H1N1 pneumonitis treated with intravenous zanamivir

I Michael Kidd, Jim Down, Eleni Nastouli, Rob Shulman, Paul R Grant, David CJ Howell, Mervyn Singer

Lancet 2009; 374: 1036
Published Online September 4, 2009
DOI:10.1016/S0140-6736(09)61528-2

Department of Virology (I M Kidd FRCPath, E Nastouli FRCPath, P R Grant PhD) **and Department of Critical Care** (J Down FRCA, R Shulman DHCPharm, D C J Howell MRCP, Prof M Singer FRCP), **University College London Hospitals NHS Foundation Trust, London, NW1 2BU, UK**

Correspondence to:
Dr I Michael Kidd, University College London Hospitals NHS Foundation Trust, 235 Euston Road, London, NW1 2BU, UK
Michael.Kidd@uclh.nhs.uk

For additional laboratory test results and further reading see Online for webappendix

On July 8, 2009, a 22-year-old woman, neutropenic after chemotherapy for Hodgkin's disease, was referred to ICU with 3 days' (d) increasing dyspnoea, bilateral chest infiltrates, and laboratory-confirmed pandemic H1N1 2009 influenza virus infection not responding to oseltamivir 75 mg twice daily and broad-spectrum antimicrobials (meropenem, teicoplanin, and caspofungin). No other organisms were detected from blood or respiratory tract. Deterioration necessitated invasive ventilation from ICU d 3 (figure). She remained in single organ failure requiring high inspired oxygen, protective lung ventilation (tidal volumes ≤6–8 mL/kg), and neutral fluid balance. Hydrocortisone was given (d 3–6), then gradually reduced and discontinued (d 13). Neutropenia recovered by d 6, although lymphopenia remained (webappendix). High level H1N1 RNA was detected in bronchoalveolar lavage (BAL) on d 10, despite 6 d oseltamivir given nasogastrically; in view of high volume gastric aspirates, this was replaced by nebulised zanamivir (d 6–13). Treatment escalation on d 13–16 delivered neither clinical nor virological response (figure).

On d 16, intravenous zanamivir 600 mg twice daily (provided by GlaxoSmithKline, Brentford, Middlesex) was started as unlicensed antiviral monotherapy; agreement for use was granted by the Hospital Formulary Committee and next of kin. Methylprednisolone was also started. Our patient's condition improved within 48 h, with a decrease in BAL viral load on d 21. She was extubated on d 21 and discharged to the ward on d 24. Antiviral and steroid treatment were stopped on d 26 and d 28, respectively. Since ICU discharge she remains stable. Of four nasopharyngeal swabs taken post-ICU, the third, taken on d 10 post-ICU, showed H1N1 RNA C_t of 24, although a repeat sample taken the next day was negative. In view of her immunosuppressed state and ongoing lymphopenia, inhaled zanamivir was started as a precaution, although her clinical status remained unchanged.

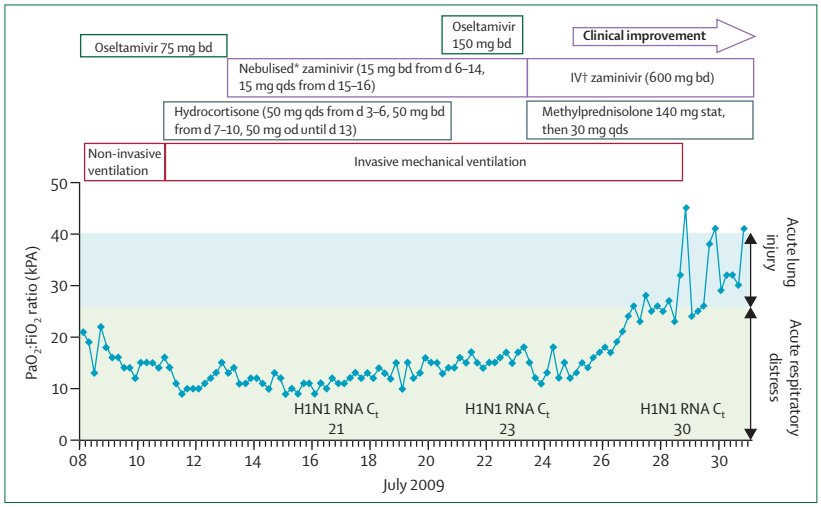

Figure: **Temporal course**
*Unlicensed route. †Unlicensed preparation.

Deaths due to pandemic H1N1 are primarily related to severe respiratory failure.[1] Our patient did not respond to extensive antiviral treatment and 2 weeks' mechanical ventilation. RT-PCR detects viral RNA rather than infectious virus, but is used to semi-quantitatively assess replication. The small difference in C_t between d 10 and 16 implied continued high-level replication. Effective treatment depends on adequate enteral absorption (oseltamivir) and an uninhibited access to the infected respiratory tissue (zanamivir). In view of high volume gastric aspirates, we used nebulised zanamivir. Since her inflamed, atelectatic lungs were probably impeding adequate drug absorption, and clinical improvement was not forthcoming, we used intravenous (unlicensed) zanamivir. High dosing achieves effective respiratory epithelial concentrations and is well-tolerated.[2,3] Our patient recovered with no side-effects. Despite inherent sampling inconsistencies, the change in BAL C_t from 23 to 30 after 5 d treatment indicates an approximate 128-fold fall in viral load. Persisting high-level H1N1 replication may drive ongoing lung inflammation and fibrosis (implied by our patient's poor lung compliance). We reasoned that synergism could exist between intravenous zanamivir and high-dose corticosteroids, although this approach may be considered controversial and is not recommended in treatment guidelines.[1] However, controlled trials are lacking and a rationale does exist for the use of corticosteroids in ARDS.[4] Although this is a single case report and direct cause and effect cannot be confirmed, the improvement in clinical status following intravenous zanamivir encourages prompt further investigation, both alone and in combination with high-dose methylprednisolone.

Contributors

All authors contributed to patient care and writing the report.

Acknowlegdments

Support provided by the UK DoH NIHR CBRC funding scheme.

References

1 CDC. Interim guidance on antiviral recommendations for patients with novel influenza A (H1N1) virus infection and their close contacts (May, 6 2009). http://www.cdc.gov/h1n1flu/recommendations.htm (accessed August 21, 2009).
2 GSK. Guidance document: zanamivir aqueous solution for compassionate use in serious influenza illness. July 29, 2009, GSK: Greenford, UK.
3 Calfee DP, Peng AW, Cass LM, Lobo M, Hayden FG. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 1999; **43:** 1616–20.
4 Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med* 2009; **37:** 1594–603.

THE LANCET

Supplementary webappendix

We post this webappendix as supplied by the authors.

Supplement to: Kidd IM, Down J, Nastouli E, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet* 2009; published online September 4. DOI:10.1016/S0140-6736(09)61528-2.

Web appendix

Table: Change in white blood count and lymphocyte count (x 10^9/L) before, during and after ICU admission

Date	Location	Total white cell count	Neutrophill count	Lymphocyte count
02/07/2009	Ward	10.29	10	0.08
04/07/2009	Ward	3.27	3.12	0.06
05/07/2009	Ward	0.6	0.55	0.02
06/07/2009	Ward	0.03	-	-
08/07/2009	ICU Day 1	0.04	-	-
12/07/2009	ICU Day 5	0.29	0.1	0.08
13/07/2009	ICU Day 6	1.65	1.24	0.13
14/07/2009	ICU Day 7	3.65	2.8	0.21
16/07/2009	ICU Day 9	13.28	10.01	0.33
23/07/2009	ICU Day 16	11.61	9.57	0.36
31/07/2009	ICU Day 24	10.9	8.8	0.96
07/08/2009	Ward	13.24	11.19	0.95
14/08/2009	Ward	6.27	5.07	0.54

Additional information on H1N1 and ARDS

1. Pandemic H1N1 2009 Clinical Practice Note – Managing critically ill cases. Joint advice from the Royal College of Anaesthetists, The Health Protection Agency, and the Intensive Care Society. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1248854036293

2. Writing Committee of the Second World Health Organization consultation on clinical aspects of human infection with avian influenza A (H5N1) virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008; **358**: 261-73

3. Stockman L, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoSMed* 2006; **3**: e343.

4. Lew TWK, Kwek TK, Tai D et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; **290**: 374-80

5. Fowler RA, Lapinsky SE, Hallett D et al. Critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; **290**: 367-73.

6. Gomersall CD. Pro/con clinical debate: steroids are a key component in the treatment of SARS. Pro: Yes, steroids are a key component of the treatment regimen for SARS. *Crit Care* 2004; **8**: 105-7.

7. Kargel MJ, Lapinsky SE. Pro/con clinical debate: steroids are a key component in the treatment of SARS. Con: No, steroids are not a key component of the treatment regimen for SARS. *Crit Care*. 2004; **8**: 105-7.

8. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med*. 2009; **37**: 1594-603.

9. Calfee CS, Matthay MA. Nonventilatory treatments for acute lung injury and ARDS. *Chest* 2007; **131**: 913-20.

10. Ottolini M, Blanco J, Porter D, Peterson L, Curtis S, Prince G. Combination anti-inflammatory and antiviral therapy of influenza in a cotton rat model. *Pediatr Pulmonol* 2003; **36**: 290-4

11. Baskin CR, Bielefeldt-Ohmann H, Tumpey TM, et al. Early and sustained innate immune response defines pathology and death in nonhuman primates infected by highly pathogenic influenza virus. *Proc Natl Acad Sci USA* 2009; **106**: 3455-60

12. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* 2006; **12**: 1203–07.

13. Fedson DS. Confronting an influenza pandemic with inexpensive generic agents: can it be done? *Lancet Infect Dis.* 2008; **8**: 571-6.

14. Marshall RP, Bellingan G, Webb S, et al. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *Am J Respir Crit Care Med* 2000; **162**: 1783-8.

15. WHO. Pandemic (H1N1) 2009 - update 62 (revised 21 August 2009) http://www.who.int/csr/don/2009_08_21/en/index.html