Letter to the Editor

Serum interleukin 6 (IL-6) as a potential biomarker of disease progression in active pulmonary tuberculosis following anti-tuberculosis drug therapy

Dear Editor,

We would like to thank Agilli et al., for their interest on our recent paper entitled “Alteration of serum inflammatory cytokines in active pulmonary tuberculosis following anti-tuberculosis drug therapy” and appreciate for their thoughtful comments. With great pleasure, we would like to address the concerns highlighted by Agilli et al. and further clarify the readers on our interpretation of the inflammatory cytokine markers in the context of tuberculosis included in that manuscript.

We agree with Agilli et al. that the intensity and duration of muscle contraction determine the magnitude of increase in plasma IL-6 in exercise. In our study, we quantified the serum levels of different inflammatory cytokines in hospitalized TB patients. The reasons for hospital admission were varied and included severe forms of TB, hypoxia, adverse drug reactions to anti-tuberculosis drugs (ATD), further investigations and also socioeconomic reasons such as inadequate caregiver support at home. Lifestyle during hospitalization was predominantly sedentary and sampling of venous blood was done in all subjects between 10:00 AM and 12:00 AM, when they were at rest. Therefore, occupation and exercise are factors unlikely to have influenced serum inflammatory cytokine levels, such as IL-6 in these patients.

Our data suggested that a lower body mass index (BMI) was associated with the higher systemic levels of inflammatory cytokines prior to the commencement of ATD therapy. The underlying reason behind this temporary association could be due to a number of reasons. Firstly, the reaction of the host immune system to invading Mycobacterium tuberculosis (Mtb) in the form of higher activity of inflammatory cytokines including IL-6 (van Lettow et al., 2005). Secondly, Mtb infection leads to persistent anorexia and an increase catabolism of energy reserve of the host (van Crevel et al., 2002; Lee et al., 2013). As the ATD therapy progressed, the systemic levels of inflammatory cytokines gradually approached to an immune homeostatic level and the association of inflammatory cytokines with BMI weakened. It is likely that an immune homeostatic cytokine level is necessary to achieve the energy homeostasis and support normal metabolism (Djoba Siawaya et al., 2009). Hence, the physicians encourage proper nutrition and plenty of rest in TB patients. These practices may unknowingly prevent any exercise induced alteration in the cytokine levels and thus help to attain the homeostatic cytokine and energy levels in the patients.

Agilli et al. highlighted that in the exercise, IL-6 causes the elevation in serum IL-10 levels, and thus acts as an anti-inflammatory cytokine. IL-6 is a pleiotropic cytokine produced by a number of immune cells including macrophages, T cells and endothelial cells in addition to the skeletal muscle cells in exercise (Pal et al., 2014). IL-6 plays direct roles in Mtb infection including the inhibition of interferon gamma signaling in macrophages, production of acute phase proteins and promoting B cell growth and differentiation (Nagabhushanam et al., 2003). On the other hand, IL-10 is an anti-inflammatory cytokine that inhibits the anti-mycobacterial activity of macrophages (Murray et al., 1997). The pattern of alteration in the serum IL-6 and IL-10 levels evident in our study were also in consistence with others (Djoba Siawaya et al., 2009). The fact that the TB patients included in our study had a sedentary lifestyle in the hospital and were under a supervised condition of physical rest, any exercise induced IL-6 leading to an elevated level of serum IL-10 can only be marginal. The observed cytokine levels were a reflection of those contributed by a variety of immune cells affected by Mtb infection (Nagabhushanam et al., 2003). As previously demonstrated in numerous occasions (Nagabhushanam et al., 2003; Sahiratmadja et al., 2007), the most likely mechanisms of action of IL-6 and IL-10 in Mtb infection are mediated via interferon gamma rather anti-inflammatory myokine origin.

In consistent with our findings, another recent in vitro study (Singh and Goyal, 2013) also demonstrated that IL-6 can be used as a potential biomarker of Mtb infection. However, due to a pleotropic nature of IL-6 and its tissue specific regulation and functionality (Pal et al., 2014), we agree with Agilli et al. that measuring of additional markers would be beneficial. While the level of C-reactive protein (CRP) would reflect the level of acute inflammation and thus distinguish from exercise mediated contribution of IL-6 as we have previously demonstrated in a related study (Sen et al., 2011). As Agilli et al. highlighted, the neopterin level can also be explored as a marker for diagnosis of inflammation. Neopterin is produced from guanosine triphosphate by activated monocytes, macrophages, dendritic cells, and endothelial cells and to a lesser extent in renal epithelial cells, fibroblasts, and vascular smooth muscle cells upon stimulation mainly by IFN-γ (Hoffmann et al., 2003). So the level of neopterin could be associated with the level of IFN-γ in serum and activation of macrophages. The neopterin as a biochemical marker with a distinct advantage as it can be measured in serum as well as in urine. We hope to incorporate the idea of measuring CRP in serum and neopterin in serum and urine to further understand the role of inflammatory cytokines in tuberculosis in the near future and look forward to share interesting data with the readers.

In conclusion, the serum inflammatory cytokine data presented in our manuscript reflect the immune response of the TB patients pre-dominantly due to the Mtb infection and/or the effect of subsequent ATD therapy with only minimum effect of confounding factor such as the exercise induced myokines (IL-6 and IL-10). Our future studies will explore the use of CRP and neopterin as markers to better understanding of the inflammatory immune response in active pulmonary tuberculosis.

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References


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