

New Guidelines for Cytomegalovirus Infection Management in Transplant Recipients

Antonio Volpi

Department of Public Health, University of Rome, 'Tor Vergata', Rome, Italy.

THIS ISSUE OF *Herpes* publishes guidelines covering the management of cytomegalovirus (CMV) infection in transplant recipients, which were generated at an IHMF® workshop and approved by a panel of experts. Of course, therapeutic strategies differ from one setting to another, to account for different degrees and types of immunosuppression, short- and long-term effects of CMV infection and effective treatments available.

Two possible approaches to controlling CMV infection are prophylaxis with low- or high-potency antivirals, or pre-emptive therapy. Both types of intervention need close monitoring of CMV load, which appears to be an excellent indicator of the degree of immune response to the virus or of the efficacy of the adopted treatment. However, it appears difficult to establish the best method to detect the viral load and the optimum threshold to be used in different settings. Immunofluorescence staining of CMV lower matrix protein pp65 (UL83) in peripheral blood leucocytes (PBL) is commonly used to detect active CMV infection. In the pp65 antigenemia (pp65Ag) assay, the number of CMV-positive cells in peripheral blood reflects viral load: high numbers of pp65-positive cells correlate with CMV disease. Over 10 positive cells/200 000 PBL and >1–2 positive cells/200 000 PBL are the thresholds suggested to guide pre-emptive therapy in solid organ and stem cell transplant (SCT) recipients, respectively. However, the pp65 antigen-based diagnostic test has some disadvantages. In particular, it has low sensitivity for detecting early-active CMV infection or disease that occurs before engraftment (due to the lack of leucocytes found during the period of aplasia: neutrophil counts $>0.5 \times 10^9$ cells/l are required), and low positive-predictive value for the occurrence of CMV gastroenteritis. Furthermore, the pp65Ag assay requires blood samples to be processed within a few hours of collection, is time-consuming, requires skilled personnel and – despite some attempts – cannot be automated.

Recently, polymerase chain reaction (PCR)-based methods have been evaluated for diagnosing and monitoring post-transplant CMV infections. However, it remains difficult to evaluate the exact role of the previously reported PCR assays

in guiding pre-emptive CMV therapy in allogeneic SCT recipients, due to differences in sample origin (whole blood, plasma, serum, PBL, peripheral blood mononuclear cells [PBMC]) and the type of PCR procedures (qualitative versus quantitative) used for monitoring. Some studies have shown that the presence of CMV in plasma or serum indicates active viral replication, and there appears to be a high predictive value for CMV disease in SCT recipients and in HIV-infected patients. In addition, plasma offers the opportunity to detect active CMV infection during periods of severe cytopenia, when cell-based assays (PCR on leucocytes and pp65 antigenemia) perform poorly.

There is much interest in the quantification of CMV load in blood for monitoring and predicting CMV disease development and progression. Many studies have shown that the amount of CMV DNA is significantly associated with disease development. However, while evidence indicates that high CMV load is associated with a higher risk of progression to CMV disease in solid organ transplant recipients, the association may be less clear for allogeneic SCT recipients. Further, low levels of CMV viral load are frequently detected following allogeneic SCT, and CMV disease may still develop in some allogeneic SCT patients who have negative pp65Ag or undetectable DNA. The research need recommendation proposed by the IHMF®, namely the need for formal studies to obtain standardized assays for universal use, appears appropriate.

Recently I heard the sad news that Drs Charles Alford Jr and Thomas Weller passed away a few days apart. Dr Weller, who was awarded a Nobel Prize in Medicine in 1954 for showing how to cultivate poliomyelitis viruses, was one of the three scientists who first isolated CMV; Dr Alford, who performed an infectious diseases fellowship with Tom Weller at Harvard, was one of the group which defined the natural history and pathogenesis of congenital CMV infection. Drs Alford and Weller played important roles in my life: Weller's review on CMV published in 1971¹ activated my interest in CMV, which I was to develop when I was a fellow in the division created by Charlie Alford. I would like to dedicate this issue of *Herpes* to them both.

Reference

1. Weller TH. The cytomegaloviruses: ubiquitous agents with protean clinical manifestations. I and II. *N Engl J Med* 1971;**285**:203–214, 267–274.