CHRONIC KIDNEY DISEASE

CMV status affects hemoglobin levels and epoetin need

Hemoglobin levels are associated with seropositivity to cytomegalovirus (CMV) in patients with end-stage renal disease (ESRD), according to Michiel Betjes and colleagues at the Erasmus Medical Center in The Netherlands.

Responsiveness to the administration of recombinant human erythropoietin (epoetin) varies greatly between patients with ESRD, and the effect of known variables, such as serum concentration of iron or deficiency of vitamin B12 or folic acid, do not completely account for this variability. 60–80% of patients with ESRD are CMV seropositive, and evidence indicates that CMV seropositivity in these patients is associated with a remarkable increase in levels of proinflammatory T cells. Specifically, in CMV-seropositive patients with ESRD, the absolute levels and the overall proportion of $CD4^+$ T cells that do not have the co-stimulatory molecule CD28 ($CD4^+CD28null$) may increase substantially compared with levels in CMV-seronegative individuals. The proportion of circulating $CD4^+$ T cells that are CD28null with respect to the total $CD4^+$ T-cell population may increase from ~0.5% in CMV-seronegative individuals to 40–60% in CMV-seropositive patients with ESRD. $CD4^+CD28null$ T cells may be highly cytotoxic, as their levels seem to be associated with the production of interferon γ in response to CMV antigen and polyclonal stimulation.

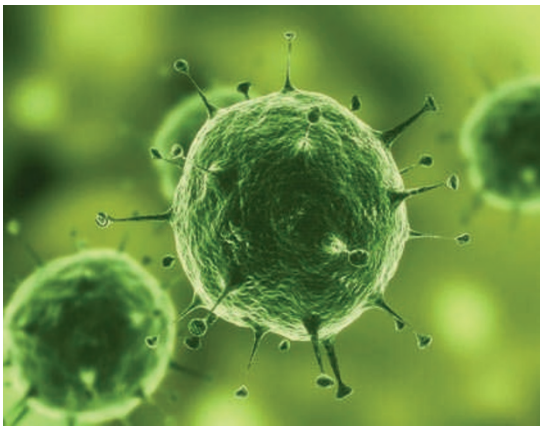
Betjes *et al.* carried out a cohort study of 129 stable patients with ESRD to investigate the possible association between CMV status, $CD4^+CD28null$ T-cell numbers and patient responsiveness to epoetin therapy. Multivariable linear regression analysis showed that in patients with ESRD on dialysis ($n = 84$) CMV seropositivity was the only parameter associated with epoetin dosage. CMV-seropositive patients on dialysis needed higher median doses of epoetin than their CMV-negative counterparts (12,000 U per week versus 6,300 U per week, respectively), even though median hemoglobin levels were not different between groups. Moreover, both increased percentage and absolute numbers of circulating $CD4^+CD28null$ T cells were associated with increased epoetin dosage. For instance, a 10% increase in serum $CD4^+CD28null$ T cells was associated with a median 20–40% increase in epoetin dose.

Among patients with ESRD who did not receive renal replacement therapy ($n = 45$)—most of whom did not receive epoetin—the average concentration of hemoglobin was significantly lower in CMV-seropositive than in CMV-seronegative individuals (115 g/l versus 125 g/l, respectively).

Betjes and colleagues also found that, following polyclonal stimulation, the average percentage of $CD4^+$ T cells that produced interferon γ and tumor necrosis factor (TNF) was significantly higher in patients on dialysis who were CMV seropositive than in their CMV-seronegative counterparts. Furthermore, following stimulation, $CD4^+CD28null$ T cells expressed higher levels of interferon γ and TNF than $CD4^+CD28^+$ T cells. In fact, on average 2% of $CD4^+CD28null$ T cells produced TNF in the absence of any stimulation, whereas only 0.6% of unstimulated $CD4^+CD28^+$ T cells did so.

In the researchers' opinion, these results are strongly suggestive of a pathophysiologic relationship between CMV status, serum levels of $CD4^+CD28^+$ T cells and hemoglobin regulation in patients with ESRD. Betjes *et al.* also conclude that, in stable patients on dialysis, the negative effect of increased numbers of $CD4^+CD28null$ T cells on erythropoiesis might be explained by the increased basal production of the proinflammatory cytokine TNF by these cells.

Betjes points out that decreased responsiveness to epoetin therapy has been associated with increased cardiovascular mortality in patients with ESRD and that results from a *trans vivo* animal model study suggest that $CD4^+CD28null$ T cells can cause atherosclerotic plaque instability and rupture. On the basis of the current study and on research published by his reasearch group in 2007 showing an association between CMV seropositivity and cardiovascular risk in patients with ESRD, Betjes states that he and his colleagues "believe that that expansion of the $CD4^+CD28null$ T-cell population may link epoetin responsiveness to increased cardiovascular mortality."



© Stockxpert

Betjes *et al.* are currently carrying out a clinical study to explore a possible relationship between increased circulating levels of $CD4^+CD28null$ T cells and cardiovascular disease. Another question that the group would like to explore in the future is what determines the number of $CD4^+CD28null$ T cells in CMV-seropositve patients with ESRD, given the high variability of this parameter in this patient population. An understanding of this regulatory mechanism may help devise therapeutic strategies to reverse the increase in levels of $CD4^+CD28null$ T cells in patients with ESRD.

Baldo Lucchese

Original article Betjes, M. G. H. *et al.* CMV seropositivity determines epoetin dose and hemoglobin levels in patients with CKD. *J. Am. Soc. Nephrol.* **20**, 2661–2666 (2009)