



## **AVG discussion meeting on clinical trial endpoints for studies of antivirals in hospitalised and at risk influenza patients**

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### *Background*

A discussion meeting was convened by the isirv antiviral group (AVG) during the 'Options for the Control of Influenza VIII' conference in Cape Town in order to share current information and promote discussion on the selection of clinical trial endpoints for studies of influenza antiviral agents in hospitalised and at risk patient populations. The meeting brought together a group of clinicians, virologists and industry representatives with interest and expertise in the field of antiviral agents for the treatment of severe influenza virus infection. The goals were to review currently available data and identify areas that still need to be addressed in order to provide a more accurate assessment of the effectiveness of influenza antiviral agents and facilitate the design of clinical trials that are both feasible and address regulatory requirements.

The meeting aimed to examine the data published since the 2010 review by Ison *et al* that summarised the evidence to support the use of primary virologic end points in studies of antiviral agents (1) and to build upon previous discussions of the AVG group.

In opening remarks to the audience, Professor Frederick Hayden acknowledged the diversity of perspectives and the lack of consensus in identifying endpoints to support rapid regulatory approval of drugs for use in seriously ill patients, a group for whom the risk-benefit assessment differs markedly to that for patients who have uncomplicated illness.

### *Review of available evidence*

Dr Michael Ison presented data on virologic endpoints and sampling strategies in hospitalised patients with influenza virus infection. He highlighted the variability in clinical disease and presentation amongst specialised populations such as hospitalised adults, immunocompromised hosts and paediatric patients, and then summarised the currently available data on the course of virologic illness in these patient groups. The key issues around standardising virologic methods were discussed, including the site of sampling (upper versus lower respiratory tract), the types of

samples (swabs, washes, aspirates) and the assays used to detect virus (cell culture assays and quantitative PCR assays). Dr Ison provided an overview of a number of clinical trials that are currently underway within the United States to validate virologic endpoints and biomarkers which may act as surrogates for clinical responses against clinical outcomes.

Professor Nelson Lee provided a summary of a number of studies that have been undertaken to correlate virologic measures and clinical outcomes in hospitalised patients and highlighted some issues relating to the use of virus culture as a virologic method. He summarised issues around influenza virokinetics including the impact on decisions about the site and timing of virologic sampling, and how virokinetics correlate with clinical variables in severely ill patients. Data from hospitalised patients demonstrate the correlation between viral RNA concentration and symptoms, the factors associated with persistence of viral RNA detection, and complications that may arise following delayed RNA clearance.

Data were presented on a number of intervention studies that have been undertaken to assess the impact of antiviral therapy on virus clearance, the emergence of antiviral resistance, and the occurrence of prolonged viral shedding. In addition, data were also presented showing the correlation between viral RNA detection, inflammatory responses, clinical presentation and clinical outcome.

Professor Jonathan Nguyen-Van-Tam discussed data from a worldwide systematic review and patient-level meta-analysis of anti-influenza drug effectiveness (PRIDE) undertaken after the 2009 influenza A(H1N1) pandemic (2). The study aimed to address two main outcomes of public health importance: mortality and admission to critical care. The analysis found a protective effect of influenza neuraminidase inhibitor (NAI) use compared to no treatment, and a significant reduction in mortality according to early versus late administration of antiviral medication.

A reduction in severe outcome, defined as admission to ITU or death, was associated with early treatment versus late treatment, whilst an increase in severe outcomes was observed when looking at NAI use versus no use. However, there is a strong likelihood that this finding was due to confounding by underlying disease severity and propensity to treat severe (end stage) disease.

Unpublished data from the PRIDE consortium, comprising 80 research groups in 38 countries, indicate that NAI use during the 2009-10 influenza A(H1N1) pandemic reduced the likelihood of mortality, especially if given early. Further analyses of influenza related pneumonia, high versus low risk patients, and corticosteroid use will follow.

Dr Michael Ison presented data on behalf of BioCryst on phase 2 and phase 3 studies of intravenous peramivir in hospitalised influenza patients. Such studies in hospitalised patients

reflect a number of challenges, since Food and Drug Administration (FDA) regulation currently requires proof of superiority against oseltamivir. Superiority studies may require between 1,600 and 5,000 subjects to demonstrate a statistically significant difference between two different neuraminidase inhibitors from data from completed studies; this would likely require decades of recruitment to complete. Oseltamivir is now considered standard care for treating hospitalised patients in most countries but has not been accepted by regulatory authorities for this indication. There are also considerable logistical challenges in conducting trials in hospitalised patients as a small number of sites generally end up recruiting the majority of the patients, and recruitment criteria are largely subjective which may result in a large number of patients being screened in order to recruit a relatively small number. Significant bias may occur in studies of long duration due to changes in the standard of patient care.

Three studies on peramivir have been undertaken outside Asia using a primary endpoint of time to clinical resolution, as indicated by normalisation of five clinical markers. There were substantial differences in time to resolution when stratified according to supplemental oxygen use and ICU category at baseline, with patients who were less ill progressing to resolution more quickly than those who were severely ill. Data were presented on a number of efficacy endpoints for studies in hospitalised patients. Only changes in viral load and shedding have been found consistently to correlate with use of antiviral therapy; baseline viral load and shedding have not been associated with post-baseline complications, including influenza-related complications, post-baseline oxygen requirements or need for post-baseline intubation. For a large number of other endpoints that have been measured the relationship to disease course, the degree of viral replication and direct effects of the virus are unknown.

Dr Helen Steel provided an overview of the challenges in undertaking clinical studies of intravenous zanamivir, which is being developed for patient groups who do not respond to approved treatments or have virus resistant to other antiviral drugs, or who are unable to take oral or inhaled medications. In accordance with FDA guidance, industry has been required to undertake dose response, duration response, or superiority add-on trials as it is not possible to undertake active-controlled non-inferiority trials to prove superiority against oral oseltamivir, which is widely regarded as the current standard of care.

Additional challenges include the absence of validated clinical endpoints or accepted biomarkers for disease outcome. Regulatory authorities favour clinical endpoints, but the European Medicines Agency (EMA) is willing to consider co-primary endpoints for the study of clinical and virologic endpoints. Published data support virologic control as an important component of resolution in acute uncomplicated influenza. Quantitative RT-PCR may provide a more sensitive marker of viral response in hospitalised patients than quantitative viral culture, but the endpoint is not yet validated (e.g. log reduction in viral load at a given time point; change from baseline or time to viral clearance).

A composite clinical resolution endpoint has been proposed by regulators, comprising normalization of vital signs (temperature, respiratory rate, oxygen saturation, heart rate and systolic blood pressure), with clinical improvement defined as hospital discharge. It was proposed that 'time to' analyses provide a useful means of differentiating between different patient groups over time.

Data from a phase 2 clinical trial have been published and include the correlation of clinical outcomes in an adult cohort (3). These data may provide insights into defining clinical endpoints and correlates of effectiveness.

Dr Nahoko Shindo presented some perspectives from the World Health Organisation (WHO) regarding the issue of guidance in the event of a public health emergency. Under such circumstances, rapid advice and interim guidance is required based on previously published data and expert opinion. As a result, documents are time-limited and scope-limited and are not subject to peer review; the corresponding medicines must be available once recommendations have been made. A PICOT (population, intervention, comparator, outcome, time) framework is used. Within this framework, five outcome measures are used: prevention of infection in higher risk individuals; prevention of disease progression; time to resolution of severe illness; reduction in hospital or ICU admission or length of hospital stay; reduction in mortality.

It was acknowledged that the formal WHO guidance development process does not consider case series or *ad hoc* analysis sufficient to weight recommendations, and values graded evidence instead. This is challenging when dealing with severe, acute disease especially in an evolving situation. The WHO has developed a public health research agenda so that clinicians know what data WHO require to inform guidance development. In addition, antiviral susceptibility data generated through the WHO Global Influenza Surveillance and Response System (GISRS) are also taken into consideration.

Dr Shigeru Saito provided some perspectives of influenza in pregnancy, and described how guidance was developed and disseminated in Japan during the 2009 influenza A pandemic. Key messages were communicated on the importance of vaccination, the safety and benefits of antiviral medication, good respiratory hygiene and self-isolation against close contact with influenza virus infection. Data indicate that there were no pregnancy-associated deaths in Japan during the 2009 pandemic.

### *Discussion of key issues*

The scientific presentations covered a range of issues including clinical and public health perspectives, challenges in study design and difficulties in interpretation of observational data.

It was suggested that co-primary endpoints of time to discharge or death and sustained negativity in viral RNA detection might be considered, as these will help to control for underlying co-morbidities in different patient populations. Current guidance suggests that superiority would have to be demonstrated for both endpoints, which could further challenge studies utilizing such co-primary endpoints. Either the 'time to' endpoint or proportion of patients who meet the endpoint at a relevant time point could be used, but it was noted that differences will occur based on the age of the patient, underlying co-morbidities, and geographical variation in clinical management of patients.

Return to pre-morbid functional status may be more clinically relevant to both the clinician and the patient, as it takes into consideration the fact that hospitalised patients will be discharged into a variety of different medical settings. The current FDA endpoint 'time to clinical stability' has not been demonstrated to be a meaningful endpoint in clinical studies. Fever was generally the only component of the 'time to clinical stability' endpoint that had clinically significant changes and it generally resolved very rapidly following antiviral therapy. Rate of change of clinical parameters was also proposed as a useful clinical endpoint.

It was noted that the association between virologic and clinical endpoints has never been fully determined in hospitalised or seriously ill influenza patients. Early virologic data from ambulatory patients were based on virus culture rather than viral RNA detection methods that have become available more recently. Virologic endpoints are of interest as they may provide a method of interpreting the person-to-person variability in clinical illness. It was proposed that virus culture is no longer a useful endpoint as the technique is not widely used clinically and may be less robust than molecular methods. However, many experts thought that both detection methods should be used at present since virus culture allows for documentation of replication-competent virus and phenotypic resistance testing. A more useful endpoint might be a change in viral RNA detection, or the use of biomarkers, although a number of cytokine levels do not change rapidly enough to be sensitive indicators.

The selection or stratification of patient populations is an important factor in obtaining useful data, as seriously ill patients may not recover. In young children prolonged viral shedding is a characteristic of infection, so consideration of how to define reduced shedding in children may require a different approach to adults.

It was noted that discussion has predominantly focused on primary endpoints for regulatory approval of drugs which require phase 3 studies involving clinical endpoints. However, drug development involving new drugs or combination therapies will require an endpoint indicating whether the drug has antiviral effects and clears virus more efficiently. Virologic endpoints are therefore very important in early stage clinical trials and more emphasis should be devoted towards using primary virologic end points to support early acute phase interventions, given the correlation between virus detection and disease development.

Since a number of agencies are interested in the topics under discussion at this meeting, it is proposed that current evidence and data will be summarised in a peer-reviewed publication to

form the basis for further discussion with the regulatory authorities. A number of studies are still underway which may give rise to further datasets to support future dialogue.

## References

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