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Interleukin-1 receptor antagonist, a biomarker of response to anti-TB treatment in HIV/TB co-infected patients

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Summary *Objectives:* Despite the high frequency of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in human immunodeficiency virus (HIV)/TB co-infected patients, no diagnostic test is available. Here, we investigated whether monocyte/macrophage activation markers can predict TB-IRIS occurrence and if they are modulated by anti-TB treatment.
Methods: Frozen plasma was obtained from 127 HIV/TB co-infected adults naïve for antiretroviral therapy, enrolled in the CAMELIA trial, 36 of whom developed TB-IRIS. Concentrations of IL-1Ra, sCD14, and sCD163 were measured at anti-TB treatment onset (baseline), after 8 weeks of anti-TB treatment and at TB-IRIS time.
Results: At baseline, IL-1Ra and sCD14 concentrations were similar in TB-IRIS and non-IRIS

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patients. sCD163 concentrations, although significantly higher in TB-IRIS patients, did not remain associated with TB-IRIS occurrence in multivariate analysis. At the time of TB-IRIS, patients displayed higher concentrations of IL-1Ra ($p = 0.002$) and sCD14 ($p < 0.001$). The most striking result was the significant decrease in IL-1Ra after 8 weeks of anti-TB treatment (median reduction: −63% ($p < 0.0001$)).

Conclusions: None of the biomarkers tested was associated with TB-IRIS occurrence. However, repeated measurement of IL-1Ra could help for the diagnosis of TB-IRIS. The substantial reduction of IL-1Ra under treatment suggests that IL-1Ra could be a surrogate biomarker of anti-TB treatment response in HIV-infected patients.

Introduction

Tuberculosis (TB) remains the most common opportunistic infection in human immunodeficiency virus (HIV)-infected patients. Even in the context of expanded access to potent antiretroviral therapy (ART), HIV/TB co-infection is still a major worldwide health threat.[1] Early initiation of ART in HIV-TB co-infected patients has been shown to significantly decrease morbidity, AIDS progression, and mortality.[2–5] However some patients experience clinical deterioration shortly after ART initiation despite virological efficacy. This clinical condition, known as immune reconstitution inflammatory syndrome (IRIS),[6,7] is associated with an exaggerated inflammatory response to either a previously diagnosed and treated infection (paradoxical IRIS) or to an unrecognized and untreated infection (unmasking IRIS).[8] Paradoxical TB-associated IRIS (TB-IRIS) occurs more frequently in patients starting ART early after initiation of TB treatment, especially when they are severely immunosuppressed.[9,10] The Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) clinical trial (ANRS 1295 − CIPRA KH001)[3] was a prospective, multicenter, randomized, open-label 2-arm superiority trial conducted in Cambodia, designed to determine the optimal timing of ART initiation after TB treatment onset in ART naïve, HIV-infected adults with CD4 counts $\leq 200/mm^3$ and newly diagnosed smear-positive TB.[3] Three hundred thirty two and 329 patients were randomized to initiate ART at 2 weeks (early arm) and 8 weeks (late arm) after anti-TB treatment, respectively. TB-associated IRIS occurred in 26% of patients irrespective of the study group. On the one hand, it was demonstrated that early ART initiation after TB treatment onset significantly reduced mortality in severely immunosuppressed HIV-TB co-infected patients; on the other hand, shortening the delay to initiate ART after anti-TB treatment onset increased the risk of developing TB-IRIS, especially when TB was extrapulmonary or disseminated.[3,9,11,12]

IRIS has been related to exaggerated innate and/or adaptive immune responses.[13–16] TB-IRIS was associated with exuberant Th1 response and increased proportions of KIR-negative $\gamma\delta^+$ T cells.[17] TB-IRIS was also associated with high levels of pro-inflammatory cytokines including IL-1β, IL-6 and IL-18,[15,16,18–21] elevated levels of acute phase proteins,[15,22,23] and D-dimer,[22–24] as well as high levels of NK-cell degranulation.[25]

We put forward the hypothesis that the degree of activation of monocyte/macrophages before anti-TB treatment and ART could predict the occurrence of TB-IRIS in HIV/TB co-infected patients. The frequency of activated monocytes was associated with several pro-inflammatory cytokines before and after ART initiation.[13] Monocytes and macrophages are innate immune cells that play a pivotal role in the pathogenesis of TB infection by initiating inflammatory response at the early stage of infection.[26] In their activated state, monocytes and macrophages release soluble forms of receptors including CD14 and CD163, and cytokines including the IL-1 receptor antagonist, IL-1Ra. Secreted by monocytes, neutrophils and epithelial cells, IL-1Ra is a naturally occurring competitive inhibitor of the pro-inflammatory cytokines IL-1α and IL-1β[27] secreted in concert with IL-1β.[28] Indeed, IL-1β, although released, cannot be reliably measured due to its short half-life in plasma.[28,29] In the present study, we thus chose to measure concentrations of circulating IL-1Ra rather than IL-1β. By binding to IL1-R1 receptor, IL-1Ra inhibits IL-1 signaling thereby performing a regulatory function on monocyte activation.[27] IL-1Ra levels were reported to be increased in broncho-alveolar lavage and serum of patients with pulmonary TB.[30] Also, gene polymorphisms of IL-1Ra have been associated with severe manifestations of sepsis.[31]

CD14 is a glycosylphosphatidylinositol-anchored protein, expressed on monocytes and macrophages that facilitates the transfer of lipopolysaccharide (LPS) to the TLR4/MD-2 receptor complex and modulates LPS recognition.[32] A soluble form for CD14 (sCD14) is secreted by monocytes/macrophages following LPS stimulation and by liver cells as an acute-phase protein.[33] In HIV-infected patients, plasma concentrations of sCD14 are increased, correlate with disease progression and predict all-cause mortality.[34,35] In primary HIV infection, sCD14 and IL-1Ra levels predict the T-cell activation set point, itself predictive of progression.[36]

Soluble CD163 (sCD163) is a hemoglobin−haptoglobin scavenging receptor that is shed from activated monocyte/macrophages. Even though sCD163 is associated with monocyte activation and inflammatory reactions, it has also an anti-inflammatory effect and is believed to be involved in resolving inflammation.[37] Elevated levels of sCD163 have been reported in HIV-infected patients, particularly in association with arterial inflammation and cardiovascular disease.[38,39] In addition, sCD163 concentrations were suggested to predict mortality in TB patients, independently of HIV status.[40]

These biomarkers, IL-1Ra, sCD14 and sCD163 are of potential interest for the diagnosis or the prediction of TB-IRIS. In addition, they could also be potential biomarkers for the evaluation of anti-TB treatment responses.