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Different Indications Between Fluoroquinolone and Amoxicillin

To the Editor—We read with great interest the recent study that investigated the association between the use of oral fluoroquinolone and the risk of acute liver injury [1]. Based on the findings of this nationwide cohort study, fluoroquinolone versus amoxicillin was associated with a higher risk of acute liver injury. Although many confounding factors have been adjusted in this study, we have serious concerns regarding the confounding effect of different indications between fluoroquinolone and amoxicillin.

First, although these 2 comparators—oral fluoroquinolone and amoxicillin—are commonly used in the treatment of lower respiratory tract infection, only fluoroquinolone can be used in the treatment of atypical pneumonia, such as legionellosis. However, atypical pneumonia can have more extrapulmonary manifestations, including liver involvement. Thus, it is possible that acute liver injury is caused by atypical pathogen rather than fluoroquinolone.

Second, in addition to lower respiratory tract infection, fluoroquinolone can be indicated in biliary tract infection. In patients receiving fluoroquinolone for treating hepatobiliary tract infection, liver injury could be directly caused by infection itself, rather than fluoroquinolone. Moreover, patients with hepatobiliary infection may take liver function tests frequently and more likely to find abnormal liver function. By contrast, amoxicillin is not a recommended for the treatment of biliary tract infection. Therefore, the role of infection indication, especially hepatobiliary tract infection, should be clarified.

Finally, the severity of infection is an important factor for clinicians to select the appropriate antibiotics. For example, the severity of infection of patients receiving fluoroquinolone would be more complicated than those receiving amoxicillin. Furthermore, more severe and complicated infection would be associated with a higher risk of acute liver injury than mild infection. Therefore, the infection severity could be another important confounding factors.

In conclusion, because fluoroquinolone is an antibiotic with broad-spectrum activity and commonly used in many types of infection, further study is needed to clarify the complicated association between risk of acute liver injury, infection and antibiotics.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Safety of Dengue Vaccine?

To the Editor—I write in response to the recent publication from Takeda Pharmaceuticals about the safety of their dengue vaccine (Patel et al, Clinical Safety Experience of TAK-003 for Dengue Fever: A New Tetravalent Live Attenuated Vaccine Candidate) [1]. The authors conclude that "no important safety risks were identified, and TAK-003 was well tolerated irrespective of age, gender, or baseline dengue serostatus in recipients aged 4–60 years." This conclusion does not accurately reflect recently published data for baseline seronegative children who received the vaccine [2].

In baseline seronegative children, Rivera et al [2] reported modest efficacy for serotype 1 (43.5%), high efficacy for serotype 2 (92%), and no efficacy for serotypes 3 (−23%) and 4 (−105%) over the first 36 months of the trial. By year 3 (months 24–36), the vaccine was only efficacious against serotype 2 (85%). Of special concern was a trend of more severe hospitalized dengue virus serotype 3 (DENV3) cases in the vaccine arm compared to the placebo arm (efficacy −183%) in baseline seronegative children. Although the investigators attribute this signal to high rates of dengue hospital admissions in Sri Lanka, this is not a satisfactory explanation.

The global public health community suffered a major setback when Sanofi's dengue vaccine (Dengvaxia) approved in some countries was subsequently discovered to be unsafe in seronegative children [3]. A lesson learned from the Dengvaxia experience was that the performance of dengue vaccines must be independently assessed by baseline serostatus and for each dengue serotype. In baseline seronegative children, TAK-003 clinical data do not demonstrate efficacy against serotypes 3 and 4 at any time point and serotype 1 after 24 months. The data also point to an enhanced risk of disease and hospitalization in vaccinated children infected with serotype 3. The results do not support the use of this vaccine in baseline seronegative children. The large body of pre- and post-clinical research on TAK-003 indicate that immunogenicity is mainly driven by the serotype 2 vaccine component with minimal to no contribution from the other 3 components [4].

Notes

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Institutes of Health, US Centers for Disease Control and Prevention, and US Department of Defense; receipt of royalties for human antibodies discovered by A. D. and others and licensed by Vanderbilt University, Tennessee; standard honoraria for academic lectures at Universities from Harvard, Scripps, Cornell, Albert Einstein, and University of Illinois; role as an inventor on issued, pending, and planned patents filed by the University of North Carolina related flavivirus diagnostics and vaccines; participation as unpaid member on dengue vaccine Scientific Advisory Board for Merck Pharmaceuticals, unpaid member on Dengue Immunology Advisory Board for Takeda Vaccines, and member on Zika Vaccine advisory board for Moderna; and other financial or nonfinancial interests: currently collaborating with Moderna on the development of mRNA vaccines to flaviviruses.

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