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The Potential Host Directed Therapy in Tuberculosis and COVID-19

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Abstract

World Health Organization (WHO) on April 2020 stated that patient with both tuberculosis and COVID-19 may have poorer treatment outcomes. The COVID-19 and tuberculosis both primarily affect the lungs and show similar symptoms such as cough, fever, and severe lower track respiratory syndromes. Even the biological agents and incubation period from exposure to disease are different. Understanding the fundamental CD4+ T-cells exhaustion role in underlying the clinical manifestations of COVID-19 and tuberculosis is vital for the identification and rational design of effective therapies. Here, the perspective of how anti TNF and IL-6 antagonist agents could be the potential rational host directed therapy in tuberculosis and COVID-19.

Keywords: Tuberculosis; COVID-19; Host directed therapy; CD4+; WHO

Introduction

By the end of 2019, multiple cases of unknown etiology of pneumonia emerged in Wuhan, China, caused by a novel coronavirus named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1,2]. On March 11th, 2020, the Public Health Emergency of International Concern (PHEIC) and World Health Organization (WHO) declared the outbreak of SARS-CoV-2 a global pandemic, which caused over one million cases and 60,000 deaths worldwide by the start of April 2020 [3,4]. In Indonesia on mid of May 2020, COVID-19 affected more than 16,000 citizens with mortality rate around 6.25% [5]. On the other hand, the incidence of tuberculosis in Indonesia remains high. In 2018, the incidence of tuberculosis was more than 450,000 cases with mortality rate around 2.5% [6].

In April 2020, WHO has issued an information note about continuing tuberculosis care during COVID-19 pandemic? This action was to anticipate patients both COVID-19 and tuberculosis may have poorer treatment outcomes, especially if tuberculosis treatment is interrupted [3]. Both COVID-19 and tuberculosis commonly involve the lungs and have similar symptoms such as cough, fever and severe lower track respiratory syndromes. Even the biological agents and incubation period from exposure to disease are different. While fever and cough in COVID-19 have a rapid onset and an incubation period of about one to two weeks, the clinical manifestations of tuberculosis typically develop over more than two months. Then, when shortness of breath occurs in COVID-19 develops early after onset; in tuberculosis this usually happens at a much later stage or as a long-term sequela. Outbreaks of COVID-19 in the same household or in a congregate setting usually becomes apparent within a week or two while in tuberculosis the progression is rarely abrupt and may only become apparent after several months [3,7,8]. As the pandemic advances, tuberculosis patients of all ages might have been exposed to COVID-19. A positive result for COVID-19 infection also could not exclude the possibility of concomitant tuberculosis, particularly in high tuberculosis burden settings. An early diagnosis of both COVID-19 and tuberculosis is important in the care of people who are vulnerable to unfavorable outcomes, including death. The tuberculosis patients who have lung damage from past tuberculosis sequelae or chronic obstructive pulmonary disease may suffer from more severe illness if they are infected with COVID-19. The outcome of COVID-19 could even worse whenever other risk factors - such as malnutrition, renal failure and liver disease or certain comorbidities like diabetes mellitus, HIV in tuberculosis patient is still developing. Programs need to be wary to obtain diagnostic of tuberculosis while COVID-19 testing is rolled out [3,7,9]. The transmission ways of tuberculosis was known by airborne, while COVID-19 develop from droplet into airborne transmission [2,10,11].

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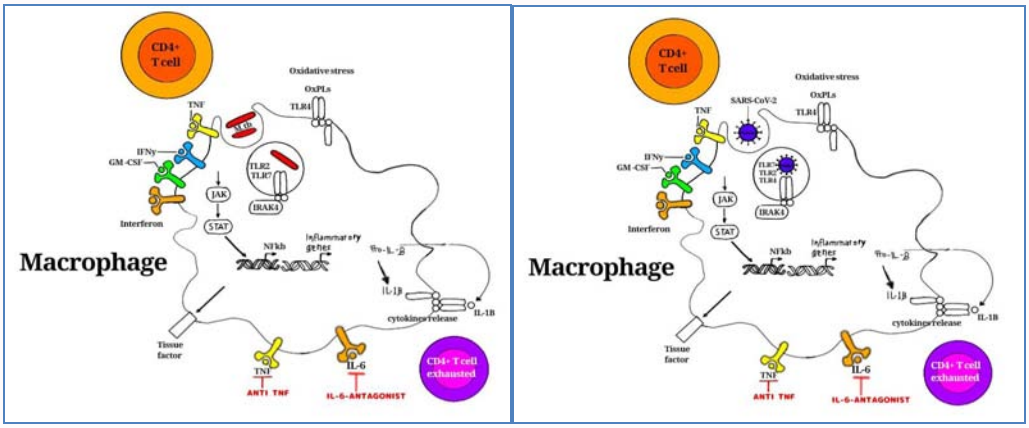

Figure 1: How host directed therapy works to enhance the immunity against M.tb (A) and SARS-CoV (B).

T-Cell Function in COVID-19 and Tuberculosis

T-cells in human immune system use to prevent infections in two ways, through cytotoxic mechanism (CD8 T-cell) and directly attack (CD4+ T-cell) the cells where a virus, bacteria or other kind of pathogen has entered and multiplied along with the cancer cells. The severity of a disease can greatly depend on the responses of the T cells [12].

After binding to Toll Like Receptors (TLRs) - TLR2, TLR4, TLR7, both SARS-CoV and *Mycobacterium tuberculosis* (*M. tb*) activated Nuclear Factor Kappa-Beta (NFκβ), the transcription factor of macrophage that function as mediators pro-inflammatory relishing factors [12-14], as seen in Figure 1. *In vitro* studies show that early infection of SARS-CoV results in delayed cytokine release in respiratory epithelial cells, dendritic cells, and macrophage cells. Furthermore, cells secrete small amounts of antiviral factors interferons and proinflammatory cytokines (Interleukin (IL) -1β, IL-6, and Tumor Necrosis Factor (TNF)) and Chemokines (CC Chemokine Ligand motif (CCL)-2, CCL3, and CCL5) [12,15]. This phenomenon leads to granuloma forms in COVID-19 patients.

Surprisingly, host immunity response against *M. tb* pathogen causes tuberculosis has similar mechanism. The chemokine CCL5 has been detected in patients with TB and implicated in control of *M. tb* infection. The CCL5, as well as CCL4, CCL3, and CCL2, promoted a large proportion of early T cell migration to *M. tb* infected sites. The CCL ligands attached to the receptor (CCR), and then localized infected cells in spreading to other cells, formed granulomas, and controlled *M. tb* infection [16]. Activated inflammation process related to the increased secretion of cytokines including TNF-α, IL-6, and IL-10 in COVID-19 patients [12,17]. This phenomenon is name "cytokine storm", an excessive inflammatory reaction thus cytokines are rapidly produced in large amount in response to microbial infection. The "cytokines storm" phenomenon has been considered an important contributor to Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Dysfunction Syndrome (MODS) in COVID-19 patients [2,12], and contributed to-cell exhaustion phase [18].

The constant presence of high viral load and antigen levels, anti inflammation mediators like Interleukin (IL)-10 and Transforming Growth Factor (TGF)-β, and regulatory T (Treg) cells, contribute to loss of T-cell function. The T-cell exhaustion is described as a state of T-cell dysfunction that happen during many chronic infection, such as Tuberculosis, chronic HBV infection [12,18]. These exhausted T-cells lead to dysfunction of T-cell function, proliferative capacity, and increased apoptosis rate. Even COVID-19 is not a chronic disease; it shows decreased number of T-cell, CD4+ and CD8 among the patients with COVID-19 [12].

The mechanism of T-cells exhausted more or less similar in tuberculosis and COVID-19. Elevated of Interleukin 6 (IL-6) and Interleukin 10 (IL-10) was the key roles of T cell exhaustion in this case. Direct action of IL-6 has been shown by STAT 3 activation in CD4.

T cells [18], IL-6 blockade significantly improved differentiation of CD4 T-cell into IFN γ. IL-6 can also suppresses the development of TGFβ induce Treg (Regulatory T-cells). Whenever Treg inhibited, an excessive immune processes occurs. The inhibition of IL-6 affected to the maturation of Dendritic Cell (DC) and decreased potential of clearance of pathogens [12]. Moreover, IL-10 as an inhibitory cytokine also induced T cell exhaustion. In both cases, COVID-19 and tuberculosis patients have high level of serum IL-10. In several studies showed that blocking IL-10 restored T cell function and improves viral control so reverse exhausting [18].

Host Directed Therapy in COVID-19 and Tuberculosis

Isoniazid, rifampicin, ethambutol, and pyrazinamide are known as directed anti M. tb agents [19-21]. However, Multidrug-Resistant (MDR) tuberculosis extensively occurs and poses a major threat to global tuberculosis control [22]. Therefore, potential host-directed therapeutic in COVID-19 patients, currently remains no evidence from Randomized Clinical Trials (RCTs) potential therapy improves outcomes in COVID-19 patients [23]. Even though, Ribavirin, Lopinavir/Ritonavir and other anti-retroviral agents where use to eliminate SARS-CoV [23,24], Host Directed-Therapy (HDT) is also been considered. This review focused in Anti-cytokine or Immunomodulatory Agents Monoclonal use to reduce "cytokine storm" and prevent T-cells exhaustion is one of HDT target.

Anti-Cytokine or Immunomodulatory Agents Monoclonal

Protective T-cell immunity against M. tuberculosis at the site of

infection is mediated by Th1 cytokines, such IFN-γ, TNF-α, IL-2, and IL-6. The exhausted T-cell might incriminate *M. tb* and SARS-CoV elimination process. Monoclonal antibodies directed against the inflammatory cytokines, such as tocilizumab, sarilumab, and bevacizumab use as adjunctive therapy in COVID-19 [23], and thalidomide use as HDT in tuberculosis [14,22,25]. The rationale use is based on underlying pathophysiology of significant organ damage in the lungs and other organs are caused by an amplified immune response and "cytokine storm", as seen in Figure 1.

Anti TNF: Thalidomide and its analog (IMiD3): Thalidomide is known as anti-emetic agents. Later discoveries have shown its potent anti-inflammatory and immunomodulatory effects [20,22]. Thalidomide suppresses TNF-α production in macrophages and thereby reduces systemic inflammation. Thalidomide has a costimulatory effect on T cells, preferentially targeting CD8+ T-cells [26]. Moreover, thalidomide shows promising effects against severe, overt inflammatory reactions associated tuberculosis, especially for extra pulmonary tuberculosis [22,27]. Thalidomide is also considered in attenuating inflammatory complications in patients with COVID-19 by reducing the "cytokines storms" [26].

IL-6 receptor antagonist: tocilizumab, sarilumab, and bevacizumab: Tocilizumab is humanized monoclonal antibody works as an antagonist in IL-6 receptor. Tocilizumab is FDA approved in safety and effective to treat Rheumatoid Arthritis (RA) [23]. The results of long-term toxicity tests on animals showed that tocilizumab was well tolerated, and no significant abnormalities were observed in histopathological evaluations. Tocilizumab competitively inhibits IL-6 binding to IL-6R, both forms - the membranous and soluble. Tocilizumab slowed down tuberculosis through the inhibition of *M. tb* multiplication in blood stem cells [28]. It also may potentially be effective and safe way to reduce mortality of COVID-19 by calm inflammatory "storm" through inhibiting IL 6. Recently, several RCTs of tocilizumab in COVID-19 patient with severe pneumonia remains underway [23,29].

Discussion

Tuberculosis status should be assessed carefully at patient admission and management and therapeutic strategies adjusted accordingly to prevent rapid development of severe COVID-19 complications. Thalidomide and tocilizumab may consider as adjunctive therapy in both COVID-19 and tuberculosis.

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