An update on the prevention and treatment of influenza infection

Influenza poses a heavy burden to the global and local health services. Every year, it causes substantial morbidity and mortality, especially among high-risk populations with weakened immunity, in elderly people, very young children, and people with chronic illnesses. WHO estimates that seasonal influenza causes 250,000–500,000 deaths worldwide every year. In the year 2014–15, the antigenically drifted influenza A/Switzerland/9715293/2013 (H3N2)-like virus caused major outbreaks in Europe and North America. More recently, in the year 2018, 80,000 people died from H3N2 infection and its complications, which was highest in the last 3 decades. Moreover, avian influenza viruses, such as influenza A H5N1 and H7N9 are associated with even higher mortality. Therefore, any strategy that could improve and expand the antigenic breadth of the protective immune response from influenza vaccination would be especially important in an outbreak setting. New antiviral and other treatment strategies are also important in the management of patients hospitalized for severe influenza infection.

The best way to prevent influenza infection is by annual influenza vaccination. Nevertheless, the efficacy of influenza vaccination has been variable depending on whether the circulating influenza strain matched the predicted vaccine strains and also on the uptake rate. Furthermore, influenza efficacy in the elderly population is far from satisfactory due to their immunosenescence status. Various methods including high dose and adjuvanted influenza vaccination, intradermal influenza vaccinations have been shown to improve the vaccine efficacy. Improving the children vaccination rate has also been shown to provide herd immunity in the prevention of influenza infection in the elderly.

Recently, our team has successfully translated our study, first from mouse models to a study of elderly patients and then to a study of young healthy subjects, given trivalent influenza vaccine after imiquimod pretreatment. Both the elderly and the young adults studies showed a significantly expedited (at day 7, normally day 21) and improved immunogenicity. Importantly, our study in the elderly population showed that imiquimod improved clinical protection from subsequent hospitalized influenza infection, emphasizing the clinical relevance of these findings, especially in this vulnerable population. Furthermore, this improvement in immunogenicity was achieved without an increase in adverse events, both in the young and elderly subjects, suggesting that topical imiquimod pretreatment before influenza vaccination is safe and well tolerated.

An even more important novel finding of the later study in the young subjects is the occurrence of cross-protective immune responses after topical imiquimod pretreatment and intradermal influenza vaccination against heterologous non-vaccine influenza strains. Enhanced immune responses were detected against not only the vaccine strains of A/California/H1N1, A/Victoria/ H3N2 and B/Massachusetts (B/Yamagata lineage) strains in the vaccine, but also against non-vaccine strains (the newly antigenically drifted A/Switzerland/9715293/2013-like influenza strain, A/WSN/1933[H1N1], prepandemic seasonal H1N1 and the B/Victoria lineage). In comparison to the elderly subjects, seroconversion was more pronounced in the young subjects, confirming the reduced vaccine
responses secondary to immunosenescence or immunosuppressive medications.

In the treatment of influenza infection, oseltamivir, a neuraminidase inhibitor, has been the predominant antiviral used for the past decade. Nevertheless, it’s effect is limited by the time of patient’s presentation and meta-analyses were unable to demonstrate oseltamivir treatment reduce the risk of hospitalization or death in high risk population. The new antiviral baloxavir marboxil, an endonuclease inhibitor, however, has demonstrated promising results with significantly better influenza virus suppression and clinical outcome when compared with oseltamivir treatment in outpatient setting. Further trial is underway for treatment of hospitalized patients.

Other treatment modalities have been studied including the use of convalescent plasma and hyperimmune intravenous immunoglobulins (H-IVIG). Studies performed by our team for treatment of severe H1N1 2009 infection in 2009-2010 have demonstrated that both convalescent plasma and H-IVIG could reduce mortality and shorten hospitalization by suppressing the viral load and cytokine/chemokine in patients hospitalized for severe influenza infection. Such findings were confirmed by a multi-centre trial performed in the US. Other treatment modalities by studies from our team and others have included the use of combination treatment of oseltamivir with NSAIDs, clarithromycin, COX-II inhibitors and other immunomodulators with variable success.

In this lecture, I will summarize the latest development in both influenza vaccination and antiviral treatment.