group and 16 (5%) in the fluconazole or itraconazole group (P = 0.01) [1, p. 353]. The resultant absolute risk reduction of 3% yields a number needed to treat of 33.3.

We do agree that the numbers alone do not tell us of the value of 1 life. Furthermore, that assessment cannot be made in the abstract but must be considered in relation to each individual and his or her circumstances and, especially, his or her personal wishes.

In response to Jain and Pottinger [4], who raised the issue of gastric acidity affecting posaconazole absorption, we requested further information from Schering-Plough, the sponsor of posaconazole [5]. Per the sponsor, “concomitant use of posaconazole and cimetidine should be avoided. The effects of other histamine-2 receptor antagonists that may suppress gastric acidity for several hours on plasma levels of posaconazole have not been studied, but a reduction in bioavailability may occur so that coadministration should be avoided, if possible” [5].

Acknowledgment

Potential conflicts of interest. S.D. is an advisory board member of Schering-Plough and Ortho-McNeil (Johnson & Johnson) and serves on the speakers’ bureau for Merck, Ortho-McNeil (Johnson & Johnson), Schering-Plough, Pfizer, Wyeth, and Cubist. V.N.: no conflicts.

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References


Antiviral Therapy and Outcomes in Hospitalized Patients with Influenza

To the Editor—It can be difficult to design studies that involve patients who are hospitalized with influenza; challenges include definition of the patient population, determination of the primary study end point, study design, and efficacy evaluation. McGeer et al. [1] should be commended for accumulating the largest prospective cohort of hospitalized patients with laboratory-confirmed influenza. During the period January 2005–May 2006, researchers identified 541 patients at acute care hospitals in the Toronto Invasive Bacterial Diseases Network. Their study corroborates other findings of substantial morbidity and mortality associated with influenza [2]. Study limitations include its observational design, sample size, diagnostic methods used, inability to compare antiviral treatment effects in different patient subgroups, insufficient power to identify effect of time to first treatment relative to symptoms, lack of generalizability, and potential confounders, such as potential bias associated with a lack of randomization.

Although the authors suggest that antiviral treatment might reduce mortality among hospitalized patients, these conclusions should be considered in the contexts of the study’s limitations and the scientific challenges involved in studying patients who have been hospitalized with influenza. First, detailed data on clinicians’ rationale for antiviral treatment was not obtained. Patients who received antivirals (106 [32%] of 327 adults) may represent an enriched subpopulation. Patients with prolonged symptom duration, poor gastrointestinal absorption, or other factors may have been excluded from treatment on the basis of a low clinical likelihood of benefit. Second, the study did not include a randomized control arm and was underpowered to distinguish efficacy differences between patients who received antivirals and those who did not. Third, there is no evidence-based, standard-of-care antiviral treatment for hospitalized patients with influenza. Although this challenge could be addressed using superiority study design, no such studies (to our knowledge) have been performed to date. An additional challenge to demonstrating the efficacy of drugs against serious influenza is the observation that patients may present for medical care several days after the onset of symptoms. Randomized, prospective studies evaluating the treatment effect of antivirals initiated >48 h after the onset of influenza symptoms have not been performed. Therefore, any study design considerations are complicated by the absence of evidence of benefit—or of the magnitude of benefit—of existing drugs that might be used in hospitalized patients with influenza. Fourth, the most appropriate primary end point for patients who are hospitalized with influenza is unknown. In this study, the primary end point was defined as mortality within 15 days after symptom onset [1]. Although mortality could be a reasonable end point, larger sample sizes would likely be needed to demonstrate a treatment effect. No surrogate marker has been identified as reasonably likely to predict important clinical outcomes. It is possible that a combined clinical end point may need to be determined for future studies. Such a primary end point could be derived from other studies of hospitalized patients with acute, serious, or potentially life-threatening respiratory illnesses [3, 4].

Despite the challenges discussed above, McGeer et al. [1] show that studies of patients hospitalized with influenza are feasible and can provide useful data, and they have demonstrated that studies with sample sizes in the range of several hundred patients may be able to detect differences in important clinical end points. Addi-
tional studies are needed, especially because some data suggest that patients with serious influenza illness may have prolonged viral replication and might benefit from antiviral treatment, even if such treatment is initiated >48 h after the onset of symptoms [5]. We hope that randomized, prospective studies can be performed to help determine whether antivirals—either currently approved or investigational antivirals—have a clinically meaningful benefit for patients who are hospitalized with serious, potentially life-threatening influenza.

Acknowledgments


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References


Reply to Chan-Tack and Murray

We thank Chan-Tack and Murray [1] for their thoughtful comments about our study. They highlight a current dilemma for clinicians, who have to decide on whether to use antiviral therapy for hospitalized patients in the absence of definitive data, and they raise interesting issues about the selection of outcomes in studies of severe influenza.

Randomized, controlled trials of outpatients demonstrate that antivirals are effective for improving outcomes in children and healthy adults infected with influenza virus [2, 3]. There are at least 5 cohort studies of high-risk patients (in addition to ours) that suggest significant benefits to therapy (mortality in 3 studies, length of hospital stay in 1, and progression to pneumonia in 1) [4–8]; in addition, numerous studies have demonstrated prolonged viral shedding in compromised hosts. Although it would be of obvious benefit to have data from randomized, controlled trials, it is not surprising that expert guidelines now recommend treatment for patients at high risk who have progressive disease due to laboratory-confirmed influenza, regardless of the time from onset of symptoms [9, 10].

The most appropriate end points for studies of severe influenza disease have yet to be defined. In part, this is because the epidemiology and clinical features of severe influenza in adults have not been carefully studied. Patients who require hospital admission for influenza may have primary influenza disease, disease secondary to bacterial infection, or exacerbations of underlying cardiac or respiratory illness. Mortality is the most important outcome and is the logical choice in the absence of other validated end points. However, trials will be smaller and information will be more useful if clinically important differences in outcomes in survivors can be identified. Validated outcome measures for clinical trials of severe influenza are needed.

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References