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Commentary

Repurposed Anti-IL-6 Therapeutics, Another Way to Quell the Cytokine Storm in Tuberculosis

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Abstract

Study on "cytokine storms" has been braced up in infectious diseases. The pertinence of this research begins to be evident in tuberculosis as it was observed that increased levels of Interleukin-6 (IL-6) were connected with disease severity. The IL-6 blockers therapeutics approaches for tuberculosis are currently a key line of research, with many in progress clinical trials, as IL-6 has become an important factor of the immune response to tuberculosis. Here, we focus on the role of IL-6 in tuberculosis.

Introduction

Over 10 million lives developed tuberculosis (TB) in the world and one out of four people are carrier of latent TB [1]. TB remains a worldwide disease, causing an estimated of 9.8 million deaths per year [2]. A characteristic of TB infection is a "cytokine storm". The term "cytokine storm" is more and more used by both popular media and Authors of scientific articles. The expression "cytokine storm" was first used to describe the response of uncontrolled systemic inflammation in graft versus host disease. Cytokine storms represent a wide spectrum of neurodegenerative and neoplastic diseases, infectious and non-infectious diseases. The status of systemic hyperactivated immunity in "cytokine storm" are the results of organ dysfunction, vascular leakage, transaminitis, coagulopathy and death. The abundance of numerous cytokines is implicated in this uncontrolled systemic inflammatory response, IL-6 plays an important role in its signaling pathways and pathophysiology. IL-6 signaling is studied extensively elsewhere [3].

IL-6 accumulates with other cytokines (IL-6, TNF-α and IL-1), which are crucial inducers of the acute phase response. The signalization of IL-6 is done via soluble and membrane bound IL-6R, specifically through gp130 [4]. A phosphorylation cascade implicating janus kinase/signal transducer (JAK/STAT) pathway mediates downstream signaling [5]. Afterwards, IL-6-STAT3-NF-κB pathway activation increases IL-6-regulated gene expression by provoking a pro-inflammatory arsenal including IL-18 and MCP-1. *Mycobacterium tuberculosis* provokes the release of IL-6 through mitogen-activated protein kinases (P38 MAPK) activation. IL-6 is generated by several types of immune cells, stromal cells, and tumor cells. In this study, we focus on TB and discuss about the involvement of IL-6 in the inflammatory storm. We also summarize the new IL-6 blocker treatments for TB.

TB and Inflammatory Storm

TB causes a fibrosis and chronic inflammation which might drive to genetic changes and mutations. TB diseases implicate

the parenchyma tissue of the lung, continuous cough, vascular morphological variations, lymphocytosis processes, and the generation of immune system mediators such as interleukins, are all among the components driving to the assumption regarding the implication of TB in lung cancer [6-8]. Study in patients with immune deficiency, reported that induction of necrosis and apoptosis appear to drive to an augmentation in TNF-α and IL-17, which will increase the Bcl-2 expression or lower P53 activity, diminish Bax-T and contribute to the impediment of caspase-3 expression because of the low expression of cytochrome oxidase in mitochondria [7,9].

TB is characterized by x-ray images and clinical symptoms (loss of appetite, fever, weight loss, continuous cough, hemoptysis, chest pain, and dyspnea) [10-12]. Because of nontuberculous mycobacteria (NTM), correct diagnosis is necessary for TB and respiratory infections. Actually, lung NTM or lung cancers infections are some of the cases of TB drug-resistance. Briefly, TB is believed to be one of the risk factors for certain diseases such as diabetes, cancer and HIV. Among the most substantial solutions for the respiratory diseases and TB diagnosis are acid-fast staining and histological study of phlegm and bronchial lavage, culture and polymerase chain reaction [13,14].

In these instances, a chronic inflammatory environment contributes to the neoplastic change. In order to comprehend how to block this process, it is substantial to know what component or components lead this transition and how this can be impeded. Many studies indicate IL-6 as a principal conductor responsible for TB. The role of IL-6 as a key mediator of TB has been extensively investigated; thus, the following section will focus on TB to illustrate the major role of IL-6 in TB risk and prognosis.

In lung of TB patients, IL-6 acts directly on lung epithelial cells via the NF-κB signaling pathway under conditions of inflammation and TB infection. IL-6 in turn promotes TB production and migration via STAT3 signaling [15]. A complementary source of IL-6 in TB is CD4+ T lymphocytes [16,17]. Increased levels of circulating IL-6 in patients infected by *M. tuberculosis* predicts TB risk. Moreover, elevated circulating levels of IL-6 are a biomarker of unfavorable TB patients [18].

Except its role in *M. tuberculosis*, "cytokine storm" is a toxic side effect of T cell engaged therapy. Once more, IL-6 has become a principal driver of inflammatory storm associated with TB. Furthermore, IL-6 from monocytes and macrophages induces "cytokine storm" in response to T-cell engaged therapy or other conditions.

IL-6 in TB

The pertinence of this study begins to be evident in TB as it was observed that increased levels of IL-6 were connected with disease severity and contributed to complications such as acute respiratory distress syndrome (ARDS). IL-6 is also correlated with increased bacterial load, and elevated levels are found in severe disease [19]. Monocyte derived and recruited macrophages produces IL-6 [20]. IL-6 cumulates with other cytokines, including IL-1, TNF-α and IL-6 which are important provokers of the acute phase response. IL-6 is pivotal in the protection against murine *M. tuberculosis* infection, because of the impact of the response of CD4+ T cells, [16]. Increased bacterial loads and a changed type 1 T helper response was observed in IL-6 deficient animals infected with *M. tuberculosis* [21]. IL-6 secreted by macrophages infected with *M. tuberculosis* represses the responses of uninfected macrophages to IFN-γ [22].

In the field of lung cancer, studies imply that early on in infection alveolar type II pneumocytes produces IL-6, later macrophage produce IL-6 which participate to severe disease phenotypes [23]. Moreover, finding stipulate that increased levels of IL-6 is a modification from alveolar resident macrophages to macrophages derived and recruited from IL-6-producing monocytes, which are found in bronchoalveolar lavage samples from people with severe disease [24]. A key participator to TB pathogenesis is IL-6-induced immune dysregulation characterized by lymphocytic dysregulation with CD4+ lymphopenia [25] and also by production of pro-inflammatory cytokines downstream of IL-6 by monocytes [26].

IL-6 Blocker Therapeutics Approaches for TB

The blockade of IL-6 has been displayed in the therapeutical plan successfully in numerous rheumatological diseases, malignancies and rheumatoid arthritis [3,27]. For the success of TB treatment, IL-6 was shown to be an important biomarker [28] (**Figure 1** and **Table 1**). In order to discover common mechanisms that might also repress TB, a growing number of repurposed drugs are going through clinical trials.

IL-6 inhibitors

Tocilizumab is a humanized anti-IL-6 receptor IgG1 monoclonal antibody which represses both the trans-signaling and the classic pathways and is approved for rheumatoid arthritis treatment and other chronic inflammatory diseases. The antimycobacterial activity of IL-6 can be decreased by tocilizumab [29]. In the treatment of TB patients, the safeness and effectiveness of tocilizumab was identified in a recent finding [30]. Tocilizumab is undergoing a phase III randomized controlled clinical trial, COVACTA (NCT01232569) [31].

Bruton tyrosine kinase inhibitors

Controlled by toll-like receptors that recognize viral genomes, bruton tyrosine kinase (BTK) provoke NF-κB signaling which end up at the production of chemokine and cytokine,
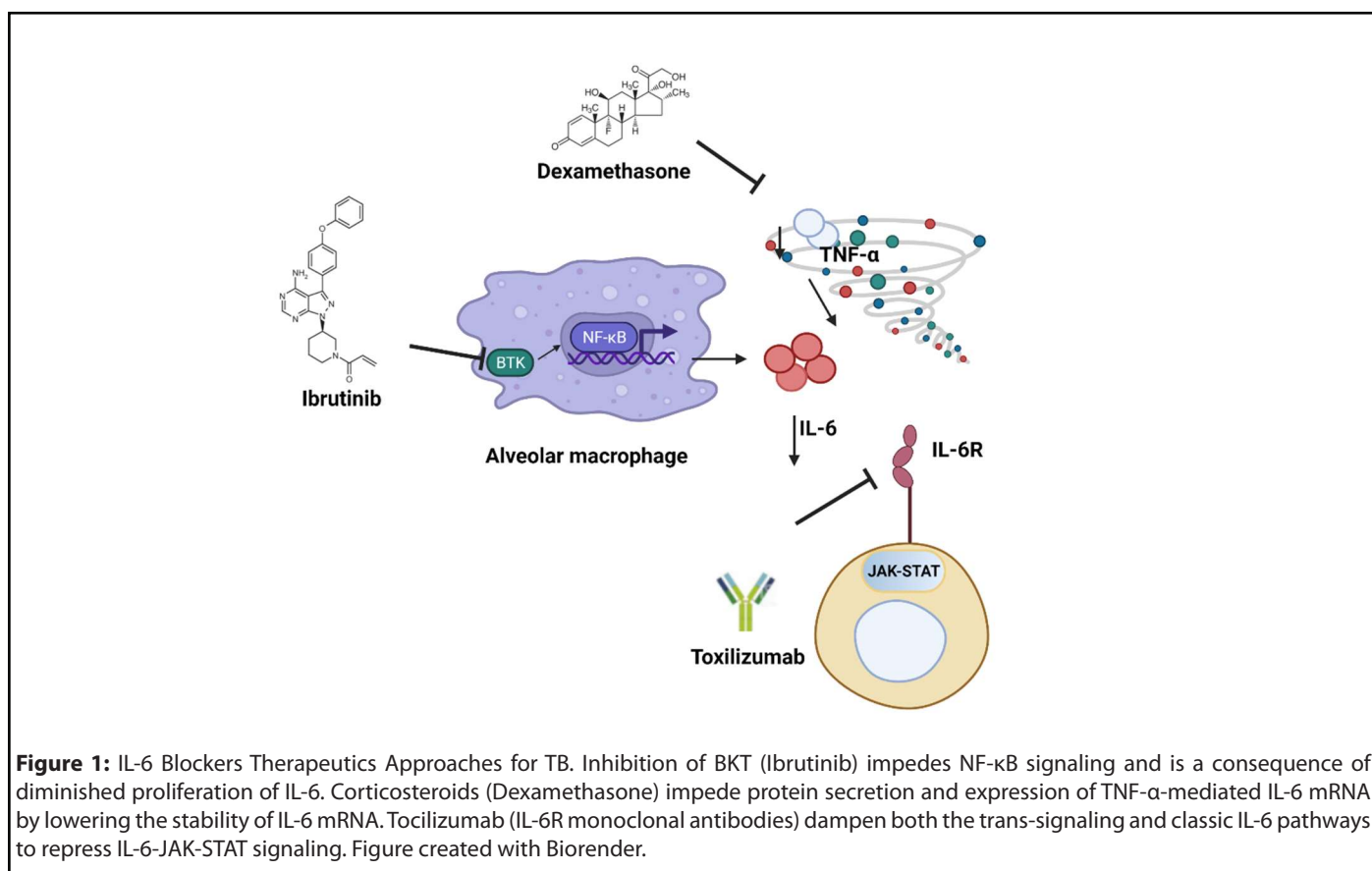
Figure 1: IL-6 Blockers Therapeutics Approaches for TB. Inhibition of BKT (Ibrutinib) impedes NF-κB signaling and is a consequence of diminished proliferation of IL-6. Corticosteroids (Dexamethasone) impede protein secretion and expression of TNF-α-mediated IL-6 mRNA by lowering the stability of IL-6 mRNA. Tocilizumab (IL-6R monoclonal antibodies) dampen both the trans-signaling and classic IL-6 pathways to repress IL-6-JAK-STAT signaling. Figure created with Biorender.

Table 1: Repurposed Anti-IL-6 therapeutics.

Repurposed Anti-IL-6	Clinical trials	Treatment	Affected pathways
IL-6 inhibitors			
Tocilizumab	A phase III randomized controlled trial, COVACTA (NCT01232569)	TB	JAK-STAT signaling
Corticosteroids			
Dexamethasone	phase-III and IV multicenter trials (NCT03100786; NCT03092817; NCT02588196)	TB meningitis	TNF-a and HDT
Prednisolone	a phase-III trial (NCT00810849)	TB pericarditis in HIV infection	
BTK inhibitors			
Ibrutinib		*M. tuberculosis* in macrophages	NF-κB signaling

including IL-6. Ibrutinib is a BTK inhibitor which was used for the treatment of specific B cell malignancies. Findings revealed that inhibition of BTK in lymphoma leads to the side effect of an invasion of aspergillosis infection, however it is usually regulated by monocytes, neutrophils, and macrophages. This raised the probability that BTK inhibitors contribute to the regulation of the inflammatory response of these cell types that are preponderant in TB [32].

In macrophages derived from patients with chronic lymphocytic leukemia, ibrutinib modifies the secretion of TNF-α and influences the polarization towards the pro-inflammatory profile against irradiated *M. tuberculosis*. In addition, ibrutinib-treated γδ T cells revealed remarkably decreased activation, as indicated by the weak expression of the activation marker CD69 and weak secretion of IFN-γ, furnishing a better sapience of the risk of contagious complications in ibrutinib-treated chronic lymphocytic leukemia patients [33]. The target of BTK inhibition are the activation of pathological monocyte and macrophage which reduce the "cytokine storm," conducting to better results. Ibrutinib represses intracellular *M. tuberculosis* growth by provoking the autophagy of macrophages [34].

Corticosteroids

Belonging to a class of steroid hormones, corticosteroids exhibit an anti-inflammatory activity via the connection of the cytoplasmic receptor of corticosteroid, which contribute to the regulation of anti-inflammatory genes transcription. The reduction of IL-6 mRNA stability is done by corticosteroids, which hinder the expression and protein secretion of TNF-α-mediated IL-6 mRNA [35].

As immunoadjuvants to standard TB therapy, numerous researches have shown corticosteroids to be beneficial. In particular, trials testing the efficacy of adjunctive dexamethasone treatment on the risk of death or disability in TB meningitis demonstrated improved patient survival rate [36,37]. Recent study suggest that dexamethasone impede necrotic cell death of cells infected with *M. tuberculosis* by facilitating mitogen-activated protein kinase phosphatase 1 (MKP-1)-dependent dephosphorylation of p38 MAPK [38].

The phase-III and IV multicenter trials are underway (NCT02588196; NCT03100786; NCT03092817). Prednisolone was investigated for TB pericarditis treatment in HIV infection, in a phase-III trial (NCT00810849). Prednisolone remarkably decreased the levels of IL-6 in plasma by 8 hours of treatment [39]. In general, it is clear that further research is needed to obtain conclusive results concerning the risks and benefits of corticosteroids as an adjunctive therapy for TB disease.

Conclusion & Future Perspective

Considering the role of IL-6 in the immune response to TB, it is important to understand the release of IL-6 mediated by monocytes and macrophages as part of the "cytokine storm" has played a role in a better comprehension of TB. The cytokine storm is real in the development of severe form of the disease in TB patients. Identification of the repurposed drugs that block IL-6 proliferation may contribute to the attenuation of the "cytokine storm" from TB. The incidence of disease might be decreased in TB patients, as TB researches are making IL-6 blocker therapeutic approaches including tocilizumab.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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