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Review Article

EFFECTIVITY OF SELECTING BALOXAVIR AS AN ALTERNATIVE TREATMENT FOR INFLUENZA: A SCOPING REVIEW

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ABSTRACT

This scoping review evaluates the effectiveness of baloxavir, a cap-dependent endonuclease inhibitor, as an alternative antiviral treatment for influenza. A scoping review followed PRISMA guidelines, utilizing databases such as PubMed, SCOPUS, Science Direct, and cochrane to identify relevant studies published until November 2024. The review included 24 studies comparing baloxavir to placebo and other antiviral agents. It indicated that baloxavir significantly reduces the duration of influenza symptoms and has a favorable safety profile compared to oseltamivir and other neuraminidase inhibitors. Specifically, baloxavir demonstrated a shorter time to symptom relief and lower incidence of gastrointestinal side effects, particularly in younger populations. However, concerns regarding the emergence of viral variants that may impact treatment efficacy were noted. Overall, while baloxavir shows promise as an effective treatment option for influenza, further research across diverse populations is necessary to validate its global applicability and safety.

Keywords: Antiviral agent, Baloxavir, Effectiveness, Influenza

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INTRODUCTION

Influenza is a respiratory disease caused by influenza A, B, or C viruses [1]. The symptoms of influenza are almost similar to the symptoms of the common cold, but the symptoms of the common cold are milder, such as coughing, stuffy nose, sneezing, sore throat and mild fever and will improve in a few days [2]. The disease can present in a variety of ways. Infection can occur without symptoms or can be a respiratory disease ranging from mild to severe symptoms such as chills, high fever, pneumonia, muscle pain, and even death [3]. In addition, the difference between influenza and avian influenza lies in the strain. The most common strain of influenza is H1N1, while avian influenza is usually the most common H5N1; there can also be specific strains such as paramyxovirus strains and, usually attacks livestock, especially poultry [4–6]. Complications from influenza can cause significant morbidity and mortality. Risk factors that cause complications may occur in young children (<5 y) or the elderly (>65 y), Caucasians, have chronic lung or heart disease, a history of smoking, people with immune disorders, pregnant women, and extreme obesity are more susceptible to severe complications of Influenza [7]. Worldwide, up to 500,000 people die each year as a result of influenza-related complications [8].

According to the World Health Organization (WHO), the global annual influenza incidence rate is between 20% and 30% among children and up to 10% among adults. The number of deaths attributed to influenza is estimated to be between 290,000 and 650,000 each year. These factors represent a significant global burden in terms of health, healthcare, and economic impact [3]. Since the beginning of 2021, the WHO has reported four influenza-related events of concern. To lessen the disease burden and safeguard global health security, it is crucial for clinicians to effectively identify and manage influenza cases, as well as to engage with the broader public and global health systems collaboratively [9].

The transmission of an infectious disease is defined as the movement of the causative pathogen from an infected host to a new host, ultimately resulting in infection. The impact of an epidemic and the speed of transmission are a consequence of the transmission level. Therefore, public health measures are usually designed to slow or stop the spread of this disease [10]. The development of influenza treatment is currently very extensive, one way is the development of previously existing drugs such as rimantadine derivatives. Rimantadine is an early class of anti-influenza drugs that have been used since 1980. At this time, the use of rimantadine has been reported to have experienced resistance to influenza a virus strains. In further developments, the synthesis of the drug was carried out on the chemical structure of L-histidyl-1-adamantylethylaminedihydrochloride monohydrate (H-His-Rim • 2HCl • H_2O) [11]. The H1N1 virus also has surface protein such as neuraminidase (NA), hemagglutinin (HA), and membrane ion channel (M2 protein) [7, 8]. Several pharmaceutical agents are employed in the treatment and prophylaxis of influenza, including amantadine, neuraminidase inhibitors (zanamivir, oseltamivir, peramivir, laninamivir), and cap-dependent endonuclease inhibitors (baloxavir) [3].

Baloxavir marboxil, or cap-dependent endonuclease inhibitor (CENI), has been reported effective for influenza A and B, including strains that are resistant to oseltamivir [12]. After oral administration, the active form of baloxavir acid is liberated through hydrolysis in the liver, circulation, and intestinal epithelial cells. Baloxavir's mechanism of action involves the targeted binding of the baloxavir molecule to the Polymerase Acidic Protein (PA) of the Ribose Nucleic Acid (RNA)-dependent RNA polymerase complex of the influenza virus, thus inhibiting the proliferation of the influenza virus. Transcription of viral RNA (vRNA) occurs in the host cell nucleus via one particular polymerase that consists of three subunits comprising polymerase. Influenza A genome consists of eight negative-sense RNA segments, namely Polymerase basic 1 (PB1), Polymerase basic 2 (PB2), Polymerase acid (PA) [13].

Clinical trials have been conducted to assess the safety and efficacy of baloxavir for prevention or the treatment of influenza in different patient populations. In determining the selection of drugs for influenza therapy, health workers or doctors can educate patients how to prepare drugs, how to use it, and how to dispose it such as drug's expired and its good storage. Thus, patients get drugs according to their needs and prevent negative impacts such as drug irrationality, inappropriate doses, and inappropriate periods [14]. This literature review attempts to establish the effectiveness of baloxavir marboxil as an alternative medicine in treating influenza virus infection.

MATERIALS AND METHODS

Search strategy

Following the reporting standards of the Preferred Reporting Items for Scoping Reviews and Meta-Analyses (PRISMA), we carried out a scoping review. Reviewers searched PubMed, SCOPUS,

ScienceDirect, and cochrane beginning on the date each database was relevant studies published until November 2024. Keywords used in the search strategy included ''influenza'', "Baloxavir'', "Baloxavir Marboxil". The search was limited to publication years in the last ten years, only English Language, and research subjects only in humans. We also manually searched for included reference lists.

Eligibility criteria

We searched for cross-sectional, cohort, prospective post marketing surveillance, randomized control trial (RCTs), and meta-analyses that tested the effectiveness of baloxavir compared with placebo for treating communicable diseases including influenza. Dosage form, duration of treatment, and side effects were not restricted. Other scales for evaluating the virus included laboratory tests (Rapid influenza diagnostic test (RIDT), Reverse Transcription Polymerase Chain Reaction (RT-PCR), Enzyme-Linked Immunosorbent Assay (ELISA), and serology). Books, letters, and review publications without peer review were excluded.

RESULTS AND DISCUSSION

Selection of inclusion and exclusion studies

Five authors participated in the article. Four authors screened manually using the PRISMA Flowchart tool to assess abstract titles and full texts of eligible studies after removing some duplicate records, and books. Researchers conduct independent screening and review of each study. The inclusion criteria for selection were as follows: (1) patients with influenza infection; (2) baloxavir intervention; (3) compared with placebo, standard of care, or other anti-influenza agents; (4) clinical efficacy and safety profile results. If there are differences regarding the criteria included, we discuss this together. Then, the criteria included in this journal are based on the results of the discussion. We extracted or extracted data regarding baseline characteristics using pre-existing methods, including author, year of publication, country, number of research centers, infectious disease, age, study sample, gender, duration of treatment, intervention, comparison, efficacy, and safety of results from individual studies.

Table 1: Study characteristics

Author	Country	Study design	Sample size (n)
(Ikematsu *et al.*, 2020) [15]	Japan	Randomized, double-blind, placebo-controlled clinical trial	752 patients
(Portsmouth *et al.*, 2021) [16]	Japan and the United States of America	Phase 3 trial, double-blind, placebo-and active comparator-controlled, randomized trial	117 patients
(Ishiguro *et al.*, 2021) [17]	Japan	Multicenter, open-label, randomized, active-controlled trial	200 patients
(Yoshino *et al.*, 2020) [18]	Japan	Prospective observational study	43 patients
(Ikematsu *et al.*, 2024) [19]	Japan	A placebo-controlled, double-blinded	495 patients
(Komeda, Takazono, Hosogaya, Miyazaki, *et al.*, 2021) [20]	Japan	Population-based, active comparator, retrospective, cohort study	339.007 patients
(Komeda, Takazono, Hosogaya, Ogura, *et al.*, 2021) [21]	Japan	Cohort	225 families
(Wagatsuma *et al.*, 2022) [22]	Japan	Observational study	159 patients
(Umemura *et al.*, 2020) [23]	Japan	Retrospective, single-center study	169 patients and the household members living with them.
(Sonoyama *et al.*, 2021) [24]	Japan	Multicenter, open-label, noncontrolled study	45 patients
(Liao *et al.*, 2023) [25]	China	Observation study	246 patients
(Cai *et al.*, 2024) [26]	China	Ambispective, observational, and multi-center design	590 patients
(Li *et al.*, 2024) [27]	China	Cross-sectional	Oseltamivir: 15,104 patients baloxavir marboxil: 1,594 patients
(Ge *et al.*, 2024) [28]	China	Cohort Retrospective with Control	865 patients
(Nakazawa *et al.*, 2020) [29]	Japan	Prospective post marketing surveillance (PMS)	3197 patients
(Qiu *et al.*, 2024) [30]	China	Prospective, randomized, parallel-controlled trial.	200 patients
(Uehara *et al.*, 2020) [31]	Japan	Phase 3, double-blind, placebo-and active comparator-controlled, randomized trial.	456 patients
(Yoshii *et al.*, 2020) [32]	Japan	Multicenter, Observational Study	295 patients
(Goto *et al.*, 2024) [33]	Japan	Non-randomized, prospective, observational, investigator-initiated research study	73 patients
(Gong *et al.*, 2025) [34]	China	Cohort study (non-randomized)	811 patients
(Macesic *et al.*, 2021) [35]	Australia	Case report	2 patients
(Retout *et al.*, 2021) [36]	Switzerland	Retrospective study	1781 patients
(Baker *et al.*, 2020) [37]	United States, Mexico, Costa Rica, Spain, Poland, and Russia.	Phase 3, randomized, double-blind, active-controlled clinical trial	176 patients
Collins *et al.*, 2023) [38]	USA, Switzerland	Phase III randomized, placebo-controlled, Capstone-2 trial	1242 patients

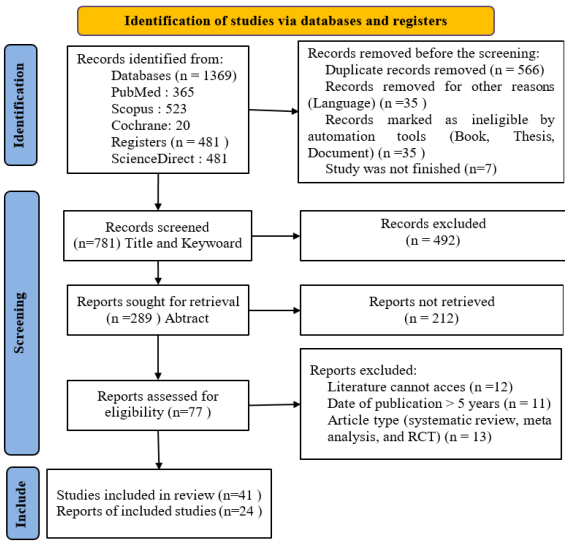

Fig. 1: PRISMA flowchart diagram

RESULTS

Various databases were used such as PUBMED, Scopus, Science Direct, and cochrane and 1369 articles were identified based on the search strategy. After screening based on exclusion and inclusion, and removing duplicates, 24 articles were included in this scoping review. Studies were conducted in Japan, the United States, and China. Four Studies discussed influenza transmission in households, five studies discussed influenza transmission in adults with an age range of 20-81, and nine studies discussed influenza in children. All journals discussed the comparison of baloxavir to placebo or other drugs for influenza treatment.

Table 2: Study result

Author	Patient/population	Intervention	Comparison	Outcome
(Ikematsu *et al.*, 2020) [15]	The present study included participants who resided in the same household as an influenza patient (index patient) during the 2018–2019 influenza season in Japan. Index patients were defined as those who were initially confirmed to have influenza in the household and had received antiviral treatment.	Subjects were randomly assigned in a 1:1 ratio to receive a single, weight-based oral dose of baloxavir or a matching placebo.	Placebo	Preventing clinical influenza in household contacts and the safety of influenza infection events.
(Portsmouth *et al.*, 2021) [16]	Healthy adolescents with acute influenza confirmed by RT-PCR, aged 12–17 y, in Japan and the United States	A single dose of baloxavir marboxil is administered at a dosage of 40 or 80 mg.	Placebo	Time to symptom relief (TTAS) was shorter in the baloxavir group (54.1 h) compared with placebo (92.7 h).
(Ishiguro *et al.*, 2021) [17]	Children aged 6 to<12 y with confirmed influenza virus infection in Japan. The study population included children with symptoms of fever and at least one moderate or severe respiratory symptom (such as cough or nasal congestion.	A single dose of baloxavir is given according to the approved dose in Japan, which is based on the child's body weight (10 mg for weight ≥10 to<20 kg, 20 mg for ≥20 to<40 kg, and 40 mg for ≥40 kg)	Administration of oseltamivir, given twice daily for 5 d, as an active comparator to determine the relative efficacy and safety between baloxavir and oseltamivir in pediatric patients.	Efficacy and safety of baloxavir as an antiviral treatment option for Japanese children infected with influenza.
(Yoshino *et al.*, 2020) [18]	Patient with diagnosed influenza and focused adult	The primary intervention tested was the administration of Baloxavir Marboxil.	The comparators in this study were oseltamivir and laninamivir.	Baloxavir Marboxil may have better antipyretic effects, potentially improving treatment compliance.
(Ikematsu *et al.*, 2024) [19]	The study population consisted of index cases with confirmed influenza and their household.	The intervention tested was treatment with Baloxavir Marboxil (BXM), given as a single dose to index cases. This was compared with treatment with Oseltamivir (OTV), which is the standard therapy for influenza.	Oseltamivir	Secondary attack rate (SAR). The results showed that the SAR for household contacts of the index case treated with BXM was 10.8%, while for OTV it was 18.5%.
(Komeda, Takazono, Hosogaya, Miyazaki, *et al.*, 2021) [20]	Patients aged 1 year and older who received treatment for influenza were continuously registered in the database for at least six months before treatment.	A single-dose baloxavir marboxil oral antiviral medication approved for treating influenza, known for its novel mechanism as a cap-dependent endonuclease inhibitor.	Neuraminidase Inhibitors (NAIS), specifically oseltamivir, zanamivir, and laninamivir.	The incidence of hospitalization was significantly lower in the baloxavir group compared to both oseltamivir (risk ratio [RR] 1.41) and zanamivir (RR 1.85) groups.
(Komeda, Takazono, Hosogaya, Ogura, *et al.*, 2021) [21]	Japanese families who had a first-in-household influenza diagnosis during the 2018–2019 season. This group included index patients (IPS) with influenza receiving one of four treatments: zanamivir (inhaled), laninamivir (inhaled), baloxavir marboxil, or oseltamivir (oral neuraminidase inhibitor).	Treatment with baloxavir marboxil reduces the viral load quickly, hence minimizing the transmission of influenza in households.	Treatment with neuraminidase inhibitors (oseltamivir as the primary control) and two other comparison groups, namely zanamivir and laninamivir.	The Household transmission was lower in the baloxavir group after adjusting for variables.
(Wagatsuma *et al.*, 2022) [22]	Japanese children under 19 y of age who were infected with influenza B/Victoria lineage or influenza A(H1N1) pdm09 during the 2019–2020 flu season.	Treatment with baloxavir marboxil, an antiviral drug given once orally to suppress symptoms and fever due to influenza.	Oseltamivir	Baloxavir shortened the duration of fever in influenza A(H1N1) pdm09, but the duration of symptoms was similar to oseltamivir.
(Umemura *et al.*, 2020) [23]	Patients diagnosed with influenza A and hospitalized at Tosei General Hospital, Japan, between October 2018 and March 2019, and their household members.	Treatment with baloxavir marboxil	Oseltamivir	Baloxavir and oseltamivir had similar rates of secondary attacks, with evaluation of TTIA, fever, viral titer, and safety.
(Sonoyama *et al.*, 2021) [24]	Pediatric patients aged less than 12 y with confirmed influenza, specifically those weighing less than 20 kg. The study involved 45 patients, predominantly under the age of 6.	Administration of baloxavir marboxil in a granule formulation at a dose of 2 mg/kg for patients weighing less than 10 kg or 20 mg for those weighing between 10 to less than 20 kg.	-	The primary outcomes measured included time to disease resolution (TTIA), time to fever resolution, and change in viral titer over 22 d to baloxavir.
(Liao *et al.*, 2023) [25]	Adults and adolescents in China, aged 12 y or older, who were diagnosed with influenza A and were seeking outpatient treatment.	Treatment with baloxavir marboxil, a single-dose antiviral medication aimed at reducing the duration of symptoms and fever in patients with uncomplicated influenza.	Oseltamivir	The primary outcomes measured included the duration of fever, duration of symptoms, changes in viral load, lymphocyte counts, and improvements in health-related quality of life (QoL).
(Cai *et al.*, 2024) [26]	Outpatient patients aged 12 y and older who are experiencing Influenza A	Baloxavir Marboxil	Oseltamivir	Baloxavir Marboxil is more effective than Oseltamivir in reducing the duration of symptoms and fever of Influenza A when given within 12–48 h, with minimal side effects.
(Li *et al.*, 2024) [27]	Participants in this study included reports from various healthcare professionals (such as doctors, nurses, and pharmacists) as well as general consumers who reported drug side effects.	There was no direct intervention because it was observational and used existing data (secondary	This study analyzes the safety profiles of two antiviral drugs, Oseltamivir and Baloxavir Marboxil, by	This study assessed the safety profile of Oseltamivir and Baloxavir through detection of side effects.

		data) from the FAERS reporting system.	examining adverse events (AEs) reported in the FDA Adverse Event Reporting System (FAERS) over a prolonged period.	
(Ge *et al.*, 2024) [28]	Patient diagnosed with influenza type A in China Children aged 0 to 18 y old	Baloxavir Marboxil (single dose)	Oseltamivir dose twice daily for 5 d	Baloxavir had a lower rate of side effects and reduced the duration of fever more quickly than oseltamivir in children with influenza.
(Nakazawa *et al.*, 2020) [29]	The demographic breakdown showed that approximately 6% were under 6 y old, about 23% were aged 6 to 12 y, and around 7% were 65 y or older. The majority of patients received baloxavir within two days of symptom onset, aligning with treatment guidelines.	Baloxavir Marboxil once, weight-based doses	-	Baloxavir is not only well tolerated but also effective in the treatment of influenza, regardless of patient age or the specific type of influenza virus.
(Qiu *et al.*, 2024) [30]	Patient diagnosed with influenza A Age 14-85 y old	Baloxavir Marboxil 40 mg once (Single dose)	Oseltamivir capsules, 75 mg twice a day, for 5 consecutive days	Baloxavir marboxil and oseltamivir are equally safe and effective in treating influenza A, and there are no appreciable variations in the groups' main outcomes.
(Uehara *et al.*, 2020) [31]	Patient diagnosed with Influenza without complications, Adults and adolescents Patients who did not have other antivirals besides baloxavir	Baloxavir Marboxil (single dose)	Patients treated with baloxavir who did not develop the PA/138X-substituted virus variants.	The studyThe PA/I38X variant may prolong symptoms and transmission, even when baloxavir is effective.
(Yoshii *et al.*, 2020) [32]	Patients with Influenza type A diagnosed	Baloxavir Marboxil	Neuraminidase Inhibitors (nais), Oseltamivir, Zanamivir, Peramivir Laninamivir	Baloxavir shortened the duration of fever compared to neuraminidase inhibitors (1.94 vs 2.35 d).
(Goto *et al.*, 2024) [33]	Patient diagnosed with influenza A during the 2022-2023 influenza season	Baloxavir Marboxil (single dose)	Neuraminidase Inhibitors	On day 5, virus detection was lower in BXM (11.1%) compared to OTV (60%) and other NAIs (52.9%). The duration of fever was similar in all groups.
(Gong *et al.*, 2025) [37]	Patients aged ≥14 y with RT-PCR-confirmed influenza B	Baloxavir marboxil (single oral dose: 40–80 mg based on body weight)	Oseltamivir	Baloxavir has shortener time to fever resolution, better symptom relief, and minimal adverse events
(Macesic *et al.*, 2021) [38]	Two immunocompromised patients with influenza A/H1pdm09 resistant to oseltamivir (confirmed H275Y neuraminidase mutation)	Baloxavir marboxil (single and repeated oral doses); in Patient 1, used in combination with zanamivir	Oseltamivir and peramivir	Baloxavir less effective when used as monotherapy
(Retout *et al.*, 2021) [39]	Adults and adolescents (≥12 y old) with confirmed influenza A or B, either otherwise healthy (OwH) or high risk (HR) for complications	Single oral dose of Baloxavir marboxil	Placebo	Baloxavir hast ime to alleviation of symptoms (TTAS), defined as sustained mild or no symptoms across 7 specific flu symptoms for ≥21.5 h
(Baker *et al.*, 2020) [37]	Children aged 1 to<12 y, with confirmed acute influenza (A or B)	Single oral dose of baloxavir marboxil	Osetalmivir	Baloxavir has shortener time to fever resolution, better symptom relief, and minimal
(Collins *et al.*, 2023) [38]	Adults (≥12 y old) with confirmed influenza and renal impairment	Single oral dose of baloxavir marboxil	Osetalmivir and Placebo	Baloxavir achieved faster viral clearance (TCVS) compared to both oseltamivir and placebo

Table 3: Missing evaluation of study quality cochrane risk of bias tool for RCTs

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Ikematsu *et al.* (2020) [18]	Low	Low	Low	Low	Low	Low
(Ishiguro *et al.*, 2021) [17]	Low	Some concern	Low	Some concern	Low	Some concern
(Yoshino *et al.*, 2020) [18]	-	-	Low	moderete	Low	Moderete risk
(Ikematsu *et al.*, 2024) [19]	Low	Low	Low	Low	Low	Low
(Komeda, Takazono, Hosogaya, Miyazaki, *et al.*, 2021) [20]	-	-	Low	Moderate	Low	Moderate
(Komeda, Takazono, Hosogaya, Ogura, *et al.*, 2021) [21]	-	-	Low	Moderate	Low	Moderate
(Wagatsuma *et al.*, 2022) [22]	-	-	Low	Moderate	Low	Moderate
(Umemura *et al.*, 2020) [23]	-	-	Low	Moderate	Low	Moderate
(Sonoyama *et al.*, 2021) [24]	-	-	Low	high	Low	high
(Liao *et al.*, 2023) [25]	Some concerns	High	Low	Some concerns	Some concerns	High
(Cai *et al.*, 2024) [26]	Low	Moderate	Low	Low	Low	Low
(Li *et al.*, 2024) [27]	Low	Moderate	Moderate	high	Low	Moderate
(Ge *et al.*, 2024) [28]	-	-	Moderate	High	Moderate	High risk
(Nakazawa *et al.*, 2020) [29]	Low	Low	Low	Low	Low	Low
(Qiu *et al.*, 2024) [30]	Low	Low	Low	Moderate	Low	Low
(Uehara *et al.*, 2020) [31]	Low	Low	Moderate	Low	Low	Low
(Yoshii *et al.*, 2020) [32]	Low	Low	Low	Low	Low	Low
(Goto *et al.*, 2024) [33]	Low	Low	Low	Low	Low	Low
(Gong *et al.*, 2025) [37]	High	Low	Low	Some concerns	Some concerns	Moderate to high
(Macesic *et al.*, 2021) [38]	High	Some concerns	Low	Some concerns	Some concerns	High
(Retout *et al.*, 2021) [39]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
(Baker *et al.*, 2020) [37]	Low	Low	Low	Some concerns	Low	Low to moderate
(Collins *et al.*, 2023) [38]	High	Some concerns	Low	Some concerns	Some concerns	Some concerns

Table 4: Tabulate adverse event rates baloxavier

Author	Sample size (n)	Any adverse events (n (%))											
		Pharyngitis or nasopharyngitis		Headache		Nauseaandvomiting		Diarrhea		Rash		Bronchitis, bronchopneumonia)	
		B	C	B	C	B	C	B	C	B	C	B	C
(Ikematsu *et al.*, 2020) [15]	752 patients	28(7,5)	26(7,0)	8(2,1)	6(1,6)	2(0,3)	1(0,3)	1(0,3)	1(0,3)	1(0,3)	0	-	-
(Portsmouth *et al.*, 2021) [16]	117 patients	-	-	1(1,3)	2(4,9)	-	-	3(3,9)	2(4,9)	-	-	1(1,3)	2(4,9)
(Yoshino *et al.*, 2020) [18]	43 patients	-	-	-	-	-	-	4(28.57)	5(35.7	-	-	-	-
(Sonoyama *et al.*, 2021) [24]	45 patients	8 (17.8)	-	-	-	-	-	5 (11.1)	-	-	-	2 (4.4)	-
(Cai *et al.*, 2024) [26]	590 patients	-	-	-	-	-	-	-	-	1(0,3)	-	-	-
(Ge *et al.*, 2024) [28]	865 patients	-	-	0	4(1,9)	10(5,0)	54(23,7)	4(2,2)	12(7,6)	2(1,2)	3(1,3)	-	-
(Nakazawa *et al.*, 2020) [29]	3197 patients	-	-	46 (1.49)	-	57(1,84)	-	189 (6.11)	-	8 (0.26)	-	-	-
(Qiu *et al.*, 2024) [30]	200 patients	-	-	2(2)	4(4)	-	-	3(3)	2(2)	0	1(1)	-	-
(Gong *et al.*, 2025) [34]	811 patients	1(0,3)	0	5(1,3)	0	0	55(13,2)	1(0,3)	7(1,7)	-	-	4(1,0)	0
(Baker *et al.*, 2020) [37]	176 patients	-	-	-	-	7(6,1)	9(15,5)	6(5,2)	1(1,7)	-	-	3(2,6)	1(1,7)

Note: B=Baloxavir group, C= Control group, (-) = without control group or not mentioned it's kind of adverse event, articles not listed in the table = do not mentioned adverse events.

DISCUSSION

Influenza is a respiratory disease that is brought on by influenza viruses A, B, or C [1]. There are several drugs used for the treatment and prophylaxis of influenza, including amantadine (M2 ion channel blockers), oseltamivir (neuraminidase inhibitors), and cap-dependent endonuclease inhibitors (baloxavir marboxil) [3]. This study analyzed 19 journals and obtained findings related to the effectiveness of baloxavir marboxil compared to other drugs in terms of length of treatment and duration of symptom reduction.

Baloxavir marboxil is one of the Cap-dependent endonuclease inhibitors, which works to inhibit the strong and selective replication of influenza viruses. One study conducted by Portsmouth *et al.*, (2021) explained that Time to Alleviation Symptom relief (TTAS) was shorter in the baloxavir group (54.1 h) compared to the placebo (92.7 h). That result was supported by 3 studies conducted by (Liao *et al.*, 2023; Wagatsuma *et al.*, 2022; Yoshii *et al.*, 2020) which showed a decrease in the duration of fever symptoms and lymphocyte count in influenza infection. Baloxavir marboxil showed a shorter treatment time than oseltamivir and other neuraminidase inhibitor drugs. This suggests that baloxavir marboxil has the same effectiveness as other neuraminidase inhibitors in terms of time to reduce symptoms [16]. Mechanism of action Baloxavir and others antiviral showed in above (fig. 1).

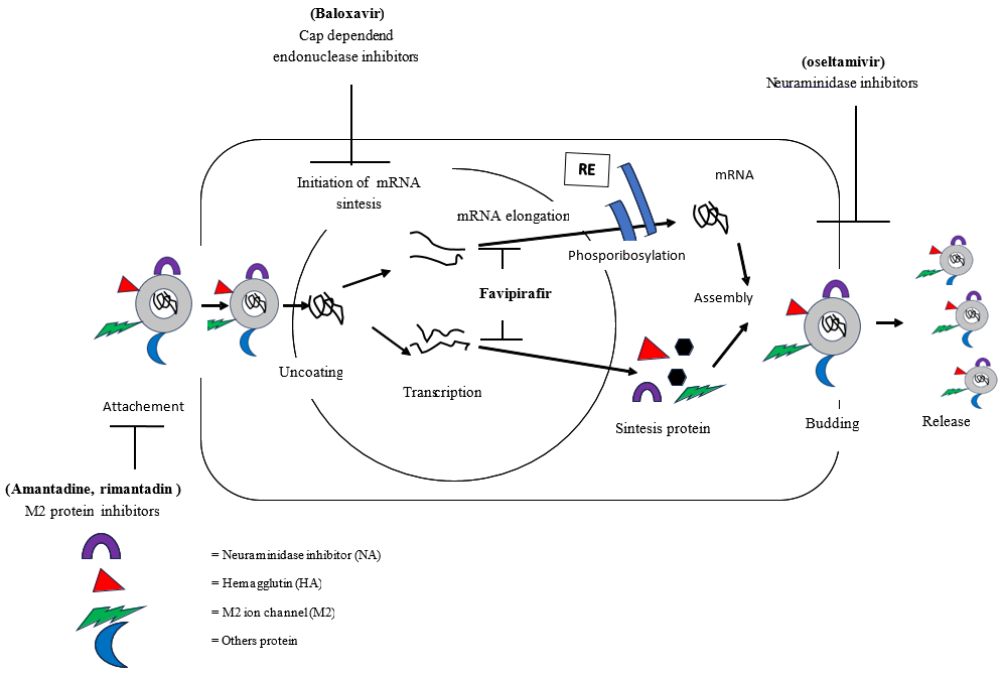

Fig. 1: Schematic diagram for pharmaceutical mechanisms of baloxavir, favipiravir, oseltamivir and other anti-influenza drugs [20, 16, 35]

Baloxavir is associated with a lower risk of side effects, when compared to other antivirals, such as oseltamivir has side effects of nausea, vomiting, epilepsy, and arrhythmia [39]. A study conducted by Li *et al.*, (2024) stated that the safety of baloxavir marboxil was based on age, the most significant safety against general symptoms was age<15 y and age>64 y. The safety profile is one of the important factors that must be considered when using new drugs. In a study conducted by Ishiguro *et al.*, (2021) which examined children aged<12 y who suffered from influenza and were given therapy in the form of baloxavir had a lower risk of gastrointestinal disease compared to oseltamivir [17]. The most common side effects experienced by patients taking this drug are diarrhea and vomiting, but these were lower than oseltamivir. A Research conducted by Afni (2022) which used molnupiravir, which works in almost the same way as baloxavir marboxil, namely by inhibiting the replication of the influenza virus, but also has the most common side effect, namely diarrhea [40]. Diarrhea adverse effects could be caused by the secretion of baloxavir and its active metabolites in the stool, food-binding metal ions in the colon, or increased osmosis pressure. The use of baloxavir in persons with liver disease revealed decreased hepatic toxicity [27].

Baloxavir can be used as prophylaxis for children under 12 y of age because influenza virus transmission is more frequent in household settings such as children to siblings or parents. However, the incidence is more common in children in households. Research conducted by Ikematsu *et al.*, (2020) showed that 73.6% of patients consisting of 19% children showed a higher incidence than adults. Patients treated with baloxavir showed clinical improvement or lower clinical risk than placebo. Laboratory tests for the efficacy of protection against influenza using baloxavir showed a fig. of 86% comparable to oseltamivir (68-89%) and zanamivir (82-84%) [17].

Experiments using mice showed that one-time administration of baloxavir 72 h after Inoculation significantly reduced virus titers within 24 h after administration. In phase 1 clinical trials, the plasma concentration of baloxavir acid increased with increasing dose with pharmacokinetic results that have a long half-life, so it is effective in single-dose administration. A phase 3 clinical trial showed that a single dose of baloxavir was more effective than placebo in relieving influenza symptoms [13]. Research conducted by Watanabe *et al.*, (2019), revealed that a phase 2 study examining dose and antiviral activity showed a decrease in time and an improvement in symptoms. In addition, there was a greater reduction in viral titer within 24 h in all baloxavir groups compared to placebo [35].

CONCLUSION

Nineteen studies showed that Baloxavir Marboxil was generally more effective than Oseltamivir and other neuraminidase inhibitors in reducing the duration of influenza symptoms, including fever. Treating influenza is essential for alleviating symptoms, preventing complications, limiting transmission, and supporting public health initiatives. Studies involving various populations in Japan and China found that Baloxavir can reduce household transmission rates and has a similar safety profile to Oseltamivir. In addition, Baloxavir also showed advantages in reducing the duration of virus detection and having a faster antipyretic effect.

However, there are concerns regarding the emergence of viral variants such as substitution to threonine (T), methionine (M), or phenylalanine (F) at position 38 of the PA (PA/I38X) that rise after Baloxavir treatment. *In vitro* characterization showed that laboratory strains with PA/I38X substitutions have reduced susceptibility to Baloxavir. Those that may affect the duration of symptoms and transmission of the virus, posing additional challenges in influenza treatment.

In addition, the limitation of studies that were only conducted in a few countries, especially in Asian regions such as Japan and China, indicates that the effectiveness of Baloxavir requires further research to ensure its validity on a global scale. Thus, while Baloxavir shows high potential as an influenza treatment option, additional evaluations in more geographically and demographically diverse regions are needed to strengthen the evidence for its overall effectiveness and safety.

ABBREVIATIONS

PRISMA = Preferred Reporting Items for Scoping Reviews and Meta-Analysis, WHO=World Health Organization, CENI= Cap-dependent Endonuclease Inhibitor, VRNA= Viral RNA, PB1=Polymerase Basic-1, PB2=Polymerase Basic-2, PA= Polymerase Acidic protein, RCT= Randomized Control Trial, RIDT= Rapid Influenza Diagnostic Test, RT-PCR= Reverse Transcription Polymerase Chain Reaction, ELISA= Enzyme-Linked Immunosorbent Assay, GRADE= Grading of Recommendations Assessment, Development, and Evaluation, PICO= Patient, Population, Intervention, Comparison, and Outcome, SD= Standard Deviation, IQR= Interquartile Range, TTAS= Time To Alleviation Symptom Relief, TTIA= Time To Illness Alleviation, QOL= Quality of Life, AE=Adverse Event, FAERS= FDA Adverse Event Reporting System, PMS= Post Marketing Surveilens, NAIS= Neuramininidase inhibitors.

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AUTHORS CONTRIBUTIONS

DU and FD have contributed in conceptualizing the research and designing the methodology. FD, RP, HN have contributed to collecting data and developing theory. RP and AF contributed to data analysis and assisted with the literature review. DU, FD, and HN have contributed regarding the interpretation of the results. All authors contributed and discussed to review and edit the manuscript.

CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work.

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