Journal of Advanced Zoology

ISSN: 0253-7214

Volume ***44*** *Issue 05* ***Year 2023*** *Page* ***2451-2456***

Immunity Risk Associated With Cytomegalovirus Infection After Organ Transplantation

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Article History

Received: 30/09/2023
Revised: 15/10/2023
Accepted:30/10/2023

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Abstract

Cytomegalovirus (CMV), a member of the Herpesviridae family, is frequently seen in hematopoietic cell transplant (HCT) and solid organ transplant (SOT) patients and is a major cause of morbidity and mortality in absence of antiviral prophylaxis in the transplant patients. CMV infection can cause serious problems in organ transplant patients following transplantation, in which the virus could reactivate or could contract a new infection, both result in signs of an active CMV infection consequently leading to organ rejection. CMV generates a robust and diverse innate and adaptive immune response and infects epithelial cells, macrophages, and T lymphocytes. During a three tier infective reaction cycle, it establishes lifetime latency within its host. Ganciclovir , Valganciclovir and Foscarnet though remain successful as treatment strategies against CMV infection, they suffer from some major side effects like leukopenia, drug toxicity and some resistance development. So more recent medicines like letermovir and maribavir have provided new insights as therapy of drug resistant CMV infection. The demand for efficient and well-tolerated medicines still remains a challenge. Early clinical trials have shown potential for adoptive immunotherapy, which involves the virus specific T-cells (VSTs) as drug regime for highly resistant viral infections. With a focus on the clinical strategy for the challenge of CMV infection, this review encompasses positive findings and problems of the widespread use of VSTs to treat immunocompromised patients.

Keywords: Adoptive immunotherapy, Cytomegalovirus, Letermovir, Maribavir, Organ Transplantation, Virus-specific T-cells.

1.Introduction:

Cytomegalovirus (CMV), a frequent infection in the immunocompromised transplant recipient, has gained increasing clinical importance during the past three decades since the advent of human organ donation. After transplantation, Cytomegalovirus infection is a common complication. Patients may experience severe infection symptoms as well as the risk of eventual death. In immune-competent people, Human Cytomegalovirus (HCMV) only causes minor to no symptoms, the infection being persistent creates another round of infection that lasts long in host body (Azevedo *et* al. 2015) Significant morbidity and mortality are caused by recurrent infections as seen in case of AIDS patients and those that received transplantation(Ramamurthy *et* al. 2012 & Ramanan *et* al. 2013). Most high-risk Solid Organ Transplant (SOT) patients get CMV infection without antiviral prophylaxis, which can cause illness, viremia and end-organ damage. (Karrer *et* al. 2015) Due to its immune-modulatory actions, patients may become more vulnerable to opportunistic infections and graft rejection. Organ rejection risk can also increase if having an active CMV infection and in such a situation another transplant might be required (Ramanan *et* al. 2013 & Haidar *et* al. 2020). The number of individuals experiencing severe issues due to active CMV infection has significantly decreased because of preventative treatments. After the transplant, CMV may increase your chance for developing certain chronic disorders -two of these are Diabetes and atherosclerosis (Shivaswamy *et* al. 2016). Organ reactivation of latent infection or after a primary infection. Typically, this syndrome appears 30 to 90 days following transplantation particularly with hematopoietic stem cell transplantation, infection typically happens within the first 30 days of transplantation, and in the presence of graft-versus host disease. The main risk factors are when the recipient is cytomegalovirus sero-negative and the donor is seropositive and using lymphocyte-dependent antibodies (Azevedo *et* al. 2015) .People may get CMV due to contact with body fluids (Cannon *et* al. 2011), directly, the virus is spread. These consist of breast milk, (Osterholm *et* al. 2020), blood, urine, saliva, semen and vaginal secretion (Pass *et* al. 2018). Many people contract CMV for the first time as children. Additionally, a pregnant woman can transmit CMV to her unborn child (Pass *et* al. 2018). Organ transplant recipients are more likely to develop an active CMV infection. Solid organ, bone marrow, and stem cell transplants are examples of transplants (Eid *et* al. 2010). If someone undergoes a transplant, to keep the immune system away from attacking the donated tissue they must take medication for the rest of life. Because the body perceives the new organ as a threat, immune system cells may target the transplanted organ which is more commonly known as organ rejection (Snydman *et* al. 2006). The medications patients take after transplantation keeps sthe donor organ in good condition but they might affect the immune system in various ways (Biron *et* al. 2006). They make it more difficult to fight off infections like CMV. When it comes to CMV infection, the majority of transplant patients who experience these complications have already that remain encrypted within body for years (Jordan *et* al. 1983). CMV infection thus is contracted while a patient undergoes transplantation or while taking blood transfusions. (Roback *et* al. 2002).

2. CMV: Structure & Pathogenesis, Gene Expression

Cytomegalovirus is a kind of herpes virus which usually causes very mild symptoms in an infected individual, but may cause severe neurological damage, in people with weakened immune systems and in the newborn. This is a genus of viruses that belongs to the kingdom Heunggongvirae, phylum Peploviricota, class Herviviricetes, order Herpesvirales, family Herpesviridae, and subfamily Betaherpesvirinae. The natural hosts are humans and other primates with 11 species, including the one that infects people, human betaherpesvirus 5 (HCMV, human cytomegalovirus, HHV-5). Cytomegalovirus (CMV) are enveloped, with icosahedral, spherical to pleomorphic, round geometries, and T=16 symmetry, the diameter of which is around 150–200 nm .The genome is linear and non-segmented and around 200 kb in length. With 162 capsomers that make up the capsid are surrounded by an amorphous integument (Gibson *et* al. 1996), Glycoproteins Complexes are embedded in the lipid envelope. Herpesviruses have some of the biggest genomes among human viruses, frequently encoding hundreds of proteins. The double-stranded DNA (dsDNA) genome of wild-type HCMV strains is around 235 kb length, making it one of the longest human viruses overall and longer than all other herpesviruses. For example, the 235 kb double-stranded DNA (dsDNA) genome of wild-type HCMV strains encodes at least 208 proteins. As a result, it has a genome that is longer than those of all other human herpesviruses and among the longest of all human viruses. Its genome structure is typical of herpesvirus class E, with two unique sections (unique long UL and unique short US) surrounded by two pairs of inverted repeats (terminal/internal repeat long TRL/IRL and internal/terminal repeat short IRS/TRS). The so-called "a sequence," which spans a few hundred bps and is shared by both sets of repeats, and the other repeat regions are sometimes referred to as "b sequence" and "c sequence".

Each viral transcript usually encodes a single protein and typically contains a promoter/regulatory sequence, a TATA box, (Suoniemi, *et* al. 1996) a transcription start site, a 3' untranslated sequence of 10–30 bp, a poly A signal, a 5' leader sequence of 30–300 bp (not translated), , and a 3' untranslated sequence of 30–300 bp. Many Gene overlaps are there. But only a few spliced genes. Antisense relationships exist between several of the expressed ORFs. There are several ORFs that can be accessible from multiple promoters. By a leaky scanning from an upstream ORF some proteins are down regulated translationary (Renbaum *et* al. 1996).
Following viral release, HCMV can now cause a number of illnesses. There are 61 genes associated with the infectious stage barring two (miR-UL148D and miR-US29) are newly found (Ye *et* al. 2020).

2.1 CMV Infection Cycle:

CMV infection stages can be seen as a phase of systemic replication in numerous peripheral tissues that activates the innate immune system and specific NK cells populations and and primes a variety of antibodies and effector/memory T cell responses. It may result into a tissue-localized persistent phase that lasts for months to years and continues to influence innate and adaptive immunity, multi-site latency with restricted viral gene expression, which encourages the immune "inflation" over a subsequent lifespan. Despite this prolonged and multifaceted interactions with its host, normally CMV only causes acute disease in people with weakened or naive immunity (Gaëlle *et* al. 2018 , Karrer *et* al.2022 & Klenerman *et* al. 2016).

2.2 T cell responses to human cytomegalovirus in lytic and latent infection:

HCMV primary infection and periodic reactivation are effectively controlled by T cell responses in healthy individuals, CMV disease can be a serious issue in those whose immune systems are weakened, such as those who have undergone transplantation, or have underdeveloped immune systems. Periodically, the virus reactivates, producing distinct memory $CD4^+$ and $CD8^+$ T cell populations, characteristics of this infection and antigenic activation of HCMV-specific secondary immune responses. HCMV alters a variety of immunological markers, alters serum proteins and enhances T cell effector memory populations. HCMV latent viral carriage in vivo has been demonstrated to occur in bone marrow resident $CD34^+$ progenitor cells and $CD14^+$ monocytes generated from these progenitors. However, HCMV latent infection of $CD34^+$ and $CD14^+$ cells can still be distinguished from active infection depending on the virion titre. Certain viral genes, such as UL138, LUNA (latent undefined nuclear antigen; UL81-82 , US28, and UL111A (vIL-10) , have been identified in earlier investigations as being transcribed during latency and being crucial for maintaining the latent infection. The secretome of CD34+ cells that have been latently infected with HCMV in vitro is altered, and this alteration results in increased expression of chemokines that can attract $CD4^+$ T cells as well as immune-suppressive cytokines including IL-10 and TGF-β. Additionally, $CD4^+$ T cells that are specific to certain HCMV proteins produced during latency can secrete IL-10 and have antiviral effector functions. This shows that latent HCMV infection alters the immune response in a way that is more suppressive as opposed to the mainly antiviral effector phenotype of $CD4^+$ T cells that are specific to HCMV proteins produced during lytic infection, such as pp65, IE, and gB. (Jackson *et* al. 2019).

3. Risk for CMV disease: Type of Transplantation & Symptoms

CMV risk may be increased with specific transplant types. These include a small intestine or lung transplant. A normal individual without any prior history of infection can be recipient but the donor is the one who had the infection at some point of their life, then they too have an increased risk for the disease. Additionally, if the immune system is not functioning properly, they may be at an increased risk of CMV infection. The particular risk may vary depending on the age & other health issues (Ramanan *et* al. 2013).

A flu-like condition may result from an active CMV infection. Symptoms could be fever, chills, fatigue, muscle pain, swollen lymph nodes (Rafailidis *et* al. 2008). Invasion of CMV results life-threatening complications, even death and may also affect a transplanted organ negatively. These symptoms appear between 1 to 4 months after the donation. Taking antiviral medication leads them to start later and those might appear after stopping this medication. A patient having CMV infection has numerous health hazards that entails hepatitis, pneumonia & pancreatic infection with additional problems like bacteremia. Other symptoms could result from these medical issues, they can need special treatment strategies intensive care unit (ICU) support. Even death may result from these consequences (Azevedo *et* al. 2015).

4. Clinical Diagnosis

The healthcare provider keeps an eye on the patient for any signs of an active CMV infection after the transplant. They will conduct a physical inspection and inquire about any existing symptoms. The most used serologic test for detecting CMV antibodies is the enzyme-linked immunosorbent assay (ELISA). A positive test for CMV IgG fails to identify the exact time of infection, but it does show that they had the virus at some point in their life. Other tests like Basic blood tests to detect infection symptoms in the blood, testing nucleic acids for detection of the pathogen of which name should be mentioned of the pp65 antigen test for CMV infection , which immediately provides information on the presence of CMV infection, Tissue samples are examined under a microscope for disease confirmation (Ljungman *et* al. 2002). The pp65 antigenemia assay and polymerase chain reaction (PCR) are the two techniques used to diagnose cytomegalovirus infection. While histology of the affected tissue and broncho alveolar lavage studies are helpful in the diagnosis of invasive disease. Serology is useless for detecting active disease (Azevedo *et* al. 2015).

There are four categories in which recipients may experience the effects of CMV infection. First, the CMV virus itself produces a number of infectious illness syndromes that are caused by the virus. Second, CMV is frequently linked to other infectious disease processes, which may be explained by the fact that this association goes beyond the immunosuppressive state that is brought on by using immunosuppressive medications. Third, CMV infection has been linked to allograft dysfunction. Fourth, CMV infection has been related to a worse survival rate among transplant recipients (Suwansirikul *et* al. 1977)

4.1 Plausible Prevention Strategy through Antivirals

The healthcare team will take every precaution to help patients against an active CMV infection. Preventive antiviral medications may be started if the doctor determines that the patient is at stake of contracting another infection or having an existing one reactivated. Immediately following the transplant, patients may take an antiviral medication such as valganciclovir. Patients might need to continue these medicines for several months. The probability of developing an active CMV infection will be significantly reduced by the medication. But sometimes, after stopping these medications, people get an active CMV infection. The healthcare providers will work to reduce the chance that the patient contracts CMV if they have never had the infection from transplanted organs. It enables faster therapy. Patients will experience fewer problems as a result (Paya *et* al. 2004).

Treatment is necessary for symptomatic patients. Ganciclovir or valganciclovir, these types of antiviral medicines can help to control the virus. The four commercially available agents—ganciclovir, valganciclovir, foscarnet, and cidofovir—are frequently the only ones that can be used to treat CMV infections in individuals who have undergone transplantation. The mentioned drugs are successfully applied as drug regime for treatment (Asberg *et* al. 2009), but they have major side effects such as leukopenia and the potential for resistance development. New treatment drugs with safer profiles are required for better CMV therapy due to the high occurrence of significant toxicities, such as myelotoxicity related with ganciclovir and nephrotoxicity associated with foscarnet and cidofovir. Few other drug choices are currently utilized against CMV in transplant recipients, despite this unmet need (Asberg *et* al. 2009).

Maribavir : US FDA approved the use of the benzimidazole nucleoside maribavir to treat R/R CMV infection in adults and children after transplantation (age 12 and up and weight at least 53 kg). It shows antiviral effect by Inhibiting UL97, which has an impact on viral DNA replication, DNA encapsidation, and nuclear egress). But Maribavir is not effective against the other herpes viruses except Epstein-Barr virus *in vitro*.

Letermovir : Antiviral medicine letermovir prevents the CMV-terminase complex from working. Week 14 after transplantation, CMV-seropositive transplant recipients who were 18 years of age or older were randomly assigned in a 2:1 ratio to receive letermovir or a placebo, administered orally or intravenously; randomization was stratified according to trial site and CMV disease risk. (Khawaja *et* al. 2023).

Early CMV treatment after transplant is difficult. It's critical to evaluate each patient's immunosuppressive strategy in order to make predictions about the duration and intensity of T-cell impairment. In the presence of recent lymphocyte-depleting agents, adaptive immunity will be difficult to develop. Lowering Prednisone dosing, reducing or stopping mycophenolate mofetil and reducing tacrolimus through concentration may need to be taken into account when necessary. Antiviral chemotherapy has made significant advancements in the last ten years for the prevention and treatment of CMV disease. There are now a variety of regimens for managing CMV disease, including risk factor identification, early stage detection along with prophylactic managements, , administration of intravenous along with monitoring are required. Specimens may be used for surveillance viral monitoring when clinically necessary. Routine cultures of urine and blood carried out

during the first two months following transplantation can help anticipate CMV disease in liver transplant recipients.

4.2 Adoptive Immunotherapy for Prophylaxis and Treatment of Cytomegalovirus Infection:
A logical approach of treatment is to encourage immunological reconstitution using adoptive immunotherapy, given its significant relevance to the management of viral illness. Adoptive immunotherapy, works via the administration of transfer of viral-specific T-cells (VST). Interleukins like interferon-ɣ (IFNɣ) are proinflammatory mediators produced by innate immune cells in response to primary CMV infection. Early CMV infection control depends on NK cells, and abnormalities in NK cell activity have been related to this pathogenicity. NK cells are used as effective candidates to work in adoptive immunotherapy. Low CD4+ T-cell quantitative levels in those with human immunodeficiency virus infection put them at the greatest risk for developing severe illness. As there is little doubt that the use of antiviral medication has decreased mortality linked to the infection this immunotherapeutic regime is a possible clinical measurement that is effective against the disease (Ouellette *et* al. 2022).

Conclusion:

The past few years have seen significant advancements in CMV infection prevention following transplant. Despite significant progress, persistent infection continue to be serious consequences after transplantation. We emphasize novel treatments that can challenge the issue. Since letermovir was approved for use as prophylactic in adult HCT recipients who tested positive for CMV, there have been significant changes in the prevention of CMV infections after transplant. The fully enrolled phase 3 trial for extended period of prophylaxis (NCT03930615) will be used to assess whether it is required to extend the duration of primary letermovir prophylaxis in high-risk allogeneic HCT recipients beyond day 100 following transplant. Despite significant improvements, R/R CMV infections and breakthrough CMV reactivation continue to be serious post-transplant consequences. Maribavir was just approved, however it remains to be seen whether this would lower the burden of these problematic and dangerous CMV infections and enhance outcomes.

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