石甘湯
Yinqiaosan	银翘散	銀翹散
King medicine	君	君
Minister medicine	臣	臣
Assistant medicine	佐	佐
Ambassador medicine	使	使
Zhimahuang	炙麻黄	炙麻黃
Zhimu	知母	知母
Qinghao	青蒿	青蒿
Shigao	石膏	石膏
Yinhua	银花	銀花
Huangqin	黄芩	黃芩
Chaoxingren	炒杏仁	炒杏仁
Lianqiao	连翘	連翹
Bohe	薄荷	薄荷
Zhebeimu	浙贝母	浙貝母
Niubangzi	牛蒡子	牛蒡子
Gancao	甘草	甘草

- Significant ↓ in the estimated median time to fever resolution seen with oseltamivir, MY, & oseltamivir +MY vs the control group.
- Time to fever resolution ↓ by 19% (CI, 0.3% to 34%; $P = 0.05$) comparing oseltamivir+MY vs oseltamivir.
- Ephedra is the main ingredient; its biological effects due to its ephedrine & pseudo-ephedrine content

Chinese medicinal herbs for influenza (Review)

Jiang L, Deng L, Wu T

Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD004559.

Main results

We included 18 studies involving 2521 participants. The methodological quality of 17 included studies was poor. Included RCTs separately compared medicinal herbs with different antiviral drugs, precluding any pooling of results. Only three indicated that compared with antiviral drugs, Chinese medicinal herbs may be effective in preventing influenza and alleviating influenza symptoms. 'Ganmao' capsules were found to be more effective than amantadine in decreasing influenza symptoms and speeding recovery in one study (in which adverse reactions were mentioned in the amantadine group although no data were reported). There were no significant differences between 'E Shu You' and ribavirin in treating influenza, nor in the occurrence of adverse reactions. Ten studies reported mild adverse reactions.

Authors' conclusions

Most Chinese medical herbs in the included studies showed similar effects to antiviral drugs in preventing or treating influenza. Few were shown to be superior to antiviral drugs. No obvious adverse events were reported in the included studies. However, current evidence remains weak due to methodological limitations of the trials. More high-quality RCTs with larger numbers of participants and clear reporting are needed.

Agents with more uncertainty

- **Mycophenolic acid** had antiviral activity against 8 different clinical isolates of A(H1N1), A(H3N2), A(H7N9) and flu B viruses (IC50 <1 μM) on plaque reduction assay. The antiviral effect of MPA completely reverted by guanosine supplementation. *To KK. J Gen Virol 2016.*
- **PPAR- γ agonist (pioglitazone)** ↓ mononuclear cells & neutrophils in BAL & ↑ peripheral CD4 & CD8 cells in mice exposed to A(H1N1) & smoke. *Bauer CM, et al. PLoS One 2010*
- Significant improvements in survival rates in the BALB/c mice treated with a triple combination of **zanamivir, celecoxib & mesalazine vs zanamivir alone** 48 hrs after challenged with flu A/H5N1/ VN/1194 /04. *Zheng B et al. PNAS 2008*
- **Chloroquine** inhibited autophagy in mouse lung induced by H5N1 while viral loads & proinflam cytokines not significantly affected. CQ raises lysosomal pH, leading to inhibition of both the fusion of auto-phagosomes with lysosomes & lysosomal protein degradation (inhibiting influenza virus endocytotic cell injury). *Yan Y. Cell Res 2013*

Agents with more uncertainty

- In mice, infection with A H5N1 virus results in downregulation of ACE2 expression in the lung and increased serum angiotensin II levels. Genetic inactivation of ACE2 causes severe lung injury in H5N1-challenged mice. Administration of recombinant human **ACE2** ameliorates avian influenza H5N1 virus-induced lung injury in mice. *Zou Z, Nature Commun 2014*
- Early Rx with intraperitoneal **pamidronate** ↓ morbidity & mortality of H7N9-infected mice through controlling both viral replication & inflammation in affected lungs. Antiviral effects of pamidronate partly mediated by IFN-γ secreted from human Vδ2-T cells which could directly kill virus-infected host cells in a perforin-, granzyme B- & CD137-dependent manner. *Zheng J, PLoS One 2015*
- **Human mesenchymal stromal cells** improved alveolar fluid clearance in vitro & in vivo in A/H5N1-infected aged mice through secretion of soluble paracrine growth factors (Ang1 & KGF). *Chan MC. PNAS 2016*
- **Anti-C5a treatment** (blocking complement activation products) in H7N9-infected monkeys led to: a) ↓ALI, with ↓ in lung histopath injury b) ↓systemic inflammatory response; body temp changes minimal & ↓ in plasma levels of inflammatory mediators. c) ↓ virus titers in the infected lungs. *Sun S, et al. CID 2015*
- Influenza virus infection activates endosomal NOX2 oxidase & restricts TLR7 signaling, and that an **endosomal NOX2 inhibitor** ↓ viral pathogenicity. *To E. Nat Commun 2017.*

General comments related to adjunctive therapies and immunomodulatory agents for the treatment of severe influenza.

	Therapeutic approach	Summary of findings
I. Agents with some evidence of patient benefit	Passive immunotherapy such as convalescent plasma and hyperimmune immunoglobulin *	Case reports, a non-randomized study and a RCT have shown benefit if given early in the disease course. Efficacy may be limited by the availability of donors and timing of administration.
	IVIG * Macrolide + NSAID Sirolimus	May have neutralizing activities against influenza viruses but caution with thrombo-embolic side effects.
II. Agents of uncertain value	*N*-acetylcysteine *	Data limited to a case report related to H1N1pdm09 influenza and in vitro testing.
NTX	PPAR agonists	Data limited to animal studies.
MPA	Macrolides	Favorable in vitro data but limited human data for influenza.
Herbal med	Statins	Cheap and readily available. Conflicting epidemiological data for outcome of influenza in chronic users. No data on acute use of statins for severe influenza.
Chloroquine		
ACE2		
Pamidronate	Combination of Cox II inhibitors and mesalazine	Data limited to animal studies.
Human mesenchymal stroma cells	Plasmapharesis	May play a role as rescue therapy but need more data than case series.
Anti C5a Ab	Haemoperfusion	May play a role as rescue therapy but need more data than a case report.
NOX2 inhibitor		
III. Agents with evidence of harm	Systemic corticosteroids	The risks of mortality and morbidity (e.g. secondary infections) were increased by administration of systemic corticosteroids in severe H1N1pdm09 influenza, especially when there was delay or lack of effective antiviral therapy. Systemic corticosteroids may prolong viremia

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Antiviral Research

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Review Article

Antiviral Research 150 (2018) 202–216

The role of adjuvant immunomodulatory agents for treatment of severe influenza

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- **A severe inflammatory immune response with hypercytokinemia occurs in patients hospitalized with severe influenza.**
- **Systemic corticosteroids administered in high dose may ↑ the risk of mortality & morbidity.**
- **Passive immunotherapy such as convalescent plasma & hyperimmune globulin may be useful as an adjunctive therapy.**
- **Confirmation of the efficacy of triple therapy (oseltamivir, clarithromycin, & naproxen) would be of great interest.**
- **Other agents esp sirolimus, NAC, NTX, etc deserve more investigation by RCTs**

Thank you!