Post Hoc Subgroup Analysis

To the Editor:

I am surprised by the published conclusions of Hung et al1 in a recent issue of CHEST (August 2013). The authors’ stated methods are not adequate to support their conclusion that hyperimmune IV immunoglobulin (H-IVIG) benefits mortality if given within 5 days to patients with severe 2009 influenza A(H1N1) infection.

The primary outcome analysis of 34 patients presented in Table 1 of the study1 shows that five patients who received H-IVIG died, and four control subjects died. The authors subsequently performed a subgroup analysis of 22 patients who received treatment within 5 days of symptom onset. All five of the H-IVIG fatalities were excluded from this analysis, but all four of the control subjects’ deaths were retained. This is not explicitly explained by the authors but can be seen by comparing survival data in Tables 1 and 2. There is no mention of any plan to perform this subgroup analysis in the Materials and Methods section; therefore, there is no guarantee that this subgroup was not specifically formulated to elicit a presupposed conclusion. This is an excellent example of why unplanned subgroup analysis should not be acceptable as a basis for scientific conclusions.

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REFERENCES


Response

To the Editor:

We thank Dr Raschke for his comments on our article on hyperimmune IV immunoglobulin treatment.1 The subgroup analysis of the 22 patients who received treatment within 5 days of symptom onset was based on the fact that the viral load between the treatment and control arms became significantly different on day 5 from symptom onset (3.3 log10 copies/mL vs 4.67 log10 copies/mL, P = .04). We agree with Dr Raschke that there is a limitation in performing such a subgroup analysis, and we should have stated the plan to perform subgroup analysis according to the viral load result in the Materials and Methods section.

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Cilostazol

Same Evidence, Different Conclusions

To the Editor:

The risk-benefit ratio of cilostazol in claudication was recently reevaluated by the European Medicines Agency (EMA).1 Around the same time, the topic was discussed during the development of the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9).2 The differences between the two entities in interpreting the evidence are of concern. Having participated in both processes, we highlight here the most important discrepancies.

The EMA stated that the modest benefits of cilostazol are only greater than its risks in a limited subgroup of patients. It has restricted its use in patients with claudication disease who have had recent coronary events or undergone coronary stent treatments and also stated cilostazol should not be given to patients also receiving two or more additional antiplatelet or anticoagulant medicines.

In contrast, the AT9 panel concluded cilostazol is more likely to confer benefits than harm in patients with claudication and that the rate of adverse effects is similar to that of placebo. Confidence in the evidence, however, is low.

The safety of cilostazol can be further evaluated by taking indirect evidence in coronary patients into account. In studies comparing patients receiving aspirin and thienopyridine to other patients receiving aspirin, thienopyridine, and cilostazol, the addition of cilostazol showed a protective effect in major adverse cardiovascular events (myocardial infarction, stroke, and death) and no differences in major bleeding (OR, 0.72; 95% CI, 0.60-0.86; 547 events; and OR, 1.07; 95% CI, 0.86-1.73; 68 events, respectively).3,4

On what basis did the EMA restrict the drug? The EMA reevaluation was initially triggered by a safety report on cilostazol. No one disputes that drug safety reports are crucial to monitor and evaluate adverse events, but these data were not considered during the evaluation process. In our opinion, however, such action in this case was appropriate because it was unclear whether the adverse events detected in the safety report were due to the drug, to the patients’ cardiovascular condition, or to other concomitant drugs. Reading the EMA recommendations, it seems that the

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REFERENCES


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