A Step Forward in the Treatment of Influenza

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For many years, antiviral treatment of influenza has consisted of monotherapy with a neuraminidase inhibitor. The Food and Drug Administration (FDA) approved the neuraminidase inhibitors oseltamivir (oral administration) and zanamivir (oral inhalation) in 1999 and peramivir (intravenous administration) in late 2014. These drugs work by binding to the viral neuraminidase protein and interfering with the release of influenza virus particles from infected respiratory tract cells. Neuraminidase inhibitors are FDA-approved for the treatment of uncomplicated influenza within 2 days after onset in outpatients, on the basis of randomized, controlled trials, but they are also recommended for the treatment of patients with severe influenza, including hospitalized patients, by the Centers for Disease Control and Prevention and the World Health Organization.1,2 The adamantane antiviral drugs (amantadine and rimantadine) are approved for the treatment of influenza A virus infections but are not recommended, owing to a high prevalence of adamantane resistance among circulating influenza A viruses.1

Because influenza viruses are continuously evolving, global surveillance of circulating influenza viruses is essential to inform recommendations on the use of antiviral drugs for influenza. This was highlighted by the emergence of oseltamivir-resistant influenza A(H1N1) viruses in 2007 that became prevalent worldwide until replacement by the 2009 H1N1 pandemic virus (influenza A(H1N1)pdm09).3 Sporadic emergence of oseltamivir resistance, including clusters of oseltamivir-resistant influenza A(H1N1)pdm09 virus infections, further emphasizes the need for drugs with mechanisms of action distinct from neuraminidase inhibitors.3

In this issue of the Journal, investigators report the results of two randomized, double-blind, placebo-controlled trials of baloxavir marboxil (baloxavir), a new antiviral drug that targets the polymerase complex of influenza A and B viruses.4 After oral administration, baloxavir is converted to baloxavir acid, which selectively inhibits the function of endonuclease within the polymerase acidic (PA) protein subunit of influenza viral polymerase. The trials involved outpatients 12 to 64 years of age without underlying high-risk medical conditions who presented within 48 hours after the onset of laboratory-confirmed influenza in Japan and the United States. In the phase 2 dose-ranging trial involving 389 Japanese adults, a single baloxavir dose (10 mg, 20 mg, or 40 mg) resulted in a significantly shorter time to alleviation of symptoms and greater reductions in levels of influenza virus at 1 and 2 days after administration of the trial regimen than did placebo. In the phase 3 trial in Japan and the United States, patients 20 to 64 years of age were randomly assigned to receive a single dose of baloxavir (40 mg or 80 mg, depending on body weight), oseltamivir at a dose of 75 mg twice daily for 5 days, or placebo; patients 12 to 19 years of age were assigned to receive either baloxavir or placebo. Among the 1064 patients who had a diagnosis of influenza confirmed by a reverse transcriptase–polymerase chain reaction assay, baloxavir resulted in a significantly shorter time to alleviation of symptoms than did placebo in patients 20 to 64 years of age (median difference, 25.6 hours) and those 12 to 19 years of age (median difference, 38.6 hours). However, there was no significant difference in the median time to alleviation of symp-
toms between baloxavir recipients and oseltamivir recipients.

These findings indicate that baloxavir has a clinical benefit that is similar to that with oseltamivir for the early treatment of otherwise healthy outpatients 12 to 64 years of age with uncomplicated influenza. Owing to its longer half-life, a single baloxavir dose provides the advantage of avoiding adherence concerns with treatment with 5 days of twice-daily oseltamivir. However, in the phase 3 trial, more than half the patients in the baloxavir group received the drug within 24 hours after symptom onset, and such patients had a greater clinical benefit regarding a reduction in the duration of influenza symptoms than those who received it later. This is consistent with data on neuraminidase inhibitors — the greatest clinical benefit is when antiviral treatment is started soon after the onset of influenza. Thus, implementing early treatment with baloxavir or neuraminidase inhibitors will remain challenging for clinicians and patients with influenza worldwide.

The virologic findings of single-dose baloxavir treatment are both encouraging and cause for concern. In the phase 3 trial, baloxavir resulted in significantly greater reductions in influenza viral RNA levels in upper respiratory specimens at 24 hours and a shorter duration of infectious virus detection than did oseltamivir or placebo. However, in both trials, baloxavir treatment induced the emergence of viral escape mutants with reduced susceptibility through changes from isoleucine to other amino acids at position 38 (I38) of the gene encoding PA. Influenza A(H1N1)pdm09 virus was the predominant virus among patients in the phase 2 trial, and 2.2% of the baloxavir recipients with paired sequenced samples had escape mutants. In the phase 3 trial, influenza A(H3N2) virus predominated, and 10% of the baloxavir recipients with paired sequenced samples had escape mutants detected, typically 5 days or more after baloxavir treatment. Furthermore, in the phase 3 trial, infectious virus was detected 5 days after baloxavir treatment in 91% of the patients with escape mutations conferring a switch at I38 to threonine or methionine (I38T/M), and their duration of symptoms was substantially longer than the duration in baloxavir recipients without these escape mutants. In a related, but separate, cohort study involving children, 19.5% of baloxavir recipients had I38T mutations detected, and these escape mutants conferred reduced susceptibility to baloxavir by a factor of 30 to 50 in influenza A viruses and by a factor of 7 in influenza B viruses. The issue for public health is whether these influenza viruses with reduced susceptibility to baloxavir are transmissible, and surveillance for I38T and other markers will be needed.

These two randomized, controlled trials reported in the Journal should be viewed as a first step and the findings tempered by the need for data on baloxavir efficacy and safety through clinical trials involving patients with influenza who are most likely to benefit from antiviral treatment. These include persons at higher risk for influenza complications because of age (young children and elderly persons), pregnancy, or chronic coexisting medical conditions. Data are also needed on the clinical benefit of administering baloxavir treatment more than 48 hours after illness onset to outpatients who are in a high-risk group and to patients of all ages who are hospitalized with severe influenza complications, including critical illness. Pharmacokinetic and pharmacodynamic data are needed to inform appropriate dosing and to determine whether additional baloxavir doses are beneficial in patients with severe influenza. Can combination treatment with oseltamivir and baloxavir provide greater clinical benefit than oseltamivir monotherapy in hospitalized patients and severely immunocompromised patients with seasonal influenza, as well as in hospitalized patients with zoonotic influenza, such as those with avian influenza A(H7N9) virus infection? Can baloxavir successfully treat patients with neuraminidase inhibitor–resistant influenza virus infection?

The significant reduction in influenza viral replication with baloxavir treatment suggests the potential for reducing influenza virus spread to close contacts and should be studied through randomized, controlled trials in households and during institutional influenza outbreaks such as in long-term care facilities. If a single dose is successful in reducing influenza virus transmission, baloxavir could be a useful tool for seasonal and pandemic influenza preparedness and response. Further clinical, virologic, and transmission studies, and global surveillance for influenza viruses with reduced drug susceptibility, will in-
from the usefulness of baloxavir for clinical use and public health benefit.

The views expressed in this editorial are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Imaging Coronary Anatomy and Reducing Myocardial Infarction

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In 1998, the Journal published one of the early studies evaluating the sensitivity and specificity of coronary computed tomographic angiography (CTA), as compared with invasive coronary angiography, for the detection of obstructive coronary artery disease.1 Subsequent studies have established that CTA has excellent sensitivity (95 to 99%) and high specificity (64 to 83%) for the detection of coronary stenoses of 50% or greater.2 An analysis from the Prospective Multicenter Imaging Study for the Evaluation of Chest Pain (PROMISE) showed that CTA predicted subsequent cardiovascular events at least as well as, and perhaps better than, functional testing (C-statistic, 0.72 vs. 0.64; P=0.04).3 The National Institute for Health and Care Excellence of the United Kingdom now suggests that CTA is the most appropriate test in patients with stable chest pain in whom angina pectoris cannot be excluded by means of clinical assessment alone.4

The Scottish Computed Tomography of the Heart (SCOT-HEART) trial investigators now report in the Journal that an initial diagnostic strategy that incorporated CTA in addition to standard care was associated with a 41% lower rate of the primary end point (death from coronary heart disease or nonfatal myocardial infarction) after almost 5 years of follow-up than standard care alone.5 This observed lower rate of the primary end point was driven almost entirely by a lower rate of nonfatal myocardial infarction in the CTA group than in the standard-care group and was achieved without resulting in a higher rate of subsequent invasive coronary angiography or coronary revascularization. This is a new finding that is in contrast to previous trials that have shown higher rates of invasive coronary angiography and coronary revascularization after anatomical imaging with CTA than after functional testing.

The relative risk reductions observed in the SCOT-HEART trial are similar to those observed in recent secondary prevention trials,6 which prompts speculation about the mechanism. In trials of diagnostic testing strategies, it is the downstream management — presumably driven by the testing results — that affects outcomes. It is unlikely that revascularization played a major role in the difference between the groups in the rate of the primary end point, and specifically in the difference in the occurrence of nonfatal myocardial infarction, given the similar rates of revascularization in the two groups. Therefore, the benefit seen in the CTA group might be attributable mostly to changes in medical management that were made on the basis of testing results. The authors speculate that the mechanism by which myocardial infarctions were prevented may, in part, be related to more appropriate use of preventive therapies in the CTA group — a