


# Reduced Prescription of Baloxavir After Suspected Prevalence of a Baloxavir-Resistant Influenza Virus Strain and the Emergence of SARS-CoV-2 in a Tertiary Hospital in Japan

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**Objective:** The use of baloxavir, a new anti-influenza agent, began in Japan from the 2018 to 2019 season and became the focus of attention due to its efficient viral reduction ability; therefore, we should know the prescription changes of anti-influenza agents.

**Methods:** We analyzed the changes in the prescription of anti-influenza agents between the 2018–19 season and the 2019–20 season in our hospital.

**Results:** The share of baloxavir was 15%, while the shares of oseltamivir and laninamivir were 42% and 31%, respectively in the 2018–2019 season. However, in the 2019–20 season, the share of baloxavir and laninamivir was reduced to 3% and 17%, respectively, in contrast to an increase in the share of oseltamivir (66%). The total prescription of anti-influenza agents for patients decreased in the 2019–20 season (205 patients), compared with the 2018–19 season (509 patients).

**Conclusion:** These results suggest significant changes such as a reduction in the prescription of anti-influenza agents, especially baloxavir, likely due to the suspected prevalence of a baloxavir-resistant strain of influenza virus and the emergence of SARS-CoV-2 in Japan.

**Keywords:** anti-influenza agents, oseltamivir, laninamivir, zanamivir, peramivir, novel coronavirus-2019, COVID-19

## Introduction

Influenza virus infection is a major respiratory infectious disease that generally induces bronchitis, pneumonia,<sup>1</sup> and acute febrile illness with malaise that can be fatal with complicating pneumonia, especially in elderly people.<sup>2–4</sup>

The neuraminidase inhibitors (NAIs) oseltamivir, zanamivir, peramivir and laninamivir are approved for therapeutic and prophylactic treatments of influenza virus infection in Japan.<sup>5</sup> The novel cap-dependent endonuclease inhibitor (CEI) baloxavir marboxil (baloxavir; S-033188) was approved in 2018 to treat influenza and has recently become the predominant anti-influenza agent in Japan because it only requires a single oral dose.<sup>6,7</sup>

However, recent studies have associated an I38T substitution in the polymerase acidic subunit (PA) with reduced susceptibility of influenza viruses to baloxavir, and a Phase III clinical trial detected PA I38T and I38M substitutions after exposure to baloxavir in 9.7% of 370 A (H3N2) viruses related with the prolonged median amount of elapsed time to symptom alleviation although these baloxavir-resistant

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strain were proven to keep the susceptibility to NAIs.<sup>7–10</sup> Therefore, we recently described the possibility of substituting and/or combining CEIs and NAIs when they have little to no effect against influenza infections, especially during the H3N2 season.<sup>11</sup>

In addition, novel SARS-CoV-2 infection spread from Wuhan, China, and a Public Health Emergency of International Concern (PHEIC) was declared by the World Health Organization (WHO) globally.

In this study, we compared the prescription of anti-influenza agents between the 2018–19 season and the 2019–20 season, and explored the effects of the emergence of COVID-19 and a suspected baloxavir-resistant strain of influenza virus.

## Methods

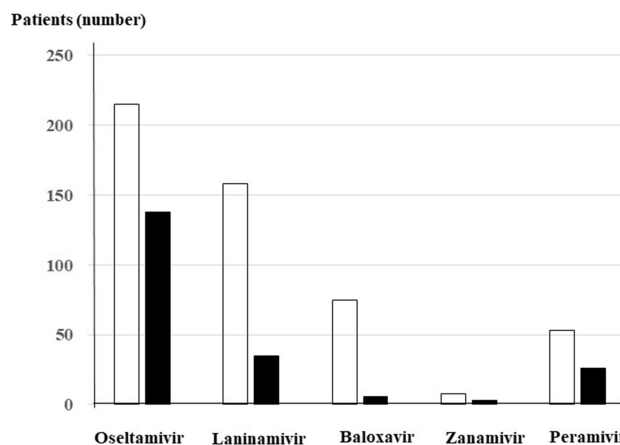
We used data from the prescription database maintained by the department of pharmacy in Tohoku Medical and Pharmaceutical University Hospital (600 beds).

The patients were diagnosed as influenza by rapid antigen tests (rapid influenza diagnosed kit: RIDTs), and/or clinically signs, such as temperature  $>38.0^{\circ}\text{C}$  with cough or sore throat with an onset of symptoms within 7 days after close contact with influenza patients. More than 90% patients were diagnosed as influenza by both RIDTs and clinical symptoms and the other were diagnosed by clinically. Both inpatient and outpatient were registered, and the anti-influenza agents were prescribed and used. The rates of inpatient and outpatient were 14% and 86%, respectively.

This study was complied with declaration of Helsinki and approved by the Committee for Clinical Scientific Research of Tohoku Medical and Pharmaceutical University Hospital in Feb, 2020 as No. ID2019-2-028. Written informed consent was provided by the patients to use their data in this study.

## Results

In the 2018–19 season, in which both A/H1N1pdm09 and H3N2 influenza virus infections were prevalent, a total of 509 patients received anti-influenza agents. In contrast, Only 205 patients received anti-influenza agents in the 2019–20 season, in which A/H1N1pdm09 infections were most prevalent. However, novel corona virus infection 2019 (COVID-19) has become a much larger cause for concern than influenza in 2019–20 season. Five anti-influenza agents, oseltamivir, laninamivir, baloxavir, zanamivir, and peramivir, were prescribed in both the 2018–19



**Figure 1** Total prescription of anti-influenza agents in Tohoku Medical and Pharmaceutical University Hospital in the 2018–19 season (white bars) and the 2019–20 season (black bars), respectively.

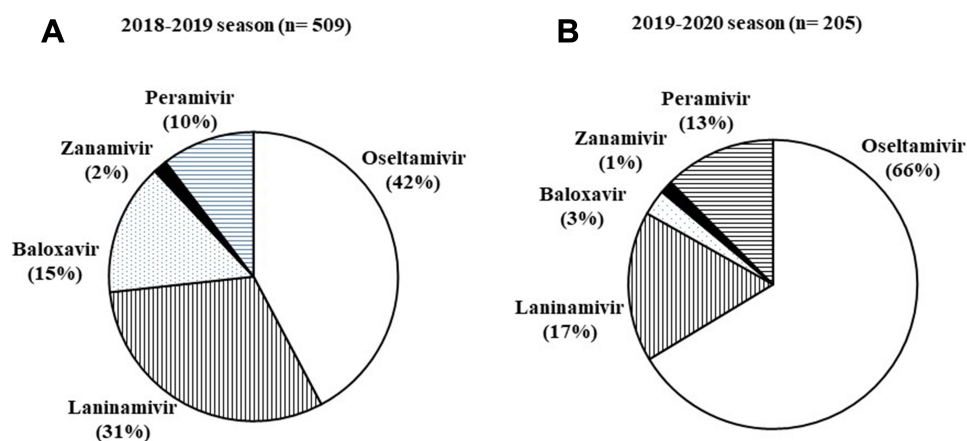
season and the 2019–20 season although the total prescription of the anti-influenza agents decreased in the 2019–20 season (Figure 1).

Figure 2 shows the share and ratio of each anti-influenza agent in the 2018–19 season (Figure 2A) and the 2019–20 season (Figure 2B). Among the five anti-influenza agents, the ratio and share of baloxavir and laninamivir significantly decreased from 15% to 3% and from 31% to 17%, respectively. In contrast, oseltamivir increased from 42% to 66%. Zanamivir remained constant, while peramivir showed a slight increase.

## Discussion

In Japan, many NAIs have been available and recently the use of a new CEI, baloxavir marboxil, began. Baloxavir is reported to be equally clinically effective, have a better viral reduction ability and only require a single oral dose to be effective when compared with oseltamivir, which must be administered twice per day for five days to be effective.<sup>7</sup>

In this study, we observed a large ratio of baloxavir prescription among the anti-influenza agents in our hospital with a relatively high share of 15% even though the 2018–19 season was the novel year of prescription. However, the clinical efficiency of baloxavir is reduced in patients with an I38 substitution of PA regions, which is consistent with drug susceptibility, and 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, especially against H3N2 in its seasonal peak, should be considered after the 2018–19 season.<sup>6,8–10</sup>



**Figure 2** The ratio and shares of prescribed anti-influenza agents in the 2018–19 season (A) and the 2019–20 season (B), respectively. White area: oseltamivir, vertical line area: laninamivir, dot area: baloxavir, black area: zanamivir, and horizontal line area: peramivir, respectively.

Furthermore, viruses with I38 substitutions suggest human-to-human transmission because these viruses were isolated from patients who had not been treated with baloxavir but had siblings who were.<sup>6</sup> NAI-resistant viruses, for instance, NA H275Y mutation confers resistance to oseltamivir and peramivir although laninamivir might be still relatively susceptible, and it is also well confirmed human-to human transmission of NAI-resistant viruses.<sup>12,13</sup> These data suggest that appropriate treatment to avoid selecting mutant viruses should be performed, since treatment for the whole household is impractical. Therefore, careful use of baloxavir might become the trend among Japanese clinicians in the 2019–20 season. As an effect, we found a significant reduction in the prescription of baloxavir from a 15% to 3% share among anti-influenza agents in our hospital. We did not find actual large number of baloxavir-resistant strain in 2019–2020 because H1N1 strain, which considered low-resistant for baloxavir, was dominant in this season, however, the informative support and education for the appropriate use of antimicrobial agents by the infectious diseases physicians and pharmacists, such as one of the antimicrobial stewardship program may result the improvement of the anti-influenza agents use, especially for use of baloxavir.<sup>14,15</sup>

In addition, the total prescription of the anti-influenza agents significantly decreased in our hospital in the 2019–20 season, compared to the 2018–19 season. This might be an effect of the COVID-19 pandemic.<sup>16</sup> The general population has been very cautious about the transmission and infection of the virus in Japan, with masks and proper hygiene procedures being strongly recommended. Therefore, influenza virus transmission and infection may

also reduce, and the total use of anti-influenza drugs, including laninamivir were reduced although prevalence of laninamivir-resistant strain have not been reported and shown continuously clinical effects in contrast to baloxavir.<sup>17</sup> The share of osertamivir alone increased clearly because it was considered as the most standard anti-influenza agent globally,<sup>18</sup> but the total amount of osertamivir use also reduced in 2019–2020 seasons, compared with 2018–2019 seasons. Further studies and clinical observation of anti-influenza agents and emergence of resistant strains and novel viruses are needed.

In summary, we analyzed the prescription of anti-influenza agents and compared their shares in the 2018–19 season and the 2019–20 season. We found a significant decrease in the total prescription of anti-influenza agents, especially of the new CEI baloxavir, in our hospital in Japan. The suspected prevalence of the baloxavir-resistant influenza strain and emergence of SARS-CoV-2 might have affected the use of anti-influenza agents in the 2019–20 season. This could be in line with the antiviral stewardship and infection control philosophy; however, more comprehensive and nationwide data analysis will be needed.

## Disclosure

The authors report no conflicts of interest in this work.

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