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Safety and Effectiveness of Xofluza (Baloxavir Marboxil) for Respiratory Viral Illness: A Systematic Review

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Abstract

Randomized Controlled Trials (RCTs) have provided evidence of the safety and effectiveness of Baloxavir Marboxil (BXM) in antiviral activity of uncomplicated influenza virus. The objective of this article was to perform a narrative review of RCTs of BXM for reduced time to alleviation of symptoms and risk of complications in influenza patients and identify uncertainties and gaps resulting from the design of individual studies. A literature search was conducted for RCTs of BXM of adult and pediatric human trials and Time to Alleviation of Symptoms (TTAS) either as a primary or secondary endpoint. A total of 6 RCTs were identified; target population baseline characteristics, outcome measures, statistical methods, and clinical trial limitations were reported. RCTs of BXM showed consistent overall beneficial effects for TTAS of influenza in comparison to placebo and other antiviral medications like oseltamivir and favipiravir. Only one study included clinical outcome of BXM on SARS-CoV-2; all other RCTs used composite TTAS as the primary endpoint of influenza. An understanding of the deficiencies of individual RCTs of BXM in TTAS of Influenza and SARS-CoV-2 is important in creating a patient specific therapeutic clinical decision and tailoring future research.

Keywords: Covid-19; Baloxavir marboxil; Influenza; Cap-dependent endonuclease inhibitors; Randomized controlled trials; Systematic review

Introduction

Despite mitigation plans to prevent human to human transmission, respiratory illness caused by the novel SARS-CoV-2 is emerging and rapidly evolving and search for vaccinations and treatment is still ongoing. In the United States, the Public Health, Commercial and Clinical laboratories have reported increase in overall percentage of positive respiratory SARS-CoV-2 specimens during week 25 of this pandemic. Since March 1, 2020, the COVID-19 related hospitalization rate is at 98.4 per 100, 000. The highest rates are seen in people aged 65 years and older (297.6 per 100,000) and 50-64 years (148.6 per 100,000). The cumulative hospitalization rate for COVID-19 is also higher when compared to past 5 influenza seasons, particularly in adults 18-64 years of age. As many as 80% of COVID-19 cases considered mild-illness, not requiring hospitalization [1]. This demand cost effective efficacious outpatient care that will help reduce time to alleviation of symptoms and reduce hospitalization.

While COVID-19 and Influenza (flu) can look remarkably similar in symptom presentation, the two illnesses are caused by different viruses. Just like the flu, most people with COVID-19 will experience fever, cough, shortness of breath, fatigue, anorexia, myalgia, and sputum production [2]. Atypical presentation of headache, confusion, rhinorrhea, sore throat, hemoptysis, nausea, vomiting, diarrhea, ageusia and anosmia have also been recorded in COVID-19 patients. The incubation period of COVID-19 is thought to extend 14 days, with one study reporting 97.5% of patients developing symptoms will do so within 11.5 days of SARS-CoV-2 infection [3]. The only potential antiviral drug under evaluation for COVID-19 recommended by National Institute of Health includes Remdesivir, a nucleoside analogue for hospitalized patients with severe COVID-19 who are not intubated [4].

Enveloped viruses like SARS-CoV-2 have biological membrane that forms the envelope derived from the host cell, originating from host endoplasmic reticulum or Golgi apparatus or plasma membrane [5]. Therefore, this envelope becomes harder for the host immune system to efficiently destroy. The FDA approved antiviral, Baloxavir Marboxil (BXM) is an orally available cap-dependent endonuclease (CEN) inhibitor, CEN an enzyme required for viral replication [6]. CEN is found on the PA subunit of the influenza virus polymerase and it mediates the cap-snatching process during viral mRNA biosynthesis [6]. This structural similarity of Influenza and SARS-CoV-2 allows BXM a good chance to inhibit the SARS-CoV-2 homolog. No studies determine efficacy of Baloxavir Marboxil (BXM) in influenza patients presenting after 48 hours of symptoms onset and in critically ill patients who are hospitalized [7]. There is lacking evidence of its use in patients with significant comorbidities, morbidly obese, elderly, and pregnant patients.Based on mechanism of action of BXM, the objective of this systematic review is to assess benefit and safety of BXM in mildly symptomatic COVID-19 patients, based on Randomized Controlled Trial (RCT) data.

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Materials and Methods

We followed the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) [8].

Search strategy

We used databases like PUBMED, PUBMED CENTRAL, COCHRANE LIBRARY, and GOOGLE SCHOLAR for searching relevant articles to answer our research question. We customized our search to include any clinical trial or review articles that had stated the efficacy of Baloxavir Marboxil in viral illness. We searched for English language studies conducted in human subjects. We searched these databases in Title Abstract Keyword using the following terms: ["marboxil", "acid"] efficacy ["effectiveness", "outcome"] treatment, Viral illness ["Virus"," influenza", "Coronavirus", "COVID 19", "Viral disease", "flu"]. All the articles were initially screened by ten reviewers independently and excluded articles based on duplication, title non-significance. After obtaining the significant articles after reviewing the abstract, we five reviewers independently obtained the full text of these articles and finally selected the studies based on our predetermined inclusion and exclusion criteria. The reviewers then independently extracted data and performed a quality assessment of the eligible trials. We resolved disagreements through discussion and consensus.

Study selection

The criteria for including studies in this systematic review were:

- Human Subject trials
- Clinical Trial (Phase 2 and/or 3)
- Time To Alleviation of Symptoms (TTAS) either as a primary or secondary endpoint
- Any RCT assessing the efficacy of Baloxavir in any viral illness
- To include Any RCT done either in children, adolescents, adults, or elderly population

The criteria for excluding studies in this systematic review were:

- Ongoing Clinical Trials
- Non-Human Subject Trials
- Phase 1 Trials

Data extraction

We reviewed the eligible studies in full text and extracted the following data: (i) participants in and control groups (ii) duration of follow-up (iii) participants characteristics like mean age, % of the current smoker, sex, mean BMI, Race (iv) Dose of (v)Baseline body temperature(degree C) (vi) % of influenza vaccination (vii) Time to treatment from symptom onset(hours) (viii) Rapid antigen test result (ix) eligibility criteria (x) study design (xi) method and mode of statistical analysis (xii) primary and secondary endpoints of the study.

Quality assessment

We assessed the quality of the eligible RCTs by the criteria developed by the US Preventive Services Task Force (USPSTF) and rated as good, fair, or poor [9]. The USPSTF Quality Assessment tool for RCT has 10 criteria to check the study validity and acknowledge the risk of biases in each study. Risk of bias assessment was accomplished independently by 5 reviewers and any disagreements were resolved through discussions and consensus.

Analysis of outcomes of included studies

We analyzed the clinical outcomes of the included RCTs in terms of time to alleviation of symptoms from the start of the trial regimen, time to resolution of fever, time to a return to usual health. We considered the outcome and trial statistically significant if $P<0.05$.

Dosing

Baloxavir is taken by mouth (PO), given as a single dose. Patients in all trials were dosed with the recommended weight based single dose of Placebo/Baloxavir: 40 mg PO as a sing dose for 40 to <80 kg and 80 mg PO as a single dose for ≥ 80 kg. When tested positive for rapid influenza virus test, patients were given recommended weight-based dosing within 48 hours of onset of symptoms and time to alleviation of symptoms was recorded.

Results

We identified 1556 articles according to our search strategy. After removing 390 duplicate articles, 1166 articles were screened according to title and abstract. We excluded 852 articles as their title and abstract were not relevant. We reviewed the remaining 314 articles with full text independently and assessed them based on predetermined eligibility criteria. We rejected 308 articles as these articles were review articles, phase 1 trials, non-human studies, had non-clinical outcomes, and were still ongoing. Finally, 6 RCTs were eligible to be included in our systematic review. The flowchart of our search strategy is shown below. Table 1 shows the characteristic features of different trials.

The quality assessment of all 6 RCTs included in this review was done and included in the supplementary material. Table 2 shows patient demographics and Table 3 shows the outcomes of different trials. Five trials were statistically significant but the trial of Baloxavir in COVID 19 could not attain statistical significance. In five of the six clinical trials, all participants experienced shorter duration for alleviation of influenza symptoms when compared to placebo or other antiviral medications like Favipiravir or Oseltamivir. Patients taking Baloxavir also did not experience clinically significant adverse events, suggesting safety and efficacy in both pediatrics (1 to <12 years old) and 12-64 years old age groups. Only phase II, CAPSTONE I and MINISTONE II trials collected patient history of smoking and influenza vaccination (Figure 1).

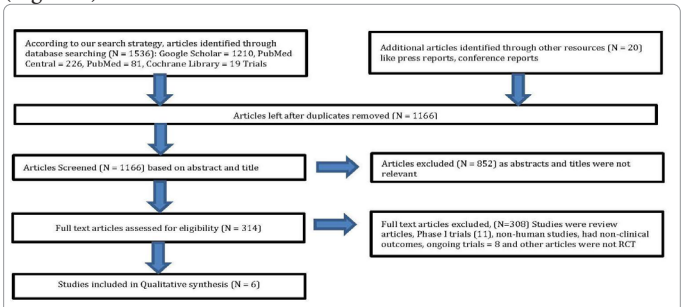

Figure 1: Search strategy for articles, publications, and clinical trials selection for this systematic review.

Study	Participants	Drug/Control	Drug/Control dosing	Follow up Duration	Time to treatment from symptoms onset
Phase 2 [10]	N=400	1:1:1:1	10 mg:20 mg:40 mg and Placebo	14 Days	Average% 0 to <12 h: 11.2% 12 to <24 h: 37% 24 to <36 h: 26.5% 36 to <48 h: 25.2%
CAPSTONE 1 [11]	N=1436	Age 20 to 64 2:2:1	Age 20 to 64 Single dose Baloxavir or Placebo: 75 mg Oseltamivir BID or Placebo for 5 days: Placebo only	14 Days	0-48 hours
		Age 12 to 19 2:1	Age 12 to 19 Baloxavir or Placebo:Placebo		
CAPSTONE 2 [12]	N=2184	1:1:1	Baloxavir:Oseltamivir:Placebo	22 days	0-48 hours
MINISTONE 2 [13]	N=173	1:1	Baloxavir:Oseltamivir	Up to 29 days	≤ 48 hours
Pediatric JAPANESE PEDIATRICS TRIAL [14]	N=104	1	Baloxavir	14 days	≤ 48 hours
COVID-19 TRIAL [15]	N=30	1:1:1	Baloxavir:Favipiravir:Control	14 days	≤ 48 hours

Table 1: Study characteristics.

Study	Age, years (Standard deviation)	Baseline temperature (°C)	Current smokers (%)	Influenza vaccinated (%)	Race	BMI (kg/m^2)	Sex, N (%)
Phase 2 [10]	Median: 10 mg: 36 20 mg: 36.5 40 gm: 38 Placebo: 37	Mean: 10 mg: 38.5 20 mg: 38.5 40 mg: 38.5 Placebo: 38.5	10 mg: 33 20 mg: 32 40 mg: 31 Placebo: 33	10 mg: 34 20 mg: 20 40 mg: 37 Placebo: 31	Asians 10 mg: 100 20 mg: 99 40 mg: 100 Placebo: 100	Weight kg (SD) 10 mg: 23.1 20 mg: 22.7 40 mg: 22.6 Placebo: 22.6	male or female patients aged ≥20 years to <65 years)
CAPSTONE 1 [11]	12-64 years	Mean (SD): Baloxavir: 38.4 (0.5) Oseltamivir: 38.5 (0.5) Placebo: 38.4 (0.5)	Baloxavir: 23.7% Oseltamivir: 26% Placebo: 23.8%	Asian: 832 Black: 38 White: 185 Hispanic: 68 Other: 9	Asian: 832 Black: 38 White: 185 Hispanic: 68 Other: 9	Baloxavir: 23.9 (4.6) Oseltamivir: 24.4 (5.0) Placebo: 24.3 (5.1)	Male: N=570 (53.6%) Baloxavir: 232 Placebo: 120 Oseltamivir: 218
CAPSTONE 2 [12]	Baloxavir: 52.3 Oseltamivir: 51.9 Placebo: 51.1	Not known	Not known	Not known	Asian: 487 Black: 98 White: 560 American Indian: 6 Or Alaska native Other: 12	Not known	Female: Baloxavir: 195 (50.3) Placebo: 206 (53.4) Oseltamivir: 198 (50.9)
MINISTONE-2 [13]	Mean: 6.1 (3.0)	Not known	Not known	Baloxavir: 51.3 Oseltamivir: 44.8 Total: 49.1	Black: 11 White: 149 Other: 13	Baloxavir: 26.1 (12.3) Oseltamivir: 28.1 (16.0) Total: 26.8 (13.6)	Female: N=92 Baloxavir: 60 Oseltamivir: 32
JAPANESE PEDIATRICS TRIAL [14]	7.4 (2.6)	38.78 ± 0.60	Not known	Total: 26.9	Asian (Japanese)	Not known	Male: 53 (51) Female: 51 (49)
COVID-19 TRIAL [15]	Baloxavir: 53.5 Favipiravir: 58.0 Control: 46.6	Baloxavir: 36.9 (36.2-38.4) Favipiravir: 36.9 (36.3-39.6) Control: 36.9 (36.0-37.9) Total: 36.9 (36.0-39.6)	Not known	Not known	Asians (100%)	Not known	All Male

Table 2: Patient demographics.

Discussion

In this systematic review, we analyzed evidence from 6 RCT of Baloxavir for patients with influenza (flu). In 2018, Baloxavir Marboxil (BXM) was approved in the USA and Japan for the treatment of uncomplicated influenza in a population of age ≥ 12 years with clinical symptoms for ≤ 48 hours [16]. A single dose of Baloxavir demonstrated efficacy in both healthy and high-risk flu patients. Baloxavir was well tolerated and associated with faster recovery and reduced risk of complications in influenza patients compared to placebo groups. It also had superiority to Oseltamivir, an antiviral, in shortening of duration of viral replication and resolving influenza illness. These studies reveal that the time to alleviation of symptoms for the Baloxavir-dose group was shorter than the placebo group, with a greater difference in patients who initiated treatment within 24 hours after symptom onset [17]. Studies discovered that a single dose of baloxavir caused considerable decrease in the influenza virus level within 24 to 48 hours after administration

Study	Endpoint of study				Other outcomes
	Primary endpoint		Secondary endpoint		
	Definition	Result	Definition	Result	Result
Phase 2 Trial [10]	TTAS® from trial dosing to time when patient rates all seven influenza-related symptoms as mild or absent for at least 21.5 hours.	Median TTAS in each of Baloxavir dose groups significantly shorter than placebo [P=0.009, P=0.02 and P=0.005 for 10 mg, 20 mg, 40 mg respectively].	Time to resolution of fever, return to usual health, and newly occurring complications leading to antibiotic use	Time to resolution significantly shorter for patients treated with all 3 doses of Baloxavir compared to placebo; Time to resumption of normal activity significantly improved in 20 mg group compared to placebo; There were 3 reports influenza-related complications-bronchitis, otitis media and acute sinusitis.	Significantly greater reductions in influenza virus titers on day 2 and 3 than placebo in all dose groups In three Baloxavir dose groups, adverse events were reported in 23%- 27% of patients while 29% of patients in placebo group reported adverse effects However, there were no significant differences in rates of specific events between each Baloxavir dose group and placebo.
CAPSTONE 1 [11]	TTAS of influenza in patients randomized in, Baloxavir, Placebo and Oseltamivir groups.	Baloxavir group showed a shorter median TTAS than the placebo group, among both of the intention to treat infected population (53.7 hours vs. 80.2 hours, P<0.001) and intention to treat population (65.4 hours vs. 88.6 hours, P<0.001); with a median difference of, 26.5 hours corresponding to 95% CI, 17.8 to 35.8 and 23.2 hours corresponding to CI, 34.2 to 14.0 respectively.	Time to Resolution of Fever in Participants Randomized to Baloxavir or Placebo	The median time with Baloxavir to resolve fever was shorter than with placebo (24.5 hours versus 42.0 hours, P<0.001).	Baloxavir was associated with significantly faster declines in viral infectious load as compared to placebo or oseltamivir. Within 1 day upon initiation of the trial protocol, the median baseline reductions of viral load in, Baloxavir, oseltamivir and placebo groups were 4.8, 2.8 and 1.3 log 10 TCID 50 per milliliter, respectively.
CAPSTONE 2 [12]	TTAS of Influenza symptoms	Time to recover and decrease in influenza symptoms was significantly shorter in Baloxavir than placebo (median 73.2 hours vs. 102.3 hours, P<0.0001) and numerically shorter than oseltamivir (81.0 hours, P=0.8347).	Time to Resolution of viral shedding. Percentage of Participants with Influenza-related Complications.	Baloxavir significantly reduced time to viral shedding (48.0 hours) versus placebo and oseltamivir (96.0 hours; P<.0001), reduced the use of antibiotics and incidence of flu-related complications (3.4% and 2.8%, respectively) versus placebo (7.5% and 10.4%, respectively; P=.01 and P<.05).	In assessing for safety, patients on the investigative therapy had a lower incidence of reported adverse events (25.1) than those on placebo (29.7%) or oseltamivir (28.0%).
MINISTONE 2 [13]	Safety of Baloxavir (i.e., Incidence, timing, and severity of adverse events)	The total incidence of adverse effects was similar between the group Baloxavir (46.1 percent) and the group oseltamivir (53.4 percent). Gastrointestinal disorders (vomiting or diarrhea) were the most common adverse effects in both groups, experienced by 12 children (10.4 percent) for Baloxavir and 10 (17.2 percent) for oseltamivir.	TTASS¥ of influenza.	TTASS was similar between both treatment groups, with a median of 138.1 [95% confidence interval (CI) 116.6 -163.2] hours for Baloxavir and 150.0 (95% CI: 115.0-165.7) hours for oseltamivir.	The median duration of fever was similar between the Baloxavir and oseltamivir groups: 41.2 (95% CI: 24.5-45.7) versus 46.8 (30.0-53.5) hours, respectively.
JAPANESE PEDIATRIC TRIAL [14]	TTAS and reduction of a fever less than 37.5°C measured at the axilla.), upon the administration of Baloxavir.	Median TTIA€ recorded at 44.6 hours with a 95% CI, 38.9-62.5 hours. 81.6% of patients' symptoms were alleviated at 120 hours after treatment of Baloxavir. The median TTIA for fever was 21.4 hours 95% CI, 19.8-25.8 hours. Patients that were afebrile had fever recurrence on day 3 and day 4 were recorded at 11.1% (11/99) and 10.7% (11/103), respectively.	Times to sustained termination of viral detection, time to resolution of fever.	The median time to sustained termination of infectious viral detection was 24.0 hours (95% CI, 24.0-48-0). 21.4 hours (95% CI, 19.8-25.8 hours) was the median time to resolution of fever.	Time to return to normal activity was 126.3 hours (95% CI, 99.4-130.7).

COVID 19 TRIAL [15]	Patients (%) that were confirmed viral negative by Day 14 and time to clinical improvement of symptoms.	Viral negative by Day 14 Baloxavir-70% Favipiravir-77% Control-100% Total-83% Time to clinical improvement-median no. of days (IQR): Baloxavir-6-49 Favipiravir-6-38 Control-6-24	Patients that were confirmed viral negative in Day 7 and the incidence of mechanical ventilation.	Viral negative in Day 7 (%) Baloxavir-60% Favipiravir-44% Control-50% Total-52% Mechanical ventilation Incidence (%) Baloxavir-10% Favipiravir-0% Control-0% Total-3%	Time to viral negative-median no. of days (IQR) Clinical improvement-no. (%) were measured in Day 7 and Day 14.
®Time to alleviation of symptoms ¥Time to alleviation of signs and symptoms €Time to illness alleviation					

Table 3: Study outcome.

and alleviation of symptoms is a short time duration (Table 3).

None of the clinical trials clearly indicated whether those who did not receive influenza vaccine were at a higher risk of having the flu or experienced difference in efficacy of Baloxavir. The number of other races other than majority Asians followed by Whites was limited amongst all clinical trials. There were no gender differences notes regarding adverse effects occurrences. The adverse effects occurrence regarding races were not determined effectively due to the limited number of races involved in the trials, however, it was noted to be equal amongst Whites and Asians. Adverse effects occurrences amongst age groups 12 and older were noted to be similar. Adverse Events (AEs) related to Baloxavir were relatively lesser than patients in the placebo groups. The most common treatment emergent adverse events noticed in Phase II and MINISTONE II placebo-controlled trials included diarrhea, bronchitis, nasopharyngitis, headache and nausea; however more common in placebo and other drug groups compared to Baloxavir. With limitations of RCT to compare safety outcomes, Baloxavir appeared to be relatively safe. It is approved at the 40 mg and 80 mg single dose for adults and children >12 years old at <80 kg and >40 kg single dose. A 10 mg dose is recommended for children <12 years of age and weight 10-19 kg [18].

As only a single dose is needed, the patient may be more adherent to baloxavir-treatment than if the oseltamivir dose is required twice a day for five days. Treating with antivirals may encounter the potential problem of the emergence of resistant mutants. The same is with the case of this novel antiviral drug. However, researchers have proposed some treatment regimens to overcome this drug resistance problem. Based on data, treatment of uncomplicated influenza with high-dose BXM for several days would be a reasonable approach [19]. The clinical trials showed viral load reduction with baloxavir compared with oseltamivir, however time to alleviation of symptoms between the two groups was not significantly different. Combination therapy of neuraminidase inhibitor Oseltamivir and CEN inhibitor Baloxavir may lessen concerns about the development of resistance [20]. The safety and efficacy of combination therapy will be assessed in the NCT03684044 trial in patients with severe influenza. Safety and effectiveness of Baloxavir in treatment of acute uncomplicated influenza has been established in people 12 years of age and older, but not in Japanese pediatric patients less than 12 years of age. In contrast to other medications used for influenza like oseltamivir, the safety and efficacy of baloxavir have not been shown to be safe for pregnant and lactating patients. As explained by CAPSTONE 2 trial, more evidence-based data is required concerning safety and efficacy in patients less than 12 years old, older than 65 years old and risks for smokers. As BXM has no antibacterial effects, it cannot treat the bacterial infections occurring with or superimposing on the viral infection.

There was one COVID-19 clinical trial of thirty patients for the use of Baloxavir in COVID-19 patients aiming to evaluate the clinical outcomes and plasma concentrations of Baloxavir marboxil and favipiravir. Statistically significant difference was not seen in percentage of patients for negative viral test after 14 days treatment between these groups. Baloxavir showed in-vitro antiviral activity with the half-maximal effective concentration (EC50) of 5.48 μM in comparison to arbidol and lopinavir, but no antiviral activity was observed up to 100 μM of Favipiravir. However, there were several limitations to this trial. Due to rapidly evolving COVID-19 situation, researchers could not screen subjects who did not receive other treatment. Majority of patients in comparison of favipiravir group were on average older in age and experienced shorter time from symptom onset to randomization. There are 2 registered trials on Chinese Clinical Trial Registry (ChiCTR2000029548, ChiCTR2000029544) where Baloxavir (component) is being used for the treatment of COVID-19; an open-label, controlled trial for evaluation efficacy and safety of BXM, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia patients and a randomized controlled trial for the efficacy and safety of BXM, Favipiravir tablets in novel COVID-19 patients who are still positive on virus detection under an ongoing antiviral therapy, respectively (Supplementary Table S2).

Conclusion

In conclusion, single dose oral baloxavir in previous clinical trials did not result in apparent safety concerns and was associated with clinical benefit in antiviral activity of uncomplicated influenza patients. Due to structural similarities of both influenza and SARS-CoV-2, Baloxavir could provide an option for patients with infections caused by such viruses. A randomized, controlled trials involving patients with positive COVID-19 test should be conducted to assess safety and effectiveness of Baloxavir.

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