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Review Article

Immune Restoration Disorders in Patients with AIDS and Tuberculosis: Novel Treatment Approaches

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Abstract

Tuberculosis (TB) is the most frequent and treacherous opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) worldwide. In this review, we discuss the pathological immune restoration in AIDS patients coinfected with Mycobacterium Tuberculosis after starting ART (antiretroviral therapy). We overview how the immune deregulation predisposes to and drive the immune reconstitution inflammatory syndrome (TB-IRIS). We describe how poor recovery and maturation of T and NK cells, and the exuberant cytokine response produced by innate and adaptive immune cells marks the manifestations of TB-IRIS.

We conclude by discussing the various standard-of-care and novel treatment approaches.

Keywords: Immune Reconstitution Inflammatory Syndrome; Tuberculosis-IRIS; TB-IRIS; AIDS; HIV; Interferons; Cytokines; T Cell Response; Innate Immunity

Introduction

Immune reconstitution inflammatory syndrome in AIDS patients co-infected with MTB

Tuberculosis (TB) is the most frequent and treacherous opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) worldwide. In late-stage HIV-infected patients, Tuberculosis (TB) is the most frequent opportunistic infection and is the major reason for morbidity and mortality, and TB-IRIS is a major clinical concern after ART initiation [1-3]. The leading manifestations of TB-IRIS are fever and exacerbating respiratory symptoms of miliary tuberculosis with worsening consolidations and pulmonary infiltrates [4,5].

Extrapulmonary TB-IRIS manifestations primarily include tuberculous meningitis, intracranial tuberculomas, or osteomyelitis [6,7]. The mortality and morbidity rates attributable to paradoxical TB-IRIS are elevated in settings where there are limited options for diagnosis and treatment [8-11].

The manifestations of TB-IRIS usually occur within 2-3 months of ART initiation or regimen change because of treatment failure [12,13]. The early-onset (< 1 month on ART) and late-onset (> 1 month on ART) TB-IRIS forms had been reported [14]. Recently proposed international network for the study of HIV-associated IRIS (INSHI) case definition system includes few radiographic imaging and immunological parameters with the proven diagnostic ability for either form of TB-IRIS. These include elevated levels of C-reactive protein (CRP), abnormal chest radiographs, and low pre-ART CD4+ T cell counts (< 100 cells/μl) [15]. Unfortunately, there is no laboratory diagnostics to definitively confirm TB-IRIS syndrome.

Kinetics of immune reconstitution in patients receiving antimicrobial and antiviral therapies

During Immune reconstitution, the kinetics of immune mediators in blood and cerebrospinal fluid (CSF) demonstrated increased levels of the innate pro-inflammatory cytokines IL1, IL6, IL8, and TNFA (tumor necrosis factor alfa) in patients co-infected with HIV and Mycobacterium tuberculosis (MTB) [16-18]. Before the beginning of ART, there has been an increased level of IL6 and IL18 and low levels of IL27, in patients at risk for TB-IRIS, and then followed by the expansion of inflammatory monocyte subsets and inflammasome activation during TB-IRIS events [19-23]. Cytokines such as granulocyte-colony stimulating factor (GCSF), CRP, interleukins IL1B, IL1RA, IL6, IL8, IL18, IFNG (interferon-gamma), TNFA, and soluble tissue factors increased in plasma and serum after ART initiation [24,25] (Figure 1). Along with these cytokines, the increases of IL12p40, IL1β, GMCSF, TNF, IL10, IL6, IL2 and IL8 in serum and in PBMC (peripheral blood monocyte cell) culture supernatants render TB patients susceptible to TB-IRIS and early mortality [20,26]. These parameters represent the baseline risk factors for TB-IRIS, followed by the kinetic that is different from favorable cellular immune reconstitution on ART and that, which accelerates toward TB-IRIS event [27-29].

Recent genetic studies found the association of IRIS onset with KIR2DS2 (Killer Immunoglobulin-like Receptor, two Immunoglobulin Domains and Short cytoplasmic Tail 2), HLA-B*41, and KIR+/HLA-C genotypes among TB-HIV co-infected patients [30]. In patients at risk, NK/T cells have shown higher expression of the cytotoxic mediators (granzyme B and perforin) and certain effector T cell receptor subunits, which in turn amplifies the degranulation potential of effector T cells, creating a pro-inflammatory environment [31-33]. There has been a higher degranulation capacity of NK cells in patients with TB-IRIS before ART and after 2 weeks of TB treatment initiation, followed by lower expression of mature NK cell activating receptors (NKp30/p46, NK Group NKG2D) [28]. The expression of NKG2D (CD314+) on NK/T cells is lower in HIV-TB patients after ART initiation and the killer cell immunoglobulin like receptors (CD158a) expression was higher in TB-IRIS compared to non-IRIS patients before ART [34]. NK cells are activated during TB-IRIS events, and express higher readiness to migrate (CXCR1+, CXCR2+) in response to several pro-inflammatory mediators (C-reactive protein, IL8, etc.) [35].

During inflammation, MTB antigens and residual live mycobacteria activate toll-like receptor (TLR) signaling and inflammasome cascade, thereby causing notable damage to target cells and tissues [36-38]. Inflammasome, a multiprotein intracellular complex, is activated in macrophages, monocytes, and neutrophils and a role in systemic inflammation and fatal TB-IRIS outcomes [38-42]. Multiple elements of inflammasome activation occur via NLR- TREM1-pathways (NOD-like; and triggering receptor expressed on myeloid cells 1), representing exaggerated innate cells' response toward ongoing viral replication and microbial antigens [43]. Studies have also found that the inflammasome pathway is a driver of CD4+ T cell depletion in HIV1-TB infection which delays immune reconstitution and serves as a biomarker of immune restoration pathology [44]. Thus, the inflammasome pathway overexpression in cells of the innate immune system represents a biomarker of systemic inflammation and significant pathology at the site of IRIS, e.g., the central nervous system in cases of TB-meningitis IRIS [21,45-47].

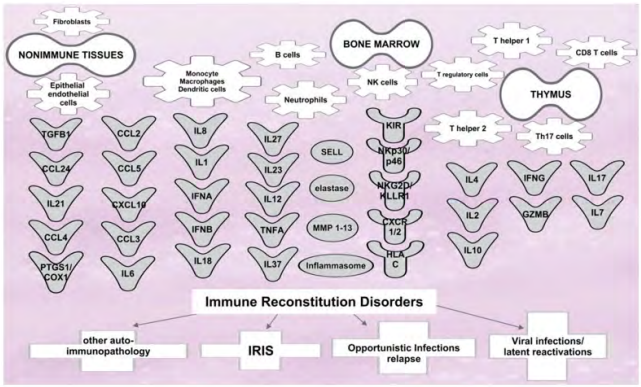

Figure 1: Cytokines, soluble factors, and cellular receptors, which play role in tuberculosisassociated immune reconstitution disorders.

In the early stages of immune restoration, CD4+, CD8+ T cells, NK/T cells express markers of lymphocytes exhaustion [48]. The expression of KLRG1 and PD-1 (programmed cell death 1) on CD4+ T cells and NK cells during recovery is similar in patients who developed TB-IRIS and survived, but low expression confers protection against MTB reactivation and over-exaggerated immune response to MTB antigens during IRIS [29,49,50]. Adaptive CD4+ T cells (together with CD8+ T cells) prompt to secrete higher amounts of IFNG and many other pro-inflammatory cytokines in

response to TB antigens, which may lead to the over-exuberant cytokine response (Figure 1) [51,52]. This may particularly be attributable to early-onset forms of TB-IRIS since late-onset TB-IRIS patients showed a T cell maturation shift towards more mature T cell subtypes [14].

In the search for potential biomarkers, a recent study tested a panel of seven anti-neutrophil cytoplasmic antibodies (ANCAs) in the blood of patients who developed TB-IRIS after ART initiation. Only one marker, an anti-elastase antibody found to be significantly lower at ART initiation, and the other (anti-proteinase 3, anti-myeloperoxidase, anti-bacterial permeability-increasing protein, anti-cathepsin, -lysozyme, -lactoferrin) are not [53]. Taken into account that expression of elastase increases at the time of TB-IRIS events [41], exploration of anti-elastase as a potential therapeutic agent to decrease neutrophils activation is plausible.

Novel and standard-of-care treatment approaches to counteract TB-IRIS

Since inflammatory responses discussed above are major drivers of TB-IRIS symptoms (Figure 1), the adjunctive corticosteroid therapy and co-trimoxazole prophylaxis has been associated with decreased inflammation and improved outcomes [54-56]. The use of prednisone is helpful to bring down acute symptoms in the short term in patients with TB-IRIS [57,58]. However, corticosteroids had shown to decrease the survival of T cells by augmenting apoptosis [59]. The addition of adjunctive treatment with IFNG, IFNA, or vitamin D supplementation, to prednisone therapy, has been useful to improve immune cell survival and decrease inflammation [60-63]. The serum concentration of cytokines such as IL10, IL12p40, IFNG, and chemokine CXCL10 decreased during 4 weeks of prednisone therapy [55].

The monoclonal antibody against IL6 has been reported to decrease severe forms of IRIS pathology in preclinical models [25]. Biologics such as adalimumab, infliximab, and other anti-TNF agents like chloroquine or thalidomide can be useful if administered with ART to treat as well as to prevent TB-meningitis and TB-IRIS [63-65]. A combination of empirical doses of anti-TNF and corticosteroid treatment have been reported in recent literature as successful [66]. Other drugs such as pentoxifylline and hydroxychloroquine have been shown to be helpful in treating IRIS patients, with some reported benefits [67-69]. Other biologics such as Bevacizumab (anti-vascular endothelial growth factor, anti-VEGF) have been reported in the treatment of paradoxical worsening of TB-IRIS with retinal detachment [70]. Anakinra, a recombinant IL1 receptor antagonist, has been used as a therapeutic option for protracted paradoxical inflammation in HIV-associated TB IRIS [48].

In cases of steroid-refractory and leukotriene-driven inflammatory forms of TB-IRIS, treatment with Montelukast, a leukotriene antagonist, had shown prosperous outcomes [71,72]. Leukotrienes stimulate proinflammatory and antimicrobial properties by recruiting neutrophils to the sites of inflammation and increase immune responses [73,74]. Formal clinical trials need to be conducted to define the success of these therapies.

A randomized, double-blind, placebo-controlled clinical trial CADIRIS had assessed the effectiveness of CCR5 inhibitor Maraviroc. The inclusion of Maraviroc therapy into ART regimens (a combination of tenofovir, emtricitabine, and efavirenz) could not prevent TB-IRIS, thus did not confer meaningful protection [75].

Conclusion and Future Prospective

Deregulation of innate and adaptive immunity (Figure 1) had shown a primary role in the pathogenesis of immune reconstitution inflammatory disorders [76,77]. Many pro-inflammatory mediators, produced by natural killer (NK), intermediate NK/T, and innate immune cells have been shown to take part in controlling the immune responses during immune reconstitution.

As discussed above, a combination of abnormal frequencies of NK-cell receptor expression, high levels of IL6, IL10, TNFA, and IFNG, etc. represent the immune parameters that characterize TB-related IRIS. Thus, anti-inflammatory regimens that composed of corticosteroid therapy and several biologics may be clinically useful to manage TB-IRIS and improve patients' outcomes.

Conflict of Interests

The authors declare no conflict of interest.

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Ethical Approval

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