

## Finding the right combination antiviral therapy for influenza

Influenza results in annual epidemics and global pandemics of acute respiratory illness that increases morbidity, mortality, and hospital admissions. Fortunately, there are currently two classes of antivirals licensed for the treatment of influenza in much of the world: the M2 inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir, peramivir and zanamivir). There are also other antivirals licensed in Asia (laninamivir and favipiravir) and Russia (umifenovir). Additionally, a wide range of novel antivirals have been or are being studied in the treatment of influenza.<sup>1,2</sup> Available therapies reduce the duration of clinical symptoms and duration of viral shedding.<sup>3</sup>

Despite the expanding number of available treatments, there are limitations to our current antivirals for influenza. Decay in viral shedding with the use of current antivirals is modest at best, clinical improvement is better the earlier the antiviral is started relative to onset of symptoms, and resistance is a constant threat. Resistant variants of influenza virus could be detected frequently during the use of M2 inhibitors. Widespread circulation of M2 inhibitor resistance emerged in 2003–04 and is currently established in all circulating influenza A strains.<sup>4</sup> All influenza B viruses are intrinsically resistant to the M2 inhibitors. Neuraminidase inhibitor resistance can emerge from changes in the neuraminidase gene, the haemagglutinin gene, or both genes.<sup>5</sup> Although most circulating strains of influenza remain susceptible to the neuraminidase inhibitors, emergence and persistence of resistance can occur, which was clearly shown with the emergence and global circulation of oseltamivir resistance, due to the His275Tyr mutation, in seasonal influenza A H1N1.<sup>6</sup>

One approach to improving the outcomes of infections and to mitigate resistance emergence is to make use of antiviral combinations.<sup>7</sup> Although a number of combinations have been studied in vitro and in animal studies, not all combinations have shown consistent additive or synergistic activity. Several clinical studies have been done to better define the efficacy of combination antivirals. One of the earliest studies<sup>8</sup> combined oral rimantadine with placebo or nebulised zanamivir. Because of enrolment challenges, the study

was ended prematurely with only 41 of the intended 100 participants enrolled. The combination therapy was found to have a trend to less cough (55% in the intervention group vs 94% in the control group) on day 3 of treatment and to result in less frequent detection of rimantadine-resistant virus during therapy (0 of 20 vs 2 [10%] of 21). Oseltamivir and zanamivir monotherapy was compared with a combination of the two neuraminidase inhibitors in a study of 541 participants.<sup>9</sup> The study found that the oseltamivir-zanamivir combination was less effective than oseltamivir monotherapy, and not more effective than zanamivir monotherapy. A phase 2 study of oseltamivir plus plasma<sup>10</sup> has shown that the combination was no different from oseltamivir in time to normalisation of patients' respiratory status but was associated with a numerical reduction in duration of hospital stay and days of mechanical ventilation. Several studies of other combinations, including oseltamivir and nitazoxanide compared with placebo (NCT01610245) and the individual drugs and oseltamivir plus either influenza-specific convalescent plasma or hyperimmune globulin (NCT01052480, NCT02572817, NCT02008578) are being done.

In vitro and animal data suggest that a triple combination of amantadine, oseltamivir, and ribavirin has improved efficacy against influenza, even in amantadine-resistant viruses.<sup>11–13</sup> In *The Lancet Infectious Diseases*, John H Beigel and colleagues report the results from a randomised, double-blind study of a triple combination (oseltamivir 75 mg, ribavirin 600 mg, and amantadine 100 mg twice a day) compared with oseltamivir (75 mg twice a day).<sup>14</sup> 394 (62%) of 633 participants randomly assigned to treatment had confirmed influenza and had virology samples on day 3. The combination treatment resulted in fewer patients having detectable virus on day 3 (80 [40%] of 200 participants) than in the monotherapy group (97 [50%] of 194 participants,  $p=0.046$ ), but had no effect on the duration of symptoms (4.5 days vs 4.0 days,  $p=0.21$ ).

Although a scarcity of clinical benefit is frustrating, the improvement in viral shedding and the theoretical benefit in preventing resistance emergence suggest that studies of combination therapy should continue



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to be investigated. Furthermore, newer antivirals are becoming available that have different mechanisms of actions. Combinations of two or more drugs with different mechanisms of action hold greater promise in enhancing the outcomes of influenza compared with monotherapy and should continue to be studied.<sup>7</sup> Combination therapies should be studied in populations that have prolonged shedding and enhanced risk of emergence of resistance, including patients admitted to hospital and immunocompromised patients. Additionally, studies of virus subtypes with enhanced risk of resistance emergence, such as influenza A H7N9, which has been documented to have resistance develop due to Arg292Lys, Glu119Val and Ile222Lys mutation and results in increased IC<sub>50</sub>s for all of the available neuraminidase inhibitors, should be considered.<sup>15</sup>

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