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# Cytomegalovirus Immunoglobulin After Thoracic Transplantation: An Overview

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**Abstract:** Cytomegalovirus (CMV) is a highly complex pathogen which, despite modern prophylactic regimens, continues to affect a high proportion of thoracic organ transplant recipients. The symptomatic manifestations of CMV infection are compounded by adverse indirect effects induced by the multiple immunomodulatory actions of CMV. These include a higher risk of acute rejection, cardiac allograft vasculopathy after heart transplantation, and potentially bronchiolitis obliterans syndrome in lung transplant recipients, with a greater propensity for opportunistic secondary infections. Prophylaxis for CMV using antiviral agents (typically oral valganciclovir or intravenous ganciclovir) is now almost universal, at least in high-risk transplants (D+/R–). Even with extended prophylactic regimens, however, challenges remain. The CMV events can still occur despite antiviral prophylaxis, including late-onset infection or recurrent disease, and patients with ganciclovir-resistant CMV infection or who are intolerant to antiviral therapy require alternative strategies. The CMV immunoglobulin (CMVIG) and antiviral agents have complementary modes of action. High-titer CMVIG preparations provide passive CMV-specific immunity but also exert complex immunomodulatory properties which augment the antiviral effect of antiviral agents and offer the potential to suppress the indirect effects of CMV infection. This supplement discusses the available data concerning the immunological and clinical effects of CMVIG after heart or lung transplantation.

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Cytomegalovirus (CMV) (Figure 1) is one of the most common pathogens in humans, infecting more than 60% of the general population and as many as 100% within some geographic areas. In the immunocompetent host, it usually has a benign, asymptomatic course, but in the immunocompromised or immune-immature host—such as transplant recipients or newborns—it may develop clinically meaningful clinical syndromes. The biology of CMV lifecycle is among the most complex of the known human viruses thanks to its ability to interact with the immune system via several strategies by which it modulates and escapes host immune response.[1] Indeed, fewer than 30% of CMV genes are required for virus replication and many of the others relate to regulation of the host's cellular mechanisms.[2,3] Despite intensive efforts to reduce the toll of CMV infection after thoracic transplantation, it remains the most clinically relevant infectious agent in this setting, representing a major cause of morbidity and, if untreated, mortality. The intense immunosuppression required after heart or lung transplantation compared with other solid organ transplants places these recipients at particularly high risk for CMV events, compounded after lung transplantation by a high transfer of latent CMV in grafts from seropositive donors.

Despite the long experience with CMV immunoglobulin (CMVIG) in thoracic organ transplantation, there is still a wide variability among centers regarding its use in the prophylaxis and treatment of CMV infection or CMV disease (Table 1). Randomized trials are rare in this setting[4] such that evidence-led decision-making, although desirable, is difficult. Against this background, a meeting of heart and lung transplant experts was convened in San Diego, CA, in April 2014. The purpose of the discussions was to review the available data relating to CMVIG therapy in the setting of thoracic organ transplantation and to consider the most appropriate strategies for its deployment to help reduce the impact of CMV infection on patient outcomes. The key

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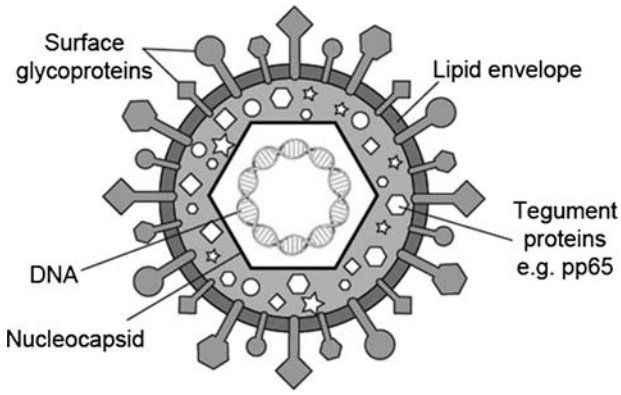


**FIGURE 1.** The CMV virion.

findings and conclusions of the expert panel are reported in this supplement.

## The Burden of CMV

Estimates of CMV infection rates vary, partly due to differences in diagnostic criteria, but recent studies using modern CMV prophylaxis regimens have reported incidences of 11% to 30% in heart transplant recipients[5-8] and 20% to 40% in lung transplant recipients.[9-11] Encouragingly, markedly lower rates have been observed in patients treated with a mammalian target of rapamycin inhibitor[5,7,12,13] or given extended antiviral prophylaxis.[14]

High-level CMV infection can manifest as the well-characterized CMV syndrome typified by mononucleosis-like fever. If the infection progresses to organ-invasive CMV disease, it most often affects the gastrointestinal system (colitis, ulceration), the liver (hepatitis) and, particularly in lung transplant recipients, the lungs (pneumonitis), with potentially life-threatening consequences. In addition, however, persistent low-level CMV infection can exert a number of damaging indirect effects.[15] Notably, CMV infection seems to be associated with a significant increase in the risk of acute rejection after thoracic transplantation even in the era of valganciclovir prophylaxis.[9] The CMV infection upregulates major histocompatibility complex antigens in the graft, likely by stimulating interferon-γ production by activated $CD4^+$ cells, thus increasing graft immunogenicity[16] and prompting rejection. The CMV infection also promotes the development of cardiac allograft vasculopathy after heart transplantation[16-20] by triggering an early inflammatory response in the graft vasculature, ultimately leading to enhanced intimal thickness and a reduced lumen.[16] Similarly, there is evidence that CMV infection or CMV pneumonitis increases the risk of bronchiolitis obliterans syndrome (BOS) in lung transplant recipients,[21-25] again by provoking interferon-γ release by $CD4^+$ cells[26] and other immunomodulatory effects,[27] although conflicting results have been reported.[28-30] The CMV infection is also associated with an increased risk of opportunistic secondary infections, such as invasive fungal disease, again due to CMV-induced modulation of the host immune system.[31]

## Issues in the Management of CMV

Host defences are severely curtailed in solid organ transplant patients receiving chronic immunosuppression, particularly in the first weeks posttransplant when the high risk of rejection necessitates potent regimens. Since the 1990s, antiviral prophylaxis for CMV using antiviral agents has become more widely used after heart[32-34] or lung[35,36] transplantation, particularly in high-risk D+/R– transplants.[35] Evidence from kidney transplantation that extending antiviral prophylaxis to a minimum of 6 months reduces the risk of CMV disease[37] has been mirrored in heart[8,38] and lung[39-41] transplantation. Prophylactic treatment for CMV after lung transplantation is almost entirely based on oral valganciclovir, preceded by intravenous ganciclovir at approximately half of specialist centers.[35] If, alternatively, a preemptive strategy is followed, prevention of primary CMV infection or viral reactivation from latency sites requires constant immune surveillance. Preemptive therapy, although effective,[42,43] seems to be less frequently used than prophylaxis; 1 international survey reported its use in only 14% of lung transplant centers.[36]

Despite the improvements in CMV infection rates after adoption of modern antiviral protocols, considerable challenges remain. Even using extended valganciclovir regimens within the controlled environment of a clinical trial, CMV infection occurs in at least 10% of heart[6] and lung[14,41] transplant patients. Furthermore, late-onset primary CMV infection after withdrawal of antiviral agents routinely occurs in a proportion of patients receiving universal prophylaxis,[44,45] whereas cases of recurrent CMV disease and, in particular, CMV strains resistant to ganciclovir or valganciclovir require alternative treatment approaches, such as foscarnet.[46] Patients with severe hypogammaglobulinemia, for example, induced by immunosuppressive therapies, such as mycophenolic acid, are another instance in which conventional antiviral therapy alone may not be adequate. Additionally, the dose-limiting hematological side effects of ganciclovir[47] can necessitate a switch of strategy.

## CMV Immunoglobulin Therapy

The highly sophisticated mechanisms by which CMV modulates cell signalling pathways to adapt the host immune system[1] may support a rationale for a combination approach to prevention and treatment of CMV infection. The CMVIG and antiviral agents have complementary modes of action: CMVIG eliminates virus particles before they reach the host cell, whereas antiviral agents (ganciclovir, foscarnet and cidofovir) target viral DNA polymerase to block viral replication within the cell. The importance of an effective immunoglobulin G response to CMV infection was highlighted by the randomized VICTOR study, in which solid organ transplant patients (predominantly kidney transplant recipients) with negative CMV serostatus at the point when antiviral therapy

**TABLE 1.**

**Possible settings for CMVIG administration in thoracic organ transplantation**

| |
|---|
| Component of universal prophylaxis in D+/R– transplants, in combination with antiviral therapy |
| Intolerance to antiviral therapy necessitating dose reductions or withdrawal/interruption |
| Recurrent CMV disease, e.g., if unresponsive to antiviral therapy |
| Treatment of CMV disease in the presence of hypogammaglobulinemia |
| Treatment of ganciclovir-resistant CMV infection (clinically suspected or laboratory confirmed) in addition to effective antiviral agents (cidovofir, foscarnet, maribavir, or letermovir, according to the sensitivity of the responsible strain) |

Note that these are not evidence-based indications.

started were significantly more likely to develop recurrent CMV disease than those who were positive for CMV IgG.[48] The high titers of CMVIG in commercial preparations provide passive CMV-specific immunity in heavily immunosuppressed patients, neutralizing free viral particles by promoting opsonization and phagocytosis, and stimulating lysis by complement- and antibody-mediated responses. After the initial viremic phase, CMVIG enhances the antibody-dependent cellular cytotoxicity response to CMV infection such that its effect peaks a few weeks after first administration, when cytokine-producing $CD4^+$ cells are produced. As discussed in the subsequent section "The immunology of posttransplant CMV infection: Potential effect of CMV immunoglobulins on distinct components of the immune response to CMV" CMVIG has complex immunomodulatory properties. In addition to augmenting the antiviral effect of antiviral agents, these may potentially suppress the indirect effects of CMV infection, such as allograft rejection, transplant vasculopathy, and BOS.

The CMVIG preparations are, essentially, concentrated doses of endogenous immunoglobulins from healthy individuals and as such, safety is not considered a major concern. Adverse events are rare and where they occur are typically mild injection site reactions. For example, in 1 series of 377 heart transplant recipients given CMVIG as sole prophylaxis, all patients received the full dose without any overt side effects,[49] confirmed in a smaller early series of 15 patients.[50] Postmarketing surveillance for the Cytotect preparation found only 4 events with a possible or certain relation to CMVIG administration across a total of 13 716 applications in 2286 patients during a 3-year period, comprising 1 case of headache, 1 infusion-related reaction, and 2 cases of anti-hepatitis B surface antibody positivity.[51] Given this level of safety, virtually all the studies described in this article do not report safety endpoints, and little evidence of adverse events associated with CMVIG is available in the literature.

CMV-specific hyperimmunoglobulin preparations have been used to treat or prevent CMV infection after thoracic transplantation for more than 30 years.[52] During that time, production methods have evolved and now incorporate sophisticated viral inactivation procedures which ensure high-quality and safety profiles and generate CMV-specific immunoglobulin.[53] Before effective antiviral agents became available, CMVIG was used more widely than now to prevent CMV infection. In the United States, data suggest that CMVIG is currently given prophylactically in fewer than 10% of heart transplant recipients overall,[33,34] but with higher usage in D+/R– patients (~40%).[36] A recent international survey of lung transplant centers also found that 30% to 40% use CMVIG for prophylaxis in D+/R– transplants.[35,36] Information on the application of CMVIG therapy for the treatment of established CMV infection or disease is more sparse, but across all types of solid organ transplants, it has been reported that approximately 10% of clinicians routinely administer CMVIG as an adjunct to antiviral treatment, mostly in D+/R– cases.[36]

Use of CMVIG in heart and lung transplant recipients has increased in recent years, possibly in response to growing problems with CMV management based on antiviral therapy alone, notably the emergence of ganciclovir-resistant strains. Current consensus recommendations, however, note that there are only limited data to support prophylactic use of CMVIG when appropriate antivirals are given.[15,54] Guidelines from the Transplantation Society and the American Society of Transplantation do not advise CMVIG prophylaxis after kidney or liver transplantation, but include the option for CMVIG as adjunctive therapy to antiviral prophylaxis after heart or lung transplantation in high-risk D+/R– patients.[15,54,55] Regarding use of CMVIG to treat CMV disease, the recommendations point out that the evidence is unclear but suggest that it could be considered in severe forms, such as pneumonitis.[15,54,55]

The relative scarcity of high-quality trials in this area prohibits development of robust, evidence-based guidance. The articles in this supplement discuss the available data concerning the immunological and clinical effects of CMVIG as prophylaxis or treatment for CMV infection after heart or lung transplantation.

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