^{18}F-FDG PET/CT as a Sensitive and Early Treatment Monitoring Tool: Will This Become the Major Thrust for Its Clinical Application in Infectious and Inflammatory Disorders?

In the June 2011 issue of *The Journal of Nuclear Medicine,* Sathekge et al. (*1*) examined the reliability of ^{18}F-FDG PET/CT in differentiating tuberculosis-infected HIV patients who respond to anti-Koch therapy from those who do not respond. The authors reported that at 4 mo there was an excellent sensitivity, specificity, and negative predictive value and a modest positive predictive value. Such an observation is important, because shifting to alternative regimens is a crucial and defining step in patients who have multidrug-resistant and extensively drug-resistant tuberculosis. Both these entities pose a significant challenge to health care, and their early definitive identification will prove extremely useful in the management of tuberculosis. Hence, such studies need to be increasingly undertaken, and the countries of the developing world, where the prevalence of this disease is relatively high, can play an active role. The paper of Sathekge was a highlight of the June issue, and I would like to congratulate the authors on their work. In our own initial experience with a few patients (unpublished data; 2010–2011), a significant response was documented as early as 6 wk after treatment initiation. For a standard case of tuberculosis, the most common regimens adopted upfront after diagnosis are either isoniazid, rifampicin, ethambutol, and pyrazinamide daily for 2 mo, followed by 4 mo of isoniazid and rifampicin, or streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 2 mo, followed by 4 mo of isoniazid and rifampicin. It can be presumed that if ^{18}F-FDG PET/CT could reliably differentiate responders from nonresponders at 2 mo, a time point at which physicians choose a battery of tests (e.g., assessment of sputum, smears, and cultures in addition to clinical and radiologic assessment) to detect treatment response or failure, ^{18}F-FDG PET/CT could be used as an important objective parameter in the management of tuberculosis. In line with the observations of the authors, our preliminary experience suggests that the change in ^{18}F-FDG uptake after initiation of anti-Koch therapy in tuberculosis is certainly not so dramatic as is observed in patients with tumors such as gastrointestinal stromal tumors on imatinib therapy, and thus there is a need to generate appropriate PET metrics in subsequent studies to distinguish responders from nonresponders.

The role of ^{18}F-FDG PET/CT in monitoring therapeutic efficacy has been relatively more successful in several systemic inflammatory conditions and granulomatous diseases such as sarcoidosis (*2*) and vasculitis (*3*), for which the initiation of steroid therapy normalizes ^{18}F-FDG uptake in disease foci and indicates clinical response simultaneously with or even before normalization of laboratory data. Several other infectious inflammatory conditions are being examined, and multiple anecdotal case reports and series in the literature document the utility of this modality in monitoring the efficacy of antiinfective therapy. One would expect that these investigations will have a positive outcome and that this promising molecular imaging technique will find a useful role in clinically challenging patients with this group of disorders.

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Sandip Basu
Radiation Medicine Centre (BARC)
Tata Memorial Hospital Annexe
Jerbai Wadia Rd.
Parel, Mumbai 400 012, India.
E-mail:drsanb@yahoo.com

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REPLY: We thank Dr. Basu for his thoughtful and detailed suggestion that ^{18}F-FDG PET/CT might also reliably differentiate responders from nonresponders at 2 mo. It is correct and important to conduct a microbiologic evaluation 2 mo after initiation of treatment. However, patients with positive cultures after 2 mo of treatment should undergo careful evaluation to determine the cause. In patients who have not been under direct observation during therapy, the most common reason for positive cultures after 2 mo is nonadherence to the regimen. Other possibilities are, of course, drug resistance and biologic variation in response (*1*). Hence, our study was designed as per the guidelines, in that patients whose sputum cultures remain positive after 4 mo of treatment should be deemed treatment failures (*1*). Also, second-line drug susceptibility testing is done only in reference laboratories and is limited to specimens from patients who have positive cultures after more than 3 mo of treatment.

Furthermore, our recent publication (*2*) was based on the fact that we wanted to evaluate the results without possible confounding factors such as immune reconstitution disease associated with tuberculosis. Immune reconstitution disease is rather common in HIV-associated tuberculosis because some of the risk factors include early initiation of antiretroviral therapy during tuberculosis treatment, low baseline CD4 cell counts, disseminated tuberculosis, and rapid immune and virologic responses to antiretroviral therapy (*3,4*). As such, the impact of immune reconstitution disease on PET/CT needs to be addressed when one is considering the use of ^{18}F-FDG PET during treatment.

Finally, we agree that the timing for follow-up imaging is unclear and should be revisited, even more so because common regimens adopted upfront after the diagnosis of tuberculosis are isoniazid, rifampicin, ethambutol, and pyrazinamide (HREZ) daily for 2 mo, followed by 4 mo of isoniazid and rifampicin (HR), or

streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 2 mo, followed by 4 mo of HR. The consideration of response to treatment at 6–8 wk may determine the extension of 2 mo of HREZ and 4 mo of RE to 3 and 6 mo, respectively, or to 3 and 9 mo, respectively, or the use of a second-line regimen. This type of work may also help to determine whether one can justify regimens such as either 3 mo of HREZ and 6 mo of HR or 3 of HREZ and 9 mo of HR, which have not been objectively validated. This would have potential implications in identifying cases of drug-resistant tuberculosis and tailoring the treatment.

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Mike Sathekge*
Alex Maes
Christophe Van de Wiele
**University of Pretoria*
Pretoria Academic Hospital
Private Bag X169
Pretoria 0001, South Africa
E-mail: mike.sathekge@up.ac.za

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