Foreword: Oseltamivir for seasonal, avian and pandemic influenza: 10 years of clinical experience

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As molecular analysis and computational techniques improved during the 1980s, the chemical structures of many biological molecules were accurately determined for the first time. With these advances came the prospect of rational drug design to target specific sites, aimed at successful human treatment. One such target was the neuraminidase (or sialidase) enzyme of the influenza virus, which is essential for viral replication and is largely conserved across influenza A and B strains. A number of molecules blocking the action of neuraminidase were synthesized and tested, the most active of which, zanamivir (Relenza®), became the first commercially available neuraminidase inhibitor (NI) for the treatment and prophylaxis of influenza. However, zanamivir could only be delivered by inhalation or intravenously (because of rapid deactivation in the gastrointestinal tract); thus research continued to identify a related compound that could be administered orally. The result was oseltamivir (Tamiflu®), which, after initial development by Gilead Sciences in 1997, was brought to market by F. Hoffmann-La Roche in late 1999. Oseltamivir was unique in that it was delivered orally via a bioavailable prodrug that was converted in the liver into the potent and selective NI, oseltamivir carboxylate. As highlighted by Brian E. Davies in the first part of this Supplement, the predictable and consistent pharmacokinetic profile of the drug and low level of significant drug interactions observed in early clinical studies suggested that a product had been created that was practical to administer and usable by a broad spectrum of patients.

In the Phase III trials that followed, oseltamivir was shown to be an effective intervention for the symptomatic treatment and prophylaxis of influenza A and B infections in children ≥1 year and adults of all ages, as described by Regina Dutkowski in the second part of this Supplement. Oseltamivir was also found to be generally well tolerated by all patient groups, with a similar overall adverse event profile to placebo. Despite successful licensure of the drug, the key limitation of the clinical trial data was the somewhat modest reduction in the duration of symptoms seen with all NIs and, initially, somewhat limited data relating to ‘harder’ public health outcomes, such as reductions in complications, hospitalizations and mortality. These data have emerged more widely over the last decade and, whilst still hotly debated in some circles, the balance of probability is, in my view, still in favour of NIs reducing hospitalizations and mortality. Even small individual effects can have a large impact when applied across whole populations, as eloquently pointed out by the late Geoffrey Rose, and the current H1N1 pandemic is certainly one situation where such potential benefits might be realized, as well as further data generated that might settle the debate.

Despite the above findings, adoption of the drug into routine clinical practice for seasonal influenza has been slow (except in Japan); concerns about massive consumer demand have proved unfounded, and organizations such as the National Institute for Health and Clinical Excellence (NICE) in the UK have limited prescribing in some territories. However, by far the biggest issue has been the lack of awareness among physicians and patients that influenza could be specifically treated, as well as an over-riding (and largely misguided) opinion that influenza was not sufficiently serious to warrant specific intervention. The latter has been driven by unusually mild seasonal disease activity since 1999–2000, and persistent under-ascertainment of influenza as a cause of hospital admission in adults and children.

Apathetic attitudes towards the use of oseltamivir were radically altered by the re-emergence of highly pathogenic avian influenza A (H5N1) in South-East Asia, which has caused a substantial number of human infections and deaths since 2003, and provoked a serious global focus on pandemic preparedness. Experts generally agreed that H5N1 had (and still has) the potential to pose a pandemic threat comparable to that which swept the globe in 1918–19, causing an estimated 40 million deaths. Oseltamivir was shown to be active against the H5N1 virus in animal models and, as reported by James R. Smith in the third part of this Supplement, to improve survival in human H5N1 cases, particularly when started early in the course of illness. Thus, the stockpiling of oseltamivir...
became central to the pandemic preparedness plans of many countries.  

As we now know, the pandemic virus that appeared in early 2009 originated not from birds but, most probably, from swine. Pandemic (H1N1) 2009 influenza currently appears to cause mild and uncomplicated illness in the majority of patients, but may also lead to severe disease and death, both in patients with and without underlying illnesses or medical conditions. In the UK, it has been reported that pandemic influenza deaths have been most numerous in people aged 25–44 years, and almost one-fifth did not have underlying conditions of any sort.6  

As described by David Reddy in the final part of this Supplement, the pandemic (H1N1) 2009 virus is largely susceptible to oseltamivir (although a small number of H275Y resistant mutations have almost inevitably occurred), and early clinical data indicate that oseltamivir is an effective treatment. A number of studies are now underway which may have the ability to determine if individuals infected with the pandemic virus who were treated early with an NI were less likely to be admitted to hospital and suffer severe outcomes. There is already at least some early suggestion that this may be the case.7,8  

The WHO and other public health bodies recommend oseltamivir for the treatment of pandemic (H1N1) 2009 in patients who have developed or are likely to develop severe disease. Nevertheless, the transition from minimal to extensive oseltamivir use during the initial stages of the pandemic has not been completely smooth. Broad prescribing of oseltamivir for suspected pandemic (H1N1) 2009 infection in countries such as the UK, where patients have hitherto been largely unfamiliar with the drug, has led to media stories surrounding side effects and resistance. It will therefore be important to educate both healthcare providers and the general public on the best use of oseltamivir as the pandemic unfolds. I hope that readers will find the content of this Supplement, which offers an engaging and helpful perspective on ‘the story so far’, useful.

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References

1 Godlee F. We want raw data, now. BMJ 2009; 339: b5405 (and related articles).
2 Schwartz S, Diez-Roux R. Causes of incidence and causes of cases—a Durkheimian perspective on Rose. Int J Epidemiol 2001; 30: 435–9.
3 National Institute for Health and Clinical Excellence. Amantadine, Oseltamivir and Zanamivir for the Treatment of Influenza (Review of Existing Guidance No. 58). http://guidance.nice.org.uk/TA168 (14 December 2009, date last accessed).
4 Nicholson KG, McNally T, Silverman M et al. Influenza-related hospitalizations among young children in Leicestershire. Pediatr Infect Dis J 2003; 22 Suppl: S228–30.
5 Van-Tam J, Sellwood C. Introduction to Pandemic Influenza. Wallingford, UK: CAB International, 2010. ISBN:9781845935788.
6 Donaldson LJ, Rutter PD, Ellis BM et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009; 339: b5213.
7 Jain S, Kamimoto L, Bramley AM et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 2009; 361: 1935–44.
8 Institut de Veille Sanitaire. Intérêt d’un traitement précoce par antiviral pour réduire la sévérité et la mortalité par grippe A(H1N1)2009: données issues de la surveillance des formes graves. http://www.invs.sante.fr/ surveillance/grippe_dossier/docs_professionnels/antiviraux_grippe_a_h1n1 _211209.pdf (17 January 2010, date last accessed).