Journal of Microbiology, Immunology and Infection 58 (2025) 490–492

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

journal homepage: www.e-jmii.com

Oseltamivir-resistant influenza in a fatal immunocompromised adult

ARTICLE INFO

Keywords:
Neuraminidase inhibitor
Oseltamivir
Antiviral resistance
Influenza A
H1N1

Dear Editor,

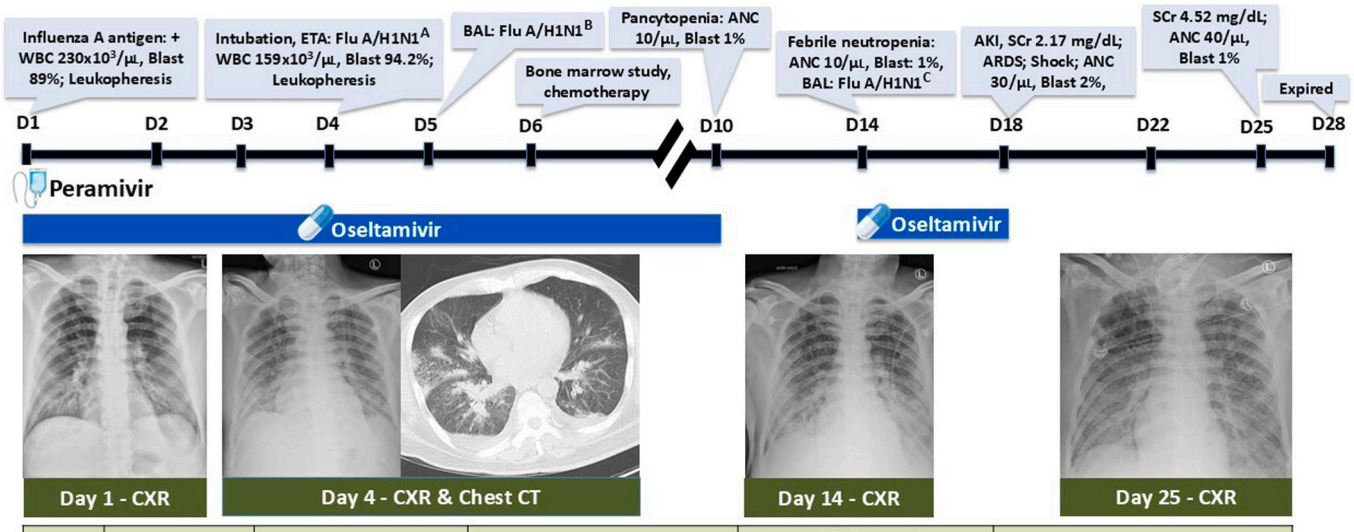
Antiviral resistance to oseltamivir, a frontline drug for influenza is a significant concern. Resistance often due to influenza A(H1N1)pdm09 virus with H275Y mutation in the neuraminidase gene, and can lead to prolonged viral shedding, delayed recovery, and severe complications. Notably, oseltamivir resistance also causes cross-resistance to other neuraminidase inhibitors (NAI), such as peramivir.[1] Here we reported a fatal case of oseltamivir-resistant influenza-related respiratory failure (see Fig. 1).

A 58-year-old man with a history of acute myeloid leukemia (AML) suffered from fever and productive cough for four days was admitted to the medical floor with hyperleukocytosis and positive influenza A antigen. His AML was in complete remission after chemotherapy but he lost follow-up for three years. He did not receive any influenza vaccine. The initial blood white cell count was 230,200/μL with 89 % of blast cells, platelet 8000/μL, and hemoglobin 8.8 g/dL. Chest X-ray revealed faint patches at bilateral lower lung fields. He received one intravenous dose of peramivir 300 mg and subsequent oseltamivir. However, he experienced hypoxemic respiratory failure on D4 and tracheal intubation was performed. He underwent emergent leukapheresis on hospital day 1, 2, 4 and 5 (D1, D2, D4, D5). Bone marrow study showed relapsed AML, so he received chemotherapy with high-dose cytarabine since D6. Chest computed tomography (CT) revealed bilateral fine reticulonodular infiltration and patchy wedge-shaped consolidations. Nucleic acid of influenza A was detected in endotracheal aspirate (ETA) on D4 and influenza A/H1N1 viruses were isolated from ETA on D4 and bronchoalveolar lavage (BAL) on D5. Hence, oral oseltamivir was kept for 10 days. Febrile neutropenia developed on D10 and bilateral pneumonia progressed. Influenza A virus was isolated again in BAL specimen on D14. Oseltamivir was administered for another five days. Hypoxemic respiratory failure did not respond to neuromuscular blockade and prone positioning. With persistent neutropenia and multiorgan failure, he expired on D28.

The susceptibility of influenza virus isolates to oseltamivir was assessed by determining the 50 % inhibitory concentration (IC_{50}) fold change using a fluorescence-based neuraminidase inhibition assay.[2] The fold change was compared to the local reference median IC_{50} of the same subtype strains from the same season. Following the WHO guideline, normal inhibition, reduced inhibition (RI), and highly reduced inhibition (HRI) is defined as a less than 10-fold increase, a 10- to 100-fold increase, and an at least 100-fold increase, respectively.[3] The influenza A/H1N1 virus isolate obtained from ETA and BAL showed HRI, with 709- and 689-fold increase of the local reference median IC_{50} in 2020, *i.e.*, 0.23 nM. However, the IC_{50} of the isolate on D14 showed an 11-fold increase, indicative of RI. To detect single nucleotide polymorphism, a published protocol was followed to reveal the presence of H275Y amino acid substitution in these three influenza virus isolates.[4] Partial sequences of the NA gene determined by Sanger dideoxy sequencing were respectively deposited as PV076893, PV076933, and PV076934 at the National Center of Biotechnology Information (NCBI) website.

In Taiwan, clinical cases of oseltamivir-resistant influenza were rarely reported, with approximately 1 % of influenza A (H1N1) virus isolates noted by the Taiwan CDC. Recognized risk factors for oseltamivir resistance include immunocompromised status, suboptimal dosing, receipt of prophylactic regimens, young age, and prior NAI exposure.[5] Influenza caused by resistant strains heralds a higher risk of adverse outcomes, including increased treatment failure, delayed recovery, increased risk of secondary infections and 28-day crude mortality rate, and underscores the need for effective antivirals.[6] Oseltamivir resistance typically results from amino acid mutations in neuraminidase, as noted in this case. Notably, the fold change of IC_{50} in the last virus isolate was less than that of the other two isolates. This decrease in oseltamivir resistance was noted after the discontinuation of oseltamivir therapy for four days. The possibility of the emerging oseltamivir-sensitive virus in mixture with oseltamivir-resistant virus on D14 warrants further studies. Peramivir, another NAI, shares cross resistance with oseltamivir, while zanamivir with a distinct binding site shows a lower risk of cross resistance.[1,7] There are two potential therapeutic non-NAI antiviral agents to treat oseltamivir-resistant influenza in Taiwan. First, baloxavir marboxil, a polymerase acidic endonuclease inhibitor, can inhibit the viral RNA polymerase complex and prevent viral replication. Baloxavir has been shown to be *in vitro* active against NAI-resistant influenza virus strains.[8] and clinically effective for limited cases of oseltamivir-resistant influenza A infection.[9] Second, favipiravir,

https://doi.org/10.1016/j.jmii.2025.03.006
Received 6 January 2025; Received in revised form 9 March 2025; Accepted 15 March 2025
Available online 17 March 2025



Isolate	Hospital day	Virus type/subtype	Clinical specimen	Fold change in oseltamivir IC_{50}	Oseltamivir susceptibility
A	D4	A/H1N1	Sputum	709	Highly reduced inhibition
B	D5	A/H1N1	Bronchoalveolar lavage	689	Highly reduced inhibition
C	D14	A/H1N1	Bronchoalveolar lavage	11	Reduced inhibition

Figure. Hospital course of an immunocompromised patient with bilateral pneumonia due to oseltamivir-resistant influenza A/H1N1 virus.
Note: WBC: white blood cell; ETA: endotracheal aspirate; BAL: bronchoalveolar lavage; Flu: Influenza; ANC: Absolute neutrophil count; AKI: acute kidney injury; SCr, serum creatinine; ARDS: acute respiratory distress syndrome; CXR: chest X-ray; CT: computed tomography; IC_{50}: half maximal inhibitory concentration.

a nucleoside analogue, inhibits viral RNA polymerase and effectively blocks replication of a broad range of RNA viruses, including NAI-resistant influenza viruses. No significant differences in favipiravir susceptibilities were found between NAI-resistant and NAI-susceptible influenza viruses.[10] However, clinical effectiveness of favipiravir monotherapy for oseltamivir-resistant influenza infection remains to be studied. Both drugs are not used as front-line agents for influenza treatment in Taiwan.

In conclusion, the present case reinforces the clinical scenario of antiviral resistance in the treatment of human cases of influenza. Documentation of viral clearance is warranted for the patients with unresolved or worsening influenza pneumonia. Frontline antiviral agents, such as oseltamivir or peramivir alone or in combination, may be ineffective for those with NAI-resistant influenza virus infection. Early detection of antiviral resistance is crucial to prevent miserable outcomes.

CRediT authorship contribution statement

Hao-En Jan: Writing – original draft, Data curation, Conceptualization. **Yi-Ting Huang:** Methodology, Data curation. **Cong-Tat Cia:** Writing – review & editing, Investigation. **Huey-Pin Tsai:** Supervision, Methodology, Data curation, Conceptualization. **Wen-Chien Ko:** Writing – review & editing, Supervision, Conceptualization.

Funding statement

This study was supported by the grants from National Cheng University Hospital, Tainan (NCKUH-11402042), and National Science and Technology Council, Taiwan (NSTC 113-2321-B-006-007).

Declaration of competing interest

All authors had no conflicts of interest.

References

1. Whitley RJ, Monto AS. Resistance of influenza virus to antiviral medications. *Clin Infect Dis*. 2020;71:1092–1094.
2. World Health Organization (WHO). Practical guidance for national influenza centres establishing or implementing neuraminidase inhibitor susceptibility surveillance. Published https://www.who.int/publications/i/item/practical-guidance-for-national-influenza-centres-establishing-or-implementing-neuraminidase-inhibitor-susceptibility-surveillance; 2018. Accessed January 6, 2025.
3. Krishna S, Jayaram A, Shetty U, Varamballi P, Mukhopadhyay C, Jagadesh A. Detection of H275Y oseltamivir resistance gene mutation among Influenza A(H1N1) pdm09 patients by allelic discrimination real-time RT-PCR. *J Med Virol*. 2023;95, e28764.
4. World Health Organization (WHO). Real-time RT-PCR allelic discrimination analysis for detection of the substitution at amino acid 275 in the neuraminidase (NA) of A (H1N1)pdm09 influenza viruses. Published https://cdn.who.int/media/docs/default-source/influenza/antiviral-wg-surveillance/allelic_discrimination_analysis_na275.pdf?sfvrsn=4e616506; 2023. Accessed February 16, 2025.
5. Mitha E, Krivan G, Jacobs F, et al. Safety, resistance, and efficacy results from a Phase IIIb study of conventional- and double-dose oseltamivir regimens for treatment of influenza in immunocompromised patients. *Infect Dis Ther*. 2019;81:613–626.
6. Behillil S, May F, Fourati S, et al. Oseltamivir resistance in severe influenza A(H1N1) pdm09 pneumonia and acute respiratory distress syndrome: a French multicenter observational cohort study. *Clin Infect Dis*. 2020;71:1089–1091.
7. Holmes EC, Hurt AC, Dobbie Z, Clinch B, Oxford JS, Piedra PA. Understanding the impact of resistance to influenza antivirals. *Clin Microbiol Rev*. 2021;34.
8. Omoto S, Speranzini V, Hashimoto T, et al. Characterization of influenza virus variants induced by treatment with the endonuclease inhibitor baloxavir marboxil. *Sci Rep*. 2018;8:9633.
9. Fujita M, Matsumoto H, Inafuku Y, Toyama J, Fujita J. A retrospective observational study of the treatment of a nosocomial infection caused by oseltamivir-resistant influenza virus A with baloxavir marboxil. *Respir Investig*. 2020;58:403–408.
10. Takashita E, Ejima M, Ogawa R, et al. Antiviral susceptibility of influenza viruses isolated from patients pre- and post-administration of favipiravir. *Antivir Res*. 2016;132:170–177.

Hao-En Jan[a,b,c,1], Yi-Ting Huang[d,1], Cong-Tat Cia[a,c], Huey-Pin Tsai[d,e,*], Wen-Chien Ko[a,f,**]
[a] *Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

[b] *Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[c] *Center for Infection Control, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[d] *Department of Medical Laboratory Science and Biotechnology, College of Medicine, National Cheng Kung University, Tainan, 701, Taiwan*
[e] *Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, 704, Taiwan*
[f] *Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

[*] Corresponding author. Department of Medical Laboratory Science and Biotechnology, College of Medicine, National Cheng Kung University, Tainan, 70101, Taiwan.

[**] Corresponding author. Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, 704, Tainan, Taiwan.
E-mail addresses: tsaihp@mail.ncku.edu.tw (H.-P. Tsai), winston3415@gmail.com (W.-C. Ko).

[1] Hao-En Jan and Yi-Ting Huang contribute equally.