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Monitoring Response to Therapy

Mike M. Sathekge, MD, PHD,* Alfred O. Ankrah, MD,*,† Ismaheel Lawal, MD,* and Mariza Vorster, MD, PHD*

Monitoring response to treatment is a key element in the management of infectious diseases, yet controversies still persist on reliable biomarkers for noninvasive response evaluation. Considering the limitations of invasiveness of most diagnostic procedures and the issue of expression heterogeneity of pathology, molecular imaging is better able to assay in vivo biologic processes noninvasively and quantitatively. The usefulness of ^{18}F-FDG-PET/CT in assessing treatment response in infectious diseases is more promising than for conventional imaging. However, there are currently no clinical criteria or recommended imaging modalities to objectively evaluate the effectiveness of antimicrobial treatment. Therapeutic effectiveness is currently gauged by the patient's subjective clinical response. In this review, we present the current studies for monitoring treatment response, with a focus on *Mycobacterium tuberculosis*, as it remains a major worldwide cause of morbidity and mortality. The role of molecular imaging in monitoring other infections including spondylodiscitis, infected prosthetic vascular grafts, invasive fungal infections, and a parasitic disease is highlighted. The role of functional imaging in monitoring lipodystrophy associated with highly active antiretroviral therapy for human immunodeficiency virus is considered. We also discuss the key challenges and emerging data in optimizing noninvasive response evaluation.
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Introduction

Despite new antimicrobial drugs licensed in recent years, infection remains among the leading causes of death, taking the life of 10-15 million people every year.[1] This is further exacerbated by the syndesmosis of human immunodeficiency virus (HIV) and tuberculosis (TB), leading to the majority of fatal cases occurring in the developing world.[2]

Even in developed countries, treatment of patients with infections is becoming increasingly difficult because of rising rates of antimicrobial drug resistance. The evolution of antimicrobial resistance is exacerbated by the overuse and inappropriate use of antimicrobials, and complicated by the evolutionary capacity of infectious pathogens to adapt to new ecological niches created by human endeavor.[1] Complicating matters is the unpredictability of infectious diseases in general and their potential for explosive global effect, as exemplified by the current pandemics of HIV and TB. Hence, this back-and-forth struggle between human ingenuity and microbial adaptation is a perpetual challenge.[3-5] As such, our response to these challenges must also be perpetual and able to circumvent the adaptations of these microbial agents. Chief among a number of approaches to meet this ever-present challenge is to optimize monitoring of response to therapy.

*Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, South Africa.
†Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, Groningen, The Netherlands.
Address reprint requests to Mike M. Sathekge, MD, PHD, Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Private Bag X169, Pretoria 0001, South Africa. E-mail: mike.sathekge@up.ac.za

Biomarkers for Monitoring Response to Therapy

The World Health Organization defines a biomarker as an objectively measured characteristic used as an indicator of a normal or pathologic biologic process or a pharmacologic response. As such, an ideal biomarker for infection must possess diagnostic, prognostic, and follow-up therapy characteristics.[6] Furthermore, biomarkers should be both sensitive and specific, measurable with good precision and reproducibility, readily available, affordable, responsive to minor changes, and provide timely results.[7] However, in clinical practice, there is a considerable overlap of biomarker values between different infectious (bacterial, viral, parasitic) and noninfectious etiologies. These limitations have been demonstrated on both commonly used biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), white blood cell, or neutrophil count, and the still experimental and not commercially available biomarkers such as soluble urokinase-type plasminogen

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activator receptor, soluble triggering receptor expressed on myeloid cells, and macrophage inhibitory factor.[8] Some of the reasons why these biomarkers cannot be expected to become isolated "magic bullets" are the relevant causes of false-positive and false-negative results of these biomarkers. For instance, the CRP response is blunted in fulminant hepatic failure, but overall the clinical relevance of renal dysfunction, chronic liver insufficiency, and corticosteroid treatment on PCT and CRP seems to be negligible.[9] PCT levels in the absence of bacterial infections are higher in patients with chronic kidney disease than in those without, and levels decrease after renal replacement therapy with either transplant renal graft or hemodialysis. The magnitude of these differences in PCT levels depends on the method used to assay the biomarker.[10] Microbiological markers such as blood cultures and PCR methods still have relatively low sensitivity and lack accurate prognostic rules. Thus, there is an ongoing unmet need for biomarkers that can reliably distinguish between responders and nonresponders and help to optimize antimicrobial treatment decisions. The consequences of this unmet need include an increase in multiresistant pathogens, high costs for inpatient care, and potential adverse outcomes. Hence, available evidence needs to be better incorporated into clinical decision-making, including imaging.

Imaging as a Biomarker for Monitoring Response to Therapy

Given the complexities of the infection response, no 1 biomarker will be sufficient to diagnose and monitor infection. Combinations of biomarkers are needed, and molecular imaging is gaining prominence in this regard.

MRI and conventional nuclear medicine tests can be employed to assess response to therapy. However, these approaches may become accurate only months after complete eradication of the infection and therefore cannot be used to provide an early assessment of therapeutic efficacy.[11] As a result of the limitation of these imaging modalities coupled with the expression heterogeneity by pathology, molecular imaging with PET/CT is better able to assay in vivo biologic processes noninvasively and quantitatively. Molecular imaging has been a particularly attractive tool for monitoring treatment in clinical cancer practice. The radiotracer ^{18}F-FDG is widely used in clinical medicine for noninvasive imaging, staging, and monitoring treatment responses of neoplastic diseases.[12,13] ^{18}F-FDG has also been used to image infection and inflammation, because detection is proportional to the glycolytic activity of the cells that trap it.[14-16]

The accumulation of ^{18}F-FDG in inflammatory and infectious diseases is based on the high uptake in activated leukocytes, which use glucose as an energy source only after activation during the metabolic burst. Transport of ^{18}F-FDG across the cellular membrane is mediated by the glucose transporter proteins, which have increased expression on the cell membrane of inflammatory cells.[17,18] Rabkin et al showed that although hyperglycemia led to a higher false-negative rate in patients with cancer it had, in contrast, no significant effect on the detectability rate of infectious foci.[19] There is currently a lack of approved guidelines for monitoring response with ^{18}F-FDG-PET/CT; however, rapidly growing data appear to show ^{18}F-FDG-PET/CT is valuable for therapy monitoring in some infectious and inflammatory diseases. The data indicate that ^{18}F-FDG-PET/CT could even play a pivotal role in the management of infections, leading to better drug dosage, confirm the usefulness of the treatment, and early modification of the therapeutic strategy. Moreover, recent interesting findings by Kagna et al[20] demonstrate that antibiotic treatment appears to have no clinically significant impact on the diagnostic accuracy of ^{18}F-FDG-PET/CT performed for the assessment of known or suspected infectious processes, despite the long duration of appropriate antimicrobial treatment. This means that in spite of the appropriateness of the administered antibiotics, if there is poor, delayed, or lack of response, ^{18}F-FDG-PET will remain positive. Importantly, Kagna et al[20] recommended that further prospective well-designed studies are needed to determine whether serial maximum standardized uptake value (SUVmax) ^{18}F-FDG measurements will indeed be able to demonstrate therapy control and define response to antibiotics in various infectious processes.

Quantifying Response

Determining an accurate and repeatable means of evaluating response to therapy remains a challenge in patients with infection. An objective assessment of response of the primary site of infection and any metastatic foci is necessary to measure therapeutic effect. One such method makes use of SUVmax.[21]

Some problems associated with quantifying response in infection include:

- In clinical practice, a baseline study is unlikely to have been done
- Limited data and poor correlation between serum biomarkers and imaging biomarkers
- SUV cutoff value (threshold) not established
- Delta SUVmax between 2 studies (baseline and follow-up) not established
- Time point during the course of treatment when the follow-up scan must be done
- Definition of the region of interest is more difficult than with solid tumors
- No clear guidelines on interpretation of mixed response (especially in TB)
- General and technical issues of quantification of SUV

Most studies have focused on changes in SUV between baseline and follow-up scans. Treatment response is considered as decrease in SUVmax between the baseline and the follow-up studies. In a study of 38 patients with spondylodiscitis, the delta-SUVmax had a higher sensitivity for early identification of responders than CRP levels.[22] In another study, the response to antibiotic treatment was defined by a significant reduction in SUVmax between baseline and post-treatment PET/CT studies in 15 patients with infectious