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Review Article

A Review Literature on Efficacy and Comparison between the Drugs Used in Influenza

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Abstract

Seasonal flu or influenza is an acute respiratory illness caused by Influenza virus A and B. The disease is usually self-limiting, but can occasionally lead to dire complications. To prevent the occurrence of these complications, many preventive, as well as therapeutic remedies, have been implicated. Vaccines have shown to reduce morbidity associated with influenza viral infection. In addition to this, if an infection does occur, it may lead to adversities, especially in patients with extremes of ages, i.e., less than 12 and more than 65. The advent of anti-viral medications has helped in a significant reduction in the symptoms associated with this disease. But, as resistance to these chemicals has emerged, this is now contributing to the widespread endemics and pandemics. With this understanding, newer and better drugs are being introduced in the market. One such medication is Baloxavir, a modified version of the novel anti-viral drugs. We conducted a thorough electronic data search on PubMed and Google Scholar. Articles were filtered using the exclusion criteria of, "co-morbid conditions," immunodeficiency state," "Chronic Obstructive Pulmonary Disease," etc. The extracted articles were within a five-year time frame and were free full text. Further information was extracted using cross-references. Articles were screened for duplication. In this literature review, we describe in detail the advantages of Baloxavir to reduce the morbidity associated with Influenza infection.

Keywords: *Antiviral agents, Influenza virus, Virus replication, Viral RNA*

Introduction

Influenza is an acute respiratory illness caused by influenza A or B viruses, which mostly peaks during the winter season as outbreaks, epidemics, and pandemics worldwide. At the onset of disease, the signs and symptoms of upper and or lower respiratory tract involvement are present, which may include cough both dry/productive, nasal stuffiness, etc., along with this systemic illness such as fever, headache, myalgia, arthralgia, weakness, and fatigue. The influenza virus is not only known to cause pandemics but is also responsible for causing widespread infections with three to five million cases of severe disease and 290,000 to 650,000 deaths annually [1-5]. The traditional medications work by inhibiting receptors and enzymes in the virus. These may include Matrix 2 (M2) ion channel inhibitors such as Amantadine, Rimantadine, and the Neuraminidase enzyme inhibitors that were approved by the

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United States Food and Drug Administration in 1999, such as Oseltamivir, Zanamivir, Peramivir. These drugs vary in their mode of actions, kinetics, resistance, and tolerance patterns. Since there is widespread resistance to the M2 ion channel inhibitors and an emerging resistance is being seen with Neuraminidase Inhibitors such as that observed with Oseltamivir against H1N1 during 2008 to 2009 pandemic [6, 7], the need for a newer and more effective drug remains unquestioned. In the past two decades, the only new class of drug approved for Influenza is Baloxavir Marboxil (trade name, Xofluza). Baloxavir-marboxil is the prodrug that gives rise to Balxovir acid. It works by selectively inhibiting the Cap-dependent endonuclease within the polymerase subunit of Influenza A and B viruses, preventing the transcription of viral mRNA[8].

The drug is known to be effective in single doses by decreasing viral titers profoundly; in the meantime, it helps alleviate influenza symptoms [9]. In this review, we demonstrate whether the new novel drug Baloxavir offers a favorable profile compared to the already marketed Neuraminidase Inhibitors. Due to the emerging resistance to the viral particles, several trials are under study which we review here in this article. Many favorable aspects have been documented in these studies. For instance Baloxavir's association with greater reductions in viral load one day after initiation of the regimen than placebo or oseltamivir [10], it's broad and potent activity against both Influenza A and B viruses compared to other drugs in the market [11] and its once-daily dosing proves to be of benefit in improving adherence and convenience of use [12]. Aforementioned has led to the fact that drug dosing and the reduction of symptoms can be worthwhile.

Materials and Methods

A thorough electronic data search was conducted on PubMed and Google Scholar. Articles were filtered using the exclusion criteria of, “co-morbid conditions,” immunodeficiency state,” “Chronic Obstructive Pulmonary Disease,” etc. The extracted articles were within a five-year time frame and were free full text. Further information was extracted using cross-references. Articles were screened for duplication.

Review

Influenza has so far been a cause of epidemics and pandemics. Several reasons which are related to the virus itself have led to morbidity and mortality associated with the illness. A lot has been learned about the structure of this virus. Influenza virus has four types A B C, and D [13] and the most common reason for human outbreaks have been due to Influenza A and B. There is a predilection of weather for the spread of this infection, with winter being the prime season for its outbreak. Even though the outbreaks are self-limiting in modern times, influenza has been famous concerning its ability to convert into pandemic anytime and cause catastrophic death rate. For instance, the worst pandemic in 1918-1919 infected 500 million people worldwide, out of which 50-100 million cases were reported to be fatal [14]. In the USA, the annual rate of influenza-related death ranges from 1.4 to 16.7 deaths per 100,000 people [15].

Signs and symptoms

Uncomplicated Influenza: Uncomplicated influenza is self-limiting with a recovery lapse of two to seven days. It can have a variable presentation such as fever, chills, myalgia, headache, malaise and upper respiratory tract symptoms including sore throat, rhinitis and nonproductive cough but young children can present with nausea, vomiting, and diarrhea while elderly institutionalized frail people have an atypical presentation. Complicated Influenza: As explained earlier, Influenza infection is mostly self-limiting, but sometimes it can cause devastating complications especially in individuals who are at increased risk including young children, adults age more than 65 years, pregnant women, diabetics, patients with heart failure and stroke. Frequently presenting complications are dehydration, worsening of chronic medical conditions(heart failure, diabetes mellitus, Chronic Obstructive Pulmonary Disease, primary viral pneumonia and superim-posed bacterial pneumonia that can lead to acute lung injury or acute respiratory distress syndro-me, however respiratory complications like tracheitis, bronchiolitis, and otitis media are more prevalent among young children [16]. Extremes of ages are usually taken into consideration due to the risk of increased morbidity and mortality.

Taxonomy of the Virus

The annual Influenza shifts and drifts are variable due to the structure of the virus. A number of structures biochemically correspond to the ability of the drugs to function efficiently. The envelope of the Influenza virus constitutes of two main glycoproteins (GP) structures, Hemagglutinin and Neuraminidase. Both these GP structures have their own prescribed roles. Neuraminidase is functionally related to the fusion and entry of the Influenza virus [17-19]. These GP's are the fundamental clue to the classification of these

viral particles. As discussed earlier, many viral subtypes can pose severe threats to human health, leading to an increased rate of fatality and a high risk of pandemics. The most famous ones among these sub-types are H5N1, H5N6, H7N9 [20, 21]. The interior of this virus possesses eight genetic segments of negative monofilar Ribonucleic acid (RNA). This RNA structure has a diverse capability of replicating through a transcriptional complex of three protein subunits of heterotrimeric RNA polymerases. These three RNA polymerases are Polymerase (PA), Basic Protein 1 (PB1) and Basic Protein 2 (PB2) [22]. The viral replication initiates with the binding of the PB2 to Cap end of the pre-messenger RNA of the host cell. The Cap dependent endonuclease (CEN) then cleaves this PB2. These chemical interactions and the structures involved in it are the targets where most of the anti-viral drugs tend to work. The most interesting of this is the CEN, which remains unchanged among various influenza strains, owing to its property to adequately target, for therapeutic means in terms of anti-influenza drugs [23-26]. The consequen-ces of this infection can be lethal and can lead to morbidity and mortality on a large scale. Of note here is the strain H7N9 that has been known to cause five different epidemics since the year 2013, the most notable and the worst of them being in China in 2016 [21, 27]. This strain of Influenza virus has affected the entire world, increasing the death toll, killing thousands of individuals. The most recent incident that was in October of the year 2018, where H7N9 strain of Influenza A virus, infected about 1567 cases as of confirmation and incrementing the death toll to 615 affected individuals [27].

Treatment of Influenza

Due to the high rate of morbidity and mortality related to the infection by the Influenza virus, multiple drugs have been implicated in reducing the consequences. An array of drugs hit the shelves every year to drop down the adverse outcomes of this lethal infection. Most of these drugs and their mechanism of actions are now taken off from the market due to exuberant resistance to the compounds. Of note here are the chemicals working on GPs, the most common of which are M2 inhibitors and Neuraminidase inhibitors (NAIs). The prominent compounds blocking M2 ion channels such as Amantadine and Rimantadine are obsolete from the market due to their wide-spread resistance. Likewise, NAIs have been dominating the class of anti-virals. The drugs replacing the generic M2 receptor blockers are the NAIs that include Oseltamivir, Zanamivir, Peramivir, Laniniamivir. These substances have taken the place of the other classes, primarily when used for acute and uncomplicated Influenza infections [28, 29]. The most important prognostic factor in the remission of Influenza infection is that of the treatment time from the commencement of disease. A substantial number of studies conducted in this regard have proved the significance of initiation of treatment for reducing the morbidity related to Influenza infection. Most of them deem it essential to commence drug therapy as early as 48 hours since the time of onset of symptoms [30-33]. As mentioned earlier, drug resistance is an alarming sign for the lethality of this infection, leading to serious consequences. Due to this reason, a broad-spectrum anti-influenza drug “Favipiravir” was approved in Japan in 2014. It was for the fact that the drug was able to limit the drug-resistant pandemic that hit this region. The uniqueness of this drug lied with its mechanism of action. The compound had effects on the viral RNA polymerase and inhibited the replication of the Influenza virus [34, 35]. The jeopardy of the resistant strains has been claimed to be a reason for global calamity. The rate of NAI resistant strains of Influenza virus is emerging exponentially. During the worldwide pandemic that hit in late 2007 and early 2009, by the H1N1 strain of this virus, resistance to NAI was reported on a larger scale. Subsequently, to decrease mortality and lower the rate of adverse outcomes due to this infection, the drug industry provoked their thought process to look for other pharmacological options. The resistance led to the fact that NAIs were no longer able to reduce the complications related to Influenza infection. This diverted a previously self-limiting Influenza infection to complicated Influenza infection. The outcomes of which are pneumonia, hospitalization, and mortality [36-38]. It is now the need of this time to seek an alternative remedy for this potentially serious infection and due to the growing resistance to the existing therapies. The approach to this would further lead to a reduction in the health hazards related to this infection and would also help control Influenza related pandemics.

Mechanism of Action of Baloxavir

The hope for the future is the drug "Baloxavir." BXM is marketed in oral form and is therefore orally bioavailable with regards to kinetics. To cater to the risk of non-compliance, this medication offers a safer option as it is only prescribed once daily. It has a good safety profile and has a long half-life supporting the single oral dosing [39-

41]. The mode of action is such that it halts the viral replication in the beginning. BXM is hydrolyzed to its active form Baloxavir acid acting on the initiation of the replicating viral particle. Data reviewed from multiple in-vivo and in-vitro studies have suggested that the mode of action is dependent on the step of Cap snatching by inhibiting Cap dependent endonuclease working on the PA subunit of the Influenza A and B virus. This also highlights the fact that the amino acids in the CEN are well-conserved owing to the sequence of this drug's mechanism [42].

Is BXM a better drug than the generic NAIs?

Several ongoing studies and randomized trials since the year 2016-17, denoted a better outcome with the use of BXM, especially for the treatment of uncomplicated influenza infection. What makes BXM superior to the rest of the drugs is best answered by the fact that it has been shown to have a reduction in the duration of virus detection compared to Oseltamivir. This fact was studied in detail in trials such as CAPSTONE 1, which is illustrated in Table 1. The review of this trial also suggests that with the induction of therapy from the time since symptom onset, there was not much of a difference in symptom alleviation between the two drugs [10].

Table 1: Illustrates the CAPSTONE 1/Phase 3 Trail depicting the significant reduction in the resolution of symptoms with BXM vs Oseltami virvs Placebo.

CAPSTONE 1/Phase 3 Clinical Trial (Subjects with Uncomplicated Influenza A or B virus included)				
	Frequency of dosing	Amount of drug	Resolution of symptoms (hours)	Duration of Infectious Virus Detection (hours)
BXM	Once	40mg for <80kg 80mg for>80kg	53.7	24
OS	12h for 5 Days	75mg	53.8	72
PLC	-	-	80.2	96

BXM Baloxavir Mabroxil, Oseltamivir, PLC Placebo, CDC Center of Disease Control and Prevention

Another trial following the CAPSTONE 1 was conducted in 2017-18. This Phase 3 randomized clinical trial illustrated the use of BXM compared to Oseltamivir. The manifestations driven by this study showed a faster recovery with a reduced number of complications seen in patients infected with the Influenza virus. These patients were susceptible to the risk of complications by the infection. However, BXM leading the trial was able to shorten the duration of viral replication and reduced the recovery time from Influenza B illness as compared to Oseltamivir. The details of the experiment are illustrated in Table 2. It was seen that the individuals treated previously with other approved drugs continued to excrete the virus for a more extended amount of time than others. BXM not only decreases the duration of the alleviation of symptoms, but it also has a role in the reduction in viral shedding. It is known that BXM also mitigates the systemic complications driven by the Influenza virus itself compared to other therapies [43-45].

Table 2: Illustration of CAPSTONE 2/Phase 3 Clinical Trial showing the insignificant effect of BXM vsOseltamavirvs Placebo.

CAPSTONE 2/Phase 3 Clinical Trial (Subjects with increased risk of influenza complications including at least 1 High-Risk factor adapted from CDC)				
	Frequency of dosing	Amount of drug	Resolution of symptoms (hours)	Duration of Viral shedding (hours)
BXM	Once	40mg for <80kg 80mg for>80kg	73.2	48
OS	12h for 5 days	75mg	81.0	96
PLC		-	102.3	96

BXM Baloxavir Marboxil, Oseltamivir, PLC Placebo, CDC Center of Disease Control and Prevention

What's new about BXM?

BXM is, however, thoroughly studied as it seems to be a savior for the devastating Influenza infection. This year began with the publishing of a network meta-analysis comparing different aspects of the efficacy of BXM with various other NAIs. Corresponding to this study, BXM was found to be unique in multiple perspectives. The salient features are listed here. Comparison with Zanamivir suggested that BXM exhibits a significant reduction in the duration of viral shedding, drop in the viral titers measured from baseline, and effective resolution of the symptoms related to Influenza. Another NAI, Penamivir was also studied in detail. The comparison between the two drugs highlighted that BXM remained superior in altering the viral titers from baseline to 24 and 48 hours only. Oseltamivir compared with BXM illustrated greater efficacy than Oseltamivir in decreasing the titers from baseline to 23 hours and shedding of the viral particle. The drugs' adverse effects were also considered in this study, which included diarrhea and vomiting. There was no significant difference noted except for a lower odds ratio in the comparison of Laninamavir with Oseltamivir [46].

The genetic mutations causing the shifts and

drifts within the viral genome are taken into consideration to avoid resistance of future medications. In addition to genomic mutations, the Neuraminidase enzyme can cause reduced susceptibility to Oseltamivir, Zanamivir, Laninamivir when compared with BXM. The drug remains active against the mutant Influenza strains. On the other hand, BXM has shown to alter the inflammatory milieu within the host body. It has pronounced effects to reduce pro-inflammatory cytokines resulting in the limited migration of the cells of inflammation, both acute and chronic; neutrophils and macrophages, respectively. This has been noted in a study conducted in mice models with evidence of the efficacy of this marvel chemical compound in abating inflammation caused by Influenza virus in the environment within the lungs of the host; this effect was not appreciable for Oseltamivir. The main aim of all these studies encompasses the fact to reduce Influenza-related complications. In the study mentioned above conducted in mice, the main objective was to control Influenza-related infection. Hence, a combination of multiple antiviral medication regimens has proven to manifest a synergistic effect for the above-noted reasons. BXM can also be combined with Oseltamivir Phosphate which has proven to be more efficacious in decreasing the viral titer and improving survival as compared to monotherapy alone. Although BXM 15mg/kg twice daily dosing has shown to completely reduce mortality, a combination of suboptimal BXM dose (0.5 mg/kg twice a day) with Oseltamivir (10-15 mg/kg twice daily) has also shown to be protective against mortality and inflammation in the lungs [47-49].

Is BXM now under the threat of resistance?

As it is a well-known fact that mutations within the viral genome are inevitable. Similarly, the concomitant use of BXM in some instances has led to the emergence of various mutated viral strains. Among these mutations are the most commonly observed substitution of isoleucine with threonine or methionine, at position 38 (I38T/M) of the PA gene. This mutation has resulted in a decrease in the susceptibility of the virus to the drug. As discussed earlier, mutant viral particles when becoming resistant to BXM treatment like other medications can prolong the shedding of the virus. In addition to this, such individuals remain symptomatic for longer periods as well, as noticed about other drugs [9, 47]. The viruses with an I38 substitution have the relatively low capability of replication. This has been identified in various in-vitro studies. Moreover, viral transmissibility currently remains unknown and questionable [42]. The variability does exist with the type of mutation. Many other substitutions have been identified in the same enzyme, like PA N412D, V517A or P632S. However, such mutations have been shown to be ineffective in altering the susceptibility of BXM [9]. As extremes of ages is a significant contributor for complications resulting from Influenza infection, BXM is however approved for patients with uncomplicated Influenza infection. In the United States, patients above age 12 are indicated for prescribing the drug. Moreover, children age less than 12 but with a weight of 10kg or more can be given this medication in Japan [50]. The Center for Disease Control (CDC), recommends avoiding BXM in women who are pregnant or lactating. In addition to these facts, limited data is available for its use in patients who are hospitalized under 12 years or more than 65 years for its safety and efficacy. The adverse effect profile that should be taken into consideration with BXM is diarrhea, bronchitis, nasopharyngitis, nausea, and headache [51]. Every aspect of drug administration and side effect profile needs to be kept in consideration as this chemical is extremely high-cost regimen than the former NAIs.

Conclusion

BaloxavirMarboxil (Xofluza) is sure a wonder drug against Influenza, and it has miraculously proved to be a modern alternative against the conventional NAIs. It has effectively reduced the concern for increasing resistance of the Influenza virus to NAIs. Despite showing itself as a spectacular drug, more studies are needed to study its use in pandemics or epidemics as well as to answer questions about its safety and efficacy in the patients under 12 years and over 65 years of age, pregnant or lactating patients, and those with severe renal or hepatic impairment.

Conflicts of interests: None

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