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Baloxavir Treatment to Reduce Influenza Virus Transmission

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Antiviral treatment of influenza is recommended as soon as possible for hospitalized patients and for outpatients who are at increased risk for influenza-related complications.^{1,2} The Food and Drug Administration–approved oral antiviral agent oseltamivir is the most widely used antiviral medication for the treatment of influenza and for postexposure prophylaxis to control institutional outbreaks of influenza. Baloxavir marboxil (baloxavir) is an oral antiviral medication that is FDA-approved for early treatment (within 48 hours after symptom onset) of uncomplicated influenza and for postexposure prophylaxis against influenza in persons 5 years of age and older. Randomized, controlled trials of early treatment with baloxavir, as compared with oseltamivir or placebo, showed that the efficacy of a single dose of baloxavir was similar to that of oseltamivir taken twice daily for 5 days for reducing the time to alleviation of influenza symptoms in adolescents and adults, including those at increased risk for influenza-related complications.^{3,4} In addition, upper respiratory tract virus levels were significantly lower with baloxavir than with oseltamivir or placebo as early as 24 hours after treatment, a finding consistent with its mechanism of action in inhibiting viral replication.^{3,4} Early treatment with oseltamivir or baloxavir has efficacy in reducing the risks of some influenza-related complications, as compared with placebo.⁴⁻⁶

An important question for public health is what is the effect of antiviral medications when used in the household setting, where a substantial proportion of community-wide influenza virus transmission occurs? Previous trials involving households used different designs to assess antiviral efficacy in reducing influenza virus transmission. These studies included early treatment in the first symptomatic person in the household (the index patient), postexposure prophylaxis in household contacts, or a combination of the two strategies. An analysis of randomized, controlled trials in the household setting showed substantial efficacy of postexposure prophylaxis with the neuraminidase inhibitors oseltamivir (81%) or zanamivir (75%) in the prevention of symptomatic influenza in exposed household contacts.⁷ One randomized, controlled trial showed that antiviral treatment in index patients, in combination with postexposure prophylaxis with baloxavir in household contacts, reduced the risk of symptomatic influenza by 86%, as compared with placebo.⁸ A secondary data

analysis of this trial estimated that baloxavir treatment in index patients reduced the risk of symptomatic influenza in household contacts by approximately 42%, as compared with oseltamivir treatment, a finding that suggests that baloxavir treatment had an additional effect in reducing influenza virus transmission to household contacts who received baloxavir as postexposure prophylaxis.⁹

In this issue of the *Journal*, Monto and colleagues¹⁰ report the findings of a randomized, controlled trial that investigated the efficacy of baloxavir treatment, as compared with placebo, in reducing influenza virus transmission from index patients with laboratory-confirmed influenza to household contacts. Most of the 1457 index patients and 2681 household contacts in this multicenter trial were enrolled in Bulgaria, the United States, Japan, China, and Turkey from October 2019 through April 2024. The index patients were 5 to 64 years of age, were not at high risk for influenza complications, had fever or acute respiratory or systemic symptoms, tested positive for influenza and negative for SARS-CoV-2 on a polymerase-chain-reaction (PCR) assay or an antigen-based assay, were enrolled within 48 hours after the onset of illness, and had household contacts 2 years of age and older. The household contacts in the trial were mostly unvaccinated. The primary end point was transmission of the same influenza virus, as confirmed on reverse-transcriptase–PCR testing, from an index patient to a household contact by day 5 after the index patient's receipt of baloxavir or placebo. Baloxavir treatment in index patients led to a significantly lower incidence of influenza virus transmission (symptomatic or asymptomatic infection) to household contacts than placebo at day 5 (9.5% vs. 13.4%; adjusted odds ratio, 0.68; 95.38% confidence interval [CI], 0.50 to 0.93; $P = 0.02$), which translated to an adjusted relative risk reduction of 29% (95.38% CI, 12 to 45), but the incidence of influenza virus transmission by day 5 that resulted in symptoms was not significantly lower with baloxavir than with placebo (5.8% vs. 7.6%; adjusted odds ratio, 0.75; 95.38% CI, 0.50 to 1.12; $P = 0.16$); the symptoms used to define whether the criteria had been met could have occurred at any time. No new safety signals were identified. These findings indicate that early initiation of baloxavir treatment in an index patient with uncomplicated influenza can reduce the risk of influenza virus transmission (asymptomatic or symptomatic infection) to the index patient's household contact by approximately 30% (an absolute reduction of 3.9 percentage points), but they do not suggest that the risk of influenza virus transmission that results in symptoms in the household contact would be reduced.

Emergence of baloxavir resistance is a concern. In the trial by Monto et al., among the treated index patients with sequencing data, 7.2% had polymerase acidic (PA) gene substitutions associated with reduced baloxavir susceptibility, but these substitutions were not present in the viruses in the household contacts, probably because influenza virus transmission from the index patients occurred before baloxavir treatment was administered. One randomized, controlled trial showed that approximately 10% of baloxavir-treated patients had PA gene substitutions that correlated with prolonged symptoms,³ and in another randomized, controlled trial, transmission of influenza viruses with reduced baloxavir susceptibility from five treated index patients was possible.⁸ Transmission of influenza viruses with reduced baloxavir susceptibility has been uncommon, but transmission of drug-resistant viruses remains a public health concern for all antiviral medications; thus,

ongoing global surveillance for drug-resistant influenza virus is essential to inform antiviral use.

The best way to prevent seasonal influenza is through annual influenza vaccination in persons 6 months of age and older, and antiviral medications are an important adjunct to influenza vaccines. Challenges and questions remain about how to use antiviral medications most effectively because of the short incubation period and short serial interval for influenza; this includes how to operationalize early diagnosis and antiviral treatment to achieve the greatest benefit, especially for persons at increased risk for complications and those living in households with such persons. Clinical trials are needed to assess strategies to control institutional outbreaks of influenza through the use of antiviral agents with different mechanisms of action (e.g., baloxavir treatment combined with postexposure prophylaxis with oseltamivir in long-term care facility residents). Data are lacking on the efficacy, effectiveness, appropriate dose administration, or duration of baloxavir use for the treatment or postexposure prophylaxis of novel influenza A viruses of pandemic potential, including highly pathogenic avian influenza A(H5N1) virus, which limits the use of baloxavir in real-world public health strategies. During the early phase of an influenza pandemic, when pandemic influenza vaccines are not yet available, early treatment with baloxavir, with its ability to decrease viral shedding, might have greater benefit in reducing transmission than when it is used for seasonal influenza, because most exposed persons will lack specific immunity to the pandemic influenza virus and household transmission is expected to be high.

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