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Case report

Adult influenza A (H3N2) with reduced susceptibility to baloxavir or peramivir cured after switching anti-influenza agents

Masafumi Seki[a,*], Yuko Sakai-Tagawa[c], Atsuhiro Yasuhara[c], Yuji Watanabe[b]

[a] Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University Hospital, Sendai, Japan
[b] Laboratory for Clinical Microbiology, Tohoku Medical and Pharmaceutical University Hospital, Sendai, Japan
[c] Department of Virology, Institute of Medical Science, University of Tokyo, Tokyo, Japan

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ABSTRACT

We describe two adults with A/H3N2 influenza with (patient 1), and without (patient 2) polymerase acidic (PA) subunit I38 T substitution during the same season. Patient 1 had a reduced clinical response to baloxavir, a cap-dependent endonuclease inhibitor (CEI), but was cured by peramivir, a neuraminidase inhibitor. Baloxavir was clinically effective for patient 2, for whom peramivir had been ineffective. Susceptibility to baloxavir can be decreased by a PA unit mutation, but response to treatment can be increased by switching and/or combination with a neuraminidase inhibitor, even though CEI are clinically effective against influenza in adults.

Introduction

Influenza virus infection is a major respiratory infectious disease that generally induces bronchitis and pneumonia [1] and causes an acute febrile illness with malaise, which together with complicating pneumonia can be fatal [2,3]. Seasonal influenza A (H3N2) affects elderly persons and tends to lead to worse outcomes than influenza A (H1N1) [4].

The neuraminidase inhibitors (NAI), oseltamivir, zanamivir, peramivir and laninamivir are approved for therapeutic or prophylactic treatment of influenza virus infection, and favipiravir, a viral RNA-dependent RNA polymerase inhibitor, is approved and stockpiled for use against novel influenza virus infections in Japan should existing antivirals be ineffective [5,6].

The novel cap-dependent endonuclease inhibitor (CEI) baloxavir marboxil (baloxavir; S-033188) was approved during 2018 to treat influenza A and B virus infections and has recently become available [7]. Because influenza virus infections can be treated with only a single oral dose, baloxavir has become the predominant treatment, particularly for adult influenza.

However, recent studies have associated an I38 T substitution in the polymerase acidic subunit (PA) with reduced susceptibility of influenza A (H1N1) and (H3N2), as well as B viruses to baloxavir, and a Phase III clinical trial detected PA I38 T and I38 M substitutions after exposure to baloxavir in 9.7% of 370 A (H3N2) viruses [7–10]. Virus shedding and the median amount of elapsed time to symptom alleviation are prolonged in patients infected with, than without PA I38 T, I38 F or I38 M mutation [7].

Here, we describe two adult cases of H3N2 infection in one patient who had a polymerase acidic (PA) subunit I38 T substitution and in another who did not during the same season.

CASE REPORT

Patient 1

A 40-year-old man presented at an emergency room in January 2019 with a four-day history of high fever accompanied by extreme fatigue. He had been diagnosed with influenza A using the Espline A&B rapid antigen test (Fuji Rebio Inc., Tokyo, Japan) of nasal swabs at a nearby clinic three days before and had been prescribed with oral baloxavir (40 mg). However, his fever persisted, and he presented at our institution with a slight cough. He had a medical history of IgG4-related diseases that had been treated with prednisolone (7 mg/day), and no history of smoking or influenza vaccination. None of his family and colleagues had any influenza-like symptoms. His initial white blood cell (WBC) count was 5,300/uL and his C-reactive protein (CRP) value was 0.72 mg/dL. Findings

* Corresponding author at: Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University, 1-15-1 Fukumuro, Miyagino-ku, Sendai City, Miyagi, 983-8536, Japan.
E-mail addresses: m-seki@tohoku-mpu.ac.jp, seki@hosp.tohoku-mpu.ac.jp (M. Seki).

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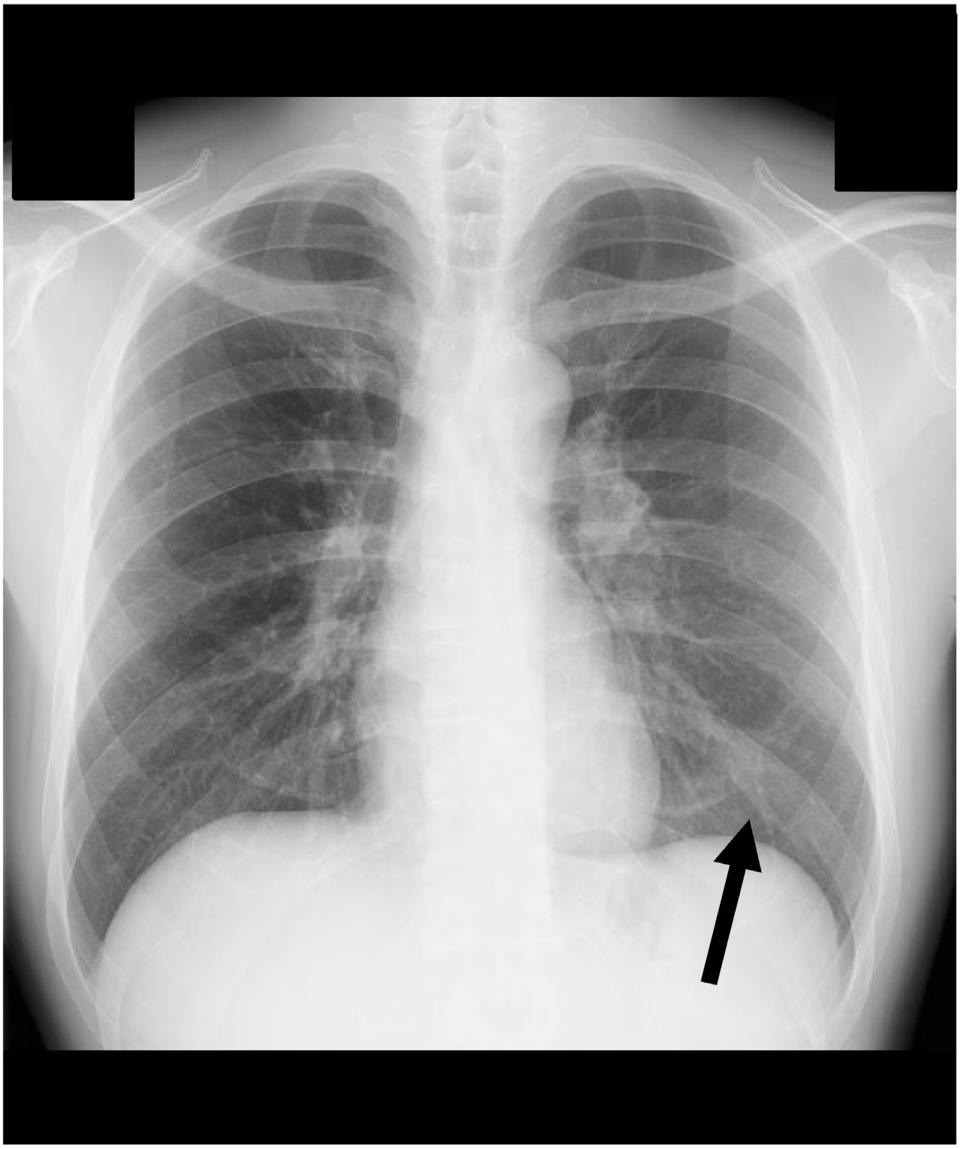

Fig. 1. Chest X-ray findings of patient 1. Slight bronchiolitis is evident in left lower lung (arrow).

of the rapid urine antigen testing for influenza were positive. A physical examination indicated the following: temperature 40.0 °C, blood pressure 130/90 mmHg, respiratory rate 22 and consciousness status E4V4M6 on the Glasgow Coma Scale. Small crackles (rhonchi) were found in the left lower lung fields, and chest radiography indicated slight bronchitis (Fig. 1).

We diagnosed influenza A that was refractory to baloxavir, and switched the medication to a drip infusion of the anti-influenza agent peramivir (300 mg). He improved and became afebrile two days later. Finally H3N2 was detected on oral swabs, and genetic analyses of the PA and NA regions revealed a I38 T substitution of PA, but no mutation of NA (Table 1).

Patient 2

A 34 year-old man with infantile paralysis presented at a clinic five days previously with high fever and was diagnosed with influenza A from a nasal swab using the Espline A&B rapid antigen test (Fuji Rebio) and was administered with a drip infusion of peramivir (300 mg). However, the fever persisted and he presented at our institution with shortness of breath in January 2019. He had no history of influenza vaccination, and a physical examination revealed the following: temperature 38.7 °C, blood pressure 125/70 mmHg, respiratory rate 24, and dehydration. Chest radiography indicated as a light shadow on the left lung field (Fig. 2A), and computed tomography of his left lower lung revealed infiltration shadows comparable to those of bronchopneumonia (Fig. 2B).

His initial WBC count was 5000/uL and CRP value was 3.37 mg/dL. Influenza A was diagnosed from a nasal swab using the Espline A&B, rapid antigen test (Fuji Rebio). We diagnosed influenza A that was refractory to peramivir, and oral baloxavir 40 mg was administered. He improved and became afebrile two days later. Influenza A H3N2 virus was detected from nasal and oral swabs, and genetic analysis of the PA and NA region showed no substitutions in either region (Table 1).

Discussion

Influenza causes serious health, economic, and societal impact despite vaccines and antivirals [1,3]. Currently,

Table 1
Characteristics of patients and influenza.

Patient No.	Male/Female	Age	Complications and Drugs	Swab	Virus subtype	Genetic substitution	
						PA	NA
1	M	40	IgG4 related diseases, Baloxavir →Peramivir,	Nasal	Not Detected	Not applicable	
				Throat	A/H3N2	I38T	None
2	M	34	Infantile paralysis, Peramavir →Baloxavir	Nasal	A/H3N2	I38	None
				Throat	A/H3N2	I38	None

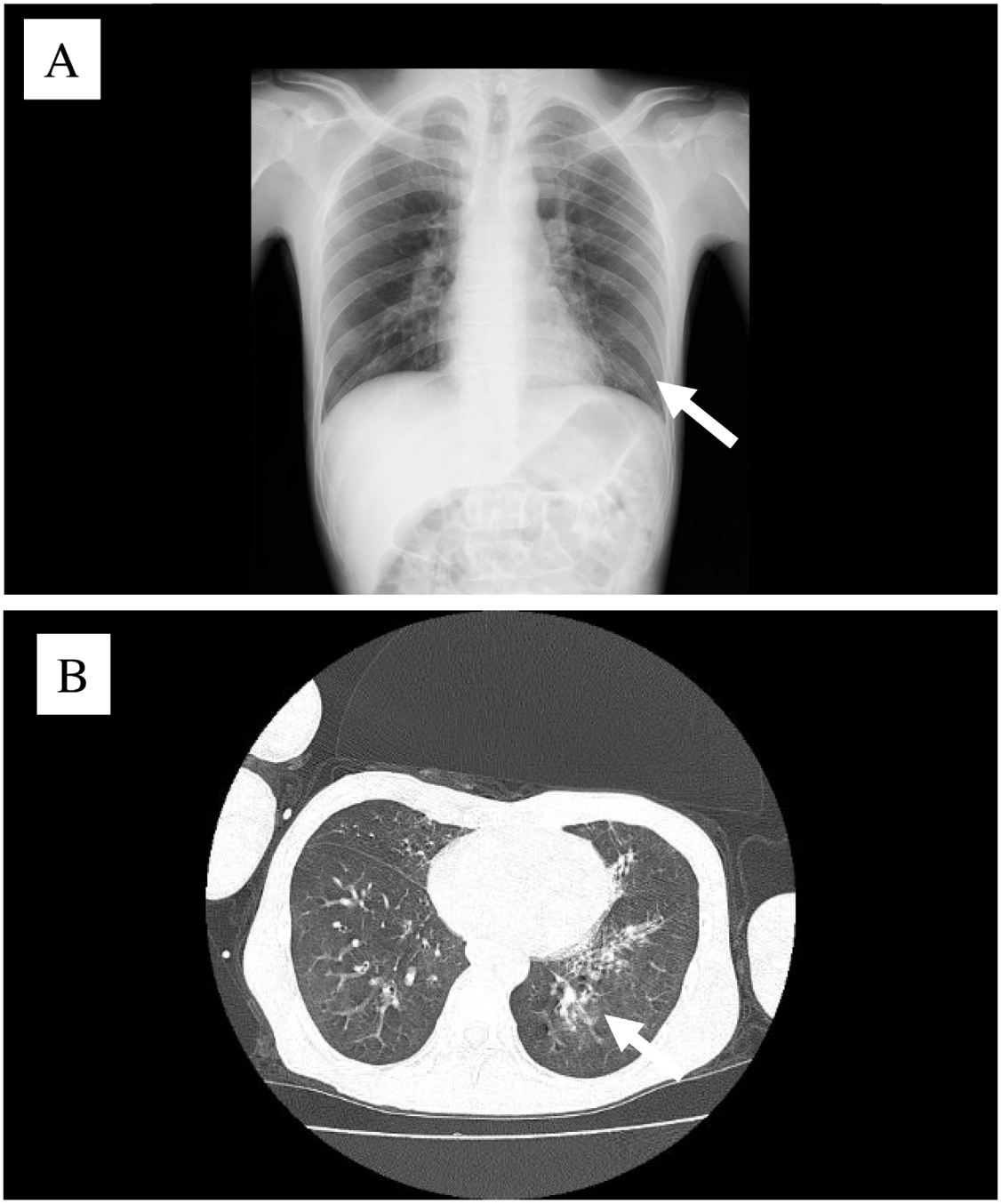

Fig. 2. Chest X-ray (A) and computed tomography (B) findings of patient 2. Infiltrative shadows in left lower lung suggest bronchopneumonia (arrows).

circulating viruses have widespread resistance to adamantanes, and neuraminidase inhibitors (NAI) are the only effective agents in most countries [5,6]. The new CEI baloxavir marboxil recently became available in Japan. However, phase 3 trials have found prolonged viral shedding, and a longer median time to symptom alleviation when patients infected with viruses harboring a PA I38 substitution were treated with this agent [7,9,10].

We described two adults with and without an I38 substitution of the PA regions who were infected with H3N2. Patient 2 without a substitution responded well to baloxavir although peramivir is the drip infusion anti-influenza agent considered as the standard NAI for treating severe influenza. Baloxavir is reportedly equally effective clinically, it has better viral reduction activity, and only a single oral dose is needed to be effective, compared with oseltamivir, which must be administered twice per day for five days [7]. We found that baloxavir might be more effective than NAI including peramivir in terms of moderate to severe influenza with pneumonia/bronchopneumonia. Our findings suggested that baloxavir could become more prevalent, especially for treating influenza A (H3N2) which is more refractory to NAI than A (H1N1) [4,5].

In contrast, the clinical efficiency of antiviral agents is reduced in patients with an I38 substitution of PA regions, which is consistent with drug susceptibility [6,8–10]. These substitutions have been found in 1.5% and 9.5% of influenza virus types H1N1 and H3N2, respectively, suggesting that the low efficiency of baloxavir against H3N2 and the seasons when this type of virus become epidemic should be considered [7]. Furthermore, viruses with I38 substitutions suggest human-to-human transmission because these virus were isolated from patients who had not been treated with baloxavir but had siblings who were [6]. These data suggest that appropriate treatment to avoid creating mutant viruses should be applied because treatment for the whole household is impractical.

Therefore, switching to a different type of anti-influenza agents such as NAI (or CEI) when other types of CEI (or NAI) should be considered when clinical effects are not evident within two to three days. In addition, combining NAI with CEI might serve as a treatment strategy against severe influenza to minimize the risk of clinical failure when patients with an I38 T substitution are infected with a virus, especially during the H3N2 season. Hayden and Shindo reported that the polymerase basic protein 2 cap-binding inhibitor pimodivir exerts antiviral effects alone and in combination with oseltamivir in uncomplicated influenza, although variants with reduced susceptibility frequently emerge during monotherapy. Furthermore, single doses of the baloxavir alleviate symptoms and rapidly inhibit viral replication in otherwise healthy and high-risk patients with acute influenza, although variants with reduced susceptibility also emerge frequently during monotherapy [11]. Synergistic effects of combining laninamivir with favipiravir that have different mechanisms: have been found in mouse models [12], but of combining drugs such as oseltamivir and zanamivir that have similar mechanisms; however, both of these agents are NAI [13]. Further studies and clinical trials of treatment with combined CEI and NAI are needed.

In summary, we described two adult patients with influenza A who were refractory to CEI or NAI, but successfully treated after switching the anti-influenza agents. The clinical efficiency after the switch found here concurred with previous reports of defining I38 substitutions from the susceptibility of viruses to CEI. Switching and/or combining CEI and NAI should be considered when drugs are less effective or ineffective against influenza, especially during the H3N2 season.

Declaration of Competing Interest

None.

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References

[1] Mandell LA, Wunderink R, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
[2] Glezen WP, Greenberg SB Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. JAMA 2000;283:499–505.
[3] Seki M, Kosai K, Yanagihara K, et al. Disease severity in patients with simultaneous influenza and bacterial pneumonia. Intern Med 2007;46:953–8.
[4] Esposito S, Molteni CG, Daleno C, et al. Impact of pandemic A/H1N1/2009 influenza on children and their families: comparison with seasonal A/H1N1 and A/H3N2 influenza viruses. J Infect 2011;63:300–7.
[5] Oikawa N, Seki M. Clinical differences in hospitalized adult influenza patients between the A(H1N1) pdm09 and the A (H3N2) seasons in Japan. J Infect Dis Ther 2018;6:1–6.
[6] Takashita E, Ichikawa M, Morita H, et al. Human-to-human transmission of influenza A(H3N2) virus with reduced susceptibility to baloxavir, Japan, February 2019. Emerg Infect Dis 2019;17:25, doi:http://dx.doi.org/10.3201/eid2511.190757.
[7] Hayden FG, Sugaya N, et al. Baloxavir marboxil Investigators Group., Baloxavir marboxil for uncomplicated influenza in adults adolescents. N Engl J Med 2018;379:913–23.
[8] Takashita E, Morita H, Ogawa R, et al. Susceptibility of influenza viruses to the novel cap-dependent endonuclease inhibitor Baloxavir marboxil. Front Microbiol 2018;9:3026, doi:http://dx.doi.org/10.3389/fmicb.2018.03026.
[9] Takashita E, Kawakami C, Morita H, et al. Detection of influenza A(H3N2) viruses exhibiting reduced susceptibility to the novel cap-dependent endonuclease inhibitor baloxavir in Japan, December 2018. Euro Surveill 2019;24:, doi:http://dx.doi.org/10.2807/1560-7917.
[10] Takashita E, Kawakami C, Ogawa R, et al. Influenza A(H3N2) virus exhibiting reduced susceptibility to baloxavir due to a polymerase acidic subunit I38T substitution detected from a hospitalised child without prior baloxavir treatment, Japan, January 2019. Euro Surveill 2019;24, doi:http://dx.doi.org/10.2807/1560-7917.
[11] Hayden FG, Shindo N. Influenza virus polymerase inhibitors in clinical development. Curr Opin Infect Dis 2019;32:176–86.
[12] Kiso M, Lopes TJS, Yamayoshi S, et al. Combination therapy with neuraminidase and polymerase inhibitors in nude mice infected with influenza virus. J Infect Dis 2018;217:887–96.
[13] Duval X, van der Werf S, Blanchon T, et al. Efficacy of oseltamivir-zanamivir combination compared to each monotherapy for seasonal influenza: a randomized placebo-controlled trial. PLoS Med 2010;7:e1000362.