

H1N1 pneumonitis treated with intravenous zanamivir

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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.

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.

Acknowledgments

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

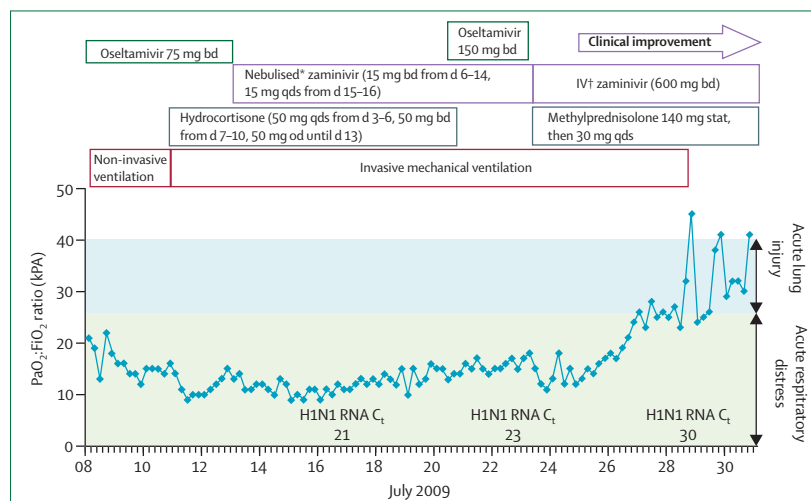


Figure: Temporal course

*Unlicensed route. †Unlicensed preparation.