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Review Article

Plasma Levels of Cytokines (IL-10) in Multidrug Resistant Tuberculosis– A literature review

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ABSTRACT

Objective: Interleukin-10 (IL-10), interferon gamma (IFN-γ) and tumour necrosis factor (TNF-α) play very important roles in anti-TB cell-mediated immunity, in both MDR-TB and drug-susceptible TB (DS-TB) patients.

Method: The databases used were PubMed and ScienceDirect. The keywords for the search were "Interleukin-10" AND "MDR-TB". The inclusion criteria was review articles and research articles published between January 2015 until August 2020 in free full text English.

Results: IL-10 plays an important role in suppressing macrophage and dendritic cell (DC) function, which helps control and initiate the immune responses. IL-10, which is a suppressor T cell or T-regulatory cytokine, is known to play a critical role during chronic and latent stages of pulmonary TB [53]. The IL-10 production is said to be elevated during the infection, promoting reactivation of TB [54]. The excessive production of this cytokine usually results in failure to control the infection, and this could account for why IL-10 was elevated in the MDR-TB participants.

Conclusions: IL-10 production in MDR-TB might also indicate suppression of the immune response, leading to an inadequate balance of pro- and anti-inflammatory cytokines.

Keywords: IL-10, MDR-TB

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by infection with Mycobacterium tuberculosis (M.tb). It is estimated that about one third of the world's population is currently infected by the M.tb. Pulmonary tuberculosis is still an important health problem in the world because this disease affects millions of people and is the second leading cause of death among infectious diseases, after Human Immunodeficiency Virus (HIV). Globally there were 9 million new cases in 2011 and 1.4 million deaths due to TB. WHO states that out of 22 countries with a high burden of TB (high burden country), Indonesia is in fourth place (after India, China and South Africa) with a TB prevalence of 289 per 100,000 population, a TB incidence of 189 per 100,000 population, and a 27 per 100,000 population.[1] Multi-drug resistant tuberculosis (MDR-TB) is defined as in vitro resistance to isoniazid (H) and rifampin (R).[2] In Indonesia it is defined as resistance to, at least H and R simultaneously , with or without resistance to other first-line anti-tuberculosis (OAT) drugs.[3] Data from WHO shows the prevalence is increasing from year to year. Worldwide it is estimated that there are 3.7% new MDR-TB cases and 20% MDR-TB with a history of previous OAT treatment.

METHOD

The databases used were PubMed and ScienceDirect. The keywords for the search were "Interleukin-10"AND "MDR-TB". The inclusion criteria was review articles and research articles published between January 2015 until August 2020 in free full text English. Studies that were published as abstract, editorial, and case report were excluded. The same articles that found on the two database also excluded.

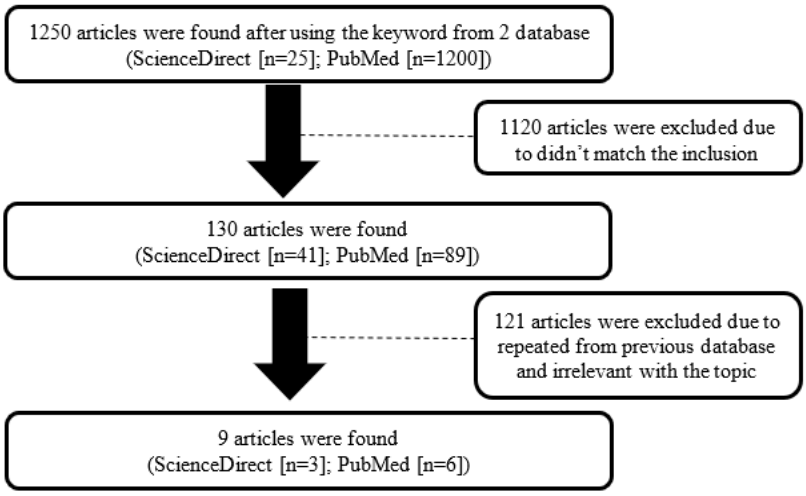

Fig.1: Article extraction flow chart. Authors' compilation.

RESULTS

Tuberculosis (TB) remains one of the world's deadliest communicable diseases.[1] Despite the availability of drugs to treat and control the disease, certain factors including patients' non-compliance, poor nutrition, and co-infection with HIV/AIDS has resulted in increased burden of TB infection, especially in resource-limited countries within sub-Saharan Africa and Asia[1,2].

In 2017, the World Health Organization (WHO) reported that 490,000 million cases of multidrug-resistant TB (MDR-TB) emerged in 2016 and an additional 110,000 cases were susceptible to isoniazid but resistant to rifampicin (RR-TB), the most effective first-line anti-TB drug[3]. The advent of multidrug-resistant cases pose a disproportionate threat to the global prospects of TB control, and frustrates diagnosis and treatment[4,5]. The regions most affected by MDR-TB cases are the former Soviet Union (Eastern European countries) and the Russian Federation, where at least one-third of TB cases presenting for treatment have MDR-TB [6,7]. In sub-Saharan Africa, South Africa is reported to have the highest number of MDR-TB cases[8]. Population rates of MDR-TB cases in a number of countries across the world have increased over time [9,10]. In Ghana, MDR-TB (resistance to at least isoniazid and rifampin, plus resistance to several drugs, excluding combined resistance to isoniazid and rifampin) among TB patients has been found to be 8.7% [11]. Cytokines have been identified to play multiple roles in the immune and pathological responses in TB. Interleukin-10 (IL-10), interferon gamma (IFN-γ) and tumour necrosis factor (TNF-α) play very important roles in anti-TB cell-mediated immunity, in both MDR-TB and drug-susceptible TB (DS-TB) patients[12,13,14]. TNF-α has been identified to play various roles in the immune and pathological responses in TB by preventing the reactivation of persistent tuberculosis, modulating the pulmonic expression of specific immunologic factors and limiting the pathological response of the host[14]. IFN-γ boosts antigen presentation, leading to the recruitment of CD4+ T-lymphocytes and cytotoxic T-lymphocytes[12], while IL-10 in response to *Mycobacterium tuberculosis* (*MTB*), may down-regulate the immune response and limit tissue injury. However, overexpression of these cytokines may have a negative impact on the capacity to control infection[13].

Effective disease management strategies must therefore consider both drug treatment and host immunity. This strategic approach can be successful if studies are conducted on the immune markers involved and devise ways of enhancing their function to maximize effective response, especially in MDR-TB. This study therefore determined the levels of cytokines (IL-10, IFN-γ and TNF-α) that are linked with the ability of *MTB* to evade the host's immune system and mediate long-term infections in the lungs, leading to chronic tuberculosis.

Table 1: Overview of systematic review and meta-analysis Plasma Levels of Cytokines (IL-10) in Multidrug Resistant Tuberculosis

Author	Objectives	Result	Grade of Recommendation (Joanna Briggs Institute)

Anthony Basingnaa,1,2 Samuel Antwi-Baffour,Dinah Obenewaa Nkansah, Emmanuel Afutu, and Enid Owusu	determined the differences in plasma concentrations of pro-inflammatory (IFN-γ and TNF-α) and anti-inflammatory (IL-10) cytokines in MDR-TB and drug-susceptible (DS) TB patients, in addition to some socio-economic factors	There were statistically significant associations between MDR-TB and factors such as education level (X2 = 9.895, p = 0.043), employment status (X2 = 19.404, p = 0.001) and alcoholism (X2 = 3.971, p = 0.046)	4B
Seok-Yong Eum, Bo-Young Jeon, Jin-Hong Min, Seung-Cheol Kim, Sungae Cho, Seung-Kyu Park, Sang-Nae Cho	examined the relationship between cytokine levels and clinical parameters indicating the state of disease in active pulmonary TB patients.	No significant difference was found in IFN-gamma production between non-MDR-TB and MDR-TB patients, but there was a marked reduction in TNF-alpha production in MDR-TB patients accompanied by a moderate increase in IL-10 levels. In contrast, the presence of cavity was associated with a significant increase in IFN-gamma, whereas no difference in TNF-alpha between the cavity and non-cavity group was observed. Those who have TB lesions in the left lung showed lower levels of IFN-gamma and TNF-alpha and higher IL-10 levels than the patients with lesions on the right side. IFN-gamma levels were significantly increased in those with moderate or advanced lesions compared with patients with mild lesions. TNF-alpha and IL-10 levels did not change with disease severity. The number of M. tuberculosis bacilli in sputum was closely associated with TNF-alpha levels. The patient group with high value (+++) of sputum culture acid-fast bacilli produced significantly reduced levels of TNF-alpha compared with medium (++) and low (+) values	3B

DISCUSSION

Chronic immune activation, which might be because of exposure to a high load of environmental antigens, has mostly characterized the immune profile of people living in sub-Saharan Africa [14,15,16]. Such exposure has been observed to impair the host's immune response to *M. tuberculosis* and HIV [17], which are widespread in sub-Saharan Africa [18]. Infection with intracellular parasites such as *Mycobacterium tuberculosis* is known to induce Th1 immune response[18]. The protective immunity against the TB pathogen is said to be mediated by cytokines such as IFN-γ, TNF-α, IL-12, IL-6 and IL-18 during the initial stage of infection [19].

IFN-γ has been identified to be significant for the function and maturation of multiple immune cells [20]. It stimulates macrophages to produce TNF-α, which is an essential component of the innate defence mechanism of the host against pathogenic challenge [21]. IL-10 plays an important role in suppressing macrophage and dendritic cell (DC) function, which helps control and initiate the immune responses [22]. TNF-α contributes to the pathogenesis of tuberculosis due to its role in the formation and maintenance of granulomas [23]. TNF-α is considered a necessity in the removal of bacteria in inflammatory lesions, and hence it has been found to be one of the key cytokines in controlling MTB infection [24,25].

Therefore, it was not surprising that elevated plasma levels of TNF-α were found in MDR-TB participants compared to the DS-TB participants. This correlated with a Chinese study that showed elevated levels of TNF-α in TB patients compared to controls [26]. Several studies have reported increased levels of TNF-α in the serum of TB patients [27,28,29]. TNF-α is a factor both in the protection against tuberculosis and in immunopathology. The high levels of TNF-α in MDR-TB patients in the current study may be due to a marked tissue necrosis during the disease occurrence that led to progressive TB and eventually MDR. This might have resulted in the release of TNF-α into circulation and eventually contributed to systemic indicators of TB, such as fever and cachexia.

The role of IFN-γ as the main macrophage-activator (Th1 cytokine) has been clearly established in animal models infected with *M. tuberculosis* [30]. Intracellular mycobacteria are destroyed due to IFN-γ action on macrophages

[31,32]. IFN-γ has been shown to stimulate macrophages, leading to the following: production of TNF-α, oxygen free radicals and nitric oxide; increase in the surface display of MHC antigens and Fc receptors; increase in the intracellular concentration of some antibiotics; and decrease in lysosomal pH [33,34,35]. The significantly higher plasma levels of IFN-γ in MDR-TB compared to DS-TB observed in this study may be because more IFN-γ action on macrophages will be needed to destroy intracellular mycobacteria that show multi-resistance to anti-TB drugs.

IL-10, which is a suppressor T cell or T-regulatory cytokine, is known to play a critical role during chronic and latent stages of pulmonary TB[36]. The IL-10 production is said to be elevated during the infection, promoting reactivation of TB [37,38,39]. The excessive production of this cytokine usually results in failure to control the infection, and this could account for why IL-10 was elevated in the MDR-TB participants. Increased production of IL-10 in patients with active disease including MDR-TB has been reported in Turkey [37,40,41,42]. This high IL-10 production in MDR-TB might also indicate suppression of the immune response, leading to an inadequate balance of pro- and anti-inflammatory cytokines.

CONCLUSION

The levels of both pro- (IFN-γ, TNF-α) and anti-inflammatory (IL-10) cytokines were observed to be significantly higher in MDR-TB patients compare DS-TB patients. The findings of this study emphasize the potential roles of IFN-γ, TNF-α and IL-10 in the host response to MTB during drug resistance development. This study also showed a statistically significant association between MDR-TB and factors such as education level, employment status and alcohol intake. Alcohol intake can be considered as a very important risk factor due to the alcoholism attitude of most Ghanaians, in both urban and rural areas..

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