



## Baloxavir marboxil: a new influenza antiviral with a novel mechanism

Brett L. Smith, PharmD, BCPS

**P**andemic and epidemic influenza infections lead to significant morbidity and mortality annually despite various vaccination and treatment options. Baloxavir marboxil, approved by the Food and Drug Administration (FDA) on October 24, 2018, offers a novel approach to treatment of acute uncomplicated influenza in adolescents and adults.<sup>1</sup> The drug received Priority Review by the FDA in June 2018 and its phase II and III trial data were published in the *New England Journal of Medicine* in September 2018.<sup>2</sup>

### Mechanism of Action

The influenza RNA-dependent RNA polymerase contains three subunits: polymerase basic protein 1 (BP1), polymerase basic protein 2 (BP2), and polymerase acidic protein (PA).<sup>2</sup> The PA subunit contains a cap-dependent endonuclease which cleaves at nucleotides 10-13 of host RNA, known as 'cap-snatching,' creating a primer for viral mRNA transcription.<sup>2,3</sup> Baloxavir marboxil is a prodrug that undergoes rapid hydrolysis to its active form, baloxavir acid.<sup>4</sup> Baloxavir acid inhibits the cap-dependent endonuclease, preventing the transcription process in its early stages.<sup>5</sup>

### Pharmacokinetics

The prodrug, baloxavir marboxil, is rapidly eliminated resulting in low concentrations following oral administration.<sup>5</sup> Baloxavir acid, however, displays two-compartment, linear pharmacokinetics for doses from 6 mg to 80 mg given when fasting.<sup>5,6</sup> In adults, the maximum concentration ( $C_{max}$ ) was reached within 3.5 hours. The mean plasma concentration 24 hours after a single dose ( $C_{24}$ ) of 6 mg (6.92 ng/mL) exceeded the mean target  $C_{24}$  (6.85 ng/mL). Baloxavir acid is 92.9 to 93.9% protein bound, with an average terminal elimination half-life of 79.1 hours (range 49-81 hours).<sup>4,5</sup> Baloxavir acid is primarily metabolized via UGT1A3 with minimal metabolism by CYP3A4. The majority of metabolized drug is excreted in the feces. When administered with food,  $AUC_{0-inf}$  and  $C_{max}$  were

decreased by 48% and 36%, respectively.<sup>4</sup> Despite decreased plasma concentrations the target  $C_{24}$  to maintain exposure was exceeded in the non-fasting state.<sup>5</sup>

Koshimichi and colleagues examined the population kinetics of baloxavir acid by analyzing data from 1109 subjects from 12 clinical studies.<sup>6</sup> The individual exposure parameters ( $C_{max}$ ,  $C_{24}$ , and AUC) decreased as body weight increased. The measures were also lower in non-Asians than in Asians. However, the recommended dosage regimen based on body weight was found to be efficacious regardless of weight or race.

Renal function does not significantly impact the pharmacokinetics of baloxavir when creatinine clearance is  $\geq 50$  mL/min.<sup>4</sup> There also appears to be no significant difference in patients with moderate hepatic impairment. However, the effects of severe renal or hepatic impairment on baloxavir pharmacokinetics have not been studied. Baloxavir is unlikely to be removed by dialysis because it is highly protein bound.

### Microbiology

In an *in vitro* study conducted by Shionogi, the company that developed the drug in Japan, baloxavir was shown to have antiviral activity against both type A and B influenza viruses.<sup>7</sup> It has broad-spectrum coverage against 6 type A subtypes (H1N2, H5N1, H5N2, H5N6, H7N9 and H9N2), including strains from human, avian, and swine hosts.

Both cell cultures and clinical studies have revealed treatment-emergent strains of influenza A and B viruses with reduced susceptibility to baloxavir.<sup>2,3,7,8</sup> The primary reason for reduced susceptibility is due to amino acid substitutions at residue 38 in the PA subunit on the viral RNA polymerase. Omoto et al. reported between 30- and 50-fold decreases in susceptibility for type A and 7-fold decreases for type B influenza in a plaque reduction assay during post-clinical monitoring.<sup>3</sup> Furthermore, A(H1N1) and A(H3N2) viruses with I38T, I38F, and I38M

substitutions had reduced replication capability compared to the wild-type virus. The type B virus with I38F and I38M substitutions, however, replicated similarly to the wild-type virus. Takashita and colleagues reported 50% inhibitory concentration values 44 times higher in an influenza virus strain containing the I38T substitution in a focus reduction assay.<sup>8</sup> Both Takashita and Omoto also found that baloxavir remains effective against neuraminidase inhibitor-resistant strains. Similarly, neuraminidase inhibitors do not exhibit cross-resistance in baloxavir-resistant strains.

In a phase II study, 2.2% of patients had viruses with I38T/F amino acid substitutions which reduced susceptibility of A(H1N1) by a factor of over ten. In the phase III trial, 9.7% of patients had I38T/ M substitutions, all in A(H3N2) viral strains. Contrastingly, no I38 substitutions were found in patients receiving placebo in a randomly selected group. At day 5, infectious virus was detected in 91% of baloxavir recipients with I38T/M substitutions, 7% of baloxavir recipients without amino acid substitutions, and 31% of placebo recipients. Time to alleviation of symptoms was also longer in patients with viral variants versus patients with strains showing no PA substitutions (63.1 hours vs. 49.6 hours).<sup>2</sup>

#### Clinical Experience

Two double-blind, randomized, controlled trials determined the safety and efficacy of baloxavir marboxil. The first study, a phase II trial, evaluated three single doses of baloxavir (10 mg, 20 mg, or 40 mg) versus placebo in Japanese adults age 20 to 64 years with acute influenza. Patients were randomized in a 1:1:1:1 ratio to one of the three doses or placebo.

The second study, a Phase III trial named CAPSTONE-1, included healthy adolescents and adult outpatients with influenza-like illness age 12 to 64 years in the United States and Japan. Patients 12 to 19 years were randomized to receive either baloxavir marboxil or placebo in a 2:1 ratio. Patients 20 to 64 years were randomized in a 2:2:1 ratio to receive baloxavir (a single dose of 40 mg for those weighing between 40 and 80 kg, 80 mg for those weighing 80 kg or more), oseltamivir (75 mg twice daily for 5 days), or placebo. Patients also received matching placebo for either baloxavir or oseltamivir for a total treatment course of 5 days for all participants.

Both trials included patients with fever (axillary,  $\geq 38.0^{\circ}\text{C}$ ), at least one respiratory symptom (cough, sore throat, nasal congestion), and at least one systemic symptom (fatigue, muscle or joint pain, feverishness or chills, headache) within 48 hours of symptom onset. In the phase II trial, influenza also had to be confirmed with a positive rapid antigen test for inclusion, as this is the standard of care in Japan. Women of childbearing age were included if they agreed to use highly

effective contraception for 3 months after the first dose of either study drug. Patients were only allowed to take acetaminophen for influenza symptom relief. Pregnant women, patients with specified underlying conditions, those weighing less than 40 kg, or those requiring hospitalization were excluded from both studies.

The primary endpoint in both trials, time to alleviation of symptoms, was determined by patient-reported absent or mild symptoms for at least 21.5 hours from the start of the trial regimen.<sup>2,6</sup> Twice daily, on days 1 through 9, participants rated the severity of the inclusion symptoms on a 4-point scale. Patients also rated their overall health on a scale of 1 (worst possible) to 10 (normal) once daily to determine time to return to usual health. Body temperature was taken four times daily for the first three days and twice daily thereafter to measure time to resolution of fever. To measure virologic endpoints, including changes in baseline of infectious virus and viral RNA titers, duration of virus detection, and frequency of emergence of amino acid substitutions associated with reduced baloxavir susceptibility, two nasopharyngeal swabs were taken at each visit up to day 8 (phase II) or 9 (phase III). In addition, serum was tested for influenza neutralizing antibody on days 1 and 22.

Overall, 389 of 400 randomized patients completed the phase II trial. The median time to alleviation of symptoms was significantly shorter in each of the three dose groups (10 mg, 20 mg, 40 mg) compared to placebo at 54.2 hours ( $P=0.009$ ), 51.0 hours ( $P=0.02$ ), and 49.5 hours ( $P=0.005$ ) versus 77.7 hours, respectively. All three dosing groups also demonstrated greater reductions in virus titers compared to placebo on days 2 and 3.

In the phase III trial, 1366 of the 1436 randomized patients completed the study. The intention-to-treat infected population included 1064 patients in the phase III trial who had influenza diagnosis confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay. In this population, the baloxavir group had a significantly shorter median time to alleviation of symptoms compared to placebo (53.7 hours vs. 80.2 hours,  $P<0.001$ ). Likewise, the intention-to-treat population baloxavir group had a shorter median time to alleviation of symptoms compared to placebo group (65.4 hours vs. 88.6 hours,  $P<0.001$ ). A shorter median time to alleviation of symptoms was also noted for both adults (median difference, 25.6 hours;  $P<0.001$ ) and adolescents (median difference, 38.6 hours;  $P=0.006$ ) receiving baloxavir compared to placebo. The baloxavir and oseltamivir groups had a similar median time to alleviation of symptoms (53.5 hours versus 53.8 hours). Patients who started the trial regimen within 24 hours of symptom onset had significantly greater median difference in the

time to alleviation of symptoms between the baloxavir and placebo groups (32.8 hours;  $P < 0.001$ ) compared to patients who started the regimen later (13.2 hours;  $P = 0.008$ ).

Baloxavir groups had a significantly shorter median time to resolution of fever compared to placebo (24.5 hours versus 42.0 hours,  $P < 0.001$ ). While the median time to return to usual health was shorter in the baloxavir group compared to placebo, it was not a significant finding (129.2 hours versus 168.8 hours,  $P = 0.06$ ).

Virologic efficacy was also shown in the phase III trial for baloxavir. Patients in the baloxavir treatment group experienced more rapid declines in viral load than placebo or oseltamivir 1 day after regimen initiation. Infectious virus was detected at a median duration of 24.0 hours for the baloxavir group versus 72.0 hours in the oseltamivir group ( $P < 0.001$ ), and 96.0 hours in the placebo group ( $P < 0.001$ ).

Ison and colleagues recently presented preliminary findings of CAPSTONE-2, a phase III, randomized, multicenter, double-blind trial examining baloxavir marboxil compared to placebo or oseltamivir in influenza patients with high risk of complications.<sup>9</sup> In addition to CAPSTONE-1 inclusion criteria participants had to have at least one criteria determining high risk of influenza complication. Patients were randomized 1:1:1 to receive one single dose of baloxavir on day 1, oseltamivir twice daily for 5 days, or placebo. The primary endpoint was time to improvement of influenza symptoms (TTIIS) in patients with confirmed influenza infection.

In the study, 2184 patients were enrolled and 1163 (53%) had confirmed influenza. Asthma or chronic lung disease and age  $\geq 65$  years were the most common risk factors. TTIIS in the baloxavir group was significantly shorter than placebo for all viral strains (median 72.3 hours vs. 102.3 hours,  $P < 0.0001$ ) and shorter than oseltamivir for type B (74.6 hours vs. 101.6 hours,  $P = 0.0251$ ). Baloxavir patients stopped shedding virus by 48 hours versus 96 hours in the placebo and oseltamivir groups.

#### Warnings and Precautions

Baloxavir has only shown efficacy against influenza virus. Practitioners should continue to evaluate for a potential bacterial infection presenting with influenza-like symptoms or as a complication of influenza and prescribe appropriate therapy as necessary.<sup>4</sup>

#### Adverse Effects

The safety of baloxavir was evaluated in all three trial phases.<sup>2,5</sup> A Phase I randomized crossover study by Koshimichi et al. evaluated drug dosing relative to food consumption in 15 healthy Japanese adult male participants.<sup>5</sup> Of the 12 participants who completed the study, five

reported a total of 8 treatment-related treatment-emergent adverse events (TEAEs). Two or more participants reported increased alanine aminotransferase (ALT), increased eosinophil count, and increased white blood cell count. A second phase I trial conducted by Koshimichi and colleagues evaluated baloxavir marboxil dosing (6 mg, 20 mg, 40 mg, 80 mg). Only one mild TEAE, headache, was reported by the 40 participants.

Adverse events were reported in 23 to 27% of patients receiving baloxavir across dosing groups and 29% of patients receiving placebo during the Phase II study.<sup>2</sup> None of the reported events had significant rate differences between treatment and placebo. The Phase III trial reported adverse events in 20.7% of the baloxavir group, 24.6% of the placebo group, and 24.8% of the oseltamivir group.<sup>2</sup> Treatment-related adverse events reported in over 1% of any patients included diarrhea and nausea. The incidence of treatment-related adverse events was more common in the oseltamivir group (8.4%) than the baloxavir group (4.4%). Overall, the adverse events reported in at least 1% of adult and adolescent participants receiving baloxavir in both phase II and III studies regardless of causality were diarrhea, bronchitis, nausea, nasopharyngitis, and headache.<sup>4</sup>

#### Drug Interactions

Baloxavir is a substrate of P-glycoprotein (P-gp), UGT1A3, and CYP3A4. However, following clinical and *in vitro* studies, baloxavir marboxil and its active metabolite do not appear to inhibit cytochrome P450 enzymes, UGT enzymes, or transporter systems.

Baloxavir acid contains a metal chelating head-group to encourage binding to two divalent cations in the cap-dependent endonuclease. For this reason cation-containing foods (e.g. dairy products) or medications (e.g. calcium, iron, magnesium, zinc) can chelate baloxavir and coadministration should be avoided.<sup>3,4</sup> While it has not been studied, concurrent administration with the intranasal live attenuated vaccine should be avoided as antivirals may decrease its effectiveness.<sup>4</sup>

A mouse model has shown synergistic antiviral activity between baloxavir acid and neuraminidase inhibitors in type A influenza.<sup>10</sup> In anticipation of potential combination therapy with baloxavir and oseltamivir, Kawaguchi et al. conducted a phase I, open-label, randomized, three-treatment crossover study to determine the effect of oseltamivir on the pharmacokinetic and safety profile of baloxavir.<sup>11</sup> In Japan, 18 healthy adult male subjects (mean age 37.7 years) received three treatments in a randomized sequence with a 21 day washout. Treatments consisted of baloxavir 40mg as a single dose, oseltamivir 75 mg twice daily for 5 days, or both medications concurrently.  $C_{max}$  and AUC were

not significantly altered for either drug during co-administration, and the mild adverse events reported were not related to the therapies, suggesting a lack of drug-drug interaction between the antivirals.

#### Availability

Baloxavir marboxil (Xofluza®) is available as 20 mg and 40 mg oblong shaped white to light yellow tablets. The tablets are packaged in blister cards to total a 40 mg or 80 mg one time dose (2 or 4 20 mg tablets; 1 or 2 40 mg tablets).<sup>4</sup> The single dose blister card is \$150, regardless of strength. Genentech has provided a coupon which can be used up to two times per influenza season. The patient will pay the first \$30 with up to \$60 additional coverage by the manufacturer.<sup>12</sup>

#### Future Studies

Two trials are currently recruiting to determine safety and efficacy of baloxavir in an otherwise healthy pediatric population presenting with influenza-like symptoms.<sup>13,14</sup> The first is a randomized, double-blind, oseltamivir-controlled study that will evaluate the percentage of patients with adverse events, pharmacokinetic parameters, and efficacy of baloxavir marboxil in patients 1 to < 12 years of age.<sup>13</sup> Patients will be randomized to receive a single weight-based oral dose of baloxavir marboxil suspension, oseltamivir suspension for 5 days, or placebo. The second, a single-arm, open-label study will evaluate similar endpoints in patients from birth to less than 1 year of age.<sup>14</sup> Patients will be recruited to one of three cohorts receiving a single oral dose of baloxavir acid at 1 mg/kg for patients < 4 weeks old, 1 mg/kg for patients ≥ 4 weeks to < 3 months old, and 2 mg/kg for patients ≥ 3 months to < 12 months old.

#### Dosing Recommendations

For acute, uncomplicated influenza in patients 12 years and older, baloxavir marboxil follows a weight-based dosing strategy.<sup>4</sup> Patients between 40 and 80 kg receive a single dose of 40 mg. Patients over 80 kg receive a dose of 80 mg. The single dose must be administered less than 48 hours from the onset of influenza symptoms with or without food.

#### Summary

Baloxavir marboxil offers a new mechanism in influenza treatment. Due to its simple dosing regimen and broad-spectrum coverage it is likely to have an important role in influenza treatment in both healthy and high-risk populations. Baloxavir also is currently being evaluated for its potential for use as a combination therapy with existing antiviral therapies.

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