

# Single-dose inhaled laninamivir: registered in Japan and its potential role in control of influenza epidemics

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To the editor:

The impact of influenza infection is felt globally each year, with approximately 20 per cent of the world's population becoming infected annually. Additionally, recent events, including human cases of avian influenza, have heightened awareness of pandemic threat and have spurred efforts to develop plans for its control.<sup>1</sup> In the spring of 2009, a pandemic influenza A (H1N1) virus emerged and caused a severe illness requiring hospitalisation that often resulted in pneumonia and death. Jain *et al.*<sup>2</sup> have described the clinical characteristics of patients who were hospitalised with 2009 H1N1 influenza in the USA from April 2009 to mid-June 2009 and have suggested that the use of antiviral drugs was beneficial, especially when initiated early during infection.

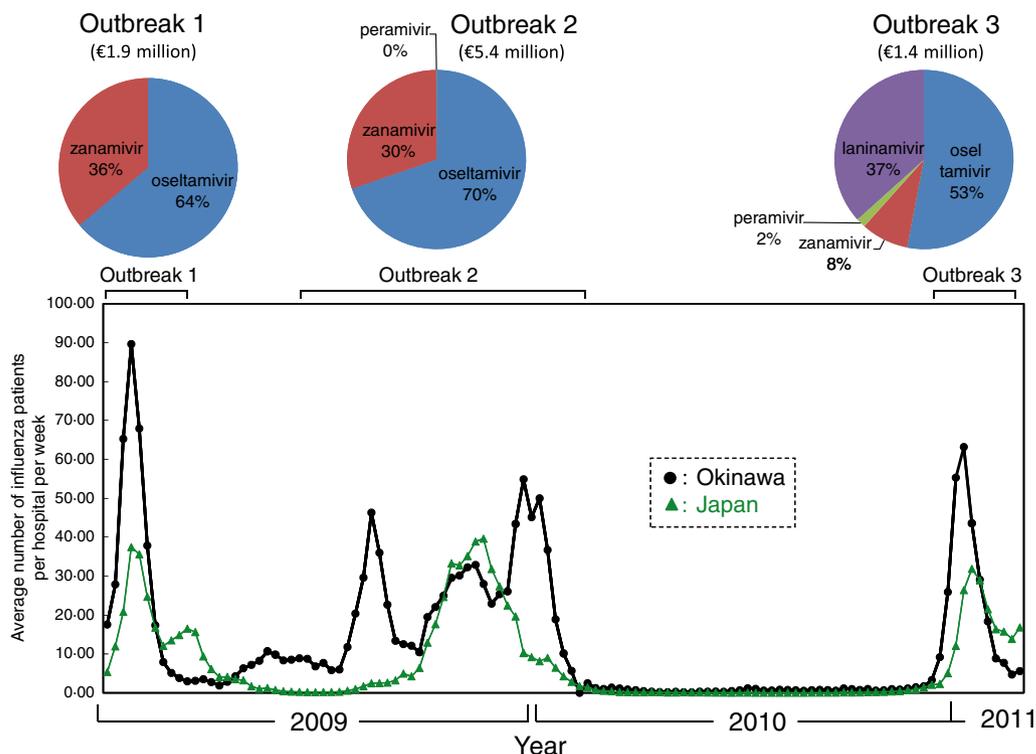
Two types of neuraminidase inhibitors (zanamivir and oseltamivir) are currently licensed worldwide for the treatment of influenza virus infection, and both drugs have been widely used in Japan. For effective treatment, these drugs require twice-daily administration for 5 days. In 2010, two newly developed neuraminidase inhibitors, peramivir and laninamivir octanoate, were introduced in Japan.<sup>3–6</sup>

Peramivir, an investigational intravenous neuraminidase inhibitor in phase three trials for hospitalised patients, was made available in the USA during the 2009 H1N1 influenza pandemic under the Emergency Investigational New Drug regulations.<sup>3</sup> Recently, it was reported that peramivir was effective for the treatment of 2009 H1N1 influenza.<sup>3,4</sup> Peramivir has been approved for use and has been commercially available in Japan since January 2010. Peramivir is used in hospitalised adult and paediatric patients that are unable to receive inhaled or oral neuraminidase inhibitors, or when drug delivery by a route other than intravenously is not feasible.

Laninamivir octanoate is an octanoyl ester pro-drug of laninamivir that exhibits neuraminidase inhibitory activity against influenza A and B viruses, including oseltamivir-resistant viruses and 2009 pandemic H1N1 viruses.<sup>5,6</sup> Moreover, laninamivir octanoate has long-lasting antiviral activities.<sup>5,6</sup> A single inhalation of laninamivir octanoate in patients affected by influenza has been shown to be comparably effective to oseltamivir as demonstrated by clinical studies.<sup>5,6</sup> Unlike other countries, laninamivir octanoate has been approved and has been commercially available in Japan since October 2010. Considering the simplicity of this one-dose drug, laninamivir octanoate appears to be a convenient anti-influenza agent.

Recently, in Okinawa, Japan, we have experienced three large influenza outbreaks. The first outbreak in the 2008–2009 season was caused by an oseltamivir-resistant H1N1 virus, the second outbreak in the 2009–2010 season was caused by the pandemic H1N1 2009 virus and the third outbreak was also caused by the pandemic H1N1 2009 virus during the 2010–2011 season (Figure 1). In the first outbreak, zanamivir and oseltamivir were available. In the end of second outbreak, peramivir was also available. In the third outbreak, all four neuraminidase inhibitors were available.

Given this background, we investigated sales of four anti-influenza drugs in Okinawa, Japan. For each season, we investigated the use (based on sales amount) of anti-influenza medications in Okinawa and calculated the ratio of each anti-influenza drug to total volume. We obtained data on monthly sales from pharmaceutical products wholesale businesses and calculated the sum total. We determined that the influenza outbreaks were finished when there were returned anti-influenza drugs to the wholesalers of pharmaceutical products. We also determined that



**Figure 1.** Plot of influenza patients from January 2009 to March 2011 in Okinawa (black circles) and all of Japan (green triangles). The three outbreaks are indicated by brackets. The associated pie charts represent distribution of influenza drug purchases during the three outbreaks. The number in the parenthesis is the amount of money spent on these drugs (in Euros).

unused anti-influenza drug stocks did not have a significant impact on the next outbreak's anti-influenza drug purchases.

As shown in Figure 1, there were substantial differences in drug sales between the third outbreak (2010–2011) compared with the first outbreak (2008–2009) or the second outbreak (2009–2010). The most striking change in the sale of anti-influenza drug was the uptake of laninamivir during the 2010 season, with a corresponding decrease of zanamivir and oseltamivir use.

To determine the reason that laninamivir octanoate was widely used in Okinawa after it was introduced, we issued a questionnaire to pharmacists in the region. Among 569 pharmacy offices, 219 offices returned the questionnaire. In the questionnaire to 169 pharmacists about which drug was easiest to instruct on its use, 138 answered that oseltamivir was easiest, 29 answered that laninamivir was easiest and only two answered that zanamivir was easiest. In Japan, most anti-influenza drugs are prescribed in pharmacies, and pharmacists often explain to patients how to use anti-influenza drugs. In Japan, although there is no absolute requirement that laninamivir is administered in the presence of and under supervision by the pharmacist, most patients opt to do so because the treatment will be complete after one inhalation. Therefore, the treatment of lani-

namivir octanoate may be finished at the pharmacy. The conclusions of the questionnaire were that laninamivir octanoate therapy was relatively simple and treatment by a single inhalation could be completed in the presence of the pharmacist. This ensured prompt treatment and full patient compliance.

At present, laninamivir octanoate is registered only in Japan but has the potential to be used around the world as a convenient anti-influenza drug. It will be interesting to investigate compliance rates between patients prescribed more traditional 5-day treatment (oseltamivir and zanamivir) and the one-dose drug laninamivir octanoate. Owing to ease of administration as shown in our study, it is likely that compliance rates would be higher among patients prescribed laninamivir than oseltamivir or zanamivir. In addition, this study suggests pharmacy-based surveys may be useful way to collect accurate information about those who are receiving treatment with anti-influenza drugs, such as age, risk factors, etc.

## Conflicts of Interest

JF has served on speaker's bureaus for GlaxoSmithKline, Abbott Japan, Boehringer Ingelheim, Pfizer, Astellas, Daiichi Sankyo, and Taisho Toyama.

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