Commentary

Tamiflu – What we Know About its Ups and Downs

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Abstract | The pros and cons of the anti-influenza drug oseltamivir (Tamiflu®) have been intensely debated lately. This article aims to sum up what is known about positive and negative effects of the drug. The available data suggests that oseltamivir treatment of uncomplicated influenza in otherwise healthy patients shortens influenza symptoms with approximately 24 hours, and increases nausea and vomiting by 3-5%. Whether oseltamivir treatment has an effect on the frequency of influenza complications or not remains controversial. Oseltamivir is still standard as prophylaxis, treatment of severely ill patients and patients with risk factors for severe influenza disease as well as an important part of pandemic preparedness plans. Resistance development is a potential problem both in treated humans and in the environment. The use of oseltamivir for treatment of uncomplicated influenza in otherwise healthy patients should be questioned.

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Oseltamivir (sold as Tamiflu® by Roche) is a neuraminidase inhibitor (NAI), i.e. it inhibits the viral enzyme neuraminidase (NA) that cleaves sialic acid and thus counterbalances the adhesive properties of hemagglutinin (HA). NA is especially important when newly formed virions are to be released from the host cell, but also to cleave bonds to mucoproteins produced as decoys by the host in the mucus of the airways. Oseltamivir is administered orally as the prodrug oseltamivir phosphate, which is rapidly converted to the active metabolite oseltamivir carboxylate (OC) by esterases in the human body. OC has a poor bioavailability which is the reason for the use of a prodrug. There are also other NAIs on the market such as zanamivir, peramivir, and laminamivir, but oseltamivir has been mostly used, mainly because of its convenient oral formulation. The effect of oseltamivir is better when treatment is started early in the course of infection, partly because the drug does not stop virus particles to infect and destroy host cells, but stops the formation of viral progeny. Thus, if the viral load in the host is already high, the benefit of treatment is much smaller.

Recently, the effect of oseltamivir in uncomplicated influenza infections has been in the focus of debate. The discussion was sparked by a Cochrane review by Jefferson et al. (2014). In this review, the authors had gotten access to previously unpublished trial data from Roche regarding effects and side effects of oseltamivir in healthy adults and children. They found that oseltamivir reduces time to alleviation of influenza symptoms by 17 hours for adults and 29 hours for children – except children with asthma in whom the reduction was non-significant. Side effects, significantly more common than in the placebo group, were nausea and vomiting among adults (3.7% and 4.6% risk difference (RD) respectively) and vomiting

among children (5.3% RD). Oseltamivir reduced the risk for self-reported pneumonia (1.0% RD) but the authors questioned the validity of this outcome and no significant effect was seen in five trials that used a more detailed diagnostic form for pneumonia. No significant reduction in the risks for hospitalizations, serious influenza complications, bronchitis, sinusitis, or otitis media was observed. According to the authors, several studies in the review contained selection bias, performance bias, attrition bias and/or selective reporting. The authors question oseltamivir's place in the treatment arsenal, and state that "the influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence". The conclusions of Jefferson et al. (2014) was widely questioned, for example in a review by Dobson et al. (2015). In this review, the authors used the same studies as Jefferson, but looked at individual patient data instead of study reports, and furthermore only included adults in the analysis. Dobson et al. (2015) found a 25-hour reduction in time to alleviation of symptoms, and similar increases in frequencies of side effects as Jefferson (nausea 3.7% RD, vomiting 4.7% RD). Furthermore, the authors found significant decreases in prescription of antibiotics for respiratory tract infections more than 48 hours after diagnosis (3.8% RD) and hospital admission of any cause (1.1% RD). However, as the authors themselves point out, these are indirect measures of influenza complications and should be interpreted with caution. The funding for Dobson et al. (2015) came from Roche through the organization Multiparty Group for Advance on Science, and although it is stated that Roche did not have any influence on the review, the funding situation has raised some concerns. Although opposite conclusions were drawn in the reviews of Jefferson and Dobson, the results as such are not that different. Taken together, current evidence suggests that oseltamivir shortens the duration of influenza symptoms in uncomplicated disease by approximately 24 hours and that nausea and vomiting are increased by 3-5%. Whether oseltamivir treatment of uncomplicated influenza infection results in a reduction of influenza complications or not is still controversial.

In influenza patients with underlying diseases and severely ill patients, the benefits of oseltamivir is much less debated. Oseltamivir is standard treatment of severely ill patients in most countries and has demonstrated positive effect in hospitalized influenza patients (Lee et al., 2010; McGeer et al., 2007). Although early initiation of oseltamivir treatment is important, and good clinical results have been demonstrated (Heinonen et al., 2010), the immunosuppressed and patients with a severe influenza infection may benefit also from a delayed start of oseltamivir treatment, possibly due to prolonged viral replication. Considering the mode of action of oseltamivir and the positive findings in early treatment, oseltamivir prophylaxis is an attractive option, and it is largely used globally both as post exposure prophylaxis in vulnerable patients and as part of pandemic preparedness plans. However, the scientific evidence for prophylaxis has weaknesses as pointed out by Jefferson (Jefferson et al., 2014).

Resistance development to oseltamivir is a concern, and was observed already in early studies in volunteers (Gubareva et al., 2001). Due to the localization of resistance mutations in or near the active site of NA, resistance was expected to result in decreased viral fitness. However, the global spread of an oseltamivir-resistant seasonal influenza A/H1N1 strain 2007-2009 without relation to oseltamivir use (Moscona, 2009) exemplified that resistance does not always result in fitness loss. At a molecular level, it has been demonstrated that several mutations can have a compensatory function, and restore NA activity caused by a resistance mutation (Abed et al., 2009; Bloom et al., 2010). Thus, resistance can prevail in human strains if induced in a virus with a suitable genetic makeup.

Another resistance scenario takes place in the environment. Oseltamivir's active metabolite OC is stable in water and sewage treatment processes (Fick et al., 2007), and will finally enter rivers and other waterways receiving sewage discharge. OC has been detected at up to 865 ng/L in river water (Takanami et al., 2010). Dabbling ducks constitute the main natural reservoir for influenza (Olsen et al., 2006), and often reside in rivers. Influenza virus is very well adapted to dabbling ducks and replicates in the epithelial cells in the gastrointestinal tract. In the aquatic environment close to outlets of sewage treatment plants, OC and replicating influenza virus can thus co-exist in the intestines of dabbling ducks, potentially enabling resistance development. It has been demonstrated that influenza viruses of subtypes H1N1, H5N2, and H6N2 infecting mallards subjected to 1-12 μg/L of OC in their water develop oseltamivir resistance (Gillman et al., 2013; Järhult et al., 2011; Achenbach and Bowen, 2013). If an oseltamivir-resistant influenza virus

is established in the pool of influenza viruses circulating among wild birds, there is a risk of transfer to humans either via assortment (the route of the last four influenza pandemics (Guan et al., 2010)) or by direct transmission (exemplified by highly-pathogenic H5N1 avian influenza). Experimental data indicates that once induced in an influenza A/H1N1 virus, resistance can persist without drug pressure (Gillman et al., 2015). An oseltamivir-resistant influenza virus capable of transmitting and causing severe disease among humans is a frightening scenario, as oseltamivir is a cornerstone in pandemic preparedness plans world-wide, especially in the first phase before vaccines can be mass-produced (Nguyen-Van-Tam et al., 2014). Billions of Tamiflu capsules have been stockpiled globally (Wan et al., 2009), and they would be useless during an outbreak of oseltamivir-resistant influenza.

In conclusion, oseltamivir constitutes an important treatment option for severely ill influenza patients and for patients with underlying risk factors. Oseltamivir is also a cornerstone of pandemic preparedness plans worldwide, both as treatment and as prophylaxis. However, oseltamivir has a modest effect in uncomplicated influenza and carries substantial side effects. Furthermore, there is a potential for resistance development in treated patients and in the environment. Therefore, the use of oseltamivir for treatment of uncomplicated influenza infection in otherwise healthy patients should be questioned.

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