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ANTIVIRAL TREATMENT IN PATIENTS WITH INFLUENZA INFECTION: A A SYSTEMATIC REVIEW

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Abstract

Introduction: *Influenza is a viral infection which is characterized by fever, cough, and runny nose. Influenza may cause a disease in varying degrees, mild to severe. Influenza is a self-limiting disease, however, patients with comorbidities may experience severe sequelae. Due to this, antiviral agents are very crucial for influenza patients.*

Objective: *This article aims to discuss treatment agents for influenza patients.*

Methods: *This manuscript was prepared based on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. PRISMA is the basis of determining the criteria used in conducting this systematic review. The desired result is a patency comparison between the two techniques. The articles included should be published between 2013 until 2023. The keywords used in search strategy were "antiviral" and "influenza".*

Results: *The results were presented in Table 1. 267 articles from PubMedn and 212 articles from SagePub were obtained from initial search. The final screening process resulted in 10 publications.*

Conclusion: *Research showed that baloxavir was more effective than NAI, while NAI was more effective than placebo. Baloxavir had more severe side effects compared to NAI, though both drugs were safe for children.*

Keywords: *Influenza Infection, Antiviral Treatment.*

INTRODUCTION

Influenza is a viral infection characterized by fever, cough, and runny nose. Influenza can cause mild to severe illnesses. Young patients who suffer from influenza generally recover within a few days or weeks. Complications that may occur including inflammation of the sinuses (sinusitis) and lungs (pneumonia) which can cause shortness of breath.[1] Influenza virus is easily transmitted through sneezing, coughing, or talking. The disease may be prevented by administering the influenza vaccine which is recommended for patients aged 6-months-old or more. Current recommendation stated that children aged nine-years-old or older were given influenza immunization once a year.[1,2]

Influenza pandemics have long been acknowledged since the "Spanish Flu" phenomenon in the 1918-19 era which was due to H1N1 virus subtype and caused mortality of up to 50 million people. Between 1957-58, the presence of antigenic shift from subtype H1N1 to subtype H2N2 causes the "Asian Flu" pandemic. The H2N2 virus was then replaced by H3N2 during the "Hong Kong Flu" pandemic in 1968, followed by the H1N1 virus outbreak in 1977 with similar characteristics to the H1N1 virus when the "Asian Flu" occurred. Since then, seasonal flu outbreaks have only involved two subtypes, H1N1 and H3N2, which often experience antigenic drift.[3,4]

The epidemiology of influenza developed worldwide, mainly in winter (4 season countries) or throughout the year (tropical countries).[3,4] The evidence of transmission of the H5N1 virus from chickens in Hong Kong in 1997 confirmed the possibility of the transmission of the avian influenza virus to humans. Between 1997-2003, 826 cases of H5N1 infection were recorded with a mortality rate of up to 53%. Although there have been reports of H5N1 transmission between individuals in Thailand, China, Vietnam, and Indonesia, there is no evidence of sustained and rapid inter-individual transmission like the "Spanish Flu" pandemic.[3]

The 2003-2007 surveillance study in Indonesia reported that there were 21,030 cases with influenza-like symptoms, of which 20.1% were confirmed to be infected with influenza viruses with similar proportions between outpatients and inpatients.[3] The largest age group suffering from influenza is school-age children. The study also stated that 64.9% of all influenza cases found were due to influenza A virus while 35.1% were caused by influenza B virus. Influenza A virus activity reached its peak in December and January, especially in western and central Indonesia.[4]

Influenza is a self-limiting disease, but it has a serious impact on patients with comorbidities. Due to this, antiviral agents' administration was important for influenza patients. This article aimed to discuss therapeutic agents for patients with influenza.

METHODS

This article was prepared based on the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), where PRISMA serves as the guidance for establishing the criteria used to monitor this systematic review. The standard was used to ensure that all relevant data has been collected and analyzed. This is a systematic review manuscript. The data source for this research was obtained from literature gathered through the internet, where the articles collected were research journals indexed by Scopus.

The databases used for article searching were PubMed and SagePub. The articles included in this manuscript discussed medical agents for treating influenza in humans, especially their efficacy and side effects. The inclusion criteria for the articles included were articles that reviewed antivirals use in influenza patients. We desired to obtain the most current literature regarding the efficacy and side effects of antivirals for influenza. The articles included had to be published from 2013 to 2023. The keywords used were "diagnosis", "antiviral" and "influenza".

Article search was performed on September 30th, 2023. The terms used included: *(("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms] OR ("antiviral"[All Fields] AND "agents" [All Fields]) OR "antiviral agents"[All Fields] OR "antivirals"[All Fields] OR "antiviral"[All Fields] OR "antivirally"[All Fields]) AND ("influenza s"[All Fields] OR "influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields] OR "influenzas"[All Fields] OR "influenzae"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter]))".*

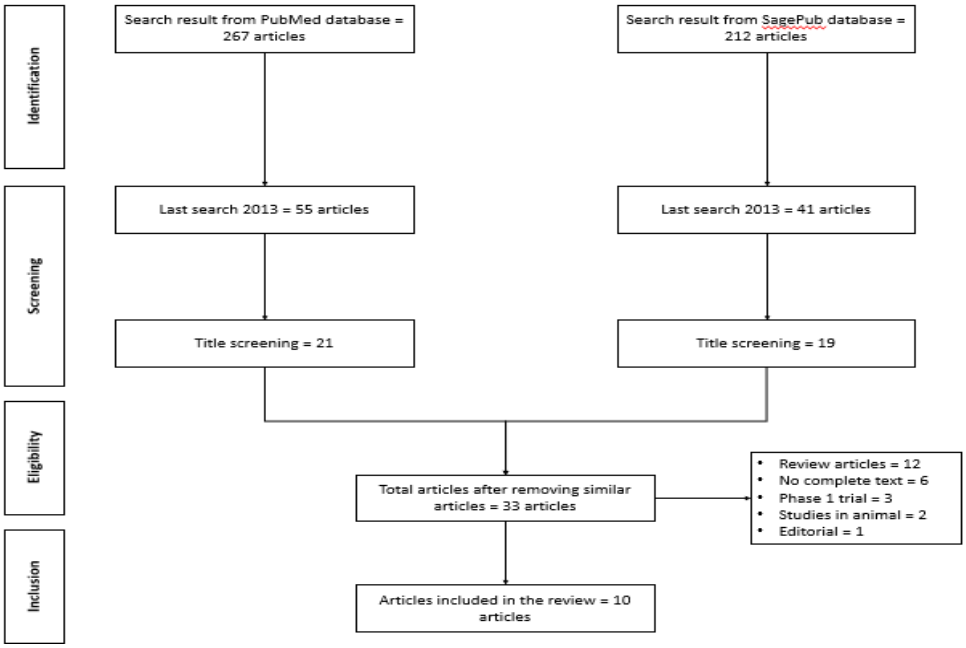

Figure 1. Research flow diagram

We excluded all studies conducted on animals and non-influenza subjects in this review. Moreover, we did not include articles that were published in languages other than English, did not have a DOI, and review or editorial articles. An independent evaluation of several articles was performed, in which we found several studies that can be presented. Title and abstract from each article were extracted and used in selecting which articles were included in this systematic review. Both data can give important information about the result of the research and help select articles for complete review.

RESULTS

The search results were presented in Table 1. Initial search performed in two databases resulted in 267 articles from PubMedn and 212 articles from SagePub. The final screening produced 10 publications for full review. Kumar, et al (2020) showed that baloxavir + NAI group was superior compared to control group. Hayden, et al (2018)[10], Baker, et al (2020)[9], and Ison, et al (2020)[8] depicted that single dose baloxavir had no clear safety concerns, was superior to placebo in reducing influenza symptoms, and was better than to oseltamivir and placebo in reducing viral load one day after the trial regiment start in patients with uncomplicated influenza. The results were also supported by latest research performed by Butler, et al (2020)[7] which concluded that the recovery time for patients on oseltamivir was shorter than those who received placebo. Another study by Hayden, et al (2022)[6] demonstrated that the favipiravir dosing regimen had significant antiviral effectiveness but was inconsistent in reducing disease in uncomplicated influenza. Other agents such as perimivir have also been tested. An open-label trial of intravenous peramivir in hospitalized subjects mainly infected with influenza A (H1N1) in 2009 showed that once- or twice-daily administration was associated with reduced viral shedding and clinical improvement.[13,14]

In regards of safety, baloxavir was comparable to placebo. Research from Ison (2020) supported early administration in patients at high risk of influenza complications to accelerate clinical recovery and reduce complications.[8] Oral baloxavir was also well tolerated and effective in relieving symptoms in healthy children suffering from acute influenza. Baloxavir provided a new therapeutic option with a simple oral dosing regimen.[9]

Author, year	Origin	Methods	Sample size	Therapeutic agents	Efficacy	Side effects
Kumar, 2022[5]	Canada	Randomized, parallel-group, double-blind, placebo controlled	366 patients with influenza	Oral baloxavir on day 1 and 4 (40 mg for BW<80 kg, or 80 mg for ≥80 kg), and on day 7 if there were no clinical improvement on day 5. NAI: oseltamivir, zanamivir, and peramivir chosen and administered according to standard operating procedure	Median time to clinical improvement was 97.5 hours (95% confidence interval = 75.9-117.2) in the baloxavir group and 100.2 hours (75.9-144.4) in the control group (median difference = -2.7 hours [95% CI = -53·4 to 25·9], p = 0·467).	Baloxavir + NAI was well tolerated. Serious adverse events occurred in 12% of patients in the baloxavir group versus 15% in the control group (orthostatic hypotension in control group). Overall, four deaths (2%) occurred in the baloxavir group and seven (6%) in the control group; none were considered treatment related.
Hayden, 2022[6]	USA	Two Phase 3, randomized, double-blind, placebo-	301 patients were given favipiravir and 322	Favipiravir (1800 mg twice daily on day 1, 800 mg twice daily on day 2 – 5) or placebo tablet	In US317 (526 favipiravir, 169 placebo), favipiravir did not significantly reduce	Apart from asymptomatic hyperuricemia, there were no significant differences of side effects.

		controlled trials	received placebo		recovery time (median 77.8 vs. 83.9 hours).	
Butler, 2020[7]	England	Open-label, pragmatic, adaptive, randomized controlled trial	3,266 patients with influenza-like syndrome	Oseltamivir administered 75 mg twice daily for 5 days	Recovery time was shorter in patients with oseltamivir (hazard risk [HR] = 1.29, 95% confidence interval [CI] 1.20–1.39) and in 30 of 36 prespecified subgroups, with estimated HR between 1.13-1.72.	Mild
Ison, 2020[8]	Japan	Double-blind, placebo-controlled and oseltamivir-controlled trial	2,184 patients with influenza-like syndrome	Baloxavir (40 mg for patients with BW <80 kg and 80 mg for BW ≥80 kg), oseltamivir 75 mg twice daily for 5 days, or placebo	The mean time to symptom improvement was shorter in the baloxavir group (73.2 hours [95% CI = 67.2-85.1]) compared to placebo (102.3 hours [92.7-113.1]; difference 29.1 hours [95% CI = 14.6-42.8]; p < 0·0001). Median result for symptom improvement in the oseltamivir group was 81.0 hours (95% CI = 69.4-91.5), differ with the baloxavir group 7.7 hours (-7.9 to 22.7)	Adverse events were reported in 25% of patients in the baloxavir group, 30% in the placebo group, and 28% in the oseltamivir group. Serious adverse events were noted in five patients in the baloxavir group, nine patients in the placebo group, and eight patients in the oseltamivir group; one case each of hypertension and nausea in the placebo group and two cases of increased transaminases in the oseltamivir group
Baker, 2020[9]	England	Double-blind, randomized, active controlled trial	173 children diagnosed as influenza	Single dose oral baloxavir or oral oseltamivir twice daily for 5 days	Median time (95% confidence interval) to relief of signs and symptoms of influenza was similar between groups: 138.1 (116.6-163.2) hours with baloxavir versus 150.0 (115.0-165.7) hours with oseltamivir.	Adverse events between groups were similar for baloxavir and oseltamivir (46.1% vs 53.4%). The most common side effects were gastrointestinal (vomiting/diarrhea) in both groups [baloxavir: 12 children (10.4%); oseltamivir: 10 children (17.2%)]. None of the patients died
Hayden, 2018[10]	Japan	Randomized, double-blind, controlled trials	400 randomized patients, 389 finished the trial	Placebo vs oseltamivir from single dose baloxavir based on body weight (40 or 80 mg). Oseltamivir was given 75 mg twice daily for 5 days	Mean time to symptom relief was 53.7 hours (95% confidence interval [CI] = 49.5-58.5) with baloxavir vs 80.2 hours (95% CI = 72.6-87.1) with placebo (P < 0.001).	Not reported
Beigel, 2017[11]	USA	Randomized, double-blind, multicenter phase 2 trial	633 patients hospitalized suspected with influenza	Combination therapy of oseltamivir (75 mg), amantadine (100 mg), and ribavirin (600 mg) or oseltamivir monotherapy twice daily for 5 days	40.0% of the combination group had detectable virus on day 3 compared with 50.0% (mean difference 10.0, 95% CI = 0.2-19.8, p =0·046) in the monotherapy group.	The most common side effects were gastrointestinal disorders, especially nausea (12% in the combination group vs. 11% in the monotherapy group), diarrhea (10% vs. 11%), and vomiting (7% vs. 4%).
Bradley, 2017[12]	USA	Randomized, double-blind, controlled trials	71 children with influenza	Intravenous zanamivir (exposure comparable to 600 mg twice daily in adult)	The mortality rate was 7%, and the average length of stay in hospital and ICU was 6 and 7.5 days, respectively.	No significant side effect
Ison, 2014[13]	USA	Randomized, double-blind, controlled trials	234 hospitalized patients	Peramivir 300 mg twice daily or 600 mg once daily	There were no significant differences in clinical or virologic endpoints between treatment groups, and the significant differences were due to disease severity differences at baseline between groups.	Peramivir is generally safe and well tolerated in patients hospitalized due to pandemic influenza
Jong, 2014[14]	Netherlands	Randomized, double-blind, controlled trials	405 patients	Intravenous peramivir (600 mg once daily) or placebo	Median (95% CI) time to clinical resolution was 42.5 (34.0-57.9) hours for peramivir versus 49.5 (40.0-61.9) hours for placebo (P = 0.97).	The incidence and severity of adverse events and laboratory abnormalities were similar between the two treatment groups.

DISCUSSION

The two drugs most reviewed in previous studies were oseltamivir and baloxavir. Baloxavir marboxil is an antiviral for flu symptoms that was given within the first 2 days or 48 hours. This drug is available in oral / tablet preparation. Baloxavir marboxil inhibits the formation of enzymes crucial for the influenza virus reproduction or replication. This drug is converted to its active form, baloxavir, through hydrolysis. Baloxavir prevents the endonuclease activity of the acid polymerase protein found in influenza viruses, therefore suppressing viral replication.[15]

Treatment should be started within 48 hours of the onset of symptoms. This medication is taken as a single dose with or without food but should not be taken with dairy products, calcium-fortified beverages, laxatives containing polyvalent cations, antacids, or oral supplements. Adverse events were reported in 20.7% of baloxavir patients, 24.6% of placebo patients, and 24.8% of oseltamivir patients in clinical trials. Adverse reactions most often reported from the two placebo-controlled trials included diarrhea (3%), bronchitis (2%), nasopharyngitis (1%), headache (1%), and nausea (1%).[15]

Oseltamivir is an antiviral neuraminidase inhibitor used for the management and prevention of influenza A (including during the H1N1 pandemic) and B virus infections. Oseltamivir works by inhibiting the viral neuraminidase enzyme detected on the surface of the virus which prevents virus proliferation, virus replication, and infectivity in host cells.[16] Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate) which is an effective and selective inhibitor of the influenza virus neuraminidase enzyme, a glycoprotein on the virion surface.[17]

Viral neuraminidase enzyme activity is essential for virus entry into uninfected cells to release newly formed viral particles from infected cells and to aid in virus spread in the body. Oseltamivir activity reduces viral shedding and infectivity. It is effective against neuraminidase of influenza A viruses (including pandemic H1N1) and influenza B.[17] Oseltamivir is an influenza drug commonly found. This drug is readily absorbed by the gastrointestinal tract after oral administration of oseltamivir phosphate and converted by hepatic esterase to the active metabolite oseltamivir carboxylate. Approximately 75% of oral dose reaches the systemic circulation as active metabolites. Pro-drug exposure <5% relative to active metabolite.[17,18]

Favipiravir was first introduced in Japan in 2014 as a new therapeutic option for influenza because of the increasing resistance of virus to oseltamivir.[19,20] This drug has broad-spectrum effects against various types of influenza viruses and has been used against other virus families, in addition to being effective against Ebola virus where its use was associated with better patient survival. Favipiravir can be combined with other antiviral drugs and shows synergistic effects. It is considered a potential drug against COVID-19. However, very little evidence present to recommend routine use of favipiravir for the treatment of SARS-CoV-2 infection.[19]

Favipiravir has significant antiviral effectiveness; however, it is inconsistent in reducing disease in uncomplicated influenza. Research showed that favipiravir was mostly well tolerated. Favipiravir was associated with a dose-related increase in serum uric acid levels that is reversible after discontinuation of the drug. Other reported side effects include mild to moderate diarrhea, asymptomatic elevation of transaminases, and decreased neutrophil count. Favipiravir is contraindicated in women who may or are pregnant due to its association with embryonic death and teratogenicity in animal studies.[6,21]

Adverse events were reported in 25% of patients in the baloxavir group, 30% in the placebo group, and 28% in the oseltamivir group. The safety of baloxavir was comparable to placebo.[8] Hypertension and nausea were reported in the placebo group and two cases of increased transaminases were noted in both the oseltamivir and balocavir groups. Baloxavir and oseltamivir are well tolerated and effective in relieving symptoms in healthy children suffering from acute influenza. Baloxavir provides a new therapeutic option with a simple oral dosing regimen.[9]

Predominant side effect of oseltamivir is skin hypersensitivity. Assessment of side effects in pediatric subjects was based on two open-label studies in patients using oseltamivir phosphate at doses ranging from 2-3.5 mg/kgBW oral suspension twice daily orally for 5 days. The safety profile of oseltamivir phosphate was similar across the age ranges studied, with vomiting (9%), diarrhea (7%) and rash (7%) being the most frequently reported adverse reactions, and typically comparable to those observed in older ages.[17,18]

CONCLUSION

Research concluded that baloxavir was more effective than NAI while NAI was better than placebo. The side effects of baloxavir were more severe compared NAI, although both drugs were safe to be administered to children.

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