Oseltamivir: over 15 years of data retention and systematic stonewalling

Oseltamivir has been authorised in the United States since 1999. It was authorised in the EU in 2002 (through the centralised procedure) for the prevention and treatment of influenza. In March 2015, the European Medicines Agency (EMA) extended the indications of *oseltamivir* to cover the treatment of flu-like syndromes in infants less than one year of age (see p. 53) (1,2).

Data retention by the company; complicit or complacent drug regulators. In 2009, while preparing its meta-analysis of *oseltamivir*, the Cochrane Acute Respiratory Infections Group found that only 40% of the assessment data had led to published reports, and that most of the data were unverifiable. With support from the *British Medical Journal* (BMJ), the Cochrane group lobbied Roche and EMA in order to obtain these missing data (3-6). In 2011, EMA provided the Cochrane group with incomplete reports and refused to ask Roche for the missing data (4). The Cochrane group then filed a complaint with the EU ombudsman, and in 2012, EMA acknowledged that Roche had concealed a number of suspected adverse effects of *oseltamivir* from regulatory agencies (4).

Finally, in 2013, Roche released 77 clinical study reports relating to the 82 trials of *oseltamivir* that the company had funded and that had been carried out between 1997 and 2001 (2,3). This lengthy delay between the end of the trials and publication of their detailed results is unjustifiable and undermines their credibility. Furthermore, they would never have seen the light of day without an administrative appeal.

Faced with this lack of transparency, the Cochrane group adapted its standard methodology to the specific case of *oseltamivir*. In particular, they focused on clinical study reports rather than on published articles. They also launched a broader reflection on the type of documents to be used by Cochrane for future meta-analyses (see p. 52) (3).

Roche reacted quickly to publication of the unfavourable results of the Cochrane meta-analysis in March 2014. In particular, the company sent the Cochrane group 69 pages of comments criticizing the results of this meta-analysis in October 2014, and even had the cheek to complain that the authors had failed to ask the company to clarify the data (7).

Data held and funded by the company. In 2013, Roche provided financial support to a group called the Multiparty Group for Advice on Science (Mugas) charged with re-analysing the assessment data on *oseltamivir* (2). In 2014, Mugas funded a meta-analysis that was published in *the Lancet* in 2015. The authors of this meta-analysis concluded that *oseltamivir* reduced the duration of symptoms and complications of seasonal influenza (8,9).

In 2014, a retrospective analysis of reviews evaluating the efficacy of antiviral drugs in influenza showed that 88% of reviews subject to financial conflicts of interests favoured the use of antivirals in influenza, compared to 17% of those with no conflicts of interest (10).

Opinions and recommendations that ignore the weakness of the evidence. Starting in 2004-2005, on the basis of these fragile and incomplete data, various countries started to stockpile *oseltamivir* in fear of an outbreak of H5N1 influenza (bird flu). The same data served as the basis for recommendations on the widespread use of *oseltamivir* during the 2009-2010 H1N1v influenza pandemic (2).

Various organisations subsequently issued recommendations without demanding more conclusive evidence. French recommendations are similar to those proposed in the United States by the Centers for Disease Control and Prevention (CDC) and the Infectious Disease Society of America (IDSA) (2,11,12).

The World Health Organization (WHO) added *oseltamivir* to its list of essential medicines in 2013, and it was still included in the 2015 update (13). Neither the CDC nor WHO responded to the authors of the Cochrane meta-analysis seeking the scientific justification for their recommendations (2,14).

In France, the opinion of the public health authority (HCSP) dated 3 March 2015 is based on a review of data funded by Roche and published in 2015, and on another systematic review published in 2013 (8,15,16). The results of the Cochrane meta-analysis published in 2014 appear to have been ignored, for reasons that remain unclear (16).

In summary. Over a 15-year period, Roche, the company that markets Tamiflu°, has hampered independent analysis of the assessment data on *oseltamivir* in the treatment of influenza. Worse yet, drug regulators and international organisations have been complicit in this data retention.

These 15 years of stonewalling represent a lost opportunity for patients and the medical community, while providing the company with an unfair advantage after successfully bringing *oseltamivir* to the market on the basis of unverified data. Yet, despite the widespread belief in the efficacy of *oseltamivir*, cleverly orchestrated by the company and other organisations, including some regulatory and health authorities, a number of independent teams were not convinced and instead went on a hunt for missing data. What they discovered was that the available trial results were neither complete nor clinically relevant and provided only weak evidence. Furthermore, they revealed that the company had not provided the information theoretically required to obtain marketing authorisation.

From the company's point of view, this deception was a success. Once health authorities and health professionals had been convinced that *oseltamivir* was effective on influenza, each new assessment that came to a dissenting or unfavourable conclusion could be countered by publication of a new company-funded analysis. This widely used strategy is called a "publication plan" (17).

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