Baloxavir Marboxil: A New Antiviral for Acute Influenza

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Abstract

Baloxavir is a newly approved, single-dose, oral influenza antiviral indicated for acute uncomplicated influenza in patients 12 years and older if symptomatic for less than 48 hours. The purpose of this article is to review currently available literature on the mechanism of action, pharmacokinetics, safety, and clinical and virologic efficacy of baloxavir. Its novel mechanism of action prevents influenza replication by targeting the viral cap-dependent endonuclease enzyme. In clinical trials baloxavir was shown to be superior to placebo and comparable to oseltamivir with regard to time to alleviation of symptoms and viral titer reduction and was well tolerated with minimal adverse effects. Baloxavir is a viable treatment option for acute uncomplicated influenza in certain age groups.

Introduction

Seasonal influenza is a major U.S. health burden characterized by widespread illness, productivity loss, hospitalization, and cost. In the 2017–2018 season, an estimated 48.8 million Americans experienced symptoms of influenza, 22.7 million required a healthcare provider visit, nearly 0.96 million were hospitalized, and 79,400 died. In 2003, the total associated cost was an estimated $87.1 billion, based on 31.4 million influenza-related outpatient visits. Of the influenza viruses, only types A, B, and C cause disease in humans. In recent seasons, influenza A H1N1 and H3N2, and influenza B Yamagata and Victoria lineages, have been the predominant circulating viral strains in the U.S. Certain individuals are at higher risk for developing influenza-related complications, including those aged 65 years and older, children less than 5 years old or with neurologic conditions, pregnant women, residents of long-term care facilities, American Indians, Alaska Natives, and patients with comorbidities including asthma, diabetes, heart disease, stroke, HIV/AIDS, or cancer. Vaccination remains the cornerstone of primary prevention of influenza and is recommended for all individuals 6 months and older without a contraindication. However, influenza vaccination is not fully protective due to challenges in accurately predicting circulating influenza strains. Considering that the complete manufacture process for the influenza vaccine can take up to 6 months, the formulation is usually undertaken at the beginning of every year in January. Due to this limited time frame, virulent strains emerging toward the middle of the year can potentially be excluded from the final cocktail. Leaving out such strains can possibly render the vaccine less effective. Due to the highly variable nature of circulating strains, vaccine composition is reevaluated annually. Viral strains selected for incorporation into the final vaccine cocktail are determined using surveillance data from influenza monitoring centers around the world. Based on data gathered from five different state study sites, vaccine effectiveness has been estimated to be 38–48% in the most recent three influenza seasons—highlighting the importance of antiviral medications for acute disease. Current guidance advocates for the use of antiviral medications in all hospitalized patients as well as outpatients at high risk of influenza complications, including pregnant women, children younger than 2 years, patients older than 65 years, or those with severe illness, chronic medical conditions, or immunocompromise. Patients who do not necessarily meet these criteria may also be treated at the treating clinician’s discretion to reduce disease severity and duration, particularly if antivirals can be initiated within 2 days of symptom onset.

Neuraminidase inhibitors (NAIs) have been the mainstays of influenza antiviral therapy. NAIs target influenza viral neuraminidase enzyme responsible for the release of newly synthesized influenza virus particles. Currently available NAIs in the U.S. include oseltamivir, zanamivir, and peramivir. All three are recommended as monotherapy for acute influenza. Adamantane class influenza antivirals, amantadine and rimantadine, are no longer recommended due to high levels of resistance among influenza A, and have no activity against influenza B. While NAI resistance in influenza remains low, in the face of continued widespread NAI use, the need for global resistance surveillance is rising. In addition to conventionally used agents, the most recent addition to the anti-influenza cohort of medications, baloxavir marboxil (BXM), provides a novel means by which influenza viruses can be targeted for neutralization. This article evaluates current available literature outlining the viability of using baloxavir marboxil as a therapeutic alternative against influenza.

Mechanism of Action

Baloxavir marboxil is a new oral influenza antiviral medication with a novel mechanism of action. BXM is a prodrug and is enzymatically converted to its active metabolite, baloxavir acid (BXA), endogenously. BXA inhibits influenza cap-dependent endonuclease (CEN), an enzyme residing within the influenza ribonucleic acid (RNA) polymerase complex, which “snatches” capped 5’ RNA primers, a critical step in viral RNA transcription. Inhibition of this enzyme by BXA prevents viral transcription and ultimately viral replication. This mechanism of action is unique to BXA, considering that the other conventionally used medications against influenza all target the viral neuraminidase enzyme.

BXA has been shown to be highly potent, with IC50 values as low as 2.5 nM for the CEN enzyme. Additionally, BXA has displayed broad spectrum activity for both influenza A and B, with IC50 values as low as 1.4–3.1 nM and 4.5–8.9 nM for the respective CEN enzymes. This broad spectrum activity seen with BXA has been linked to the conservation of the primary amino acid sequence of the CEN enzymes across several strains.
Indication, Dosage, and Administration

Baloxavir is indicated for treatment of acute uncomplicated influenza in patients 12 years and older with onset of symptoms less than 48 hours prior to initiation of therapy. The medication received Food and Drug Administration (FDA) approval on October 24, 2018. The recommended dose of the drug is influenced by patient weight. Dosage in patients weighing between 40 and 80 kg is 40 mg (supplied as two 20 mg tablets) as a single dose, and in patients weighing 80 kg or more is 80 mg (supplied as two 40 mg tablets) as a single dose. Baloxavir can be taken with or without food; however, calcium-containing laxatives, supplements, or antacids, along with calcium-containing beverages and dairy products, should be avoided at the time of administration. The dose can be taken at any time of day, but it should be taken as early as possible upon onset of symptoms. Safety and efficacy studies have not been performed in patients younger than 12 years or older than 65 years, patients weighing less than 40 kg, pregnant patients, or lactating mothers. Additionally, as with other systemic antiviral medications, it should be noted that the viral replication inhibition seen with baloxavir may render live attenuated vaccines less effective.

Pharmacokinetics

BXA shows dose-proportional increases of peak plasma concentration (Cmax) and area under the plasma-concentration time curve (AUC) for doses between 6 mg and 80 mg taken in a fasted state. Cmax values were reached between 3.5 to 4 hours after dosage with proposed first-order absorption and lag time. Additionally, BXM Cmax, AUC, and plasma drug levels attained 24 hours post dose (C24) have been shown to decrease with increased body weight for a fixed dose. Studies on the effect of feeding on BXM pharmacokinetics showed a 47% reduction in Cmax, and a 37% reduction in AUC in patients who were fed versus those who fasted. This may be, in part, explained by baloxavir chelation by divalent cations.

Endogenous conversion of BXM into its active form BXA occurs via hydrolysis in the intestinal lumen, intestinal epithelium, and liver by the enzyme serine esterase arylacetylamine deacetylase. Metabolism of BXA occurs mainly via glucuronidation by UGT1A3. Of note, greater expression of UGT1A3 exists in German Caucasians in comparison with Han Chinese and Japanese, and may explain variation observed in BXA elimination. However, no dosage adjustment is recommended based on ethnicity. No significant drug-drug interactions were observed when BXM was co-administered with CYP or UGT inhibitors, inducers, or substrates.

Approximately 80.1% and 14.7% of baloxavir is eliminated via feces and urine, respectively, as glucurononidated drug. Being 93% protein bound, BXA has an estimated clearance of 10.3 L/h and a long elimination half-life of 79.1 hours, resulting in supra-therapeutic C24 levels, thereby allowing for a single dose regimen.

Efficacy Data

Efficacy of baloxavir for treatment of acute influenza was established in one phase 2 trial and two phase 3 clinical trials. The phase 2 trial, a prospective, randomized, double-blind, placebo-controlled, dose-ranging study, enrolled 400 Japanese influenza-infected patients between the ages of 20 and 64 (Table 1). Study patients were randomized (1:1:1:1) to one of four intervention arms and received single doses of either 10 mg, 20 mg, or 40 mg of baloxavir or placebo. The majority (66.8%) were infected with influenza A H1N1. Significant reduction in time to alleviation of symptoms (TTAS) was observed for all baloxavir treatment arms compared with placebo, with an overall reduction in TTAS of 23.4–28.2 hours (P < 0.05). Additionally, at 24 hours after administration, baloxavir showed a significantly greater viral titer reduction compared with placebo: 4.5 versus 1.6 log10 TCID50/mL in 50% tissue-culture infective dose (P < 0.001). Subgroup analysis comparing patients who received baloxavir within 24 hours of symptom onset versus later than 24 hours found a mean reduction in TTAS of 32.8 hours versus 13.2 hours, respectively (P = 0.008). Additional subgroup analysis revealed that reductions in TTAS versus placebo were statistically significant only in patients with influenza A H1N1 and not in those with influenza A H3N2 or influenza B virus. However, by day 2, viral titer reductions were shown to be significantly greater in all three baloxavir groups versus placebo in patients with influenza A H1N1 and influenza B. In patients infected with influenza A H3N2, only the 10 mg and 40 mg, not the 20 mg, doses were shown to produce statistically significant viral titer reductions versus placebo. Of note, the C24 levels obtained for each dose were observed to be proportional to the degree of viral titer reduction. Doses as low as 10 mg of baloxavir were able to produce greater than 50% of maximum titer reduction.

The first prospective, double-blind, randomized, phase 3 clinical trial of baloxavir for acute uncomplicated influenza, CAPSTONE-1, randomized 1,436 patients between the ages of 12 and 64 years, from both Japan (77.2%) and the U.S. (22.8%). Patients 20–64 years of age were randomized into one of three intervention arms: single dose baloxavir 40 mg for body weight < 80 kg or 80 mg for body weight ≥ 80 kg; oseltamivir 75 mg twice daily for 5 days; or placebo in a 2:2:1 ratio. Patients 12–19 years old were randomized 2:1 to receive either baloxavir or placebo on day 1 only (Table 1). Among all treatment arms, 84.8–88.1% had influenza A H3N2.19 Baloxavir demonstrated a reduction in TTAS versus placebo of 26.5 hours (95% CI = 17.8–35.8 hours). No significant difference in TTAS was observed between baloxavir and oseltamivir. Baloxavir showed a greater viral titer reduction of 4.8 log10 TCID50/mL compared with 2.8 and 1.3 log10 TCID50/mL seen for oseltamivir (P < 0.05) and placebo (P < 0.05), respectively, one day after initiation of therapy. Infectious influenza viruses remained detectable in throat and nasopharyngeal swabs of participants for a period of 24 hours post dose for baloxavir, compared to 72 hours and 96 hours seen in the oseltamivir (P < 0.001) and placebo (P < 0.001) arms, respectively. Moreover, 3.5% of patients receiving baloxavir had complications that required treatment with antibiotics, compared with 4.3% and 2.4% for placebo and oseltamivir administered patients, respectively.

The second prospective, randomized, double-blind, phase 3 clinical trial, CAPSTONE-2, was conducted, which examined the efficacy of baloxavir compared with oseltamivir or placebo in patients with acute influenza and at least one risk factor for developing influenza-related complications. In the study, 2,184 patients ≥ 12 years old were randomized 1:1:1 into one of three treatment arms: single dose baloxavir 40 mg for body weight < 80 kg or 80 mg for body weight ≥ 80 kg; oseltamivir 75 mg twice daily for 5 days; or placebo (Table 1). Results from the study showed that mean time to improvement of influenza symptoms (TIIS) was significantly shorter.
for baloxavir (73.2 hours) compared with placebo (102.3 hours) (P < 0.0001) and not statistically different compared with oseltamivir (81.0 hours) (P = 0.8347). Baloxavir was shown to terminate viral shedding significantly earlier, with a median time of 48 hours compared with 96 hours for both placebo (P <0.05) and oseltamivir (P < 0.05). Subgroup analysis of study patients with influenza B revealed that baloxavir had significantly lower TTIIS (74.6 hours) compared with both placebo (100.6 hours) (P = 0.0138) and oseltamivir (101.6 hours) (P = 0.0261).

Although potential for combination treatment with both oseltamivir and baloxavir has yet to be investigated in humans, a study performed on mice revealed a synergistic treatment response against influenza. Similar results were observed when a combination of either oseltamivir, zanamivir, laninamivir, or peramivir was used in conjunction with baloxavir in Madin-Darby canine kidney cells infected with type A H1N1. The combination was observed to synergistically inhibit influenza viral replication.

Safety and Tolerability

The most commonly reported side effects from baloxavir during clinical trials include diarrhea (3%), bronchitis (2%), nausea (1%), nasopharyngitis (1%), and headache (1%). However, rates of these reactions were similar or lower than that observed in patients administered placebo.

The CAPSTONE-1 phase 3 trial that compared baloxavir to both placebo and oseltamivir reported adverse event rates of 20.7% for baloxavir versus 24.6% and 24.8% for placebo and oseltamivir, respectively. Although only some of the above-mentioned adverse events were linked to the study interventions, in those patients, oseltamivir was shown to have a higher rate of adverse events, 8.4% versus 4.4% in patients treated with baloxavir (P = 0.009). Two serious adverse events, an incarcerated inguinal hernia and aseptic meningitis, were reported in patients treated with baloxavir, but they were deemed unrelated to the drug. No deaths occurred during the trial; however, one patient treated with oseltamivir required hospitalization. The CAPSTONE-2 phase 3 trial reported similar safety incidence rates where all patients, irrespective of their treatment groups of either baloxavir, oseltamivir, or placebo, experienced adverse event rates between 25.1% and 29.7% for events of any kind, and rates between 0.7% and 1.2% for serious adverse events. Safety and efficacy studies have not been performed in patients younger than 12 years or older than 65 years, patients weighing less than 40 kg, pregnant patients, or lactating mothers.

Resistance

In the phase 2 trial, four patients (3.6%) who received baloxavir had influenza A H1N1 pdm09 detected with viral polymerase mutations (I38T/F substitution), demonstrating a 10-fold reduction in baloxavir susceptibility. The co-crystal structure of the mutated polymerase revealed reduced van der Waals affinity for baloxavir and thus a less stable enzyme/inhibitor complex. Notably, influenza A H1N1 pdm09 has been previously documented to exhibit a higher frequency of polymerase polymorphism.

The CAPSTONE-1 trial showed similar results, where 9.7% of patients with influenza A H3N2 receiving baloxavir...
Baloxavir has not been studied in patients younger than 2 weeks of age. Of note, none of the 95 randomly selected patients treated with placebo developed this substitution. On day 5 of the study, the 295 patients in the baloxavir arm without substitutions, 7% had detectable infectious virus. However, this percentage increased to 91% (29 out of 32) in patients with the I38T/M substitution, implying substantially increased susceptibility to baloxavir. Other studies have reported reduced susceptibilities to baloxavir as high as 76- and 120-fold in I38T substitution variant influenza A H3N2 viruses isolated from two separate children who were treated with baloxavir.

Fortunately, amino acid sequence analysis of influenza viruses from the 2016/17 and 2017/18 influenza seasons in the U.S. has shown a low incidence of reduced susceptibility to baloxavir. Reduced susceptibility to baloxavir was observed in only 0%, 0.032%, and 0.3% of influenza B, A H3N2, and A H1N1 pdm09 viruses, respectively. Similarly, 2017/18 season data from Japan also did not reveal any influenza A H1N1 pdm09, A H3N2, or B viruses with impaired susceptibility to baloxavir.

Although I38T/M substitutions are not uncommon, low rates of reduced susceptibilities in some viruses might be explained by "impaired replicative fitness" due to diminished potency of the endonuclease enzyme in these variants. In more recent data from the 2018/19 influenza season, none of 384 viruses showed polymerase amino acid substitutions of concern. In the future, increased vigilance with resistance monitoring for baloxavir is advisable with projected increase in usage in countries like Japan and the U.S.

**Compared with Other Influenza Antivirals**

One of the primary advantages of baloxavir is its single dose regimen administered orally, enhancing convenience and adherence. The most common alternative options to baloxavir, oseltamivir and, to a lesser extent, zanamivir, require 10 doses over the span of 5 days as part of their standard treatment course. Peramivir, similar to baloxavir, is administered as a single dose regimen (Table 2).

| Antiviral | Baloxavir | Oseltamivir | Zanamivir | Peramivir |
|-----------|-----------|-------------|-----------|-----------|
| Dosage Form | Tablet | Capsule; Oral suspension | Powder for inhalation | IV solution |
| Age Indication | ≥ 12 years | ≥ 2 weeks | ≥ 7 years | ≥ 18 years |
| Standard Dose | 40 – 80 mg | 75 mg BID | 10 mg BID | 600 mg |
| Duration of Treatment | Once | 5 days | 5 days | Once |
| Route of Administration | Oral | Oral | Oral inhalation | IV infusion (15–30 minutes) |
| WAC (per full treatment course) | $150 | $93 (Generic) $152 (Brand) | $59 | $950 |

Other differences include age indications, route of administration, side effects, and considerations relative to comorbidities. Oseltamivir can be used in infants as young as 2 weeks old, and zanamivir is approved for use in patients 7 years and older. By comparison, baloxavir, indicated for patients 12 years and older, is limited in its potential use in pediatric populations. However trials investigating use of baloxavir in pediatric populations are forthcoming. Peramivir is indicated for patients 18 years and older (Table 2).

Baloxavir is an oral medication, which provides advantages in terms of administration convenience compared with peramivir, a sparingly used option considering its requirement for intravenous administration, and zanamivir, which is administered via oral inhalation (Table 2). Additionally, zanamivir is also associated with potentially fatal bronchospasms in patients with asthma or chronic obstructive pulmonary disease. Unlike oseltamivir, baloxavir is not available as an oral suspension, which may be a barrier for patients who cannot tolerate tablet formulations. Additionally, in patients with renal impairment, zanamivir can be used, along with oseltamivir and peramivir, with appropriate dosage adjustment. Baloxavir has not been studied in patients with renal impairment, and therefore specific guidelines for use in this population are not available. Clinical studies conducted for both baloxavir and oseltamivir in patients with hepatic impairment do not recommend any dosage adjustments, while peramivir and zanamivir have yet to be studied in this population. The effect of baloxavir, oseltamivir, and peramivir in pregnant patients has yet to be evaluated, while small sample size studies for zanamivir have shown no signs of maternal or fetal toxicity. Accumulation of drug metabolites in breast milk, and the impact of these drugs on breast milk production in lactating mothers, has not been researched in any of the four NAIs.

A network meta-analysis performed on 19 trials comparing both safety and efficacy of baloxavir relative to other antiviral agents in the treatment of influenza showed that baloxavir has similar efficacy in comparison to other antivirals, with an equivalent or slightly improved safety profile. TTAS with baloxavir was significantly shorter versus zanamivir by 20.62 hours (95% CI = 0.20–44.95), but showed no significant difference versus the other NAIs. Time to cessation of viral shedding was shown to be significantly shorter for baloxavir compared with zanamivir.
and oseltamivir, with a median time difference of 47.00 (95% CI = 28.18–73.86) hours and 56.03 (95% CI = 33.74–87.86) hours, respectively. Moreover, reduction of viral titer levels 24 hours after initiation of therapy was shown to be significantly greater for baloxavir compared with zanamivir, oseltamivir, and peramivir, with differences of 2.49 (95% CI = 1.12–3.85), 2.30 (95% CI = 1.52–3.30), and 2.31 (95% CI = 1.19–3.49) log10TCID50/mL, respectively. The frequency of adverse drug effects with baloxavir was shown to be comparable to both zanamivir and peramivir, but less frequent versus oseltamivir 1.93 (95% CI = 1.18–3.19). Baloxavir is not currently approved for influenza prophylaxis, as it has yet to be studied for this indication in human subjects. Influenza prophylaxis, typically used in high-risk patients during an outbreak, is limited to oseltamivir or zanamivir.

Another potential niche for baloxavir use might be in the event of resistance to NAIs. Although global widespread resistance to NAIs has not been documented to levels seen with adamantanes, in 2007/08 an increase in oseltamivir-resistant influenza A H1N1 viruses with the H274Y mutation was observed in several countries, including the U.S. The novel mechanism of action of baloxavir provides theoretical viability against such NAI-resistant strains. Amongst NAI-resistant viral strains, no significant differences were seen in baloxavir susceptibility compared with those strains sensitive to NAIs.

Drug and vaccine shortages have also complicated the health and economic burden associated with influenza. Multiple documented shortages of oseltamivir, notably after the 2009 H1N1 pandemic, have led to the requirement for drug manufacturers to communicate regularly with the CDC to gauge available supply. Baloxavir provides an additional alternative for acute influenza in the event of a shortage of other influenza antivirals.

Cost of therapy is another major consideration for insurers, pharmacies, prescribers, and patients. The wholesale acquisition cost (WAC) for a single dose of baloxavir is estimated to be around $150, compared to $93, $152, and $59 for 5-day courses of generic oseltamivir, brand oseltamivir (Tamiflu), and zanamivir respectively, and $950 for single-dose peramivir (Table 2).

Conclusion

Baloxavir is the newest influenza antiviral available in the U.S., with a novel mechanism of action. Efficacy for acute influenza is comparable to current standards of treatment (NAIs) and superior to placebo. Baloxavir is administered as a single dose oral regimen and is well tolerated, making it a viable treatment option for influenza.

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