Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains

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The current outburst of a new H1N1 swine influenza strain(s) in México and the United States is causing great concern in health authorities and in the general population [1]. With the World Health Organization (WHO) reporting the pandemic potential of the new strain, it is necessary to determine which therapeutic options are available until a specific vaccine is available. Based on information from the Centre for Disease Control (CDC), the virus is sensitive to oseltamivir and zanamivir. Antivirals are strongly affected by viral mutations; thus their efficiency could be lost as the virus changes.

The cytokine hypothesis proposes that the host immune system and autoinflammation is the main cause underlying respiratory distress in severe cases of influenza. The "cytokine storm" is a consequence of disregulated immune responses to the virus [2]. Influenza virus employs human signaling pathways to replicate, interfering with normal cell physiology and leading to undesired effects such as overinduction of cytokines and chemokines. Host intracellular signaling pathways or host immune mediators, blocked by immunomodulatory drugs, are not affected by viral mutations and therefore may be suitable targets for treating severe influenza patients. A wide range of immunomodulatory drugs have been proposed for influenza treatment, but there is limited experience in their use in this context [3,4].

Macrolides are molecules with antibacterial activity that also have remarkably anti-inflammatory properties. Macrolides exert both stimulatory and inhibitory effects on leukocytes. These effects seem to be related to the activation state of the leukocytes, facilitating bacterial killing as well as resolving local inflammation [5]. The benefits of macrolides for treatment of community-acquired pneumonia appear to be mediated by both anti-bacterial and non-antibacterial properties [6]. Recent research of the immunomodulatory properties of azithromycin implies that azithromycin may have a previously unknown short-term biphasic modulatory effect on inflammation. It enhances host defence mechanisms shortly after initial administration followed by inhibition of local infection/inflammation at a later period [7]. Sato *et al*. demonstrated that administration of erythromycin at a dose of 3.3 mg/kg/d (intraperitoneally, from Days 1 to 6 after infection), significantly improved the survival rate of mice infected with a H2N2 influenza virus [6]. Erythromycin significantly decreased interferon gamma (IFNg) in infected lungs and decreased the number of inflammatory cells recovered in lung lavage fluid 6 d after virus infection. The treatment also resulted in a dose-dependent decrease in the level of nitrite/nitrate (metabolites of nitric oxide, NO) in the serum and the NO synthase (NOS)-activity in the lungs of the virus-infected mice.

Tsurita *et al*. showed an early augmentation of interleukin (IL)-12 levels in the airway of mice administered orally with clarithromycin, resulting in alleviation of influenza infection [8].

Clarithromycin has been successfully used in a clinical study in respiratory syncytial virus bronchiolitis in children [9]. Treatment with clarithromycin was associated with a statistically significant reduction in the length of hospital stay, the duration of need for supplemental oxygen, and the

need for beta2-agonist treatment. There were significant decreases in plasma IL-4, IL-8 and eotaxin levels after three weeks of treatment with clarithromycin. Readmission to the hospital within six months after discharge was significantly lower in the clarithromycin group.

Ninomiya reported beneficial effects of macrolides on the resolution of symptoms, duration of illness and complications in children with pneumonia and influenza [10].

Inmunomodulation by using steroids was extensively employed during the SARS Coronavirus outburst in 2003, with controversial results. Treatment with corticoids translated into some beneficial effects in most of the studies reported, but maintained doses of steroids could lead to bacterial infection and sepsis [11]. Macrolides could be safely employed for immunomodulatory purposes since these drugs do not pan-immune-suppress. Furthermore, it could be used to prevent secondary infections by bacteria in those patients severely affected by the novel H1N1 viruses, such as A/California 04/09 and similar strains. Leelarasamee *et al*. reported a case of rapidly progressing H1N1 influenza improving with a combination of oseltamivir and clarithromycin [12].

Clarithromycin inhibits the middle to late stage of the influenza virus replication cycle, resulting in inhibition of progeny virus production from the infected cells [13]. Macrolides could mediate this effect by inhibiting intracellular hemagglutinin HA0 proteolisis [14]. The inhibitory effects on influenza virus replication of macrolides has been known since the 80s [15] and have been observed for other viruses such as Sindibis virus [16]. Other drugs such as statins and Pentoxifylline might have beneficial effects in the treatment of severe influenza, but there is much less information available on their efficiency profiles in the treatment of influenza infection [17,18].

We propose here to utilize macrolides in the treatment of severe disease caused by the novel H1N1 swine flu reassortment influenza viruses now circulating in Mexico, the United States, Canada and other countries. We propose macrolides be used in combination with antivirals, in order to diminish the systemic inflammatory response leading to pneumonia and fatal outcome.

Macrolides are easily accessible: they are used in the hospitals of both developed and developing countries to treat bacterial infection; they are relatively cheap; and they show a good toxicity profile. Administration could be employed on the basis of a clinical score including high fever, chest X-Ray images and O2 saturation as predictors for disease outcome.

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