Zanamivir: an alternative translation

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This paper offers an alternative view to that given elsewhere regarding the value of zanamivir as an agent for treating patients who develop influenza symptoms. The position taken here has developed as a result of an analysis of the data that was undertaken by the journal *Drug and Therapeutics Bulletin*.

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1. INTRODUCTION

The views held by the National Institute for Clinical Excellence about the value of zanamivir as a treatment in otherwise healthy people are in accord with the analysis of data undertaken in *Drug and Therapeutics Bulletin*. However, differences occur when the drug's place as a treatment in patients classed as being at particularly high risk of morbidity and mortality if they develop the disease is considered, i.e. in those aged 65 years or more and in those who are immunocompromised or who have diabetes mellitus, significant cardiovascular disease or chronic respiratory disease.

2. THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE'S NOVEMBER 2000 POSITION ON ZANAMIVIR

In its guidance on zanamivir (Relenza), the National Institute for Clinical Excellence (2000) concluded that 'Zanamivir is recommended, when influenza is circulating in the community, for the treatment of at-risk adults who present within 36 hours of the onset of influenza-like illness and who are able to commence treatment within 48 hours of the onset of these symptoms' (p.1). The *Drug and Therapeutics Bulletin* (Anon. 2000) analysis argues that this position is unsustainable, at least as far as UK practice is concerned. How can the views of these two respected, UK authorities conflict?

3. BASIS FOR THE DRUG AND THERAPEUTICS BULLETIN'S POSITION

In order to reach its position, the *Drug and Therapeutics Bulletin* analysed the guidance published by the National Institute for Clinical Excellence (2000), together with the source material published by the institute, which formed the basis for its guidance. This material consisted of the 74-page *Health technology assessment report* by University of Birmingham (2000) and the subsequent eight-page supplement to the assessment report (University of Birmingham, undated). The *Drug and Therapeutics Bulletin*

also analysed a key publication that was referred to in the supplement by Murphy *et al.* (2000).

The methodology used by the *Drug and Therapeutics Bulletin* has been described in detail (Anon. 1997). In brief, material being reviewed is closely scrutinized and the products of that scrutiny are circulated to up to 100 commentators in several draft forms before publication. It is a process that the journal has developed over almost 40 years.

4. THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE'S HEADLINE CONCLUSIONS ABOUT ZANAMIVIR

In its guidance, the National Institute for Clinical Excellence (2000) makes four key statements about data on the use of zanamivir in at-risk patients.

- (i) There are no reliable data as to the impact of the drug on mortality rates.
- (ii) There are no reliable data as to the impact of the drug on hospitalization rates.
- (iii) Overall, the drug reduced the absolute risk of complications requiring antibiotics in the intention to treat (ITT) population by 6% (95% confidence interval 0–11%).
- (iv) The overall pooled analysis shows that the drug reduces the duration of influenza symptoms by 1.2 days, from *ca.* 6 to 5 days (95% confidence interval 0.1–2.2) in the ITT population.

The *Drug and Therapeutics Bulletin's* analysis of the source data is in accord with the institute's observations on mortality and hospitalization rates. However, differences emerge when assessing the drug's effects on the risk of complications and on the duration of symptoms.

After close analysis of the *Health technology assessment report* and its supplement and the Murphy *et al.* (2000) data on the reduction in the absolute risk of complications requiring antibiotics, the *Drug and Therapeutics Bulletin* (Anon. 2000) found that (i) the criteria for administering antibiotics are not clear, (ii) the severity of 'infections' is not clear, (iii) the complications requiring an antibiotic

were never a primary outcome measure, and (iv) the reduction in complications requiring antibiotic use did not reach conventional levels of statistical significance.

After similar analysis of the *Health technology assessment report* and its supplement and the Murphy *et al.* (2000) data on the reduction in symptom duration, the *Drug and Therapeutics Bulletin* noted the following.

- (i) The *Health technology assessment report* (pooled data) states that, in this population, the reduction in the time to alleviation of symptoms in the influenza-positive group was not statistically significant.
- (ii) The supplement (Murphy *et al.* (2000) data) states that, in this population, the reduction in the median time to alleviation was not statistically significant.
- (iii) Previously, a reduction of 1 day was not seen as clinically worthwhile.
- (iv) No trial has compared the drug's effect on symptoms with that provided by standard over-the-counter remedies coupled with traditional clinical measures such as going to bed and drinking water.

5. LACK OF EVIDENCE COMPOUNDED BY OTHER ISSUES

With the lack of convincing evidence relating to the benefit of zanamivir in four key domains (mortality, hospitalization, antibiotic usage and the duration of symptoms), the position of the *Drug and Therapeutics Bulletin* in arguing against the use of the drug as a treatment would appear justifiable. However, consideration also needs to be given to additional issues.

It would appear from the National Institute for Clinical Excellence's (2000) published material that the evidence base was sometimes incomplete and, when assessing the potential for zanamivir causing unwanted effects, the *Health technology assessment report* essentially dismissed the possibility with a brief note stating that 'there was no excess of adverse events in the treatment population compared to the controls' (University of Birmingham 2000, p.39). In doing this, the *Health technology assessment report* and the National Institute for Clinical Excellence have chosen to overlook the data on, for example, the adverse respiratory effects collected in post-marketing surveillance, which are referred to by the World Health Organization, the European Union summary of product characteristics and by the Food and Drug Administration. While the National Institute for Clinical Excellence may have concluded that these adverse reactions were of no clinical significance, failure to refer to these observations and to address them in any detail undermines the validity of the position it takes.

In a similar way, the National Institute for Clinical Excellence (2000) essentially dismissed any risk that

widespread use of the product might give rise to the development of resistance. Several agencies are very concerned about the development of antimicrobial resistance. By giving this possibility so little attention it could be argued that the National Institute for Clinical Excellence failed in a societal responsibility. It is certainly an issue that has taxed the *Drug and Therapeutics Bulletin*.

The National Institute for Clinical Excellence (2000) also failed to put its conclusions into a realistic clinical setting. All that the guidance advises on management is that those at risk should take zanamivir when influenza symptoms develop. It would seem that the availability of zanamivir has obscured the need for other additional approaches such as taking an antipyretic or analgesic and going to bed. This oversight is particularly questionable since these additional approaches were advocated in all of the trials of zanamivir.

Finally, there may be an explanation for the National Institute for Clinical Excellence's (2000) apparently perverse recommendation, bearing in mind the data the institute had available. Amongst its terms of reference, the National Institute for Clinical Excellence is required to take into account 'encouragement of innovation' in its decision making. Perhaps it was this requirement that held sway when the guidance was agreed. This would be perfectly legitimate, but if it were a contributing factor its influence would have been better declared in advance.

6. CONCLUSION

It has been difficult for the *Drug and Therapeutics Bulletin* to see why zanamivir should be used for the treatment of influenza based on the published evidence. Moreover, there are risks of the widespread use of zanamivir that the National Institute for Clinical Excellence (2000) does not seem to have taken into account. Nevertheless, differences of opinion are inevitable and not in themselves wrong. Translating science into public policy is fraught with problems and, if nothing else, impartiality, attention to detail, transparency and the right for honest debate must be given the highest priority.

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