Short-Course Rifampin and Pyrazinamide Compared with Isoniazid for Latent Tuberculosis Infection: A Cost-Effectiveness Analysis Based on a Multicenter Clinical Trial

Sir—We applaud the work by Jasmer and colleagues [1, 2] using a Markov model and sensitivity analysis to conduct a rigorous cost-effectiveness analysis of short-course rifampin and pyrazinamide therapy for tuberculosis (TB) based on a previously published clinical trial. Their analysis compared the rates of adverse events and completion of 6 months of isoniazid with the rates of adverse events and completion of 2 months of rifampin and pyrazinamide (RZ) in the treatment of latent TB infection (LTBI). The clinical trial found that RZ was associated with a statistically significant higher risk of hepatoxicity than was 6 months of treatment with isoniazid, resulting in discontinuation of rifampin and pyrazinamide (RZ) treatment [2]. The cost-effectiveness analysis in the current study concluded that, compared with 2RZ, treatment with isoniazid is more cost-effective, unless completion rates are quite low (i.e., <36%) [1]. This cost-effectiveness advantage is maintained even when the duration of treatment with isoniazid is extended to 9 months [3].

In addition to the recommendations of the Centers for Disease Control and Prevention (CDC; Atlanta, GA) [4] mentioned by the authors, it is important to highlight here that the CDC and the American Thoracic Society now recommend against—and the Infectious Disease Society of America endorses against—the use of RZ, and RZ should generally not be offered to either HIV-negative or HIV-infected persons with LTBI [5]. These guidelines are based on recent reports of severe liver injury and higher rates of RZ-associated hospitalizations and deaths (3.0 and 0.9 per 1000 treatment initiations, respectively), compared with isoniazid-related hospitalizations (0.1–0.2 per 1000 treatment initiations; median, 0.15) and deaths (0–0.3 per 1000 treatment initiations; median, 0.04), in the treatment of LTBI [3, 6, 7]. According to these new recommendations [5], in circumstances in which the RZ regimen is offered, clinicians should dispense no more than a 2-week supply (with a daily pyrazinamide dosage of <20.0 mg/kg/d and a twice-weekly dosage of <50.0 mg/kg/d). Patients should be reassessed at 2, 4, 6, and 8 weeks of treatment for adherence, drug tolerance, and adverse effects. The week 8 assessment should also be used to document treatment completion. At each visit, a health care provider who speaks the patient’s own language should instruct the patient to stop taking RZ immediately and seek medical consultation if abdominal pain, emesis, jaundice, or other symptoms of hepatitis develop. Provider continuity is recommended for optimal monitoring. Serum aminotransaminases and bilirubin levels should also be measured at baseline and at 2, 4, 6, and 8 weeks of treatment. Patients should be monitored throughout the entire course of treatment [5].

The CDC continues to collect reports of severe liver injury (i.e., injury leading to hospitalization or death) that is caused by any regimen of LTBI; reports can be made by calling 1-404-639-8401 (Atlanta, GA).

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References

False-Positive Aspergillus Galactomannan Antigen Test Results

Sir—Viscoli et al. [1] and Adam et al. [2] recently reported the occurrence of false-positive results of Aspergillus galactomannan assays associated with piperacillin-tazobactam therapy in patients with hematological malignancies. In view of the widespread empirical use of this drug combination in febrile neutropenic patients with cancer, this observation is a matter of concern because it may lead to inappropriate (semi-)invasive investigations, overtreatment with toxic and/or ex-
pensive drugs, or inclusion of patients in research protocols. We describe a patient who received an erroneous diagnosis of probable invasive aspergillosis and received treatment accordingly in an investigational protocol.

Diagnosis of invasive aspergillosis remains frustratingly difficult. Signs and symptoms are not specific, and no single microbiological test can yield a definite diagnosis. Even more problematic is the poor comparability and reliability of clinical research in this field, which is largely the result of a lack of standardized diagnostic criteria. Fortunately, an international panel of experts recently took the lead in developing a set of research-oriented criteria for defining the degrees of certainty of the diagnosis of invasive aspergillosis for patients who have cancer and who have received hematopoietic stem cell transplants [3]. These definitions have incorporated advances in imaging techniques and serological markers of fungal involvement and have now been widely adopted in clinical research for defining a homogeneous study population. However, it is evident that the predictive value of “pathognomonic” radiological signs depends on the underlying disorder and the neutropenic status of the patient [4]. In addition, both transient and persistent false-positive test results are being reported with the new serological assays [1, 2, 5, 6].

A 19-year-old man with refractory leukemia was treated with amoxicillin-clavulanate for neutropenic fever due to \textit{Escherichia coli} bacteremia. Serum samples were examined daily for the presence of galactomannan antigen with the use of the Plateia Aspergillus kit (BioRad). One day after the initiation of antibiotic treatment, antigen levels abruptly increased from an optical density (OD) index of 0.1 to high values (OD index, >1.5) in 5 consecutive serum samples, followed by a gradual decrease after the patient was switched to quinolone therapy. There were no other data supportive of invasive aspergillosis. One week later, treatment was started with piperacillin-tazobactam because of acute appendicitis followed by an immediate re-emergence of antigenemia (OD index, ≥2.5). The patient simultaneously developed signs of lower respiratory tract infection and bilateral nodular infiltrates, which were noted on a chest radiograph.

In accordance with the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC-MSG) criteria [3], a diagnosis of probable invasive aspergillosis was made. Therapy was switched to meropenem and an investigational antifungal; there was a decrease in the antigen level before the patient died. However, autopsy revealed massive leukemic infiltration of the lungs without evidence of fungal involvement.

The development of diagnostic criteria represents one of the most important advances in the current and future study of fungal infections, and it should not be tripped up by this or similar reported cases. However, a regular fine-tuning of these definitions based on the ongoing evaluation of these noninvasive diagnostic tools is clearly taking place. At present, we believe that patients with a diagnosis of probable invasive aspergillosis that is based on no microbiological criterion other than positive results of antigenemia assays should be excluded from clinical trials in this field if they are receiving piperacillin-tazobactam or amoxicillin-clavulanate.

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