Imbalanced pro- and anti-Th17 responses (IL-17/granulocyte colony-stimulating factor) predict fatal outcome in 2009 pandemic influenza

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Several clinical studies have confirmed an association between persistent hypercytokinemia and severe 2009 pandemic influenza, but none of these have used predictive models to analyze the relationship between the cytokines involved and disease outcome [1-4].

In the present work, we re-analyzed the results from two cohorts of critically ill patients suffering from pandemic influenza infection in 2009 [1,2]. Thirty-five critically ill patients hospitalized with primary viral pneumonia were included in the analysis.

The levels of 27 cytokines in peripheral blood measured during the first 24 hours following admission to the hospital were included in a Cox regression analysis to evaluate their association with mortality at 28 days. This analysis was adjusted by APACHE II score and the presence/absence of mechanical ventilation in order to preclude their potential influence on the results. IL-6, IL-8, IL-7, IL-17, and granulocyte colony-stimulating factor (G-CSF) yielded P-values <0.2 in the univariate analysis. In the multivariate analysis, high IL-17 levels were associated with increased probability of survival, while high levels of G-CSF were associated with increased risk of mortality at 28 days (P < 0.05; Figure 1). Kaplan Meier curves confirmed the association of IL-17 with survival and of G-CSF with occurrence of earlier death (Figure 1). Patients who died had significantly higher levels of G-CSF than those who survived (mean (standard deviation) pg/ml: 6,709.4 (17,979.1) and 2,043.9 (7,362.7), respectively; Mann Whitney U test). In contrast, surviving patients had higher levels of IL-17 than those who died (mean (standard deviation) pg/ml: 7.7 (8.1) and 1.5 (0.3), respectively; Mann Whitney U test).

A beneficial role of IL-17 in lethal influenza has been previously proposed [3]. In our experience, 9 out of the 10 patients who died had undetectable levels of IL-17. G-CSF is the principal cytokine controlling neutrophil development and function and could thus mediate excessive recruitment of neutrophils to the lungs, contributing to impairment of the respiratory system. In turn, G-CSF induces overexpression of negative regulators of Th17 differentiation [5]. In fact, G-CSF levels correlated negatively with IL-17 levels in our cohort, supporting a potential inhibitory role of G-CSF on the secretion of IL-17 in these patients (Spearman r coefficient, -0.43; P-value 0.010).

In conclusion, IL-17 has been shown to be protective in severe pandemic influenza, while G-CSF is a risk factor for mortality, indicating the existence of imbalanced pro- and anti-Th17 responses during this disease.

Abbreviations

G-CSF, granulocyte colony-stimulating factor; IL, interleukin.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

RA, ROL, DJK, IML, and JFBM assisted in the design of the study, coordinated patient recruitment, analyzed and interpreted the data, and assisted in writing the paper. LS, PR, JL, JR, CL, JB, DA, DM, EM, and JV recruited the patients, assisted in the analysis, interpretation of data, and writing the report.

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