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Commentary

Biomarkers for Identifying Risk of Immune Reconstitution Inflammatory Syndrome

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In the last 10–20 years, access to antiretroviral therapy (ART) has improved worldwide, resulting in substantial reduction in HIV-associated mortality and increased life expectancy, especially in low and middle-income countries. However, immune reconstitution inflammatory syndrome (IRIS), the clinical deterioration in patients with HIV initiating ART, is a common complication of ART initiation. The manifestations of IRIS depend on the type of opportunistic infection. With HIV-1 as the strongest predisposing factor to tuberculosis (TB) and TB as the commonest cause of death in HIV-1 infected persons in Africa, the otherwise beneficial dual therapy for HIV-1 and TB is frequently complicated by the occurrence of TB-immune reconstitution inflammatory syndrome (TB-IRIS) (Walker et al., 2015). Two forms of TB-IRIS are recognized: paradoxical, which occurs in patients established on antituberculosis therapy before ART, but who develop recurrent or new TB symptoms and clinical features after ART initiation; and unmasking TB-IRIS in patients not receiving treatment for TB when ART is started, but who present with active TB within 3 months of starting ART (Meintjes et al., 2008). Paradoxical TB-IRIS affects approximately 15.7% of all HIV-1-infected patients commencing ART while on TB treatment, and up to 52% in some populations, causing considerable morbidity and mortality (Namale et al., 2015).

While the clinical features are relatively well-described, specific diagnostic tools and treatments for TB-IRIS are lacking. The diagnosis of IRIS is clinical, and excluding other causes for a clinical deterioration, such as other opportunistic infections and drug-resistance, is challenging, especially in a resource-limited setting. While risk factors for IRIS have been identified, such as low CD4 count pre-ART initiation and the presence of a disseminated opportunistic infection, there are no biomarkers that predict which patients will develop IRIS. The identification of biomarkers for IRIS prediction may help elucidate the mechanism of IRIS pathogenesis, which may in turn facilitate the development of specific therapies and additionally, allow high-risk patients that would benefit from specific preventative strategies to be identified.

A large number of investigations have addressed the roles played by different aspects of the immune response in contributing to TB-IRIS pathogenesis, reviewed in Lai et al. (2015a). A recent unbiased whole-blood transcriptomic profiling of HIV-TB co-infected patients commencing ART showed that inflammation in TB-IRIS is driven by innate immune signaling and activation of the inflammasome, which triggers the activation of transcription factors leading to hypercytokinemia, resulting in systemic inflammation (Lai et al., 2015b). Other recent work also suggests that extracellular matrix destruction by matrix metalloproteinases may play a role in paradoxical TB-IRIS (Tadokera et al., 2014; Shruthi Ravimohan, 2015). Immunosuppressive corticosteroid therapy improves symptoms and reduces hospital admissions but is not without adverse events, and is potentially detrimental in cases of drug-resistant TB (Meintjes et al., 2010). Therefore therapeutic strategies that offer greater immune specificity should be explored.

The CADIRIS study, a double-blind, randomized, placebo-controlled trial, investigated the use of maraviroc (a CCR5 antagonist) for IRIS prevention, based on the hypothesis that inflammatory cytokines and chemokines mediate the influx of CCR5-expressing immune cells in IRIS and CCR5 blockade would prevent these inflammatory cells leaving the circulation, reducing local inflammatory reactions leading to IRIS. The study recruited HIV-infected participants with advanced immunosuppression (CD4 count $<100/\mu l$) from five clinical sites in Mexico and one in South Africa and followed them for 1 year. Patients were assigned to receive either maraviroc (600 mg twice daily) or placebo in addition to ART, the primary outcome being time to an IRIS event by 24 weeks. Maraviroc had no significant effect on development of IRIS after ART initiation. While this CCR5 inhibitor has proven antiviral activity, safety and tolerability as part of an ART regimen, its use as an immune-modulator to prevent IRIS appears un-warranted (Sierra-Madero et al., 2014).

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Well-conducted clinical trials, even if their outcome is negative, are an enormously valuable resource for further studies, such as identifying correlates of risk and/or protection. In this issue of *EBioMedicine*, Musselwhite and colleagues (Musselwhite et al., 2016) investigate plasma biomarkers predictive of IRIS in samples banked at enrolment from HIV-infected patients entering the CADIRIS trial. With the hypothesis that the risk of IRIS is most likely already present before starting ART, and can be predicted from measuring biomarkers in plasma samples collected before starting ART, they assessed twenty biomarkers in an exploratory way, and retrospectively associated them with the risk of developing IRIS. Of the 267 patients with banked plasma samples, 62 developed IRIS within 6 months of ART initiation, 31% of them TB-IRIS specifically, within median of 13 days of ART. The results indicate that baseline concentrations of vitamin D and higher concentrations of D-dimer, as well as markers of T cell and monocyte activation (interferon-γ and sCD14) were independently associated with risk of IRIS in general. Vitamin D deficiency was prevalent. Higher vitamin D levels were associated with protection against IRIS events, suggesting vitamin D plays an immune-modulatory role. However, vitamin D and D-dimer concentrations were not associated with TB-IRIS specifically, perhaps due to lack of power for this sub-analysis. TB-IRIS was associated with higher concentrations of CRP, sCD14, and interferon-γ and lower hemoglobin than other forms of IRIS and these parameters were used in a composite score to predict TB-IRIS over Other IRIS, with an area under the curve of 0.85 (CI 0.79-0.92) on Receiver Operator Characteristics (ROC) analysis.

The strength of this study lies in reasonable power to assess predictors of IRIS and the availability of plasma samples prior to starting ART on two different continents, contributing to the generalizability of the findings. Interesting comparisons are drawn between TB-IRIS and other causes of IRIS, demonstrating heterogeneity in IRIS pathophysiology. As patients with CD4 counts ≥100/μl and those with critical illness (e.g. severe laboratory abnormalities, CNS infections) were excluded, generalizability of the findings to these groups is unknown. Further work is required to confirm the findings in these and other at-risk patient populations.

Disclosure

The authors declared no conflicts of interest.

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