Editorial

The pathogenetic role of CMV in intensive care unit patients: the uncertainity remains

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More than two decades ago, Domart and colleagues (1) were the first to hint at a pathogenetic role for CMV in non-canonically immunosuppressed critically ill patients. In a cohort of 115 consecutive adult patients with mediastinitis after cardiac surgery, CMV shedding in urine, as determined by viral culture, was documented in 25% of patients of whom 79% had viremia. CMV shedding was found to be associated with persistence of local infection, prolonged hospitalization, and increased late mortality. Since then, a great body of experimental evidence has been gathered on this subject. We now know that CMV-seropositive patients frequently experience one or more CMV replicative episodes (CMV reactivations) during critical illness, most notably burn or septic patients (2-11). In fact, roughly one third of CMV-seropositive ICU patients will reactivate CMV, although the actual incidence rate may even exceed 40% in high-risk patients when highly sensitive real-time PCRs are employed for CMV surveillance, both the blood and the lower respiratory tract are concurrently screened and the frequency and length of CMV monitoring are optimal (12). A uniform finding of most of the above-quoted studies and a major conclusion of one meta-analysis (13) and one systematic review (14) is that the rate of mortality is increased two-fold, as an average, in patients experiencing CMV reactivation in comparison to that observed in CMV-seronegative ICU patients or in those seropositive not having CMV reactivation. The impact of active CMV infection in mortality is particularly striking in patients with acute respiratory distress syndrome (ARDS) (9). Moreover, the cumulative incidence of mortality in ICU patients correlates with the level at which CMV replicates, as inferred by the magnitude of peak CMV DNA load in plasma (8). Despite these observations and the pathogenetic feasibility of CMV involvement, a causal role of CMV cannot be established incontrovertibly by cohort studies, and thus definitive proof of causality awaits controlled clinical trials of CMV-specific antiviral therapy. In this scenario, Cowley and colleagues recently published the first randomized clinical trial addressing this issue (15). Although it was primarily designed to evaluate the efficacy and safety of antiviral therapy for prevention of CMV reactivation in this patients population, it provides interesting data on the potential impact of CMV replication on mortality that deserve comment.

Cowley and colleagues conducted a single-center, open-label randomized controlled clinical three-armed trial. A total of 124 CMV-seropositive adult patients with no documented congenital, acquired or iatrogenic immunosuppression were randomized (1:1:1) to receive CMV prophylaxis either with oral valacyclovir (n=34) at maintenance doses (2 g 4 times a day), or with oral valganciclovir also at maintenance doses (450 mg once a day) or no CMV prophylaxis (controls). Intravenous acyclovir or ganciclovir was given to patients unable to receive enteral medication. Anti-CMV treatment was interrupted in the presence of severe neutropenia and dose-adjusted when renal toxicity was documented. Disease severity (APACHE

II score) at admission to was comparable across groups. The primary outcome was the time to first CMV DNAemia (incidence rate), as determined by real-time PCR (limit of detection 20 copies/mL). CMV DNAemia monitoring was conducted every 5 days. Not unexpectedly, receipt of antiviral prophylaxis resulted in a significant decrease in the incidence of CMV DNAemia (12 patients in the control group *vs.* 3 in the prophylaxis arms-one in the valganciclovir group and 2 in the valacyclovir group (HR =0.14; 95% CI, 0.04–0.50; P=0.002). Both the initial and the peak CMV DNA load values within episodes occurring in controls or in breakthrough episodes developing in patients while under antiviral prophylaxis were rather low (median below 60 copies/mL) and did not differ significantly between groups. In fact, only one plasma specimen had a CMV DNA load above 1,000 copies/mL. Urinary and oral CMV DNA shedding was also examined in a large percentage of patients (85.2% and 90.7%, respectively). While the suppressive effect of antiviral prophylaxis on urine CMV shedding was evident (four patients in the control group *vs.* no patients in the combined prophylaxis groups) it was inapparent for oral shedding (four patients in the control group *vs.* three patients in the combined prophylaxis group).

Previous studies performed in the murine mCMV model of sepsis indicated that the lungs are a major site of CMV reactivation (16,17). This also appears to be the case in critically ill patients. In effect, CMV reactivation was reported to be diagnosed in around 25% of patients solely on the basis of the presence of CMV DNA in tracheal aspirates, thus suggesting that monitoring for the presence of CMV in the blood compartment may underestimate the actual incidence of active CMV infection in this population group (3,18); therefore, screening of lower respiratory tract specimens is imperative for an optimal diagnosis and monitoring of active CMV infection in ICU patients. In this sense, Cowley *et al.* examined sequentially 33 out of 118 patients for the presence of CMV in non-directed bronchiolar lavage specimens. Surprisingly, antiviral prophylaxis with valganciclovir had no effect on the rate of CMV DNA detection in the lower respiratory tract (two patients in the control group and two patients in the prophylaxis group). Although the scarce number of patients screened does not allow to draw robust conclusion on this matter, the data suggested that antiviral prophylaxis may not be equally effective at suppressing CMV replication in the lungs and the blood compartment or at other tissue or mucosal sites. This is not without relevance as poor clinical outcomes linked to CMV reactivation in ICU patients are likely to be related to local inflammation and perhaps to the generation of an immunosuppressive environment caused by CMV replication at pulmonary tissue (9,16,17).

Undoubtedly the most disappointing data, at least for those who defend the causal link between CMV and poor clinical outcomes in ICU patients, are those referring to the effect of CMV replication suppression on mortality. Although the study groups were balanced in terms of the severity of the illness at the time to ICU admission, the mortality rate was even higher in patients undergoing antiviral prophylaxis than in controls (in total, 9 of 44 patients died in the hospital in the control group compared with 15 of 34 patients in the valacyclovir group and 12 of 46 patients in the valganciclovir group). In fact the relative risk for hospital mortality was 1.3 (95% CI, 0.6–2.7) in the valganciclovir group *vs.* control and 2.2 (95% CI, 1.1–4.3) for the valacyclovir group *vs.* control. Certainly, the study was not primarily aimed at detecting significant differences in mortality across groups and perhaps it was not sufficiently powered to that purpose; despite this, the data are sound. An intriguing finding of this study was the unexpected higher early mortality rate among patients in the valacyclovir group which obligated to stop the recruitment in this arm prematurely. Independent intensive care specialists reviewed the case notes and concluded that despite APACHE II scores at ICU admission being comparable between groups all deaths were attributable to the underlying disease. Secondary clinical outcome measures including organ failure-free days (SOFA score <2) and moderate organ dysfunction-free days (SOFA score <5) at 28 days, time to discharge from the ICU and time to discharge from the hospital were also not significantly different between groups. In turn, severe neutropenia and thrombocytopenia occurred more frequently in patients in the antiviral prophylaxis arms, particularly in the valganciclovir group. This, nevertheless, could be anticipated given the known hematological toxicity of ganciclovir (in particular).

Conclusions

Cowley and colleagues (15) demonstrated that the use of anti-CMV prophylaxis in ICU patients drastically decreases the incidence of CMV DNAemia; nevertheless, this had no apparent impact on mortality, organ failure-free days or length of hospital stay. As this study was not aimed at anything but evaluating the virological efficacy and safety of two different antiviral prophylactic regimens, we are afraid that the possibility of CMV being a major factor in

the ICU setting leading to poor clinical outcomes remains unproven. To our knowledge, there are two clinical trials underway. The PTH study (NCT02152358) is investigating whether pre-emptive therapy with ganciclovir increases survival or the number of mechanical ventilation-free days. The GRAIL study (NCT01335932) is investigating the efficacy of the antiviral prophylaxis approach for treating CMV-seropositive patients who have been on mechanical ventilation for least for 24 h (GRAIL study). Let's hope these studies shed light and get us out of shadows.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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