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Oseltamivir against Influenza in Severe Acute Respiratory Infection (SARI): Review

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Abstract

Many viral diseases have been generating potential health issues to humans. Severe Acute Respiratory Infection (SARI), a disease of respiratory system, is one of them. Treatment of this disease is crucial factor to save human life using oseltamivir because it has been used by medical practitioners and received promising results. Diverse medicines are being investigated for the same purpose. In this review, we have examined the oseltamivir which is used against the infection in question for its efficiency.

Introduction:

In humanoid olden times, there were several cases of virus-related pandemic situations including polio [1], Ebola [2], smallpox [3], chickenpox [4] and HIV-AIDS [5] that placed hominoid life on severe hazard [3]. On the other hand, such sicknesses were eradicated via serum [6], cures [7] and prediction [8]. The stated infections were life-threatening and caused prospective biotic damage in the globe [9,10,11]. Of them, aerial and infectious illnesses [12] are extra difficult for people, and their prevention is challenging [13]. Viral communicable infections cause major illnesses and death in humans [14].

Lower respiratory contagions are the lethal transmissible infections, producing 3.2 million deaths universally in 2015 [14]. To fight with virus-related illnesses, serums and antiviral medications have been used mutually [14]. The acute respiratory contagions are the principal reason of deceases in early life stages all over the world [15] and give rise to 1.9 million deceases each year [16], of which 70 % occur in developing nations [17]. Additionally, it was responsible for 30% of all childhood deaths in the developing world [18].

Severe acute respiratory infection (SARI) is one of the principal reasons of deaths between young stages of life globally [19]. SARIs are termed as an acute respiratory illness of current arrival (in seven days) expressed by fever (≥38°C), cough and breathlessness necessitating hospitalization [20]. SARI is caused by both influenza and other viruses [21,22, 23], for example, respiratory synctial virus [21,23],

Parainfluenza subtypes 1, 2 along with 3 [21,22], bocavirus [22], Parainfluenza virus type 3 [22, 94], Piconavirus (EV/RV) [22], Adenovirus [19,21,22,23], Influenza A (H1N1) [22], Rhinovirus [19], Influenza B [93], Human metapneumovirus (hMPV) [22] and bacteria [21].

Hence, the effective treatment strategy of SARI becomes essential. In this review, we have investigated the oseltamivir drug for its efficiency against the influenza infection, one of the characters of SARI, since it has been used by medical practitioners and received promising results.

2. Treatment:

Treating influenza infection in SARI is one of the challenges in the medical fields. The judgement given by the clinician is the basis of criteria for the admission in hospital as well as treatment in general, and the admissions in hospitals are not always connected with severity [24]. Hence, employing a case definition is important [24]. In comparison, no scientific evidence of treatment against SARI was reported, and also, scientific case definition of SARI has not been provided.

The usual diagnosis of SARIs is conducted clinically and antibiotics are used for its treatment as per bacterial culture along with susceptibility tests with care that supports in the case where virus diagnosis facilities are unavailable [19]. Although, no scientific proof of specific antiviral drugs against SARI has been provided and according to Xuan C et al. [25] and Loeffelholz M et al. [26], antiviral drug oseltamivir is used against influenza but its properties and clinical applications against SARI has not been provided. Generally, the antiviral drug oseltamivir is used against various viral infections. GS 4104 (oseltamivir, TAMIFLU) has appeared as a guaranteed antiviral treatment as well as prophylaxis of infection by influenza in humans [77].

3. Properties and clinical applications of oseltamivir:

Oseltamivir (Tamiflu) is an antiviral drug which acts against influenza A and B [27]. To add, it creates obstruction in the function of viral neuraminidase protein [27]. Neuraminidase bearing influenza virus with reduced oseltamivir carboxylate sensitivity changed characters in vitro, and is compromised as far as infection is concerned in addition to the capacity of replication in vivo [43].There are some inhibitors that can be used to control viral infection by creating barrier in the life processes of virus.

In this sequence, neuraminidase inhibitors are able to reduce the symptoms caused by influenza including fever, head ache and myalgias within approximately 0.7 to 1.5 days if their administration occurred before 48 hours after infection [27] by inhibiting the viral release from cell (figure 1). In accordance with the current guidelines to treat pregnant women suffering from the influenza infection, one of the permitted neuraminidase inhibitors can be used [33].

Interestingly, viral neuraminidase of influenza A and B are selectively inhibited by oseltamivir carboxylate [27]. The production of oseltamivir was important success in medical field [27]. A fat soluble side chain of the active drug attaches to the neuraminidase enzyme, interrupting its capability to cleave sialic acid residues on the outer layer of the infected cell, causing an incapability to release progeny virus particles [28,29,30], hence viral natural life cycle gets disturbed.

After the infection by influenza virus, oseltamivir administrations are not able to interrupt the cellular immune responses [31]. Unfortunately, the Tamiflu has good clinical tolerance except insignificant gastrointenstinal upset [32] and therefore, more research work is required in the field of drug designing to engineer Tamiflu in such a way that gastrointestinal upset can be tolerated.

4. Pharmacokinetics and distribution:

As administration of oseltamivir in human body is considered, its fate in the body should be studied. Additionally, in the blood, gastrointenstinal tract along with the liver, oseltamivir ethyl ester that is to be administered orally is absorbed in a good way in addition to its cleavage with esterases speedily [27,33]. Then, it is finally converted to its active form oseltamivir carboxylate which is equally distributed all over the body, together with the upper and lower respiratory tract [27].

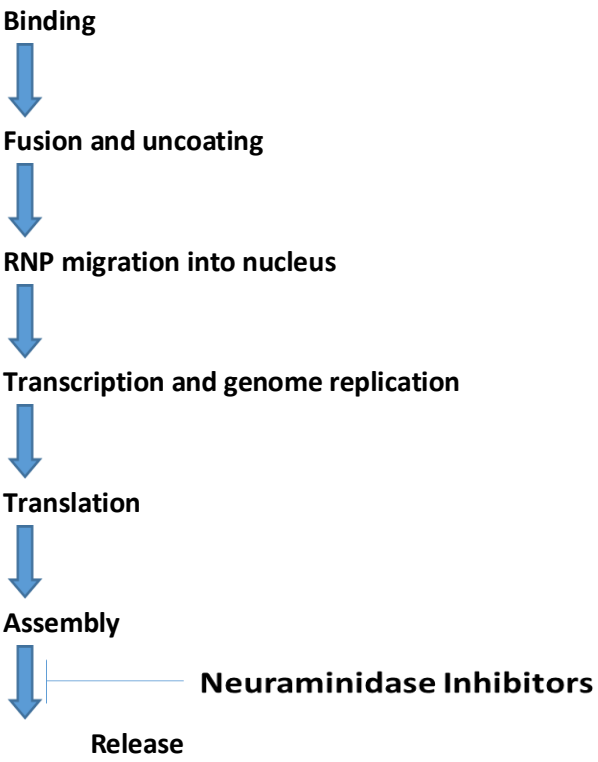

Figure 1: Target sites of the antiviral agents. Note: Reprinted from Beigel J I and Bray M [70] and modified by Tingre, G., & Dhakane, R. (2020).

5. Route of administration:

Oseltamvir can be delivered orally only in the form 75 mg, 45 mg and 30 mg tablets and white tutti-frutti flavoured suspension [33]. 75 mg two times a day for 5 days is approved dose of the medicine under study for adults [33].

6. Dosage:

The prescribed dosing of a medicine is very important to cure the disease successfully. Nevertheless, since active metabolite is observed in increased concentration, there is no requirement of the dosage adjustment [35]. Oe et al. [38] reported that it is compulsory to adjust the dose with help of increasing 2 mg/kg two times daily because the clearance rate of metabolite which was active was faster in younger than adults. This indicates that there are opposite opinions among the researchers regarding dosage adjustment of oseltamivir and hence, this area demands further scientific investigation.

Likewise, the drug is contraindicated among younger owing to its toxicity [38] which may be serious issue among the patients with respect of their health to treat disease. The combined efforts are recommended to be taken from global researchers to resolve the appeared contraindication and make the drug safe for use by younger patients. The common dose of oseltamivir can be lowered to 75 mg one time a day in order to achieve treatment as well as either 75 mg each other day or 30 mg suspension everyday for prophylaxis when a patient has a creatinine clearance of <30 mL/min [33]. Besides, doses are recommended to be given after hemodialysis [33].

However, in case of pregnant women, some studies indicated the requirement of higher doses of oseltamivir (75 mg TID) while other studies suggest that there was no need of adjustment of dose [63, 64, 65]. Making the treatment dose of oseltamivir double, the patients who are hospitalized does not show virologic efficacy increase with exception for infections by influenza B or clinical effectiveness even if one ICU based RCT suggested that making the standard dose triple was connected with the increase of clearance of viral RNA from the tract of respiratory system [66, 67, 68].

7. Prophylaxis:

The drug oseltamivir showed promising results when used practically in the patients suffering from the influenza infection. If administered in the time less than 48 hours, it showed affectivity against the infection under study [27]. 33 volunteers were treated with the drug in question (8/21 volunteers) or placebo (8/12 volunteers) for 5 days with a dose as 100 mg orally [27]. As well, it is considered to prevent the influenza infection in the patients of more than or equal to one year with dosing pattern as once in a day [33]. What is more, the effectiveness of oseltamvir with dose as 75 mg once daily for 6 weeks in the process of preventing influenza infection in healthy as well as non-immunized adult was reported as 84%, and it was 50% in the process of preventing infections by influenza regardless of symptoms [34]. In the residents of immunized nursing home, the prophylaxis efficacy was 92% against ill health as compared to placebo [39].

In a prophylaxis study of household-contact, fairly lower efficacy was observed [40]. Further, approximately 80% protective efficacy was reported in relation with seasonal prophylaxis of patients with

high-risk immune compromising pattern against influenza illness which is confirmed by RT-PCR [41]. Fortunately, Hayden et al. 1999 [42] examined not only safety but also efficiency of oseltamvir in the adults with the ages in the range of 18-40 years. Authors reported that 74% of all volunteers were protected by oseltamivir against influenza A [42].

As a conclusion, both trials indicated that in adults, oseltamivir was not only safe but also effective to prevent the influenza infection. The risk of developing influenza was reduced by 70-90 % showed by meta-analysis study of seven prevention trials [37]. However, since the prophylaxis results into the resistant mutants, the precaution should be taken while prescribing oseltamivir in patients who exposed with an index case for prophylaxis [44]. As a result, generally, monitoring is required in these cases [33].

8. Chemoprophylaxis:

Unfortunately, there is unavailability of reference to administer oseltamivir before infection prophylaxis by HIN1 for the influenza virus of the swine [27]. As soon as confirmation of H1N1 infection, chemoprophylaxis should be provided and continued for 10 days subsequent to the last diagnosis [27].

9. Merits:

In order to alleviate the non-complicated influenza illness, oseltamivir (75mg two times a day for 5 days) makes the time short with reduction of illness severity, fever duration, time required to reach at normal activity, viral shedding quantity, impaired activity duration, complications resulted due to antibiotic use especially bronchitis, compared to placebo in earlier healthy adults [45, 46, 47]. Also, oseltamivir showed effectiveness up to 72 hours after onset of symptom in children in Bangladesh [48]. The paediatric studies that included children of 2 weeks old showed that oseltamivir was not only safe but also it reduced duration and illness significantly along with the time required to resume the complete activities as well as existence of complications due to antibiotic use [49-53].

Furthermore, observational studies provided the major part of existing literature based on the efficacy as well as safety of oseltamivir in high-risk or elderly persons involving those who were suffered from immunodeficiency or cardiopulmonary conditions [54-57]. Among such hospitalized and high risk members, there was a benefit if antiviral therapy started at least 5 days and within 48 hours after onset of symptoms [58]. Likewise, the studies of adults who are hospitalized suggest that the early therapy reduced the occurrence of complications of lower respiratory tract, duration of illness, ICU-level care requirement and duration of mortality and shedding [45, 46, 56, 57, 59]. This clearly admits the value of early treatment of the infection to eradicate it easily.

10. Adverse reactions:

Oseltamivir is not exceptional among the drugs that show side effects on the body. It is connected with abdominal discomfort, nausea and emesis (less often) in the minority of the treated patients [33]. To add, in oseltamivir recipients, both vomiting and nausea exist at about 10-15 % higher frequency [33]. In contrary to this, the reports of post marketing show that oseltamivir may be connected not often with the skin rash, thrombocytopenia or dysfunction [33]. However, rash, swelling of face or tongue, epidermal necrolysis which is toxic, tests of abnormal liver function, hepatitis, seizures, arrhythmias, confusion aggravation of diabetes are other reported adverse effects [69]. Thus, the adverse effects of oseltamivir cause health concern to the patients.

Besides, there are reports of not only abnormal neurologic but also behavioural characters that have hardly ever resulted into deaths among mostly children and many of these reports arrived from Japan [33]. The pregnant women infected by influenza got clear therapeutic benefit due to oseltamivir which is safe [60, 61, 62].The available data suggest that such events are secondary to infections by influenza than oseltamivir therapy [71, 72]. Besides, steady-state pharmacokinetics of generally used immunesuppressive agents is not affected by oseltamivir [73].

Additionally, cementadine inhibitor of cytochrome P450 has no effect on the plasma levels of oseltamivir carboxylate or oseltamivir [27]. With no any modification in dose, renal excretion rate of oseltamivirmay be controlled with help of Probenecid [74]. Oseltamivir might impair immunogenicity of

concurrent intranasal influenza vaccine which is live attenuated [33]. Unless the potential advantage justifies the risk (potential) to the foetus, the oseltamivir prescription in the pediatric patients with ages less than 1 year should be avoided [75].

11. Resistance:

Developing resistance against medicaments is a natural process of life. Likewise, many strains of H1N1 influenza A virus responsible for pandemic were sensitive to neuraminidase inhibitors i.e oseltamivir as well as zanamivir [27]. Oseltamivir resistance is connected with NA mutations E119, H274Y, R292K and R152K [76]. Even if the R292K neuraminidase mutation give resistance at high level to GS 4071 (neuraminidase inhibitor) in vitro, its effect on the virulence by viruses render this mutation with limited clinical significance [78]. Following oseltamivir phosphate treatment, the H274Y mutation found in the influenza A/H1N1 neuraminidase active site leaves the viruses compromised severely both not only in vivo but also in vitro [79].

The NA inhibitors show their activity against many influenza A and B viruses and cause lesser side effects, however, the generation of resistance against oseltamivir by various influenza viruses has been reported [81]. For example, with rare incidences of limited transmission, H1N1 virus infections which are sporadic have been reported in 2009 [80,83,84,85]. In reality, H1N1 virus strains which are oseltamivir resistant emerged within 48 hours after starting of treatment [86].

The rare occurrence of spread of influenza B virus strains that are resistant to oseltamivir or 2009 H1N1 virus strains received from persons treated by oseltamivir was reported and clinical isolates with lowered susceptibility to zanamivir were obtained irregularly from immunocompromised children after prolonged therapy [87, 88, 89, 90]. During the treatment of influenza which is seasonal, the development of resistance against oseltamivir or zanamivir has been detected [91,92]. For management of the disease, the data related with variables connected with the disease was obtained including requirement of non-invasive and invasive mechanical ventilation, vasoactive drugs, corticosteroid use (inhaled or systemic), prescription of antibiotic compounds and antiviral oseltamivir [93].

12. Conclusion:

Oseltamivir is a suitable drug to treat influenza infection that occurs in the patients who suffer from Severe Acute Respiratory Infection (SARI) with exception of some adverse effects. Future research may include investigation of oseltamivir effect against viruses other than influenza which are involved in SARI although individual treatments against them were practiced with no aim to treat SARI.

Competing interest:

Authors declare that no competing interest exists among them.

Ethical Statement:

Since it is review article, no ethical permission required.

Author contributions:

GT: Wrote manuscript, RD: Developed an idea and verified the data

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