

Cytomegalovirus Intravenous Immune Globulin (CMV-IG; Cytogam®)— Literature Review

(See associated document regarding CMV-IG restrictions and dosing recommendations at The Nebraska Medical Center)

Definitions¹

CMV infection: evidence of CMV replication regardless of symptoms

CMV disease: evidence of CMV infection with characteristic symptoms; can be further described as a viral syndrome (fever, malaise, leucopenia, and thrombocytopenia) or as a tissue-invasive disease (pneumonia, gastrointestinal, hepatitis, pancreatitis, encephalitis, chorioretinitis, myocarditis, nephritis, cystitis, or mucocutaneous)

Donor CMV (+): D+ Donor CMV (-): D- Recipient CMV (+): R+ Recipient CMV (-): R-

FDA-Approved Indications for use^{2,6}

- Cytomegalovirus (CMV) disease prophylaxis associated with transplantation of kidney, lung, liver, pancreas and heart.
- Prophylaxis in combination with ganciclovir for transplantation of the above organs (except kidney) from D+ to R-

FDA-Approved Dosing and Administration²

Time frame after transplant	Kidney transplant	Liver, lung, pancreas, heart
Within 72 hours of transplant	150 mg IG/kg	150 mg IG/kg
Weeks 2,4,6,8 post transplant	100 mg IG/kg	150 mg IG/kg
Weeks 12 & 16 post transplant	50 mg IG/kg	100 mg IG/kg

*Maximum recommended total dosage per infusion is 150 mg IG/kg; max rate: 60mg/kg/hr

Infusion rate:

- Monitor closely during each rate change.
- Initial Dose: 15mg/kg/hr x 30 minutes, 30 mg/kg/hr x30min, then 60 mg/kg /hr to complete
- Subsequent: 15 mg/kg/hr x15 min, 30 mg/kg/hr x15 min, then 60 mg/kg/hr to complete
- If infusion reactions occur, slow the rate or temporarily interrupt; if severe, discontinue infusion and administer diphenhydramine and/or epinephrine

Adverse effects and management²

- Infusion related
 - Minor: flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia,
 - Potentially severe: hypotension, wheezing/anaphylaxis
- Renal failure: Increasing serum creatinine/ blood urea nitrogen , acute renal failure, progression to oliguria/ anuria requiring dialysis
 - Risk factors: diabetes, age > 65yo, hypovolemia, paraproteinemia, sepsis, otherconcomitant nephrotoxins
 - Administer at the minimum concentration & rate, monitor serum creatinine, BUN, and urine output regularly, and ensure patients are euvolemic prior to receiving
 - Discontinue if renal function deteriorates
- Aseptic Meningitis Syndrome (headache, nuchal rigidity, drowsiness, fever, photophobia, nausea/ vomiting), occurs hours - days after infusion, CSF: pleocytosis, elevated protein.

- Other adverse effects
 - General: Pyrexia, rigors, back pain
 - Neurologic: coma, loss of consciousness, seizures, tremor
 - Respiratory: dyspnea, apnea, pulmonary edema, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI)
 - Cardiovascular: cardiac arrest, thromboembolism
 - Skin: erythema multiforme, bullous dermatitis, Stevens-Johnson syndrome
 - Hematologic: Pancytopenia, leukopenia, hemolysis, positive Coombs test
 - Gastrointestinal: Hepatic dysfunction, abdominal pain

Pharmacokinetic Studies

DeRienzo et al: Half life of Cytogam in HSCT patients – approximately 7 days³

Krause et al: CMV activity of IgG⁴

- Tested 5 commercially available IVIG preparations (Isven, Omr-IgG-am, Gamimune-N, Sandoglobulin, Pentaglobin) via EIA and IFA assays
- Found no anti-CMV antibodies present in any tested IVIG product
- Concluded that each IVIG product should be tested for CMV activity when used for CMV prevention or treatment

Planitzer et al: CMV activity of IVIG vs. CMV-IVIG⁵

- Compared CMV hyperimmune globulin (Cytect, Biotest, Germany) with standard IVIG preparations (GG'LQD, Kiovig, and GG'SD, all Baxter AG, Austria) for CMV activity.
- Higher ELISA titers for CMV-IG(product is standardized for composition via this method)
- IVIG products showed approximately 50% higher CMV neutralization capacity and IgG₃ levels vs. CMV-IVIG
- Of note, this study was conducted and funded by Baxter employees

Review of International Consensus Guidelines: CMV Prophylaxis⁶

Adults

- Prophylactic strategies
 - Pre-emptive approach – regular lab monitoring for increasing viral replication, with initiation of antiviral therapy if viral replication reaches certain assay threshold. This strategy has not been well studied in lung transplant or intestinal transplant patients.
 - Universal pharmacologic prophylaxis
 - Low Risk (D-/R-) – none indicated
 - High Risk (D+/R-) – valganciclovir, IV or oral ganciclovir depending on organ transplanted for 3-6 months, immunosuppression, and other factors
- CMV-IVIG
 - FDA approved for prophylaxis of CMV disease but remains controversial
 - Potential option for D+/R- patients in heart, lung, and intestinal transplant patients in combination with antivirals
 - No randomized studies indicating superiority of adding CMV IG to ganciclovir or valganciclovir vs appropriate antiviral therapy alone
 - Level III recommendation (opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees)

Pediatrics

- Pediatrics have an increased risk of primary CMV infection; more experience with pharmacologic prophylaxis than preemptive management
- Recommended CMV prophylaxis regimens
 - Low risk (R+ renal transplants) - IV ganciclovir x 2 wks, then PO valganciclovir x 10wk
 - Intermediate risk (R+ liver, heart transplants) - IV ganciclovir x12 wk
 - High risk (All D+/R- transplants and R+ lung & small bowel transplants) - IV ganciclovir x 12 wk - 6 months
 - (D-/R-) – none indicated
- CMV-IVIG
 - Some experts recommend CMV IG for intermediate or high risk patients– lack of large randomized trials indicating clinical benefit
 - Much of the data is extrapolated from adults or is not directly compared with appropriate antiviral prophylaxis
 - Some studies have suggested benefit to a combination with antiviral therapy, while others showed no effects on rates of CMV disease and/or infection.
 - Guidelines do not provide specific recommendation, but state that when it is used, is typically given to (D+R-) small bowel, lung, and heart transplant patients.

Review of Literature: Treatment of CMV disease

Current recommendations/Standard of care

International Consensus Guidelines: Solid organ Transplantation⁶

- Non-life threatening disease: Valganciclovir 900mg po BID or ganciclovir 5mg/kg IV BID x minimum of 14 days and until viral eradication
- Life threatening disease & children: IV ganciclovir 5mg/kg IV BID as above.
- Secondary prophylaxis: Valganciclovir 900mg po QD may be given for 1-3 months for high risk patients
- Resistant disease – ganciclovir 10mg/kg BID for mild infection, foscarnet, combination ganciclovir+foscarnet, ‘alternate/experimental therapy’
- CMV-IVIG
 - Role in adults unclear; may be adjunctive for severe infection like pneumonitis
 - Recommended in pediatrics for treatment of pneumonitis & enteritis and for hypogammaglobulinemia; “on a selective basis” for other clinical entities

Infectious Disease Society of America Guidelines: CMV Encephalitis⁷

- Combination of ganciclovir 5 mg/kg IV q12h and foscarnet 60 mg/kg IV q8 h or 90 mg/kg IV q12h for 3 weeks followed by maintenance therapy
- Cidofovir is not recommended, as its blood-brain barrier penetration is poorly studied

National Comprehensive Cancer Network (NCCN) Guidelines⁸

- CMV disease: ganciclovir 5mg/kg every 12hrs x2 weeks, then 5-6mg/kg daily for at least an additional 2-4 weeks and resolution of all symptoms.
- Ganciclovir resistance: Foscarnet preferred, 90 mg/kg IV q12h x2 weeks, then 120mg/kg daily for at least an additional 2-4 weeks and resolution of all symptoms.
- CMV pneumonia: Add IVIG 400-500mg/kg every other day for the first week; formulations and dosages vary in different series.
- Alternate: cidofovir 5mg/kg IV every week x 2 weeks, then 5mg/kg every 2 weeks. Give with probenecid and hydration

The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT)⁹

- CMV Pneumonia: ganciclovir IV and high-dose intravenous immune globulin recommended despite lack of controlled data and though efficacy of immune globulin (IG) is controversial
- No data for use of IG in any manifestation of CMV disease other than pneumonia
- No data support any advantage of CMV hyperimmune globulin over standard IVIG
- Other types of CMV disease: IV ganciclovir or foscarnet alone
- Second line: Cidofovir or combination of IV ganciclovir and foscarnet

Treatment of CMV disease: Clinical Studies

Liver transplant

D'Alessandro et al, 1989¹⁰

- Retrospective case series –patients with CMV symptomatic infection post liver transplant
- N=9 patients; 4 (self-resolving viral syndrome), 2(hepatitis),1 (retinitis) 2(pneumonia)
- Treatment:
 - Hepatitis/Pneumonia: CMV-hyperimmune globulin (U of Minnesota) 200mg/kg qod x 3 doses, then weekly during hospitalization + ganciclovir (5 mg/kg bid x 10-14 days)
 - Retinitis: ganciclovir alone as above
- Outcome: complete recovery in all 4 pts receiving the combination
- Conclusion: ‘highly effective method of treatment’ for high-risk CMV disease patients
- Limitations: No comparator group in study or in literature for treatment or rates of recovery

George MJ et al, 1993¹¹

- Retrospective observational study of double blind randomized placebo controlled trial
- N=17 patient post liver transplant post CMV-IG or placebo prophylaxis
- Treatment: ganciclovir 5mg/kg BID alone (6) or ganciclovir + CMV-IG 100mg/kg IV qod (9)
- Outcome: shorter time on ventilator (combination), lower 30 day mortality 33% (ganciclovir) vs. 22% (combo); lower 1 yr mortality 83% (ganciclovir) vs. 44% (combo)
- No outcome was statistically significant
- Conclusion: no statistically significant outcomes; ‘trend towards’ improvement
- Limitations: small sample size, non-randomized treatments, no product information

Renal transplant

Brown CB et al, 1983¹² (abstract only)

- Patients: 11 renal transplant patients with CMV infection (symptomatic with fever and ‘typical clinical and lab features’)
- Treatment: “fractionated hyperimmune anti-CMV immunoglobulin” (10), passive immunization (1)
- Result: 7/11 patients showed “a striking and sustained response within 24-48 hours of therapy, with lysis of fever, resolution of pneumonitis, a rise in white cell count and improvement in renal function and liver function tests”
- Limitations: case series, no data on type of CMV disease, no comparator group in study or in literature for treatment or rates of recovery, no details on CMV-IG product used or dosing

Hematopoietic Stem Cell Transplant

Alexander BT et al, 2010¹³

- Retrospective single-center cohort study conducted from 1999-2007
- Patient population: 35 HSCT patients with probable or proven CMV disease
 - CMV disease: 74% CMV pneumonitis, 26% enteritis, 83% viremia

- CMV-IG dosing: 1999-2001: 150 mg/kg q48 hrs; 2002-2007: 150 mg/kg 2x/week.
- Concomitant treatment (combination possible): ganciclovir (83%), foscarnet (40%)
- Primary outcome: All cause mortality at discharge: 17 patients (49%)
- Secondary outcomes: virologic response (resolved in 55%), Day 30 all cause mortality (51%), adverse effects (HTN 6%, erythema/chills 3%)
- Conclusion: Mortality rate similar to what been previously reported, may be somewhat lower than with antiviral monotherapy; CMV-IG safe for use as adjunct in HSCT population

Reed EC et al, 1988¹⁴

- Prospective observational cohort study
- n=25 pts with BMT and CMV pneumonia
- Treatment: CMV-IG(Cutter) 400 mg/kg on days 1, 2, and 7 and 200 mg/kg on day 14 in addition to ganciclovir 2.5 mg/kg q 8hrs x 14 days for induction
- If clinical improvement but still symptomatic after 14 days, maintenance regimen of ganciclovir 5 mg/kg daily x 14 additional days + CMV-IG200 mg/kg on day 21
- Primary outcome: survival - 13/25 patients (52%), Survival significantly higher compared to historical controls (52% vs. 15%),
- Secondary: viral excretion ceased in 74% of pts treated more than 96 hours
- Adverse events: leukopenia: 12/18 patients (67%), only 3 discontinued
- Conclusion: combination therapy of CMV-IG and ganciclovir IV improved survival in BMT patients compared to previous trials with either agent alone or other previous regimens.

Ljungman P et al, 1992¹⁵

- Retrospective study – survey of EBMT centers
- n=49 allogeneic BMT patients with CMV pneumonia
- Treatment: all received combination ganciclovir and IG
 - Ganciclovir (2.5mg/kg BID, 5mg/kg BID, or 5mg/kg daily) x 14+ days, then maintenance therapy (6 patients)
 - IG (51% IVIG, 49% CMV-IVIG) high dose 57% (at least 0.2g/kg QOD)
- Results: response – 17/49 overall (35%), 30-day survival 31%
- No difference in survival between IVIG and CMV-IG or high dose and non-high dose IG
- Conclusions: Overall low survival in CMV pneumonia, no advantage to CMV-IG
- Limitations:
 - No dosing provided for either IG product
 - Retrospective survey; each center provided information on the survey vs. providing medical records

Verdonck LF et al, 1989¹⁶

- Retrospective observational/case series
- n=6 allogeneic BMT patients with CMV pneumonia
- Treatment
 - All: CMV-IG (Cytotect) 400 mg/kg d 0,4,8, then 200 mg/kg d12, 16.
 - 3 patients: combo with ganciclovir 2.5 mg/kg q 8hrs x 20d
- Results: survival – 0/6 patients
- Conclusion: No benefit of CMV-IG alone or in combination for CMV pneumonia
- Limitations: extremely small, non randomized

Reed et al, 1987¹⁷

- Prospective observational
- n=14 allogeneic BMT patients with CMV pneumonia
- Treatment
 - CMV-IG(Cutter) 400 mg/kg d1,2,7, then 200 mg/kg weekly until clear
- Results: survival - 2/14 patients (14%) – 1 death after 50 days, 11 after 5 days
- Higher CMV antibody in survivors; no effect on viral excretion in non-survivors
- Conclusion: CMV-IG treatment did not improve survival compared to historical rates
- Limitations: small, uncontrolled, observational only

Ljungman P et al, 1998¹⁸

- Retrospective survey of European BMT centers
- n=33 allogeneic BMT patients with CMV GI disease
- Treatment
 - 22 patients: antivirals alone (82% ganciclovir, 18% foscarnet)
 - 11 patients: antivirals + IVIG (45% IVIG, 54% CMV-IVIG)
- Results: response - 18/33 overall (55%), 13/22 (59%) antivirals; 5/11 (45%) combination
 - When adjusted for acute GVHD: no difference in outcome with/without IVIG
 - 100 day survival (overall) - 64%.
- Conclusion: No benefit of adding IVIG to antivirals for CMV GI disease
- Limitations:
 - No differentiation of CMV-IG and IVIG for outcome reporting
 - No dosing provided for either IG product
 - Each center provided information on the survey vs. providing medical records

Treatment of CMV disease: IVIG

Schmidt GM et al, 1988¹⁹

- Prospective observational
- n=13 patients post allogeneic BMT with CMV pneumonia
- Treatment:
 - IVIG (Gammagard): 500 mg/kg every other day + ganciclovir 5 mg/kg q 12 hrs x 21 d
 - Maintenance: IVIG 500 mg/kg q week and ganciclovir 5 mg/kg 5 days/week
- Results: Response 11/13, survival 9/13; elimination of detectable virus in BAL and reversal of clinical/radiographic evidence; no relapses at time of publication
- Conclusion: combination ganciclovir/IVIG is an effective treatment for CMV pneumonia in allogeneic BMT patients

Emmanuel D et al, 1988²⁰

- Prospective nonrandomized trial
- n=21 patients post allogeneic BMT with CMV pneumonia
- Treatment:
 - Intervention: IVIG (Gammagard): 500 mg/kg every other day x10 d + ganciclovir 2.5 mg/kg TID x 20 days; then IVIG 500 mg/kg twice weekly x8 doses + ganciclovir 5 mg/kg 3-5x/week x 20 doses
 - Historical control: ganciclovir alone, CMV-IG alone, or IVIG alone
- Results: Survival: 7/10 (intervention), 0/11 (control)
- Conclusion: combination ganciclovir/IVIG is an effective treatment for CMV pneumonia in allogeneic BMT patients

Discussion

- Current guidelines do not recommend routine treatment of CMV disease with CMV-IG but state that either CMV-IG or regular IVIG may be considered in pneumonitis
- No well designed randomized controlled clinical trials were found for the use of CMV-IG in the treatment of CMV disease
- Trials found are almost exclusively for CMV pneumonia and are largely uncontrolled, retrospective, observational, case-series or surveys; almost no recent evidence is available
- Some trials were conducted before ganciclovir treatment was standard of care
- No standardized dose used for CMV-IG in the literature
- No trials comparing efficacy of IVIG and CMV-IG for treatment
- No clear evidence that CMV-IG provides advantage over IVIG for treatment of CMV disease, and IVIG has also shown in some trials to be effective for adjunctive treatment of CMV pneumonia

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March 2012

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