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The paradoxical effect of IL-6 and implications for the use of Tocilizumab in Covid-19 patients

ABSTRACT

In the context of the current SARS-CoV-2 pandemic, patients affected by chronic obstructive pulmonary disease (COPD) should be more vulnerable to Covid-19, whereas they seem to be protected against severe Covid-19. That paradox has important practical implications for the use of the drug Tocilizumab in Covid-19. Interleukin-6 (IL-6) orchestrates the so-called cytokine storm leading to the Acute Respiratory Distress Syndrome (ARDS), the life-threatening condition that is responsible for Covid-19 deaths. However, IL-6 has a paradoxical effect in many viral infections. For pathogens such as HIV and Hepatitis B for example, high elevations show a toxic effect and are associated with higher mortality (e.g. they promote progression to AIDS in HIV patients), whereas mild elevations show a protective effect. IL-6 can be therefore considered as being both a pro-inflammatory and an anti-inflammatory cytokine. Several studies have shown that severe COPD is associated with extremely-high levels of IL-6, whereas mild COPD is associated with mild elevations of IL-6. It is plausible that the chronic, mildly-elevated concentrations of IL-6 found in mild COPD patients is protective against the deterioration of Covid-19, as it is the case for other viral diseases. That may explain why COPD is surprisingly an uncommon comorbidity in Covid-19 intensive care units. This may have an important practical implication for the treatment of Covid-19 patients: our hypothesis is that Tocilizumab must be used exclusively in patients with an ongoing cytokine storm. Otherwise, an early use of Tocilizumab can be harmful, especially in patients affected by COPD or other conditions with mildly-elevated IL-6.

In the context of the current SARS-CoV-2 pandemic, several studies have shown that patients with Chronic Obstructive Pulmonary Disease (COPD) seem to be protected against Covid-19, as they are underrepresented in Covid-19 hospital departments, especially in intensive care units. This is a surprising finding, since patient with that kind of comorbidity should be considerably the most vulnerable to SARS-CoV-2 infection and to Covid-19 progression into Acute Respiratory Distress Syndrome (ARDS), the life-threatening condition that is responsible for covid-19 deaths [1,2].

Why would COPD patients be protected against ARDS in Covid-19? We may find an answer in the role played by interleukin-6 (IL-6) in the pathophysiology of both Covid-19 and COPD.

Innate immunity is key in the development of Covid-19-related pneumonia, promoting the activation of the inflammasomes and a consequent hypersecretion of inflammatory cytokines including IL-1, TNF and IL-6. When the disease develops into an ARDS, IL-6 becomes fundamentally important. IL-6 orchestrates the so-called cytokine storm leading to an immune hyper-reaction and to the aggression against the pulmonary tissue [3]. This was confirmed in a meta-analysis of nine studies, which highlighted how the levels of IL-6 were higher in the severe forms of Covid-19 compared to the mild ones. The cut-off of 55 pg/ml was considered as the most accurate for identifying high-risk patients [4]. As a consequence, the drug Tocilizumab – which is a monoclonal antibody against the IL-6 receptor – is now commonly used to treat Covid-19 in hospitals [5].

However, IL-6 has a paradoxical effect in many viral infections. For pathogens such as HIV and Hepatitis B for example, mild elevations of IL-6 show a protective effect by stimulating CD4 T cells and by providing an enhanced antibody response, whereas high elevations show a toxic effect and are associated with higher mortality (e.g. they promote progression to AIDS in HIV patients) [6]. Mild elevations of IL-6 may be protective and boost the immune system also by stimulating the B cells and IL-10 for the T cells activation [6]. IL-6 can be therefore considered as being both a pro-inflammatory and an anti-inflammatory cytokine [7].

In COPD patients, the circulation of inflammatory cells such as lymphocytes and neutrophil granulocytes is more pronounced. Those cells produce IL-1, TNF, IL-17, and IL-6. The latter one is responsible for the osteoporosis that those patients can develop, as it interferes with the RANKL/RANK/OPG system and activates osteoclasts, with consequent bone resorption [8]. Several studies have shown that severe COPD is associated with extremely-high levels of IL-6, whereas mild COPD is associated with mild elevations of IL-6. It seems that the little extra IL-6 of the mild cases is produced locally, in the bronchi [9].

It is plausible that the chronic, mildly-elevated concentrations of IL-6 found in mild COPD patients is protective against the deterioration of Covid-19, as it is the case for other viral diseases. That may explain the low prevalence of COPD in Covid-19 intensive care units.

IL-6 may therefore be the key determinant of whether a SARS-CoV-2 infection develops into a mild case of Covid-19 or into a cytokine storm with consequent ARDS and a high risk of death. This may have an important practical implication for the treatment of Covid-19 patients: our hypothesis is that Tocilizumab must be used exclusively in patients with an ongoing cytokine storm. Otherwise, an early use of Tocilizumab may be harmful, especially in patients affected by COPD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110284.

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