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Baloxavir and Treatment-Emergent Resistance: Public Health Insights and Next Steps

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Drug resistance is a topic of significant concern in the treatment of infectious diseases caused by rapidly evolving RNA viruses that can persist (eg, human immunodeficiency virus and hepatitis C virus) or reinfect (eg, influenza virus). Combination drug therapy is standard of care for the treatment of infections by rapidly mutating RNA viruses [1, 2]. However, it is not a common approach for treating influenza virus infections, partly because of the limited number of anti-influenza drugs and drug targets. We now know that all of the classes of anti-influenza drugs—M2 blockers, neuraminidase inhibitors (NAIs), and the newly licensed cap-dependent endonuclease inhibitor (baloxavir marboxil)—have low genetic barriers to resistance: 1 or 2 amino acid substitutions are sufficient to gain resistance [3, 4].

In this issue of *The Journal of Infectious Diseases*, Uehara et al explore factors associated with the emergence of resistance to baloxavir [5]. They determined that an amino acid substitution, PA-I38T, in the polymerase acidic protein (PA) was the most common change detected in viruses emerging during baloxavir treatment. Based on the data obtained from in vitro studies and clinical trials, this substitution has been recognized as a principal pathway to baloxavir resistance [6, 7]. Moreover, this substitution was shown to emerge under selective pressure of another PA inhibitor, RO-7, which targets the endonuclease active site [8]. Consistent with a low genetic barrier to resistance, the emergence of PA-I38T mutants was detected as early as day 3 (range, 3–9 days) after receiving baloxavir treatment, and in most cases it occurred on day 5 [5, 6].

Pathways to drug resistance are known to differ by influenza virus type and subtype. For example, in influenza A(H1N1) viruses, the most common marker of oseltamivir resistance is NA-H275Y, whereas in influenza A(H3N2) viruses, it is NA-R292K [4]. This is due to certain structural variance in the drug-targeted enzyme, neuraminidase. Although PA-I38T is the marker of baloxavir resistance, regardless of the virus type and subtype, its effect on the level of resistance appears to be type specific, at least in vitro [7]. This difference may reflect structural variance in the PA endonuclease enzyme active site in type A versus type B viruses. Unfortunately, the study by Uehara et al does not provide additional insights on this

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matter, as there was only a small percentage of patients (8.3%) with illness due to influenza B virus. PA-I38T was not the only change detected in viruses collected after treatment. Another substitution, PA-I38M, was detected in 3 patients and appeared to provide a lower level of resistance in vitro [7]. Since emergence of PA-I38T was associated with a delay in symptom alleviation, prolonged shedding, and rebound in virus titers, detection of this substitution can be considered as a laboratory correlate of clinically relevant baloxavir resistance. The effect of other substitutions (eg, PA-I38M) on clinical outcome will require additional studies.

The rate of emergent viral resistance during treatment can influence clinical management and is also important for risk assessment modeling and pandemic preparedness. Uehara et al reported resistance rate of 7.9%–9.7% among baloxavir-treated immunocompetent adults and adolescents, depending on the availability of viral sequences for analysis. This high rate of emergent resistance commands a closer look. Although 8%–10% may seem higher than reports for emergent NAI resistance in adults, it is problematic to compare the current result with findings from previous studies of other drugs, as they were conducted using different methods to detect resistance and in different seasons with different circulating viruses.

In this study (CAPSTONE-1), most patients had illness caused by A(H3N2), the dominant circulating viruses in Japan and the United States during the 2016–2017 influenza season. Interestingly, the rate of baloxavir resistance in the previously published phase 2 study was reported as 2.2%; the majority of the participants in that study were infected with 2009 pandemic influenza A(H1N1) virus (A[H1N1]pdm09) [6]. Taken together, these findings suggest that resistance may emerge more frequently during the treatment of A(H3N2) infections. The outcome of a small pediatric study conducted in Japan during the 2016–2017 season further supports this assumption, as the rate of baloxavir resistance was 19.5% and the majority of patients were treated for illness due to A(H3N2) [7].

One of the most interesting findings in the report by Uehara et al was an association between low levels of neutralizing antibodies and the emergence of baloxavir-resistant viruses. In fact, this was the only factor statistically different between treated patients shedding susceptible versus resistant viruses. Why would preexisting neutralizing antibodies prevent the selection of baloxavir resistance? Their presence might increase the genetic barrier to resistance by combining antiviral effects of antibodies and baloxavir. Because spontaneous mutations occur at a low rate (approximately 10^{-4} mutations/nucleotide), a remaining smaller virus population reduces the chances for the emergence of virus variants carrying a resistance-conferring mutation. It is tempting to speculate that the neutralizing antibodies in the group shedding only susceptible viruses played a crucial clinical role by further suppressing the size of the virus population (and its heterogeneity) during the critical period, 48–72 hours after treatment; additional analyses could explore this hypothesis.

Consistent with this argument, the 2 studies with higher rates of resistance emergence, the CAPSTONE-1 and pediatric trial, occurred in a season with circulation of 3C.2a antigenically drifted A(H3N2) that emerged in 2014–2015 and reports of lower vaccine protection [9]. Thus, the treated population may have had lower levels of protective neutralizing antibodies against the infecting virus as compared to seasons without antigenic

drifted viruses. Conversely, the rate of baloxavir resistance might be higher in treated patients with A(H1N1)pdm09 infections if antigenic drift occurred in these viruses.

An association between underlying immunity and resistance may have played a role in the wide circulation of oseltamivir-resistant A(H1N1) between 2007–2008 and 2008–2009 [10]. Antigenic drift among circulating A(H1N1) detected by human serologic studies, a potentially more sensitive assay for detecting antigenic changes than ferret sera, was one factor suspected to contribute to the rapid spread of the oseltamivir-resistant pre–2009 pandemic A(H1N1), when viruses carrying NA-H275Y and compensatory substitutions spread via a mechanism known as “hitchhiking” [11].

Susceptibility to the infecting virus is only one factor that may contribute to the emergence or circulation of resistant viruses. Understanding the transmissibility of PA-I38T viruses from one person to another will be critical. In vitro studies suggest viruses carrying PA-I38T substitution may be attenuated as compared to wild-type viruses [7, 12]. However, A(H3N2) with PA-I38T have been identified from specimens collected from ill children not treated with baloxavir [13, 14]. While these reports are rare to date, they are concerning and suggest that non–treatment-related PA-I38T viruses may transmit among humans [14]. In addition, Uehara et al demonstrated differences in the emergence of resistance and drug serum concentrations between the Japanese and American participants. This needs to be explored more fully and could have clinical implications.

Influenza A and B viruses are contagious respiratory pathogens relentlessly evolving to escape from host immunity raised in response to previous influenza virus infections and vaccinations. This results in annual epidemics with often very large disease burdens. Anti-influenza drugs are needed to reduce morbidity and mortality caused by seasonal epidemics and to mitigate influenza pandemics before the availability of vaccines. Optimizing the use of antiviral agents will not only maximize clinical benefit but also ensure that these drugs do not become obsolete. Combination therapy using anti-influenza drugs has been explored in the past. Combination of the older antivirals (amantadine, ribavirin, and oseltamivir) did not provide an apparent therapeutic benefit as compared to monotherapy; however, combinations might prevent emergence of drug resistance [15]. Indeed, the combination of amantadine, ribavirin, and oseltamivir was shown to impede the selection of drug-resistant influenza viruses in vitro [16]. Thus, all potential benefits of combination use of baloxavir with other anti-influenza drugs must be explored.

Protecting the limited number of anti-influenza drugs available for seasonal and pandemic influenza is critical. This will require close monitoring of influenza virus resistance globally and additional studies to understand the fitness and transmissibility of resistant viruses, as well as further determination of which groups are at highest risk for the emergence of resistance during treatment. Finally, if preexisting immunity plays a role in reducing resistance, annual influenza vaccination could be an important tool to minimize the emergence of resistance and potentially optimize the benefits from current anti-influenza drugs.

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