Mixed Glycoprotein B Genotypes of Cytomegalovirus and Immunosuppression

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(See the article by Coaquette et al. on pages 155–61)

Cytomegalovirus (CMV) infection remains the most significant infection affecting the outcome of solid-organ transplantation or hematopoietic stem cell transplantation (HSCT). CMV infection causes febrile illness and end-organ disease and has been implicated indirectly in other clinically relevant outcomes. CMV infection has been shown to reduce patient survival and graft success rates and to increase the number of bacterial and fungal infections and the total cost of care [1]. Debate continues about whether the preferred treatment is prophylactic antiviral therapy for prolonged periods in all patients after receiving a transplant or preemptive use of antiviral therapy against CMV when evidence of CMV replication is present. Both approaches, however, are effective at decreasing the incidence of CMV disease in patients who undergo solid-organ transplantation or HSCT [2, 3]. Antiviral prophylaxis has also been attributed to improvement in events indirectly associated with CMV infection, such as decreases in the rate of graft rejection and improvements in the use of in-patient medical resources [4].

The remarkable achievements associated with antiviral therapy for CMV infection have also led to the development of 2 new challenges in transplant recipients: the new syndrome of late-onset CMV disease, and infection with drug-resistant strains of CMV. Late-onset CMV disease syndrome is the result of antiviral therapy delaying but not preventing the onset of CMV disease in patients who are predisposed to develop it. This observation stems from clinical studies of patients who received solid-organ transplants, were treated prophylactically with antiviral therapy, and developed CMV disease after discontinuation of therapy [4, 5]. This risk is particularly high in CMV-seronegative recipients of solid-organ transplants from CMV-seropositive donors (i.e., CMV D+/R⁻ transplant recipients); as many as 27% of such patients develop CMV disease, usually within 3–6 months after undergoing transplantation [6]. In addition, the use of high-dose methylprednisolone for immunosuppression in treating potential allograft rejection greatly increases the risk of CMV disease in solid-organ transplant recipients [6]. Late-onset CMV disease syndrome has been increasingly observed in recipients of HSCTs and occurs at a median of 169 days after transplantation in 18% of allogeneic HSCT recipients [3]. In this group, CMV disease is associated with an increase in mortality; 46% of HSCT recipients with late-onset CMV disease died, and this increased to 76% in the subgroup of patients with CMV pneumonitis [3]. An important characteristic for success after receipt of an HSCT is recovery of CMV-specific CD4⁺ and CD8⁺ cell function at 3 months after transplantation. It has been suggested that prolonged prophylaxis with ganciclovir delays recovery of CMV-specific cytotoxic T lymphocyte response by suppressing CMV replication and preventing CMV antigen expression, thus preventing adequate stimulation of the immune system [7]. Therefore, when antiviral prophylaxis is discontinued, the ensuing CMV replication in recipients of CMV D⁺/R⁻ transplants who are unable to mount a response with CMV-specific cytotoxic T lymphocytes contributes to severe late-onset CMV disease.

Additional studies have also supported the impact of steroid use in suppressing maximal reconstitution of the immune system. Patients undergoing transplantation who received 1 of 3 doses of steroids within 2 weeks after analysis of CMV-specific CD4⁺ cell functional recovery were studied [8]. The study found that, of 57 patients who received 2 mg/kg per day of steroids, only 1 (1.8%) exhibited recovery of CD4⁺ cell function at 3 months after transplantation. This compared with 35 (57.4%) of 61 patients who received 1 mg/
kg per day of steroids and 54 (74%) of 73 who received no steroid (P < .001). Multivariate analysis showed that only steroid use and CD4⁺ lymphopenia exhibited significant independent effects. Hakki et al. [8] concluded that both the maximum steroid dose and the cumulative amount of steroid received negatively influenced the recovery of CMV-specific CD4⁺ and CD8⁺ cell functions.

The amount and severity of immunosuppression is not the only factor that allows viruses to replicate; all viruses use genetic diversity to evade the immune system. The report in this issue of Clinical Infectious Diseases by Coaquette et al. [9] examines the role of mixed CMV genotype B infection in the clinical outcomes of immunocompromised patients [9]. The CMV glycoprotein B (gB) is the major envelope glycoprotein of CMV, and it is encoded by the UL55 gene of CMV. CMV gB is involved in entry into the host cell, cell-to-cell virus transmission, and fusion of infected cells [10, 11]. It is an important target for humoral and cellular immune responses to CMV [12, 13]. CMV gB is expressed on the virus surface as a precursor molecule that is glycosylated and cleaved at codon 461 to form a disulfide-linked complex with a gp55 and a gp116 subunit [14]. On the basis of gB nucleotide sequencing, the existence of 4 distinct gB genotypes have been observed among strains of human CMV [15]. Because of its role as the major viral glycoprotein initiating a strong immune response in humans, a correlation between gB genotype and CMV-associated disease in immunocompromised patients has long been sought for, but no convincing evidence has been found.

In this new study, Coaquette et al. [9] provide significant evidence that infection with >1 gB genotype (i.e., mixed infection) correlates with clinical disease better than does infection with any single genotype. In a group of 64 transplant patients who received kidney (22 patients), liver (26), or bone marrow transplants (16), Coaquette et al. [9] found that infection with a mixed CMV gB genotype was fairly common, occurring in 30 (46.9%) of 64 patients, compared with infection with a single CMV gB genotype (34 [53.1%] of 64). The study reported the surprising result that infection with a mixture of gB genotypes in immunocompromised patients was associated with a higher virus load, a higher prevalence of CMV disease, and a higher rate of graft rejection, when compared with infection with a single gB CMV genotype [9]. These differences were all statistically significant. Coaquette et al. [9] were able to extract CMV DNA from 97 CMV isolates and successfully amplify the DNA using PCR. As in many other studies, they found that the occurrence of infection with types gB1 (28.6% of isolates), gB2 (19.4%), and gB3 (23.5%) was common. The rate of infection with type gB4 was 2%. Also in agreement with other studies, they found no significant difference among gB genotypes in terms of the development of symptomatic disease. Coaquette et al. [9] cite other studies that show no significant association between gB genotype and acute graft rejection [16]. They also mention a study by Rosen et al. [17] that analyzed 53 liver transplant recipients and found that gB1 correlated with a higher number of acute graft rejection episodes, but that there was no correlation with graft-rejection severity or chronic rejection.

Coaquette et al. [9] defined CMV disease as CMV hepatitis, CMV gastrointestinal disease, CMV viral syndrome, or CMV pneumonia. Further details about CMV disease and severity are not provided. For transplant recipients, the risk of progression to CMV disease was 67.6% among patients infected with a single gB genotype and 93.3% among those infected with mixed genotypes. The difference is statistically significant (P < .05). These risks for CMV infection are very high, and this study would benefit greatly if more details were provided. Coaquette et al. [9] state that, among transplant recipients, only those who received a transplant from a donor who was seropositive for CMV and who themselves were seronegative (i.e., CMV D‘/R⁻ transplant recipients) before undergoing transplantation received antiviral prophylaxis. There are no details provided, however, on the number of CMV D‘/R⁻ recipients, the type or duration of antiviral prophylaxis administered, or the development of antiviral resistance to the prophylactic regimen.

Coaquette et al. [9] point out that patients with mixed infection are more heavily immunosuppressed, compared with the patients with single gB genotype infection. This was especially attributed to treatment with antilymphocyte globulin, suggesting a role for severe immune suppression in contributing to the inability to develop CMV-specific CD4⁺ and CD8⁺ cytotoxic lymphocyte responses. This is an attractive hypothesis, given the data they present, but it is difficult to interpret in the absence of details about the actual immunosuppressive regimens employed. No specific details about the immunosuppressive regimens used in the present study [9] are included in the paper, and the reader must refer to a prior publication [18] to find the drugs used. That report [18] states that, in all transplant recipients except for those who received kidney transplants, a combination of cyclosporine, azathioprine, and prednisone was used. The kidney transplant recipients also received antilymphocyte globulins. Cyclosporine therapy was administered on day 4 after transplantation. Mild rejection episodes were treated with methylprednisolone, and severe rejection episodes were treated with OKT3 monoclonal antibodies. No information on the dosage used is provided. In the current report [9], the authors state that mixed gB CMV infection is mostly associated with heavy immunosuppression, especially immunosuppression with antilymphocyte globulin. This suggests that a main association with mixed infection was the treatment of severe rejection episodes in kidney transplant recipients. The study [9] also provides interesting data on a higher prevalence of both Epstein-Barr virus/CMV
coinfection and herpes simplex virus/CMV coinfection in those immunocompromised patients with mixed gB infection. This supports their hypothesis that severe immunosuppression prevents the response of virus-specific cytotoxic lymphocytes to infection with diverse CMV gB genotypes and other herpesviruses.

This study [9] provides new and provocative evidence that CMV infection with mixed gB genotypes in immunocompromised patients is associated with increased progression of CMV disease, higher CMV load, and an increase in the number of graft rejection episodes. It is important that this study be confirmed by results from other centers. Additional data are also required on the details of the immunosuppression regimens and antiviral prophylaxis associated with enhanced CMV progression before the full implications of these findings can be appreciated. This study [9] should provide a strong stimulus for further research on the relationship between immunosuppression and the inability to control infection with diverse strains of CMV.

References