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Editorial

An Update on Therapeutic Strategies for Influenza

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1. Introduction

Seasonal influenza is a common acute respiratory viral infection with an estimated one billion cases annually, of which 3–5 million are severe cases responsible for 290,000 to 650,000 deaths each year [1]. The influenza virus, belonging to the family *Orthomyxoviridae*, has 4 different types (A to D) of which A, B and C are known to infect humans [2]. Influenza A and B are of public health importance being responsible for seasonal influenza whereas influenza C is rare usually causing a mild upper respiratory tract infection. Influenza A viruses are further classified into subtypes according to their haemagglutinin (H) and neuraminidase (N) surface proteins; amongst humans *H1N1* and *H3N2* are the predominantly circulating influenza A virus subtypes.

Globally, neuraminidase inhibitors (NAIs) such as oseltamivir and zanamivir have been the mainstay of treatment for influenza A and B for over a decade following the emergence of high resistance rates to the previously used adamantanes (amantadine and rimantadine) in the early 2000s [2]. Influenza resistance rates to NAIs have remained very low (<2%) since their introduction and resistance has therefore not been a major issue with NAI use thus far. In the very rare instances where NAI resistance has been identified, this has mostly been in immunocompromised patients infected with influenza A *H1N1* (with resistance to influenza A *H3N2* or B being even rarer) and these oseltamivir-resistant variants mostly remain susceptible to zanamivir [2].

2. Antivirals Recommended in the UK for the Treatment of Influenza

Influenza antiviral treatment is recommended for all individuals with severe influenza and also for those with non-severe influenza who have risk factors for severe disease [3]. There are currently 2 classes of antivirals licensed in the UK for the treatment of seasonal influenza; NAIs (targeting the neuraminidase glycoprotein on the surface of influenza viruses) and the more recently licensed cap dependent endonuclease inhibitor Baloxavir marboxil (targeting the polymerase acidic [PA] protein of influenza viruses) [3]. Both antiviral classes are generally considered safe although baloxavir is not recommended for use in pregnant women due to a lack of safety data. The oral NAI, oseltamivir, is recommended as first line treatment for influenza for a duration of 5 days although it can be given for up to 10 days in the severely immunosuppressed in view of potentially prolonged viral shedding. Where oseltamivir cannot be administered, inhaled or intravenous (IV) zanamivir is an alternative.

Several studies, albeit with varying degrees of certainty, have demonstrated that NAIs (versus placebo or standard of care) for patients with influenza reduce symptom duration, risk of lower respiratory tract complications, hospital admission rates and risk of death with the greatest mortality benefit seen when administered within 48 hours of symptom onset [2,4]. In the event of poor clinical response to first line treatment with oseltamivir, switching to zanamavir or adding baloxavir marboxil can be considered, taking into consideration that in the absence of oseltamivir resistance (which is rare), robust evidence to support either of these strategies is lacking.

Baloxavir, given as a single oral dose, has demonstrated superior efficacy to placebo and similar efficacy oseltamivir at reducing symptom duration in adults and adolescents with uncomplicated influenza A or B, although variants with reduced susceptibility to baloxavir emerged following treatment in up to 10% of patients [5]. Trials of baloxavir monotherapy in severe influenza are lacking.

3. Other Influenza Antivirals

Peramavir, another NAI (approved for use in the United States), is given as a single IV dose and is an alternative to oseltamivir where enteral administration is not suitable. However, peramivir does not retain activity against influenza A *H1N1* strains with reduced susceptibility to oseltamivir (most commonly due to the neuraminidase *H275Y* mutation) whereas zanamivir typically remains active against these oseltamivir/peramivir-resistant strains [2,6]. Laninamivir is a long-acting inhaled NAI with similar activity to zanamivir and is approved for use in Japan and South Korea [6].

Favipiravir is an oral and IV antiviral which inhibits RNA polymerases and is approved for the treatment of influenza in Japan although not first line and with strict regulations on its use [6]. Of additional note is that favipiravir does not reliably reach therapeutic concentrations in all individuals. Molnupiravir, another RNA polymerase inhibitor, was in preclinical development for use against in-

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fluenza before being redirected for use against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the coronavirus disease 2019 (COVID-19) pandemic [6]. Potent activity against influenza A viruses has been demonstrated in preclinical models and the results of ongoing human trials are awaited (NCT05818124 and NCT05648448).

Onradivir is an inhibitor of the PB2 subunit of influenza A virus polymerase and given its differing mechanism of action, it serves as an alternative agent for oseltamivir-resistant and baloxavir-resistant strains. A phase 3 trial has recently demonstrated safety of onradivir with a similar clinical efficacy to oseltamivir for uncomplicated influenza [7]. However, of concern is the high incidence of adverse effects associated with its use, particularly diarrhoea, which was reported in 49% of participants who received onradivir. In May 2025, onradivir was approved in China for the treatment of uncomplicated influenza A in adults.

4. Combination Antiviral Treatment

Theoretically, co-administration of influenza antivirals with differing mechanisms of action could be advantageous in curtailing viral replication in severe infection, particularly in immunosuppressed individuals who may have an increased and/or prolonged viral burden. The synergistic activity of various combinations of antiviral agents including oseltamivir-baloxavir, amantadine-oseltamivir-ribavirin (known as the triple combination antiviral drug [TCAD] regimen) and MS-257 (an experimental oseltamivir-zanamivir hybrid inhibitor) has been demonstrated against influenza *in vitro* and in murine studies [4]. However, human trials of these various antiviral combinations have not conclusively demonstrated improved clinical outcomes [2,4,8].

The recent Flagstone trial, in which baloxavir was combined with standard of care (NAI therapy) for hospitalised patients with severe influenza, found that combination therapy did not improve clinical outcomes compared to NAI monotherapy [8]. However, a post hoc analysis demonstrated significantly lower mortality (2.17% vs 11.76%, $p = 0.02$) in the dual antiviral group (baloxavir plus NAI, n = 92) vs the NAI monotherapy group (n = 51) in patients who met at least 1 of the following criteria: immunosuppression, diabetes or chronic lung disease [9]. Additional studies are needed to confirm these findings and further elucidate which specific groups, if any, may benefit from baloxavir plus NAI combination therapy.

5. Monoclonal Antibodies

Influenza monoclonal antibodies (mAbs) may be of particular benefit in immunocompromised individuals who respond less well to vaccines and who are at greater risk of severe disease. MHAA4549A, a human mAb targeting the influenza A hemagglutinin stalk, has been shown to neutralise influenza A virus in animal and human volunteer challenge studies [10,11]. A phase 2 randomised, double-blind, placebo-controlled trial in adult outpatients with uncomplicated influenza A found that MHAA4549A was safe but did not improve clinical outcomes [12]. A range of other anti-influenza mAbs have been evaluated in pre-clinical and clinical studies but with mixed results in terms of efficacy [13]. Future hurdles with influenza mAb development will be maintaining activity against circulating influenza virus strains, which through antigenic shift and drift will vary across different influenza seasons.

6. Corticosteroids and Other Immunomodulators

In some individuals with severe influenza, a cytokine storm occurs characterised by excessive proinflammatory cytokine production and aggressive proinflammatory responses, which can lead to acute respiratory distress syndrome (ARDS). Meta-analyses have reported that corticosteroid use was associated with increased mortality in patients with influenza pneumonia (with and without ARDS) as well as a higher incidence of nosocomial infection [14,15]. Corticosteroids are therefore not currently recommended in influenza. The specific role of low-dose corticosteroids in influenza is unclear and aiming to address this is an ongoing double-blind, placebo-controlled randomized controlled trial (RCT) in Spain evaluating the safety and efficacy of dexamethasone (6 mg/day) plus oseltamivir vs placebo plus oseltamivir in patients with severe influenza (NCT06528444).

Celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, has been shown to improve outcomes and survival in murine studies of influenza but the results of human trials are awaited [16]. Other immunomodulators including mesalazine, sirolimus, chloroquine and pamidronate have also been investigated but none have conclusively been shown to be of benefit [16].

Lastly, passive immunotherapy with IV immunoglobulin (IVIG) has shown promise in preclinical and small clinical studies [16]. However, an international RCT of anti-influenza hyperimmune IVIG (given as a single infusion) plus standard of care (most commonly oseltamivir) vs placebo plus standard of care for adults hospitalised with influenza A or B found that IVIG did not improve overall clinical outcomes [17].

7. Treatment of Secondary Bacterial Infection

Routine empirical antibiotic use is not recommended in influenza. However, clinical deterioration despite antivirals with a corresponding rise in serum neutrophil count and/or C-reactive protein, and evolving chest imaging features such as new lobar consolidation, should raise concern for secondary bacterial infection (*Streptococcus pneumoniae* and *Staphylococcus aureus* being the most common culprits). Early recognition of secondary bacterial pneumo-

nia can be challenging and unfortunately serum procalcitonin (PCT) levels, considered to rise in bacterial infection, have shown very limited clinical utility in this setting [18].

8. Conclusion

NAIs remain the cornerstone of treatment for influenza and resistance rates remain very low. Baloxavir is a welcome addition to the repertoire of influenza antivirals in view of its differing mechanism of action and requiring only a single oral dose. However, concerns regarding treatment-emergent resistance and its higher cost may limit its current use. Further studies are required to establish whether dual therapy (NAI plus baloxavir) may be of benefit in individuals at higher risk of severe influenza. Corticosteroids and other forms of immunomodulatory therapy are not generally recommended.

Key Points

• Neuraminidase inhibitors remain the mainstay of treatment for influenza and resistance rates remain low.

• Currently there is no clearly defined role for combination antiviral therapy in the treatment of influenza (particularly in the absence of antiviral resistance).

• Corticosteroids and other immunomodulators are not generally recommended in the treatment of influenza.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualisation by TL. Investigation by NP and TL. Writing—original draft by NP and TL. Supervision by TL. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

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