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Commentary

Biomarkers for Treatment Monitoring in Tuberculosis: A New Hope

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Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis* (Mtb) and can manifest as either TB infection or disease (pulmonary or extra-pulmonary TB). TB is a major public health problem worldwide with approximately 10 million new cases every year and 1.7 million deaths per year (Pai et al., 2016). Moreover, TB infection is estimated to be present in nearly one third of the world's population in a latent form and represents a source of active TB disease in the future. The need for TB biomarkers arises due to the fact that TB is hard to diagnose – the current gold standard is sputum culture, which takes weeks or a molecular diagnostic test (GeneXpert MTB/RIF), which is not universally available (Wallis et al., 2016). In fact, the most widely used diagnostic test is the detection of mycobacteria in sputum, which has a sensitivity of 34–80%. Host biomarkers are therefore needed to diagnose tuberculosis (both pulmonary and extra-pulmonary), to distinguish TB infection and disease, to provide correlates of protection against active TB and correlates of risk for the development of active disease and to determine the response to anti-TB treatment (Walzl et al., 2011).

The current regimen for treating pulmonary TB requires a minimum of 6 months, involves a combination of at least 4 drugs with varying toxicity profiles, and is therefore marked with problems of compliance and adherence. There is a great deal of interest in shortening the duration of treatment using either existing drug combinations or with the addition of new drugs as well as renewed interest in both re-purposing old drugs for TB treatment and utilizing host-directed therapy as an adjunct measure (Wallis et al., 2016). The common measure used to assess efficacy in clinical trials is the sputum culture conversion status at 2 months post-therapy in solid or liquid media. However, the major drawback of using this measure is the requirement of large sample sizes for evaluation of new trial regimens. Therefore, there is an imperative need to identify blood based biomarkers that, if found valid, would improve the efficiency of this process (Nahid et al., 2011).

Given this background, Sigal et al. have performed an elegant study of 70 different markers of infection, inflammation and metabolism in 319 sputum culture positive, pulmonary TB individuals (Sigal et al., 2017). The markers were evaluated at the beginning of treatment and at 8 weeks after treatment initiation. Samples originated from five locations on three continents, included both HIV + and HIV − individuals as well as different age groups. Apart from the inclusive nature of the individuals in this study, the study also was performed using biomarker assays that were specifically developed for this study and quantified using a multiplex platform. This helps in greatly improving the reliability of the study as it encompasses different geographic regions and also uses a validated single platform which overcomes the challenge of harmonizing different techniques. This is also aided by the fact that all the individuals in the study were Mtb culture positive and were clinically and radiologically well defined.

The authors have identified seven different proteins, SAA1, PCT, IL-1b, IL-6, CRP, PTX-3 and MMP-8 as markers of baseline TB disease severity and bacterial burdens. These proteins were also shown to be down modulated by anti-TB treatment, suggesting that they could serve as biomarkers for both TB treatment monitoring and baseline severity and/or extent of disease. Biomarkers that changed significantly following treatment also included MMP-1, IL-22 and VEGF. Thus, the authors postulate that the findings in the context of a rigorously conducted clinical trial and the consistency of these results imply an important biological association of these markers with TB disease and would need to be pursued further for validation. Of related interest, the study did not find a significant association of previously reported biomarkers including HMOX1, neopterin and cathelicidin with the treatment response. Some of the limitations of the study include the absence of follow-up samples past the early 8 week time point and absence of a comparator arm at baseline (such as latent TB controls). Typically, studies monitoring treatment response are conducted at 6 months to a year following treatment initiation. Additionally, the sample size was too small to conduct rigorous subgroup analysis by HIV status, diabetes status, age, sex or geography, which would have been informative in this context. Moreover, the genotyping of the mycobacterial strains was not reported and could be a confounding factor in the results. Finally, disease severity

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was assessed only in terms of microbiological burdens and chest X-ray results and more advanced imaging techniques including CT or PET-CT could have provided more detailed analysis of disease pathology (Cadena et al., 2017).

Nevertheless, the study has been able to replicate important findings in terms of biomarker associations with TB and to identify novel biomarkers that could be useful for evaluating disease severity and treatment monitoring (Rockwood et al., 2016, Wallis et al., 2009). It would be imperative to follow up these findings in larger cohorts with additional follow-up time points that could correlate treatment outcomes of failure and relapse. The application of these biomarkers in the setting of extra-pulmonary TB and childhood TB, wherein sputum examination is either not useful or logistically difficult could also enhance the utility of these findings. Finally, as always, the development of a point-of-care test, incorporating these parameters, is the new hope in the landscape of TB control and elimination.

Disclosure

The author declares no conflicts of interest.

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