P&T®

PRODUCT PROFILER

Cytogam®

Cytomegalovirus Immune Globulin Intravenous (Human)

FDA-Approved Indication

Prophylaxis of cytomegalovirus disease associated with transplantation of:

- Kidney
- Liver
- Pancreas
- Heart
- Lung

Contents

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SECTION THREE

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The Product Profiler

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

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Disclosure

This work was developed with CSL Behring. The authors indicate that they have no direct relationship, financial or otherwise, with CSL Behring.

PRODUCT PROFILER

Cytogam®

Cytomegalovirus Immune Globulin Intravenous (Human)

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Introduction: Disease Overview and Risk Factors

Cytomegalovirus (CMV) is a hardy and adept virus that has succeeded in maintaining its presence for many centuries. CMV has a consistent ability to circumvent human immune defenses and is able to do so in a variety of ways; its ability to thwart our defenses makes infection with CMV a challenge to prevent and treat. Specific populations affected by an infection with CMV include newborns and immunocompromised patients. Recipients of solid organ transplants (SOT) also have an exceptionally high risk of CMV infection, which may ultimately place the patient and transplanted organ at risk for loss.

Traditional prophylaxis treatments are often used to prolong the time between a possible CMV infection post transplantation. Another agent, CMV immune globulin, intravenous (CMVIG) (Cytogam®), is an effective treatment that may be used concurrently with traditional prophylaxis to help limit infection with CMV. This Product Profiler will review CMV, current therapeutic options for CMV prophylaxis, and the pharmacology, efficacy, and safety of CMVIG.

DISEASE OVERVIEW

Cytomegalovirus Host Evasion and Subsequent Pathology

CMV is a ubiquitous herpes virus that is composed of double-stranded DNA, a protective protein capsid, a tegument that houses enzymes and proteins, and a lipoprotein membrane envelope (Baden 2008, Cytomegalovirus Infections 2008, McDevitt 2006).

Like other herpes viruses, CMV has the intricate ability to establish tenure within a host cell's DNA and is subsequently capable of establishing latency and/or causing an active infection. This opportunistic pathogen often creates latent infections in various cells including monocytes, neutrophils, lymphocytes, endothelial cells, and smooth muscle cells (AJT 2004, Froberg 2004, Sia 2000). CMV is capable of causing severe illness in newborns, transplant recipients, and patients with HIV (Froberg 2004).

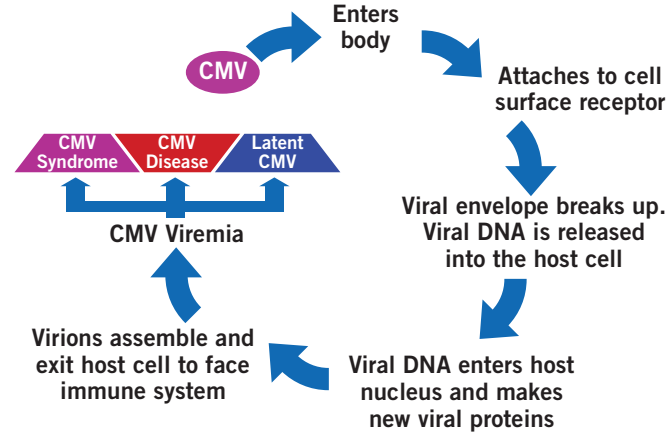
CMV is a highly evolved virus in that it has developed numerous mechanisms to evade host defenses. These evasion techniques, often referred to as "immuno evasion," have allowed the virus to develop camouflage and sabotage techniques to effectively disrupt normal immune responses. The cellular and genetic changes induced by CMV can be divided into three categories: immune escape, impaired replication, and impaired signaling (Fisher 2009).

The virus may establish a latent infection by using immuno evasion to camouflage its presence from immune detection (Froberg 2004). During a latent infection, the virus intercalates its DNA into the host genome, ensuring its survival each time the cell divides. Because little to no virions are produced during this process, the apoptotic pathway is not activated, allowing the infected cell to survive indefinitely (Froberg 2004). With a latent infection, the virus remains in a reversible, nonproductive infective state (Froberg 2004). Although CMV may establish a latent infection and remain inactive in many cells, it may simultaneously cause active and chronic infections in the salivary glands (Froberg 2004). This allows the virus to facilitate its transmission to other hosts (Froberg 2004) (Figure 1).

CMV is capable of disrupting or activating cellular immune signaling and replication (Froberg 2004). This type of activity can be seen in steps involved in the antigen presentation process common to Major Histocompatibility Complex (MHC) Class I and II cells (Froberg 2004). CMV is able to disrupt MHC class presentation on the surface of cells (Froberg 2004).

Under normal circumstances, this disruption would ini-

FIGURE 1
Lifecycle of CMV Infection



Adapted from Uknis 2005

tiate natural killer (NK) cell responses. However, through unique short (US) genetic segments, CMV effectively replicates an MHC Class I homolog that is capable of binding to host peptides (Froberg 2004). Peptides are continually expressed on the cell surface, inhibiting NK activity and curbing their normal cytotoxic effects (Froberg 2004). CMV also prevents apoptosis by binding specific viral proteins, ensuring its survival in the host cell (Froberg 2004). Lastly, CMV can replicate a G-protein-coupled receptor homolog (Froberg 2004). The CMV generated homolog binds to chemokines and initiates a sequence of complications, including vascular and atheromatous lesions in the affected host (Froberg 2004).

In addition, the presence of US genetic segments in the CMV genome allows the virus to (Froberg 2004, Pereyra 2004):

- Degrade immune complexes
- Inhibit peptide translocation (Class I)
- Bind to certain MHC molecules (Class I)
- Dislocate complexes for rapid degradation (Class I)
- Destroy proteins involved in presentation (Class II)
- Downregulate cellular responses (Class II)
- Replicate a cytokine homolog to inhibit cytokine production (Class II)

Epidemiology

CMV is widely prevalent and can be found in all geographic and socioeconomic groups (CDC 2008). However, it is more frequently found in developing countries and in lower socioeconomic conditions (Beers 2006, CDC 2008). It is common for 60%–90% of the general population to have been exposed to and to be infected by CMV because of its wide predominance in many geographical locations (Beers 2006). Naturally, as patients age, they have a higher risk of CMV infection (Beers 2006).

RISK FACTORS FOR CMV INFECTION IN SOLID ORGAN TRANSPLANT RECIPIENTS

Many factors are involved that can cause complications during and after SOT procedures. However, CMV has been noted as the most common pathogen to cause complications leading to morbidity and mortality in post-SOT recipients (EBCG 2001, Razonable 2004). True to its nature, CMV is an opportunistic virus that thrives on factors that favor infection and subsequent disease.

CMV Serostatus

The predictive risk for subsequent CMV infection lies heavily in the serostatus of both the organ donor (D) and recipient (R) (Razonable 2005). CMV serostatus is in fact, the most important risk factor for CMV infection and disease in organ transplant recipients. The pattern for CMV infection in transplant recipients is categorized by three types of infection: primary, reactivation/recurrent, and superinfection/reinfection (NIAID 2005).

Primary infection is the leading cause of CMV infection in SOT recipients (NIAID 2005, Razonable 2005). A primary infection is most prevalent when a seronegative recipient (R–) receives an organ from a seropositive (D+) donor. This type of transplant confers a high risk for developing a primary infection (Razonable 2005).

The second pattern of CMV infection is called reactivation or recurrent infection (NIAID 2005). This infection carries an intermediate risk for CMV infection and occurs through the reactivation of a latent CMV infection already present in the recipient (McDevitt 2006, Razonable 2005).

The final type of infection is the superinfection or reinfection pattern of CMV (NIAID 2005). Superinfections occur when both the donor and recipient are positive for CMV but are infected with two distinct strains (McDevitt 2006, NIAID 2005): the recipient's original latent strain and the donor's latent or active strain (NIAID 2005). This infection carries an intermediate risk for CMV infection post transplant. Table 1 lists levels of risk of CMV infection post transplant.

Additional Risk Factors for Post-transplant CMV Infection

The type of organ transplant also plays a role in the risk of acquiring CMV infection (McDevitt 2006). Liver, lung, and pancreas transplant recipients have a high risk of acquiring a CMV infection while heart, small bowel, and kidney transplantation carry a lower risk (McDevitt 2006; Razonable 2005). In most instances, CMV infection often develops within 3 months of transplantation if prophylactic viral therapy is not initiated (McDevitt 2006). CMV may cause a variety of illnesses during infection, although, tissue invasive diseases involving the transplanted organ are more likely (McDevitt 2006). The presence of CMV may also add to the risk of organ rejection. Risk factors include retransplantation, fulminant hepatitis, bacterial infections, contaminated blood products, cadaveric allograft transplantation, Human Leukocyte Antigen (HLA) mismatch, and the amount of virus present in the donor organ (McDevitt 2006, Sia 2000).

The degree of immunosuppression may influence the rate or risk of CMV infection as well (Sia 2000). For example, the type, dose, duration, and sequence of immunosup-

TABLE 1
Risk Factors for the Development of Post-transplant CMV Infection

CMV serostatus (donor/recipient)	Risk of primary infection, reactivation, superinfection
D+/R– D+/R+ D–/R+ D–/R–	High risk (primary) Intermediate risk (reactivation/superinfection) Intermediate risk (reactivation) Low risk (primary)

Source: McDevitt 2006

pressive therapy may dictate the level and speed in which CMV may flourish (NIAID 2005, Sia 2000). Many anti-rejection drugs used for prophylaxis limit the body's natural ability to mount responses by suppressing cell-mediated immune responses. They may also induce blunt antibody responses, inhibit proliferation, suppress T- and B-cell lymphocytes, and cause leukopenia (Sia 2000).

The extent of viral replication is also a considerable concern in the development of CMV infection (Razonable 2005). The reactivation and subsequent replication of latent CMV may dictate the pathogenesis and severity of an infection (Sia 2000). In addition, the rate and ability of the virus to infect and progress has been linked to the organ type and the efficiency of the immune system at the time of infection and/or transplantation (McDevitt 2006). The severity of CMV is usually categorized as either CMV infection or CMV disease. Unfortunately, these two categories are not universally defined and discrepancies may occur (McDevitt 2006). In many studies, CMV infection is defined as the isolation of the virus in any body fluid or tissue specimen (Ljungman 2002), while the disease refers to the presence of CMV in blood or body tissues with the presence of clinical symptoms (McDevitt 2006). The severity of CMV infection and its sublime opportunity to progress into disease depends on the host's immune system and the type of SOT. It is important to note that although a percentage of patients may become infected with CMV, not all will progress to CMV disease (McDevitt 2006) (Table 2).

TABLE 2
Frequency of CMV Infection and CMV Disease in Solid Organ Transplant Recipients

Organ	CMV Infection (%)[a]	CMV Disease (%)[b]
Kidney	8–32	8
Liver	22–29	29
Heart	9–35	25
Lung or heart–lung	39–41	39
Pancreas or kidney–pancreas	50	50

[a]CMV infection refers to viremia without clinical symptoms.
[b]CMV disease refers to viremia with clinical symptoms.
Source: McDevitt 2006

TABLE 3
Direct and Indirect Consequences of CMV Infection

Direct consequences	Indirect consequences
• Viral syndrome • Hepatitis • Pancreatitis • Gastritis • Colitis • Nephritis • Myelosuppression • CMV retinitis	• Increased state of immunosuppression • Opportunistic infections • Acute allograft injury • Chronic allograft injury • Post transplant lymphoproliferative disease • Decreased patient and graft survival • Increased cost and hospitalization stays

Sources: Preiksaitis 2005, Razonable 2005, Sia 2000

DIRECT AND INDIRECT CONSEQUENCES OF CMV INFECTION

Any organ transplant procedure carries inherent risks for complications. CMV infection specifically can often cause systemic and tissue invasive diseases in this population subtype (Razonable 2005). Infection with CMV acquired post transplantation often predisposes patients to both direct and indirect consequences such as febrile syndrome, myelosuppression, hepatitis, pneumonitis, gastrointestinal disease, and encephalitis (Razonable 2005). This patient population is often prone to opportunistic infections which may often lead to acute or chronic rejection of the allograft (Razonable 2005).

Active or recurrent infections with CMV after transplantation affect patient outcomes as well. For example, liver transplant patients 1 year after surgery were found to have higher mortality rates, increased medical expenses, and longer hospital stays than those of their CMV-negative transplant counterparts (Sia 2000). Similar decreased survival rates were observed when heart transplant patients were followed over a 5-year period. Patients positive for CMV disease had a 32% survival rate compared to 68% of their CMV-negative counterparts (Sia 2000). Lung transplant recipients who received CMV-positive lungs also developed severe complications related to the graft and had lower survival rates than CMV negative graft recipients (Sia 2000). Direct and indirect consequences of CMV infection in patients post transplant are summarized in Table 3.

Prophylaxis for CMV Infection

SOT recipients are naturally at a disadvantage for infection because of their immunosuppressed status. In an effort to counter effect the risks of infection, prophylaxis for CMV infection is recommended. Two classes of agents appropriate for prophylactic therapy are antiviral agents and immune globulin. The implementation and use of prophylactic treatment has many advantages (Fishman 2007), including:

- Suppression of asymptomatic viremia
- Prevention of direct and indirect effects
- Improved outcomes related to allograft survival
- Reduced incidence of opportunistic infections
- Decreased mortality

Roles and Risks of Antivirals

Strides have been made in both the number and optimal use of antivirals in recent years (Baden 2008). However, the development of antivirals poses several challenges for researchers because of the unique nature of viruses (Baden 2008). Viruses usurp host cell machinery for the intracellular replication and synthesis of viral particles (Baden 2008). These actions pose significant challenges to antiviral drug development because antiviral agents must be able to discriminate between host and viral proteins with a high degree of specificity (Baden 2008). The lack of specificity would interfere with normal host cell function, leading to unacceptable toxicity in patients (Hayden 2006).

For agents to play an effective role in the mediation of viral infection, it would be novel for the agent to inhibit viral replication or viral-directed proteins (Hayden 2006). The different stages of viral replication have allowed for a number of selective viral inhibitors to show efficacy in mediating viral infections (Table 4). Insufficient drug delivery, whether because of subtherapeutic doses, poor bioavailability, or poor adherence, may be implicated in clinical failure as well as in the development of resistance.

With the development of sensitive and specific methods that measure the concentration of virus in the blood (viral load), disease progression and appropriate modification of viral therapy can be adjusted effectively (Baden 2008). Although this test is useful and becoming more available to clinicians, test results are likely to vary because of interlaboratory variability (Baden 2008).

ADJUVANT THERAPY FOR PREVENTION OF CMV INFECTION

Solid organ transplant patients have a particular risk for becoming infected with CMV within a few months of the transplant procedure (NIAID 2005, Uknis 2005). The variables of this risk lay heavily with the serostatus of both the organ donor and recipient (Uknis 2005). Although antirejection therapy is currently used for transplant patients, the optimal prophylactic therapy and/or treatment combinations have continued to evade clinicians and researchers (Weill 2003). However, more robust clinical observations have been mainstreaming the use of adjuvant technology, such as CMV-specific immune globulin (IG), to prevent or limit the development of CMV infection and disease.

CMVIG is an immunoglobulin that contains a standardized amount of antibody to CMV (Cytogam 2008). When used as an adjuvant therapy with standard immunosuppressive therapy, it has shown statistically significant reductions and delays in the development of CMV infection and/or disease in high-risk organ transplant patients (Cytogam 2008).

Warnings With CMVIG Use

As with any therapeutic agent, there are conditions for and against its use.

CMV-IGIV is made from human plasma and carries the

TABLE 4
Possible Targets for Antiviral Agents

Stage of viral replication	Class of selective inhibitors
Cell entry	• Soluble receptor decoys • Antireceptor antibodies • Fusion protein inhibitors
Uncoating	• Ion channel blockers • Capsid stabilizers

Transcription of genome	• Inhibitors of viral DNA/RNA
	• Inhibitors of:
	  ○ Polymerase
	  ○ Reverse transcriptase
	  ○ Helicase
	  ○ Primase
	  ○ Integrase

Translation of genome	• Interferons • Antisense oligonucleotides • Ribozymes • Inhibitors of regulatory proteins
Post translational modifications	• Protease inhibitors
Assembly of virion components	• Interferons • Assembly protein inhibitors
Release	• Neuraminidase inhibitors • Antiviral antibodies • Cytotoxic lymphocytes

Source: Hayden 2006

possibility for transmission of bloodborne viral agents and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmission of recognized bloodborne viruses is considered to be low because of the viral inactivation and removal properties in the Cohn-Oncley cold ethanol precipitation procedure used for purification of immune globulin products. Until 1993, cold ethanol-manufactured immune globulins licensed in the United States had not been documented to transmit any viral agent. However, during a brief period in late 1993 to early 1994, intravenous immune globulin made by one U.S. manufacturer was associated with transmission of Hepatitis C virus. To further guard against possible transmission of bloodborne viruses, including hepatitis C, CMV-IGIV is treated with a solvent detergent viral inactivation procedure known to inactivate a wide spectrum of lipid-enveloped viruses, including HIV-1, HIV-2, hepatitis B, and hepatitis C. However, because new bloodborne viruses may yet emerge, some of which may not be inactivated by the manufacturing process or by solvent detergent treatment, CMV-IGIV, like any other blood product, should be given only if a benefit is expected (Cytogam 2008).

Immune Globulin Intravenous (human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentrations available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many IGIV products, those containing sucrose as a stabilizer (and given at daily doses of 350 mg/kg or greater) account for a disproportionate share of the total number. Cytogam® contains sucrose as a stabilizer (Cytogam 2008).

During administration, the patient's vital signs should be monitored continuously and careful observation made for any symptoms throughout the infusion. Epinephrine should be available for the treatment of an acute anaphylactic reaction (Cytogam 2008).

Concerns Regarding Manufacturing Processes and Availability

CSL Behring acquired Cytogam® from MedImmune in 2006. With that acquisition, there were minor difficulties regarding the manufacturing process and subsequent availability of product for a limited period. CSL Behring has worked diligently to improve and enhance the manufacturing process and has made strides toward the successful collaboration with new manufacturing partners. CSL Behring has overcome previous manufacturing challenges and is capable of providing a reliable and consistent flow of CMVIG to customers (CSL Behring).

Cytogam® Indications, Description, and Pharmacology

INDICATIONS AND USAGE

CMV Immune Globulin Intravenous (human) is indicated for the prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic CMVIG should be considered in combination with ganciclovir.

DESCRIPTION

Cytogam®, Cytomegalovirus Immune Globulin Intravenous (human) (CMVIG), is an immunoglobulin G (IgG) containing a standardized amount of antibody to Cytomegalovirus (CMV). CMVIG is formulated in final vial as a sterile liquid. The globulin is stabilized with 5% sucrose and 1% albumin (human). Cytogam® contains no preservative. The purified immunoglobulin is derived from pooled adult human plasma selected for high titers of antibody for cytomegalovirus (CMV). Source material for fractionation may be obtained from another U.S. licensed manufacturer. Pooled plasma was fractionated by ethanol precipitation of the proteins according to Cohn methods 6 and 9, modified to yield a product suitable for intravenous administration. A widely utilized solvent-detergent viral inactivation process is also used. Certain manufacturing operations may be performed by other firms. Each milliliter contains: 50±10 mg of immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg of sucrose; 10 mg of albumin (human). The sodium content is 20–30 mEq per liter, i.e., 0.4–0.6 mEq per 20 mL or 1.0–1.5 mEq per 50 mL. The solution should appear colorless and translucent.

CLINICAL PHARMACOLOGY

Cytogam® contains IgG antibodies representative of the large number of normal persons who contributed to the plasma pools from which the product was derived. The globulin contains a relatively high concentration of antibodies directed against cytomegalovirus (CMV). In the case of persons who may be exposed to CMV, Cytogam® can raise the relevant antibodies to levels sufficient to attenuate or reduce the incidence of serious CMV disease.

Source for Indications, Description, and Pharmacology section: Cytogam® [package insert]. CSL Behring LLC; 2008.

Summary of Clinical Trials

CMV Immune Globulin Intravenous (human) is indicated for the prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas, and heart. Summaries of key clinical studies of this product are arranged by transplant site.

KIDNEY

A Pilot Trial of a Novel Cytomegalovirus Immune Globulin in Renal Transplant Recipients

This phase 1 trial evaluated the ability of a reformulated intravenous CMVIG infusion to deliver CMV antibodies and provide increased CMV protection in renal transplant patients (Snydman 1984). The phase 1 study included 4 CMV seronegative patients and tested the safety and pharmacokinetics of CMVIG.

Study patients

Renal transplant recipients were eligible for inclusion if they had serum CMV antibody titers of <8 or <50 via indirect hemagglutination (IHA) or an enzyme-linked immunosorbent assay (ELISA), respectively.

Dosing and sample collection

The total dose of each infusion was 50 mg/kg, equaling approximately 3,500 mg of protein for the average patient of 70 kg (70–100 mL of a 3–5% solution). The starting infusion rate was 0.25 mL/min. The rate was increased to 0.5 mL/min after 30 minutes and increased to 1 mL/min after another 30 minutes. Dosing was administered for the first 3 days post transplant and then every 21 days for a 4-month period. Subsequent step increases in infusions were scheduled at 15-minute intervals.

Urine, throat washes, serum, and buffy coat preparations were taken for CMV isolation weekly for 2 months, every other week for 2 months, and then monthly for 4 months, for a total of 8 continued months of follow-up. Serum was taken 1 hour before and after each infusion and during viral isolation sampling to determine the CMV antibody titer of patients. Changes in ELISA titers were compared over time.

Results, Safety, and Conclusion

All patients following the dosage regimen were able to maintain an IHA titer >8 or an ELISA titer >50 for the first 4 months after transplant and were able to sustain detectable titers for up to 2 months after the last infusion. There appeared to be a shorter antibody half life during the first 30 days post transplant (8 days) than after the initial 60 days (13–15 days). However, the authors noted that these changes can be attributed to a number of variables and need to be reviewed more closely in subsequent clinical studies. There were no adverse reactions reported from CMVIG administration. This small-scale trial showed the initial suitability for the prevention or possible modification of CMV infection in renal transplant patients and provided a basis for further investigation.

Use of Cytomegalovirus Immune Globulin To Prevent Cytomegalovirus Disease in Renal-Transplant Recipients

A multicenter, randomized, controlled trial evaluated the prevention of primary CMV disease in renal transplant recipients by treating patients with or without CMVIG as a CMV-specific prophylactic treatment (Snydman 1987). The trial randomized 59 CMV seronegative patients who received kidneys from seropositive donors from multiple sites in the United States.

Definitions

CMV syndrome was defined as having two or more of the following:

- Unexplained fever for at least 3 days in association with pneumonitis (without other causes)
- Leukopenia (<3,000 leukocytes/mm^3) after azathioprine or ganciclovir withdrawal
- Elevated serum alanine aminotransferase level (≥2.5 times the upper limit of normal)
- Atypical lymphocytosis (>20% peripheral white cells)

Serious CMV disease was defined as occurring with one of the following: leukopenia, CMV pneumonia, fungal or parasitic superinfection, retinitis, or central nervous system involvement.

Study patients

Patients eligible for the study had to be renal transplantation candidates, have a CMV antibody titer of <8 via IHA, and receive a kidney from a CMV seropositive donor with an antibody titer of ≥8.

Dosing and sample collection

Patients prophylactically treated with CMVIG received 150 mg/kg of body weight within 72 hours of transplantation, 100 mg/kg 2 and 4 weeks after transplant, and 50 mg/kg at 6, 8, 12, and 16 weeks after transplant. The globulin was administered at a rate of 15 mg/kg/hr. Infusion rates were increased to a maximum of 60 mg/kg/hr if no adverse effects were present during infusion. Both treatment arms received standard immunosuppressive drugs following transplant.

Serum and blood baseline laboratory values were determined at study enrollment, weekly for 2 months, during follow-up visits, and clinical illness. Urine and throat wash specimens for viral isolation were collected prior to the first infusion, weekly for 2 months, then monthly for 6 months. Peripheral blood leukocytes were obtained for viral isolation every other week for the first 2 months, every month for 6 months, at the 1 year follow-up visit, and during any clinical illness during the first year. CMV antibody was measured via IHA and/or complement fixation. Seroconversion confirmations were performed via enzyme immunoassay.

TABLE 5
Outcomes in Patients Receiving CMV Immune Globulin vs. Control

	Globulin (n=24)	Control (n=35)
Outcome	Cases	Cases
Clinical		
• Virologically confirmed CMV syndrome	5 (21%)	21 (60%)[a]
• Fungal or parasitic opportunistic infections	0	7 (20%)[b]
• Death	1 (4%)	5 (14%)
• Graft loss	4 (17%)	10 (29%)
Virologic		
• CMV viremia	6 (25%)	15 (43%)
• Viral isolation (any site)	13 (54%)	20 (57%)
• Seroconversion	17 (71%)	27 (77%)

[a]Chi-square=8.86; $P<0.01$.
[b]Fisher's exact test; $P=0.05$.
Source: Snydman 1987

TABLE 6
Types of Virologically Confirmed CMV-Associated Conditions

Condition	Globulin (n=24)		Control (n=35)
	Cases	*P*	Cases
Leukopenia	1 (4%)	<0.01	13 (37%)
Hepatitis	5 (21%)	0.14	15 (43%)
CMV pneumonia	1 (4%)	0.26	6 (17%)
Thrombocytopenia	2 (8%)	0.12	10 (29%)
Retinitis	0	NS	2 (6%)
Aseptic meningitis	1 (4%)	NS	0

NS=not significant.
Source: Snydman 1987

Results

Virologically confirmed cases of CMV syndrome were significantly reduced from 60% to 21% ($P<0.01$) in patients receiving prophylactic CMVIG (Table 5). The rate of complications due to fungal or parasitic infections was also significantly reduced in the group receiving CMVIG ($P=0.05$). There were no significant differences between the mortality rate and graft loss rate in either of the groups. The rate of CMV viremia was 43% in controls and only 25% ($P>0.05$) in the globulin-treated group. Globulin use did not have an overall effect on viral isolation or the rate of seroconversion. Globulin recipients had a median onset of CMV infection at 49 days after transplant, compared to 42 days for the placebo cohort. Fungal and parasitic superinfections were limited to the control group and were fatal in all but those related to *P. carinii*.

The principal effect of the globulin was a reduction in acquired leukopenia ($P<0.01$) with reduced frequencies in CMV-associated hepatitis ($P=0.14$) and thrombocytopenia ($P=0.12$) (Table 6). The globulin-dosed group also showed an 80% reduction in the rate of CMV pneumonia.

Among patients given immunosuppressive rejection regimens, three (13%) globulin-treated patients were confirmed with serious CMV disease, compared with 16 (46%) control patients ($P<0.01$). The use of globulin reduced the attack rate of serious CMV disease from 54% to 15% ($P=0.04$). CMV syndrome, a less-serious disorder, developed in five (42%) globulin-treated patients treated for rejection, compared with 20 (77%, $P<0.05$) in the control group.

Safety considerations

Of 205 infusions given to patients, 6% (7 patients) were associated with possible side effects. Reactions were not severe enough to discontinue infusion therapy.

Reactions included:

- Flushing (3 episodes)
- Anxiety, nausea, metallic taste, headache, shortness of breath (2 episodes each)
- Palpitations, backache, and muscle cramps (1 episode each)

Key takeaway

Prophylactic CMV therapy including CMVIG provided protection for renal transplant patients at risk for primary CMV disease in this study. Reductions were demonstrated in CMV-associated syndromes, CMV-associated leukopenia, and opportunistic infections.

Final Analysis of Primary Cytomegalovirus Disease Prevention in Renal Transplant Recipients With a Cytomegalovirus-Immune Globulin: Comparison of the Randomized and Open-Label Trials

This report follows up on results of a phase 3, multicenter, randomized, prospective controlled trial (Snydman 1988) of primary renal transplant recipients using CMV hyperimmune globulin for the prevention of CMV disease (Snydman 1991). Of the original 60 patients in the

controlled trial, 36 continued in the open-label extension of the study, in which all patients received CMVIG. This report summarized the final analysis of the open-label trial and compared the results to the findings of the original controlled trial.

The open-label extension showed similar patterns to those of the randomized trial. Of those patients followed in the open-label trial, 36% developed a CMV-associated syndrome, compared with 33% in the controlled phase of the trial. Rates of graft loss, viremia, viral isolation, and seroconversion were almost identical to the globulin-treated patients in the controlled portion (Table 7). No statistical differences were observed in the overall rates of serious CMV syndrome or among those receiving cadaveric versus living organ donors.

Key takeaway

The findings of this open-label extension mimicked those of the original phase of the study that suggested that immune globulin provides a measure of protection against CMV complications following kidney transplant.

LIVER

Cytomegalovirus Immune Globulin Prophylaxis in Liver Transplantation: a Randomized, Double-blind, Placebo-controlled Trial

This phase 3, multicenter trial evaluated the effectiveness of CMVIG in the prevention of CMV disease in liver transplant recipients (Snydman 1993). Researchers enrolled 141 patients at four transplant centers in Boston.

Definitions

CMV syndrome was defined as having two or more of the following:

- Unexplained fever for at least 3 days in association with pneumonitis (without other causes)
- Leukopenia ($<4.0 \times 10^9$/L leukocytes/mm^3)
- Thrombocytopenia (platelets $<100 \times 10^9$/L) on 3 or more consecutive days after azathioprine or ganciclovir withdrawal
- Atypical lymphocytes (>5% peripheral leukocytes)

CMV disease was defined as clinical evidence of organ dysfunction, along with biopsy proof of CMV presence in the affected organ. CMV disease was considered present if the virus was isolated at the time of disease from a clinical specimen, histopathologic tissue, or via seroconversion within 1 month of transplant. Abnormal liver chemistry results were not included in this definition.

Study patients

Children and adults who had liver transplant procedures at participating study centers were eligible for participation. The CMV antibody status of the donors and recipients did not affect inclusion eligibility. Patients receiving liver transplants were given either prophylactic CMVIG or placebo.

Dosage and sample collection

Patients treated with CMVIG received 150 mg/kg body weight within 72 hours of liver transplantation. Additional doses were given at 2, 4, 6, and 8 weeks after transplant. Doses were reduced to 100 mg/kg at 12 and 16 weeks. Patients randomized to receive placebo were given 1% albumin in a manner identical to CMVIG administration. Both treatment arms received standard immunosuppressive drugs after transplant.

Baseline laboratory studies were done at enrollment, weekly for 2 months, at scheduled follow-up visits, and during any clinical problems. Urine and throat wash specimens for viral isolation were collected before the first infusion, weekly for 2 months, and then monthly for 6 months. Serum collection for CMV antibodies was collected pre- and post-infusion, weekly for 2 months, and then monthly for 6 months. Peripheral blood leukocytes were collected for viral isolation every other week for the first 2 months, every month for 6 months, at the 1-year follow-up, and during any clinical illnesses compatible with CMV disease. Complement fixation, latex agglutination, IHA, and ELISA methodologies were used to detect CMV during different stages of patient follow-up.

TABLE 7
Comparison of Outcome in Randomized and Open-Label Trials

	Randomized		Open-label CMVIG (n=36)
	CMVIG (n=24) Number (%)	Control (n=35) Number (%)	Number (%)
Clinical outcome			
• Virologically confirmed CMV syndrome	5 (21)[a]	22 (60)[a,b]	13 (36)[b]
• Fungal infection	0[c]	7 (20)[c,d]	2 (6)[d]
• Death	1 (4)	5 (14)	2 (7)
• Graft loss	4 (17)	10 (29)	6 (17)
Virologic outcome			
• CMV viremia	6 (25)	15 (43)	8 (22)
• Viral isolation	13 (54)	20 (57)	21 (58)
• Seroconversion	17 (71)	27 (77)	24 (67)

[a]Chi-square=8.94, $P<0.01$.
[b]Fisher exact test, $P=0.037$; open-label vs.control group one tail.
[c]Fisher exact test, $P=0.02$.
[d]Fisher exact test, $P=0.069$; open-label vs.control group, one tail.
Source: Snydman 1991

Results

CMV infection developed in 57% of globulin recipients and 61% of placebo recipients. The rates of viremia did not differ between the two groups. The mean onset of viral excretion in globulin recipients occurred 62.7 (±94.0) days post transplant, compared with 40.8 (±41.8) days in the placebo group. The onset of viremia was similar in both groups with 45.3 (±71.3) days in the globulin group, compared with 41.9 (±38.0 days) in the placebo group.

Twenty-seven patients contracted severe CMV-associated disease; however, the use of CMVIG therapy resulted in a greater than 50% reduction in severe CMV-associated disease (relative risk [RR], 0.39; CI, 0.17–0.89; P=0.02). Invasive fungal disease associated with CMV infection or disease occurred less frequently in the CMVIG treated group (RR, 0.35; CI, 0.13–1.02; P=0.04). When results were stratified by organ donor and recipient CMV serostatus, differences were found in CMVIG protection (Table 8).

Safety considerations

Of 73 patients randomized to receive globulin, 17 (23%) developed possible reactions, compared with 8 of 73 (11%) of the placebo group (P=0.08). Twenty-nine reactions occurred during the 436 (6.7%) globulin infusions compared to 16 reactions during the 419 (3.8%) placebo infusions (P=0.07). The most frequent adverse reactions were pain (8 cases), fever (4 cases), flushing (4 cases) in the globulin group compared with pain (3 cases), chills (2 cases), and nausea (2 cases) in the placebo group. One patient discontinued infusion therapy as a result of side effects.

Key takeaway

In this study, use of prophylactic CMVIG reduced the risk of severe CMV-associated disease in liver transplant patients.

A Further Analysis of the Use of Cytomegalovirus Immune Globulin in Orthotopic Liver Transplant Patients at Risk for Primary Infection

Twenty-one patients from a completed phase 3, multicenter, randomized, double blind, placebo-controlled trial comparing the prophylactic use of CMVIG (Snydman 1993, described above) were subsequently enrolled into a follow-up, open-label, study (Snydman 1994). Upon completion of the randomized trial, and prior to unblinding and data analysis, all CMV seronegative liver transplant recipients were administered CMVIG. CMV disease and syndrome were defined previously in Snydman 1993.

Study patients

Patients eligible to participate in the study included CMV seronegative children and adults who underwent a liver transplantation at one of the multicenter sites.

Dosing and sample collection

Detail regarding CMV antibody titers for patients were described previously in Snydman 1987. The patient dosing regimen was identical to that previously reported in Snydman 1993. After enrollment, patients were managed clinically for the first 8 weeks following transplant, monthly for the next 6 months, and at the 1-year follow-up. The clinical management was previously described in Snydman 1993.

Urine, throat, and serum analyses, as well as viral isolation techniques, were as described in Snydman 1993. Prior to liver transplantation, CMV antibody was measured in patient and donor serum samples via complement fixation, latex agglutination, or ELISA. The rates of CMV infection and disease in the open-label trial were compared to those of the randomized, controlled study.

Results

Rates of CMV infection and disease in the open-label trial were similar to those seen in the controlled trial. Among the 9 seronegative recipients of CMV seropositive donor organs, six (67%) had CMV infections. The median time from transplantation to CMV excretion was 28 days (range 9–40 days). Though three cases of CMV disease occurred, there were no cases of pneumonia or severe CMV-associated disease. Two cases of fungal infec-

TABLE 8
Effect of CMVIG on Selected Outcomes
Controlling for donor and recipient serologic status

Stratification	CMV Disease (N=141)		Severe CMV-associated disease (N=141)	
CMV serostatus	Cases			
	Globulin (n=69)	Placebo (n=72)	Globulin (n=69)	Placebo (n=72)
D–/R– D–/R+ D+/R+ D+/R– **Overall**	0/19 (0%) 2/18 (11%) 1/13 (8%) 10/19 (53%) **13/69 (19%)**	4/25 (16%) 5/16 (31%) 3/12 (25%) 10/19 (53%) **22/72 (31%)**	0/19 0/18 1/13 (8%) 7/19 (37%) **8/69 (12%)**	2/25 (8%) 4/16 (25%) 4/12 (33%) 9/19 (47%) **19/72 (26%)**
Relative risk for CMVIG (95% confidence interval)	0.58 (0.27–1.08) (P=0.08)		0.34 (0.15–0.78) (P<0.01)	

Source: Snydman 1993

tions occurred in D–/R– patients who remained free of CMV infection.

The combination of results of the open-label trial and patients who received CMVIG in the random-assignment trial revealed a significant reduction in the rate of CMV infection in the D+/R– group (P=0.04) (Table 9). There was also a trend toward a 50% reduction in severe CMV-associated disease (P=0.10). CMVIG recipients who received CMV seronegative donor organs (P=0.03) also had a significant reduction in CMV disease.

Key takeaway

This open-label study demonstrated the ability of CMVIG to prevent manifestation of severe CMV-associated disease in transplant patients.

Cytomegalovirus Prophylaxis With Ganciclovir, Acyclovir, and CMV Hyperimmune Globulin in Liver Transplant Patients Receiving OKT3 Induction

A retrospective analysis reviewed the incidence of CMV infection and disease in liver transplant patients (Ham 1995). Patients initially given muromonab-CD3 (OKT3), an immunosuppressive therapy that blocks T cell function, were given a combination of antiviral drugs and CMVIG to prevent CMV disease. CMV disease was considered present with end-organ involvement or a pathologic involvement of a distant site, in addition to fever and malaise.

Study patients

A review of 100 patients who received a liver transplant between 1991 and 1994 yielded 87 eligible subjects. Thirteen patients were ineligible due to lack of OKT3 dosing, retransplantation, or death. The remaining patients were divided into four groups based on donor and recipient CMV serologic status.

TABLE 9
Occurrence of CMV Infection and Disease
By donor status

Donor status	CMVIG-treated patients n/N[a]	Placebo n/N[b]
CMV donor seronegative		
• CMV infection	5/31 (16%)	5/25 (20%)
• CMV disease	0/31[c]	4/25 (16%)[c]
• Severe CMV-associated disease	0/31	2/25 (8%)
CMV donor seropositive		
• CMV infection	17/28 (57%)[d]	17/19 (89%)[d]
• CMV disease	13/28 (46%)	10/19 (53%)
• Severe CMV-associated disease	7/28 (25%)[e]	9/19 (47%)[e]
Graft survival at 1 year	47/59 (80%)	31/44 (70%)

[a]Totals are for CMVIG-treated patients in both the controlled study and the open-label extension.
[b]Placebo totals are for patients in the controlled study.
[c]P=0.03, Fisher exact test, one-tailed.
[d]P=0.04, chi-square, one-tailed.
[e]P=0.10, Fisher exact test, one-tailed.
Source: Snydman 1994

Dosing and CMV presence

Standard immunosuppression therapy consisted of OKT3 5 mg/d for 7–10 days; methylprednisolone 1 g initially, tapered to prednisone 50 mg/d by the end of Week 1. An additional reduction to 10 mg/d was initiated over 2 months. Cyclosporine levels were titrated for blood trough levels of 350±50 ng/mL. Azathioprine 2 mg/kg/d was titrated to leukocyte counts. Four types of CMV prophylaxis regimens were used based on serologic status:

- D+/R–: ganciclovir (G)/CMVIG/acyclovir (A)
- D+/R+: GA
- D–/R+: GA
- D–/R–: A

Ganciclovir 10 mg/kg/d was given for 14 days. CMVIG was given at 150 mg/kg within 72 hours of transplant, then reduced to 100 mg/kg on Weeks 2, 4, 6, and 8 post transplant. At Weeks 12 and 16, CMVIG was reduced to 50 mg/kg. Acyclovir 3,200 mg/d was given in divided doses for 6 weeks following ganciclovir. Ganciclovir and acyclovir regimens were adjusted for renal dysfunction as needed.

CMV infection was considered present with any of the following:

- Positive CMV cultures
- Shell vial rapid antigen assay
- Cytology from bronchial aspirates
- Tissue biopsy with CMV inclusions
- IgG CMV titer conversion to >1:16 in a previously negative patient
- CMV-IgM positivity in a previously negative patient

Results

Among the four groups, no significant differences in incidence of infection or disease were observed. The overall disease rate for the 87 patients was 10%, and the total infection rate was 25% (Table 10).

The 15 patients in the D+/R– group were considered the highest group at risk for the development of CMV disease, delineating these patients to receive combination prophylaxis. Only one of these patients developed CMV hepatitis, which was resolved with drug therapy. Of the 35 patients in the D+/R+ group, 5 deaths occurred, 2 of which were directly attributed to disseminated CMV disease and overwhelming sepsis. In this group, overall mortality was 14%, with the average time to documentation of CMV infection at 93 days following transplant; the death rate for patients with CMV disease was 50%.

The incidence of CMV disease in the D–/R+ group was 13% with 4 deaths, but only 1 death was attributed directly to CMV disease; others

deaths occurred from unrelated causes. One patient in the D–/R– group developed CMV disease 28 days after transplant. After 8 months following transplant, another patient in this group developed late CMV infection after receiving multiple treatments for organ rejection.

Key takeaway

This analysis demonstrated an effective prophylactic regimen for high-risk liver transplant patients exposed to CMV who were actively involved in an OKT3 dosing regimen. Data from this study suggest a 5-fold reduction in the rate of CMV disease in the high-risk population (D+/R–).

Cytomegalovirus Immune Globulin (CMVIG) Prophylaxis Is Associated With Increased Survival After Orthotopic Liver Transplantation

A retrospective analysis of the Snydman 1993 and 1994 studies described above was conducted to determine the effect of CMVIG prophylaxis on first-year and long-term survival after liver transplantation (Falagas 1997). Data were analyzed for 162 liver transplant patients, 90 patients of whom received CMVIG (the remaining received placebo). The median follow-up was 5.6 years and 5.4 years for CMVIG and placebo, respectively.

Patient population and dosing

This analysis involved liver transplant patients from two CMVIG prophylaxis studies previously described: a randomized, controlled trial of 141 patients (Snydman 1993) and 21 seronegative patients in an open-label study of CMVIG prophylaxis (Snydman 1994) based on a protocol identical to that of Snydman 1993. Dosing regimens are described in Snydman 1993 summary on page 9.

CMVIG recipients were more likely to have primary biliary cirrhosis (21% vs.8%, P=0.025) compared to placebo. CMVIG patients were also less likely to receive packed red blood cell infusions during transplantation (median 18 vs.22 units, P=0.06) and had less exposure to OKT3 treatment (58% vs.71%, P=0.09).

Results

Among liver transplant recipients, CMVIG prophylaxis was significantly associated with increased first-year survival (86% vs.72%, P=0.029) compared to placebo (Table 11). CMVIG patients had an approximate 20% increased survival benefit compared to placebo recipients in the first year after transplantation.

TABLE 11
1-year Survival Rates
By study medication and donor/recipient CMV serostatus

CMV serostatus	1-year survival	
	CMVIG (n=90)	Placebo (n=72)
• D–/R–	29/31 (94%)	22/25 (88%)
• D–/R+	15/18 (83%)	13/16 (81%)
• D+/R+	12/13 (92%)	7/12 (58%)
• D+/R-	21/28 (75%)	10/19 (53%)
• Total	77/90 (86%)[a]	52/72 (72%)

[a]P=0.029 (log-rank chi-square test from Kaplan-Meier survival analysis).
Source: Falagas 1997

TABLE 10
Rates of CMV Infection and Disease Using 4 Antiviral Regimens
By CMV status

CMV status	n	Infection incidence	Disease incidence
D+/R–	15	6 (40%)	1 (7%)
D+/R+	35	11 (31%)	4 (11%)
D–/R+	23	3 (13%)	3 (13%)
D–/R–	14	2 (14%)	1 (7%)
Total	**87**	**22 (25%)**	**9 (10%)**

Source: Ham 1995

Key takeaway

This study suggested that CMVIG prophylaxis may increase 1-year survival in liver transplant patients. Implementation of CMVIG effectively decreases the incidence of severe CMV-associated disease.

Combined CMV-IGIV and Ganciclovir Prophylaxis in CMV Seronegative Transplant Recipients of Livers From CMV Seropositive Donors

This study explored the use of combination prophylaxis of CMVIG with ganciclovir in high-risk (D+/R–) liver transplant patients (Snydman, Data on file). The multicenter, open-label trial included 41 patients who received liver transplants from CMV seropositive donors. Controls for this study were retrospectively obtained from Snydman 1987 and Snydman 1988 and consisted solely of CMV seronegative patients receiving liver transplants from seropositive donors.

Results from these observations showed a trend toward the reduction of both CMV infection and CMV viremia using the combined CMVIG and ganciclovir dual therapy (CMV disease P=0.007, serious CMV-associated disease P=0.004). Similar reductions in CMV pneumonia (P=0.009) and invasive fungal infection (P=0.03) were also evident in those patients on combination therapy.

KIDNEY, KIDNEY/PANCREAS, AND LIVER

CMV Prophylaxis With Combination Ganciclovir and CMV Hyperimmune Globulin Followed by High-dose Acyclovir in Solid Organ Transplant Recipients

This large, prospective, observational trial studied the seroconversion rate, asymptomatic CMV infection rate, and CMV disease in D+/R– recipients undergoing kidney (74), combined kidney/pancreas (14), or liver (12) organ transplantation at the University of Iowa (Martin, Data on file). All transplant patients received CMVIG every 2 weeks for 8 doses, ganciclovir 10 mg/kg/day for 14 days

TABLE 12
Rate of CMV Infection and Disease in Organ Transplant Patients on CMVIG, Ganciclovir, and Acyclovir Therapy

Organ	D+/R– patients (n)	Mean follow-up (months)	CMV		Severity of disease	
			Infection	Disease	Mild	Severe
Kidney	74	21	36/74 (49%)	6/74 (8%)	5	1[a]
Kidney/Pancreas	14	18	6/14 (43%)	1/14 (7%)	1	0
Liver	12	18	7/12 (58%)	4/12 (33%)	3	1[b]
Total	**100**	**22**	**49/100 (49%)**	**11/100 (11%)**	**9**	**2**

[a] CMV pneumonia.
[b] Retinitis, hepatitis, recurrent disease.
Source: Martin, Data on file.

post transplant, and acyclovir 800–3,200 mg/day for 10 weeks.

Of the 74 kidney transplant patients, 9% developed CMV disease (Table 12). One patient in the combined kidney/pancreas transplant group developed CMV syndrome, and 58% of liver transplant patients developed evidence of CMV infection. From these findings, the author concluded that combination therapy for high-risk patients is effective in reducing the severity of CMV disease.

CARDIOPULMONARY

Impact of Cytomegalovirus Hyperimmune Globulin on Outcome After Cardiothoracic Transplantation – a Preliminary Cohort Study

This preliminary cohort study, using historical controls, introduced a prophylaxis regimen intended to reduce the rate of CMV disease in high-risk cardiothoracic transplant patients (Valantine 2001). The prophylaxis was revised to include CMVIG in all high-risk cardiothoracic transplant patients. High-risk patients were defined as seronegative recipients receiving hearts from seropositive donors and all heart-lung and lung transplant patients where the donor or recipient was seropositive. The investigators sought to determine whether a dual regimen of CMVIG and ganciclovir would reduce rates of acute CMV disease and provide superior outcomes compared to ganciclovir monotherapy.

Study patients

Eighty transplant recipients – 27 heart transplant patients and 53 heart-lung and lung transplant patients – were included. Historical controls were matched up via organ transplant within the preceding 2 to 3 years, prior to the initiation of CMVIG prophylaxis.

Dosing strategies

High-risk heart transplant patients: D+/R– heart transplant patients received 150 mg/kg CMVIG 72 hours after transplantation, reduced to 100 mg/kg administered at Weeks 2, 4, 6, and 8. At Weeks 12 and 16, CMVIG dosage was given at 50 mg/kg. Patients also received ganciclovir IV after transplantation at a dosage of 5 mg/kg twice daily for 14 days, followed by 6 mg/kg/day for 2 weeks.

High-risk heart-lung and lung transplants: D+/R–, D–/R+, and D+/R+ patients received a CMV prophylaxis regimen identical to those of heart transplant patients. Patients also received ganciclovir IV for 28 days following transplant.

Results

Heart, heart-lung, and lung transplant patients treated with CMVIG dual therapy had significantly higher disease-free incidence of CMV, lower rejection incidence, and higher survival rates compared with those who received ganciclovir monotherapy. The incidence of CMV disease was reduced from 55% in the ganciclovir group to 46% in the combined group ($P \leq 0.06$) and survival was increased from 61% to 94% ($P \leq 0.001$). In heart-lung or lung transplant patients the incidence of CMV disease in patients receiving ganciclovir alone (n=25) was 85% as compared to 36% of the 33 patients receiving both CMVIG and ganciclovir ($P \leq 0.05$). Survival was 60% in the ganciclovir group and 80% in patients receiving CMVIG and ganciclovir ($P \leq 0.01$).

Key takeaway

The results of this study suggested that the inclusion of CMVIG therapy to a regimen of ganciclovir may decrease the incidence of CMV disease in high-risk heart, heart-lung, and lung transplant patient. **The authors cautioned that this was a preliminary cohort study that used historical controls and unadjusted endpoints,** but said the results provide the rationale for a follow-up prospective, randomized, double-blind study to determine the efficacy of CMVIG plus ganciclovir for preventing the acute and long-term sequelae after heart and lung transplantation.

Management of Cytomegalovirus Infection in Lung Transplant Recipients: Evidence-Based Recommendations

An expert advisory group of transplant surgeons and infectious disease specialists met in Chicago in June 2003

to develop recommendations about the optimal management of CMV in lung transplant recipients (Zamora 2005). For the purposes of these guidelines, CMV infection was defined as isolation of the virus, or the demonstration of its presence via immunologic or molecular techniques or by seroconversion. CMV disease was defined as histologic evidence of tissue invasion or a characteristic syndrome after exclusion of other causes in the presence of CMV infection.

A review of the published literature at the time showed that the inclusion of CMVIG prophylaxis in addition to traditional therapy (ganciclovir or valganciclovir) enabled reductions in the incidence of CMV disease. As such, the advisory group recommended that CMVIG be considered as part of a combination prophylaxis regimen in all lung transplant patients to reduce the incidence of CMV infection and disease. Table 13 summarizes the panel's recommendations.

Combination Prophylaxis With Ganciclovir and Cytomegalovirus (CMV) Immune Globulin After Lung Transplantation: Effective CMV Prevention Following Daclizumab Induction

A study evaluating the effectiveness of combination prophylaxis with ganciclovir and CMVIG versus ganciclovir monotherapy was studied in lung transplant patients during the first 180 days after transplant (Weill 2003).

Definition

CMV syndrome was diagnosed if blood samples contained CMV antigens or a positive buffy coat. CMV disease was defined as the presence of tissue invasion via histologic evaluation, presence of compatible symptoms with a clinical response to ganciclovir, or a positive bronchoalveolar lavage without evidence of tissue invasion but who responded to ganciclovir treatment.

Patients and dosing strategy

A historical comparison group consisting of 48 patients was used as the control for the ganciclovir monotherapy group. For the combination prophylaxis group, 38 patients received CMV prophylaxis based on donor/recipient serology and the receipt of daclizumab for immunosuppressive therapy.

To be eligible for participation in the study, patients in both groups had to have survived through the CMV prophylaxis period and be followed for 180 days after transplant. Study patients who expired from other causes besides CMV disease were excluded. Heart-lung and lung transplant recipients were excluded if they had a D–/R– serology profile.

Results

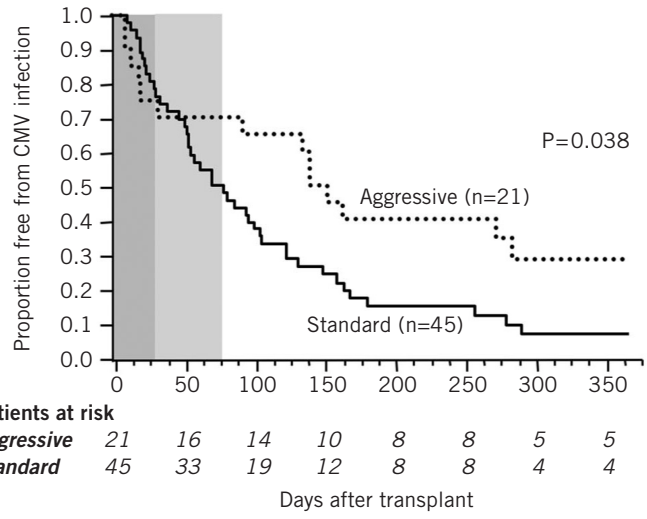
The incidence of CMV disease in the combination therapy was 7.9% (3/38) versus 33% (16/48) in the monotherapy group, (P=0.0077). Of the patients diagnosed with CMV disease, two had CMV pneumonia and one had CMV

TABLE 13
Summary of Recommendations for CMV Management in Lung Transplant Patients

Recommendation	Strength of recommendation (Category)	Quality of evidence (Grade)
1. All lung transplant patients should be considered for prophylaxis. Other risk factors include use of antilymphocyte antibody therapy and blood product transfusion.	A	II
2. Prophylaxis should consist of valganciclovir 900 mg (or dose adjusted in accordance with a dosing algorithm) for at least 100 days. Longer prophylaxis (up to 180 days) may be warranted. Combination prophylaxis with CMVIG should be considered. During the first 6 months post transplant, patients should be monitored every 2 weeks for CMV viremia.	A	II
3. Frequency of monitoring should be reduced to once per month after the first 6 months post transplant. Monitoring should preferably be performed using the LightCycler-based PCR-based assay. Breakthrough CMV infection and disease should be treated with IV ganciclovir 5 mg/kg, two times per day, for up to 3 weeks.	B	III
4. Immunosuppression should also be reassessed. Treatment with IV ganciclovir should continue until the viral load has been reduced to levels below the detection limits of a sensitive monitoring assay. For asymptomatic CMV viremia that occurs after prophylaxis, the immunosuppressive regimen should be reassessed.	B	II
5. If CMV viremia or disease occurs after prophylaxis, treatment with IV ganciclovir or valganciclovir is recommended. Patients should receive treatment until the viral load is below the detection limits of a sensitive monitoring assay. Resistance should be considered after the development of breakthrough viremia, recurrent CMV infection, or a poor clinical or virologic response after 2 weeks of treatment.	B	II
6. Genotypic analysis should be performed. Foscarnet alone or in combination with ganciclovir should be administered until the viral load has been reduced to below the detection limits of a sensitive monitoring assay.	B	II

Source: Zamora 2005

FIGURE 2
Days to CMV Infection, by Prophylaxis Regimen



Dark-gray shaded area indicates period of IV ganciclovir prophylaxis in both groups. **Light-gray shade** indicates period of valganciclovir and CMVIG administration in the aggressive prophylaxis group.

Source: Used with permission: Potena L, Holweg CT, Chin C, et al. Acute rejection and cardiac allograft vascular disease is reduced by suppression of subclinical cytomegalovirus infection. *Transplantation.* 2006;82:398-405

syndrome (Table 14). In the monotherapy group, 16 patients were diagnosed with CMV disease, 11 of which had CMV pneumonia and 5 of which had CMV syndrome. Acute rejection occurred in 66% of patients (25/38) in the combination group, as opposed to 79% (38/48) in the monotherapy group (P=0.22).

Key takeaway

In this study, the combination of CMVIG and ganciclovir reduced the incidence of CMV disease regardless of induction therapy with daclizumab.

Acute Rejection and Cardiac Allograft Vascular Disease Is Reduced by Suppression of Subclinical Cytomegalovirus Infection

A comparison phase 4 study was undertaken to determine the effects of CMV infection on acute rejection and cardiac allograft vasculopathy (CAV) in high-risk patients (D+/R–) aggressively treated with standard antiviral prophylaxis in combination with CMVIG therapy or with CMV prophylaxis monotherapy (Potena 2006).

Study patients

Patients undergoing their first heart transplant between January 2002 and February 2004 were considered for enrollment. Of the 66 patients who enrolled and completed the study, 45 received standard CMV prophylaxis monotherapy and 21 received aggressive CMV prophylaxis that included CMVIG treatment.

Dosing strategies and medical procedures

CMV-seropositive recipients received standard prophylaxis consisting of ganciclovir IV 5 mg/kg/twice daily for the first 2 weeks after transplant, and 6 mg/kg once daily during the following 2 weeks, for a total of 25±4 days. CMV-seronegative heart transplant patients (R–/D+) received aggressive prophylaxis, including standard ganciclovir therapy followed by valganciclovir (450–900 mg daily, adjusted for renal function) for 73±12 days, plus CMVIG dosed at 150 mg/kg 72 hours after transplant, then 100 mg/kg at 2, 4, 6, and 8 weeks, reduced to 50 mg/kg at 12 and 16 weeks.

Patients were monitored for acute rejection by surveillance endomyocardial biopsies. Biopsies were performed weekly during the first month, biweekly until Month 3, monthly until Month 6, and then once at Month 9 and again at Month 12. Biopsy samples were graded according to International Society for Heart and Lung Transplantation (ISHLT) classification.

Intravascular ultrasound was used to assess allograft vascular disease during the first year post transplant. The left anterior descending coronary artery was imaged within 6 weeks after transplant and again after 1 year. Images provided vessel, lumen, and intimal area measurement. An automated volumetric reconstruction of the coronary artery was also performed. Changes from baseline and 1 year post transplant were determined.

Qualitative, nested PCR was used to analyze systemic CMV infection present in peripheral blood polymor-

TABLE 14 CMV Prevention Following Daclizumab Induction

	CMV disease[a]			
	Pneumonia	Syndrome	CMV infection	Acute rejection[b]
Combination therapy (ganciclovir and CMVIG) (n=38)	2 (5%)	1 (3%)	0	25 (66%)
Monotherapy (ganciclovir)	11 (23%)	5 (10%)	1	34 (79%)[b]

[a] P=0.008 combination vs. monotherapy.
[b] P=0.22 combination vs. monotherapy.
Source: Weill 2003

phonuclear cells. Real-time PCR was used for quantification of positive samples.

The primary endpoint was the occurrence of CMV infection. The secondary endpoints were the development of acute rejection and changes in CAV.

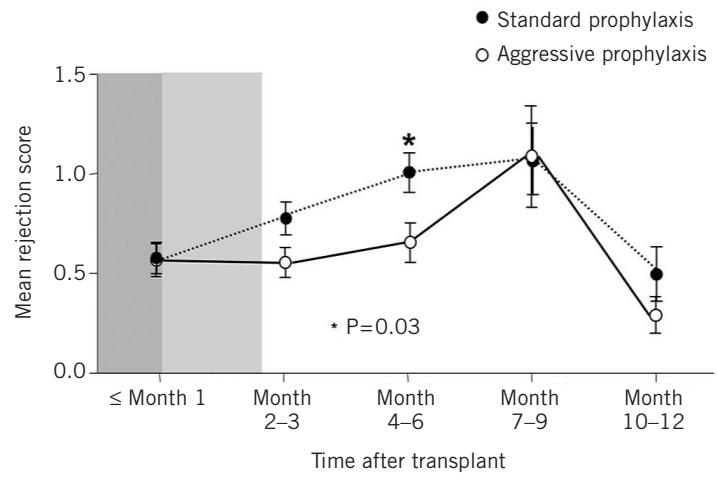
Results

In patients treated with CMVIG prophylaxis, CMV infection occurred less frequently and had a longer time to onset than those of their monotherapy counterparts (CMV infection estimated incidence 73±10% vs.94±4%, respectively; *P*=0.038) (Figure 2). Using multivariate analysis, the CMVIG treated group was independently associated with a 28% reduction in the relative risk for CMV infection (RR=0.72 [95% CI 0.52–0.96]; *P*=0.02). Patients who exhibited an increased burden of CMV infection were higher among the standard prophylaxis group (n=17, 38%) than in those with the CMVIG combination therapy (n=3, 14%, *P*=0.043).

Figure 3 depicts a comparison of the roles of CMV monotherapy and aggressive therapy in acute rejection over time. In Month 1, there was no difference between the two arms. In Months 2 to 6, however, there was no rise in the rejection score of the aggressively treated patients. These patients also remained significantly lower than the monotherapy-treated arm (*P*=0.03). At Months 7 to 9, both groups peaked with similar rejection scores, suggesting that prolonged prophylaxis delays the occurrence of rejection. The rejection-free survival was significantly longer in patients treated aggressively with the CMV prophylaxis than the monotherapy patients. Significance was shown at 6 months after ganciclovir discontinuation (Figure 4).

Between the two groups, there was an increase in intimal volume (from 119±82 to 139±95 mm^3; *P*=0.02), and decreases in both vessel lumen (from 734±219 to 639±180mm^3; *P*<0.01) and volume (from 615±182 to 500±148mm^3; *P*<0.01). These changes are consistent with vessel shrinkage and negative remodeling. However, vessel and lumen volume were significantly decreased only in the standard monotherapy patients. (–126±111 and –140±106mm^3, respectively; *P*<0.01) compared with aggressively treated patients (–28±122 and –61±96 mm^3, respectively; *P*≥0.1). When comparing absolute changes in vessel, lumen, and intimal volumes from baseline, patients with standard prophylactic therapy showed a significant reduction in vessel and lumen volumes compared with the aggressively treated group.

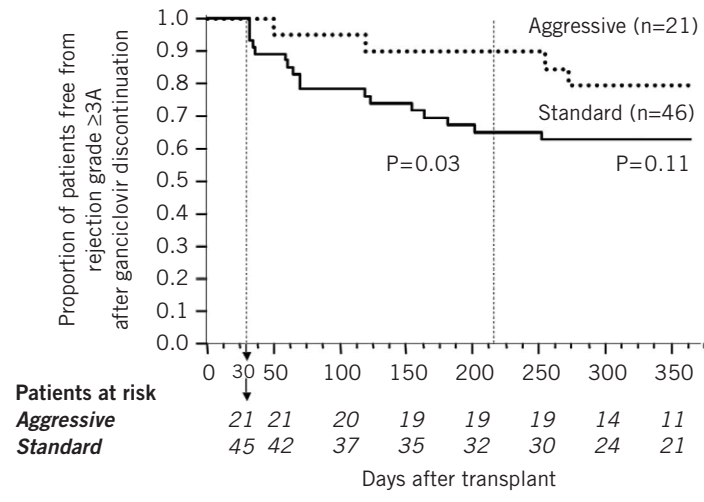
FIGURE 3
Effectiveness of Prophylaxis in Acute Rejection



Dark-gray shaded area indicates period of IV ganciclovir prophylaxis in both groups. **Light-gray shade** indicates period of valganciclovir and CMVIG administration in the aggressive prophylaxis group.

Source: Used with permission: Potena L, Holweg CT, Chin C, et al. Acute rejection and cardiac allograft vascular disease is reduced by suppression of subclinical cytomegalovirus infection. *Transplantation.* 2006;82:398-405

FIGURE 4
Kaplan-Meier Cumulative Event Curves for Freedom from Acute Rejection



Source: Used with permission: Potena L, Holweg CT, Chin C, et al. Acute rejection and cardiac allograft vascular disease is reduced by suppression of subclinical cytomegalovirus infection. *Transplantation.* 2006;82:398-405

Key takeaway

The study demonstrated that the use of aggressive CMV prophylaxis with CMVIG delayed the onset of CMV infection and lessened viral burden, delayed the onset and partially reduced the incidence of acute rejection, and delayed the temporal manifestation of CAV.

P&T Committee Considerations

DOSAGE AND ADMINISTRATION

The maximum recommended total dosage per infusion is 150 mg Ig/kg, administered according to the schedule in Table 15:

Preparation for Administration. Remove the tab portion of the vial cap and clean the rubber stopper with 70% alcohol or equivalent. DO NOT SHAKE VIAL; AVOID FOAMING. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Infuse the solution only if it is colorless, free of particulate matter and not turbid.

Infusion. Infusion should begin within 6 hours after entering the vial and should be complete within 12 hours of entering the vial. Vital signs should be taken pre infusion, mid-way and post-infusion as well as before any rate increase. Cytogam® should be administered through an intravenous line using an administration set that contains an in-line filter (pore size 15) and a constant infusion pump (i.e., IVAC pump or equivalent). A smaller in-line filter (0.2) is also acceptable. Pre-dilution of Cytogam® before infusion is not recommended. Cytogam® should be administered through a separate intravenous line. If this is not possible, Cytogam® may be "piggybacked" into a pre-existing line if that line contains either Sodium Chloride Injection, USP, or one of the following dextrose solutions (with or without NaCl added): 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, 20% dextrose in water. If a pre-existing line must be used, the Cytogam® should not be diluted more than 1:2 with any of the above-named solutions. Admixtures of Cytogam® with any other solutions have not been evaluated.

Initial Dose. Administer intravenously at 15 mg Ig per kg body weight per hour. If no adverse reactions occur after 30 minutes, the rate may be increased to 30 mg Ig/kg/hr; if no adverse reactions occur after a subsequent 30 minutes, then the infusion may be increased to 60 mg Ig/kg/hr (volume not to exceed 75 mL/hour). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during and after each rate change.

Subsequent Doses. Administer at 15 mg Ig/kg/hr for 15 minutes. If no adverse reactions occur, increase to 30 mg Ig/kg/hr for 15 minutes and then increase to a maximum rate of 60 mg Ig/kg/hr (volume not to exceed 75 mL/hour). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during each rate change. Cytogam® should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65, volume depletion, paraproteinemia, sepsis and patients receiving known nephrotoxic drugs). In these cases especially, it is important to assure that patients are not volume depleted prior to Cytogam® infusion. While most cases of renal insufficiency have occurred in patients receiving total doses of 350 mg Ig/kg or greater, no prospective data are presently available to identify a maximum safe dose, concentration or rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable.

Potential adverse reactions are: flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, wheezing, drop in blood pressure. Minor adverse reactions have been infusion rate related – if the patient develops a minor side effect (i.e., nausea, back pain, flushing), slow the rate or temporarily interrupt the infusion. If anaphylaxis or drop in blood pressure occurs, discontinue infusion and use antidote such as diphenhydramine and adrenalin. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. The syringes and needles should not be reused.

TABLE 15
Dosing Schedule

	Type of Transplant	
	Kidney	Liver, Pancreas, Lung, Heart
Within 72 hours of transplant:	150 mg/kg	150 mg/kg
2 weeks post transplant:	100 mg/kg	150 mg/kg
4 weeks post transplant:	100 mg/kg	150 mg/kg
6 weeks post transplant:	100 mg/kg	150 mg/kg
8 weeks post transplant:	100 mg/kg	150 mg/kg
12 weeks post transplant:	50 mg/kg	100 mg/kg
16 weeks post transplant:	50 mg/kg	100 mg/kg

CONTRAINDICATIONS

Cytogam® should not be used in individuals with a history of a prior severe reaction associated with the admin-

Source for P&T Committee Considerations section: Cytogam® [package insert]. CSL Behring LLC; 2008.

istration of this or other human immunoglobulin preparations. Persons with selective immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to subsequent administration of blood products that contain immunoglobulin A, including Cytogam®.

SAFETY INFORMATION

WARNINGS

See Section 2 of this Product Profiler.

PRECAUTIONS

General

Cytogam® does not contain a preservative. The vial should be entered only once for administration purposes and the infusion should begin within 6 hours. The infusion schedule should be adhered to closely (see *Infusion* section). Do not use if the solution is turbid. Although systemic allergic reactions are rare, epinephrine and diphenhydramine should be available for treatment of acute allergic symptoms. If hypotension or anaphylaxis occur, the administration of the immunoglobulin should be discontinued immediately and an antidote should be given as noted above.

Renal Function

Assure that patients are not volume depleted prior to the initiation of IGIV. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including the measurement of blood urea nitrogen (BUN) and serum creatinine should be assessed prior to the initial infusion of Cytogam® and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. The recommended rate of Cytogam® infusion for prophylaxis of CMV disease in solid organ transplant patients is 60 mg Ig/kg/hr.

Aseptic Meningitis Syndrome

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) (IGIV) treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu.mm., predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis

Immune globulin intravenous (human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis.

Transfusion-Related Acute Lung Injury (TRALI):

There have been reports of noncardiogenic pulmonary edema (transfusion-related acute lung injury [TRALI]). In patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1–6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support. IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

Thrombotic Events

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

Laboratory Tests

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and the patient serum. Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

Drug Interactions

Antibodies present in immune globulin preparations may interfere with the immune response to live virus vaccines such as measles, mumps, and rubella; therefore, vaccination with live virus vaccines should be deferred until approximately 3 months after administration of Cytogam®. If such vaccinations were given shortly after Cytogam®, a revaccination may be necessary. Admixtures of Cytogam® with other drugs have not been evaluated. It is recommended that Cytogam® be administered separately from other drugs or medications which the patient may be receiving.

Pregnancy Category C

Animal reproduction studies have not been conducted with cytomegalovirus immune globulin intravenous (human). It is also not known whether cytomegalovirus immune globulin intravenous (human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cytomegalovirus immune globulin intravenous (human) should be given to a pregnant woman only if clearly needed.

Information for Patients

Patients should be instructed to report all infections directly to their physician and to CSL Behring at 1-866-915-6958. The risks and benefits of this product should be discussed with the patient. In addition, patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, and/or shortness of breath (which may suggest kidney damage) to their physician.

ADVERSE REACTIONS

Minor reactions, such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing were the most frequent adverse reactions observed during the clinical trials of Cytogam®, cytomegalovirus immune globulin intravenous (human). The incidence of these reactions during the clinical trials was less than 6.0% of all infusions and such reactions were most often related to infusion rates. A decrease in blood pressure was observed in 1 of 1,039 infusions in clinical trials of Cytogam®. If a patient develops a minor side effect, slow the rate immediately or temporarily interrupt the infusion.

Increases in serum creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following IGIV infusion. Progression to oliguria or anuria requiring dialysis has been observed. Types of severe renal adverse events that have been seen following IGIV therapy include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. Severe reactions such as angioneurotic edema and anaphylactic shock, although not observed during clinical trials, are a possibility. Clinical anaphylaxis may occur even when the patient is not known to be sensitized to immune globulin products. A reaction may be related to the rate of infusion; therefore, carefully adhere to the infusion rates as outlined under "Dosage and Administration." If anaphylaxis or drop in blood pressure occurs, discontinue infusion and use antidote such as diphenhydramine and adrenalin.

Postmarketing

The following adverse reactions have been identified and reported during the post-approval use of IGIV products:

Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), transfusion-related acute lung injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm.

Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension Neurological: Coma, loss of consciousness, seizures, tremor.

Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis.

Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test.

General/Body as a Whole: Pyrexia, rigors.

Musculoskeletal: Back pain.

Gastrointestinal: Hepatic dysfunction, abdominal pain.

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.

OVERDOSAGE

Although few data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload.

HOW SUPPLIED AND STORAGE

HOW SUPPLIED

Cytogam®, cytomegalovirus immune globulin intravenous (human), is supplied in one single-dose vial form.

NDC No.: 44206-3101-1.

Total quantity of immunoglobulin: 2500 mg±500 mg

Volume: 50 mL

Concentration: 50±10 mg/mL

STORAGE

Cytogam®. should be stored between 2–8°C (36–46°F), and used within 6 hours after entering the vial.

Conclusion

Patients waiting for or undergoing transplantation are commonly in an immunocompromised state, leaving them vulnerable to CMV and other opportunistic infections. In addition, they are also at risk for receiving CMV positive organs, which increases their risk of acquiring a CMV infection. This is especially true in those CMV-negative patients receiving CMV-positive organs during transplantation. However, with the advent of concurrent CMVIG prophylaxis, with traditional therapy, substantial benefits have been shown to limit or prolong the time to CMV infection and/or disease in this transplant subpopulation.

Numerous clinical studies have been performed to ascertain the safety and effectiveness of CMVIG combination therapy in post-transplant patients. These findings have shown beneficial results in this subpopulation and include the reduction of CMV disease and a reduction in the onset and severity of CMV infection especially in serologically high-risk patients. More specifically, clinical studies have demonstrated a 50% reduction in primary CMV disease in renal transplant patients, and a 56% reduction in serious CMV disease in liver transplant patients when given CMVIG in addition to traditional transplant prophylaxis (Cytogam 2008). Prophylactic therapy with CMVIG was also associated with an increased 1-year survival in liver transplant recipients (Cytogam 2008).

CMVIG has also maintained a consistent safety profile with adverse events localized mainly to the infusion or infusion rate itself (Cytogam 2008). The well-established safety profile and the more than 17 years of clinical experience in transplant biology underscores its effectiveness and usability in patients undergoing transplantation of the kidney, lung, liver, pancreas, and heart.

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CSL Behring
Cytogam®
Cytomegalovirus Immune Globulin Intravenous (Human)

Liquid Formulation
Solvent Detergent Treated

℞ only

DESCRIPTION

Cytogam®, Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IGIV), is an immunoglobulin G (IgG) containing a standardized amount of antibody to Cytomegalovirus (CMV). CMV-IGIV is formulated in final vial as a sterile liquid. The globulin is stabilized with 5% sucrose and 1% Albumin (Human). Cytogam® contains no preservative. The purified immunoglobulin is derived from pooled adult human plasma selected for high titers of antibody for Cytomegalovirus (CMV) (1). Source material for fractionation may be obtained from another U.S. licensed manufacturer. Pooled plasma was fractionated by ethanol precipitation of the proteins according to Cohn Methods 6 and 9, modified to yield a product suitable for intravenous administration. A widely utilized solvent-detergent viral inactivation process is also used (2). Certain manufacturing operations may be performed by other firms. Each milliliter contains: 50 ± 10 mg of immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg of sucrose; 10 mg of Albumin (Human). The sodium content is 20-30 mEq per liter, i.e., 0.4-0.6 mEq per 20 mL or 1.0-1.5 mEq per 50 mL. The solution should appear colorless and translucent.

CLINICAL PHARMACOLOGY

Cytogam® contains IgG antibodies representative of the large number of normal persons who contributed to the plasma pools from which the product was derived. The globulin contains a relatively high concentration of antibodies directed against Cytomegalovirus (CMV). In the case of persons who may be exposed to CMV, Cytogam® can raise the relevant antibodies to levels sufficient to attenuate or reduce the incidence of serious CMV disease.

INDICATIONS AND USAGE

Cytomegalovirus Immune Globulin Intravenous (Human) is indicated for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.

CLINICAL STUDIES

Clinical studies have shown a 50% reduction in primary CMV disease in renal transplant patients given CMV-IGIV (3) and a 56% reduction in serious CMV disease (4) in liver transplant patients given CMV-IGIV. CMV-IGIV prophylaxis was associated with increased survival in liver transplant recipients (5).

In two separate clinical trials, Cytogam® was shown to provide effective prophylaxis in renal transplant recipients at risk for primary CMV disease. In the first randomized trial, (3) the incidence of virologically confirmed CMV-associated syndromes was reduced from 60% in controls (n=35) to 21% in recipients of CMV immune globulin (n=24) ($P < 0.01$); marked leukopenia was reduced from 37% in controls to 4% in globulin recipients ($P < 0.01$); and fungal or parasitic superinfections were not seen in globulin recipients but occurred in 20% of controls ($P = 0.05$). Serious CMV disease was reduced from 46% to 13%. There was a concomitant but not statistically significant reduction in the incidence of CMV pneumonia (17% of controls as compared with 4% of globulin recipients). There was no effect on rates of viral isolation or seroconversion although the rate of viremia was less in Cytogam® recipients. In a subsequent non-randomized trial in renal transplant recipients (n=36)(6), the incidence of virologically confirmed CMV-associated syndrome was reduced to 36% in the globulin recipients in comparison to a 60% incidence in control patients (n=35) in the randomized trial. The rates of serious CMV disease, and concomitant fungal and parasitic superinfection were similar to patients receiving CMV-IGIV in the first trial.

In a randomized, double-blind, placebo-controlled trial in liver transplant recipients (4), the incidence of serious CMV-associated disease was reduced from 26% in the 72 control patients to 12% in the 69 CMV-IGIV recipients (p=0.02); serious CMV-associated disease included CMV disease in 2 or more organs, CMV pneumonia, or CMV-associated invasive fungal infection, the incidence of which was 18% in controls and 7% in CMV-IGIV recipients (p=0.04). In follow-up (5) of the liver transplant patients studied in this randomized controlled trial and a subsequent open-label trial (7), the one year survival of the 72 control patients was 72% versus 86% in the 90 recipients of CMV-IGIV (p=0.03). In the randomized control trial, the reduction in serious CMV-associated disease in CMV seronegative recipients of livers from a CMV seropositive donor (7/19 in the CMV-IGIV group vs. 9/19 in control) was less than in transplants with other donor and recipient serologic status (1/50 in the CMV-IGIV group vs. 10/53 in the control group). This finding was similar to that of Merigan et al. (8) in a study of ganciclovir prophylaxis after heart transplantation. In this study, patients received ganciclovir IV at 5 mg/kg twice a day for the initial 14 days post-transplant, then at 6 mg/kg each day for 5 days per week through day 28.

Recent studies of combined prophylaxis with CMV-IGIV and ganciclovir have shown reductions in the incidence of serious CMV associated disease in CMV seronegative recipients of CMV seropositive organs below that expected from one drug alone (9-12).

Ham et al. (9) used CMV-IGIV with a dosage schedule of 150 mg/kg CMV-IGIV within 72 hours of transplant; 100 mg/kg at two, four, six and eight weeks following liver transplant and then 50 mg/kg at 12 and 16 weeks post-transplant in combination with ganciclovir (10 mg/kg/day for 14 days). The incidence of CMV disease was reduced from an expected 60-80% rate to 7% in 15 seronegative recipients of a seropositive organ.

Snydman (10) using the CMV-IGIV dosage schedule listed under **DOSAGE AND ADMINISTRATION** section in combination with ganciclovir (10 mg/kg/day for 14 days) reduced the incidence of serious CMV disease in D+R- liver transplant recipients receiving placebo or one drug from 16/47 (34%) to 3/41 (7%) in patients receiving both drugs for prophylaxis.

Martin (11) using CMV-IGIV 100 mg/kg every two weeks for six weeks followed by 50 mg/kg every two weeks with a final dose at week 16, in combination with ganciclovir 10 mg/kg/day for 14 days after transplantation, observed severe CMV disease in 1/74 (1%) of CMV seronegative recipients of a kidney from a CMV seropositive donor, in 0/14 (0%) of CMV seronegative recipients of a kidney-pancreas transplant from a CMV seropositive donor and in 1/12 (8%) of CMV seronegative recipients of a liver from a CMV seropositive donor. The incidence of serious CMV disease with combined CMV-IGIV and ganciclovir prophylaxis was lower than previous experience with single drug prophylaxis.

Valantine and Luikart (12) compared prophylaxis with CMV-IGIV (biweekly for three months) in combination with ganciclovir prophylaxis (IV at 5 mg/kg twice a day for the initial 14 days post-transplant, then at 6 mg/kg through day 28) in 16 CMV seronegative recipients of hearts from CMV seropositive donors with 16 matched controls receiving ganciclovir alone. The actuarial incidence of CMV disease was reduced from 55% in the ganciclovir group to 46% in the combined group ($p \leq 0.06$) and survival was increased from 61% to 94% ($p \leq 0.001$). In heart-lung or lung transplant patients in whom either the donor or recipient was CMV seropositive, the actuarial incidence of CMV disease in patients receiving ganciclovir alone (n=25) was 85% as compared to 36% of the 33 patients receiving both CMV-IGIV and ganciclovir ($p \leq 0.05$). Survival was 60% in the ganciclovir group and 80% in patients receiving CMV-IGIV and ganciclovir ($p \leq 0.01$).

CONTRAINDICATIONS

Cytogam® should not be used in individuals with a history of a prior severe reaction associated with the administration of this or other human immunoglobulin preparations. Persons with selective immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to subsequent administration of blood products that contain immunoglobulin A, including Cytogam®.

WARNINGS

CMV-IGIV is made from human plasma and, like other plasma products, carries the possibility for transmission of blood-borne viral agents and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmission of recognized blood-borne viruses is considered to be low because of the viral inactivation and removal properties in the Cohn-Oncley cold ethanol precipitation procedure used for purification of immune globulin products (13-15). Until 1993, cold ethanol manufactured immune globulins licensed in the United States had not been documented to transmit any viral agent. However, during a brief period in late 1993 to early 1994, intravenous immune globulin made by one U.S. manufacturer was associated with transmission of Hepatitis C virus (16). To further guard against possible transmission of blood-borne viruses, including Hepatitis C, CMV-IGIV is treated with a solvent detergent viral inactivation procedure (2) known to inactivate a wide spectrum of lipid enveloped viruses, including HIV-1, HIV-2, Hepatitis B, and Hepatitis C (17). However, because new blood-borne viruses may yet emerge, some of which may not be inactivated by the manufacturing process or by solvent detergent treatment, CMV-IGIV, like any other blood product, should be given only if a benefit is expected.

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death (18-25). Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentrations available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many IGIV products, those containing sucrose as a stabilizer (and given at daily doses of 350 mg/kg or greater) account for a disproportionate share of the total number (18). Cytogam® contains sucrose as a stabilizer. See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections for important information intended to reduce the risk of acute renal failure.

During administration, the patient's vital signs should be monitored continuously and careful observation made for any symptoms throughout the infusion. Epinephrine should be available for the treatment of an acute anaphylactic reaction (see **PRECAUTIONS** section).

PRECAUTIONS

General:

Cytogam® does not contain a preservative. The vial should be entered only once for administration purposes and the infusion should begin within 6 hours. The infusion schedule should be adhered to closely (see *Infusion* section). Do not use if the solution is turbid.

Although systemic allergic reactions are rare (see **ADVERSE REACTIONS** section), epinephrine and diphenhydramine should be available for treatment of acute allergic symptoms. If hypotension or anaphylaxis occur, the administration of the immunoglobulin should be discontinued immediately and an antidote should be given as noted above.

Renal Function:

Assure that patients are not volume depleted prior to the initiation of IGIV. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including the measurement of blood urea nitrogen (BUN) and serum creatinine should be assessed prior to the initial infusion of Cytogam® and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. The recommended rate of Cytogam® infusion for prophylaxis of CMV disease in solid organ transplant patients is 60 mg Ig/kg/hr (see **DOSAGE AND ADMINISTRATION**).

Aseptic Meningitis Syndrome:

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) (IGIV) treatment (26-29). The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu.mm., predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis:

Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis (30-32). Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (33) [See **ADVERSE REACTIONS**]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis [See **PRECAUTIONS: Laboratory Tests**].

Transfusion-Related Acute Lung Injury (TRALI):

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV (34). TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [See **PRECAUTIONS: Laboratory Tests**].

Thrombotic Events:

Thrombotic events have been reported in association with IGIV (35-37) (See **ADVERSE REACTIONS**). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See **PRECAUTIONS: Laboratory Tests**].

Laboratory Tests:

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done [See **PRECAUTIONS**].

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and the patient serum [See **PRECAUTIONS**].

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See **PRECAUTIONS**].

Drug Interactions:

Antibodies present in immune globulin preparations may interfere with the immune response to live virus vaccines such as measles, mumps, and rubella; therefore, vaccination with live virus vaccines should be deferred until approximately three months after administration of Cytogam®. If such vaccinations were given shortly after Cytogam®, a revaccination may be necessary. Admixtures of Cytogam® with other drugs have not been evaluated. It is recommended that Cytogam® be administered separately from other drugs or medications which the patient may be receiving (see **DOSAGE AND ADMINISTRATION** section).

Pregnancy Category C:
Animal reproduction studies have not been conducted with Cytomegalovirus Immune Globulin Intravenous (Human). It is also not known whether Cytomegalovirus Immune Globulin Intravenous (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cytomegalovirus Immune Globulin Intravenous (Human) should be given to a pregnant woman only if clearly needed.

Information for Patients:
Patients should be instructed to report all infections directly to their physician and to CSL Behring at 1-866-915-6958. The risks and benefits of this product should be discussed with the patient. In addition, patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, and/or shortness of breath (which may suggest kidney damage) to their physician.

ADVERSE REACTIONS
Minor reactions such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing were the most frequent adverse reactions observed during the clinical trials of Cytogam®, Cytomegalovirus Immune Globulin Intravenous (Human). The incidence of these reactions during the clinical trials was less than 6.0% of all infusions and such reactions were most often related to infusion rates. A decrease in blood pressure was observed in 1 of 1039 infusions in clinical trials of Cytogam®. If a patient develops a minor side effect, *slow the rate* immediately or temporarily interrupt the infusion.

Increases in serum creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following IGIV infusion. Progression to oliguria or anuria requiring dialysis has been observed. Types of severe renal adverse events that have been seen following IGIV therapy include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis (18-25).

Severe reactions such as angioneurotic edema and anaphylactic shock, although not observed during clinical trials, are a possibility. Clinical anaphylaxis may occur even when the patient is not known to be sensitized to immune globulin products. A reaction may be related to the rate of infusion; therefore, carefully adhere to the infusion rates as outlined under "**DOSAGE AND ADMINISTRATION**." If anaphylaxis or drop in blood pressure occurs, *discontinue infusion* and use antidote such as diphenhydramine and adrenalin.

Postmarketing:
The following adverse reactions have been identified and reported during the post-approval use of IGIV products (38):

Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension Neurological: Coma, loss of consciousness, seizures, tremor
Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
General/Body as a Whole: Pyrexia, Rigors
Musculoskeletal: Back pain
Gastrointestinal: Hepatic dysfunction, abdominal pain

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.

OVERDOSAGE
Although few data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload.

DOSAGE AND ADMINISTRATION
The maximum recommended total dosage per infusion is 150 mg Ig/kg, administered according to the following schedule:

	Type of Transplant	
	Kidney	**Liver, Pancreas,Lung, Heart**
Within 72 hours of transplant:	150 mg/kg	150 mg/kg
2 weeks post transplant:	100 mg/kg	150 mg/kg
4 weeks post transplant:	100 mg/kg	150 mg/kg
6 weeks post transplant:	100 mg/kg	150 mg/kg
8 weeks post transplant:	100 mg/kg	150 mg/kg
12 weeks post transplant:	50 mg/kg	100 mg/kg
16 weeks post transplant:	50 mg/kg	100 mg/kg

Preparation for Administration. Remove the tab portion of the vial cap and clean the rubber stopper with 70% alcohol or equivalent. DO NOT SHAKE VIAL; AVOID FOAMING.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Infuse the solution only if it is colorless, free of particulate matter and not turbid.

Infusion. Infusion should begin within 6 hours after entering the vial and should be complete within 12 hours of entering the vial. Vital signs should be taken preinfusion, mid-way and post-infusion as well as before any rate increase. Cytogam® should be administered through an intravenous line using an administration set that contains an in-line filter (pore size 15µ) and a constant infusion pump (i.e., IVAC pump or equivalent). A smaller in-line filter (0.2µ) is also acceptable. Pre-dilution of Cytogam® before infusion is not recommended. Cytogam® should be administered through a separate intravenous line. If this is not possible, Cytogam® may be "piggybacked" into a pre-existing line if that line contains either Sodium Chloride Injection, USP, or one of the following dextrose solutions (with or without NaCl added): 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, 20% dextrose in water. If a pre-existing line must be used, the Cytogam® should not be diluted more than 1:2 with any of the above-named solutions. Admixtures of Cytogam® with any other solutions have not been evaluated.

Initial Dose. Administer intravenously at 15 mg Ig per kg body weight per hour. If no adverse reactions occur after 30 minutes, the rate may be increased to 30 mg Ig/kg/hr; if no adverse reactions occur after a subsequent 30 minutes, then the infusion may be increased to 60 mg Ig/kg/hr (volume not to exceed 75 mL/hour). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during and after each rate change.

Subsequent Doses. Administer at 15 mg Ig/kg/hr for 15 minutes. If no adverse reactions occur, increase to 30 mg Ig/kg/hr for 15 minutes and then increase to a maximum rate of 60 mg Ig/kg/hr (volume not to exceed 75 mL/hour). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during each rate change.

Cytogam® should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65, volume depletion, paraproteinemia, sepsis and patients receiving known nephrotoxic drugs). In these cases especially, it is important to assure that patients are not volume depleted prior to Cytogam® infusion. While most cases of renal insufficiency have occurred in patients receiving total doses of 350 mg Ig/kg or greater, no prospective data are presently available to identify a maximum safe dose, concentration or rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable.
Potential adverse reactions are: flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, wheezing, drop in blood pressure. Minor adverse reactions have been infusion rate related – if the patient develops a minor side effect (i.e., nausea, back pain, flushing), slow the rate or temporarily interrupt the infusion. If anaphylaxis or drop in blood pressure occurs, discontinue infusion and use antidote such as diphenhydramine and adrenalin.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. The syringes and needles should not be reused.

HOW SUPPLIED
Cytogam®, Cytomegalovirus Immune Globulin Intravenous (Human), is supplied in one single-dose vial form:

NDC No.	Total Quantity of Immunoglobulin	Volume	Concentration
44206-3101-1	2500 mg ± 500 mg	50 mL	50 ± 10 mg/mL

STORAGE
Cytogam® should be stored between 2-8°C (36-46°F), and used within 6 hours after entering the vial.

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