

Cytokine Gene Polymorphisms and Viral Infections

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ABSTRACT

In 2014, over 119,000 solid organ transplants were performed worldwide, whereas, more than 30,000 were performed in the United States alone in 2015. Renal transplants were the most common transplant among all solid organ transplants. Infections are a major cause of morbidity and mortality in renal transplant and second leading cause of death in patients with allograft function. Many opportunistic pathogens have been reported in renal transplant recipients including bacterial and fungal organisms, and viruses, among these, Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and BK virus are prominent. CMV infection is the most common opportunistic infection occurs in 8% of renal transplant recipients. Individual's exposure to the virus amount and the virus's replication dynamics, presence of other viral or bacterial infections are the factors

contributes to the development of CMV infection. On the other hand, cytokines play an important role in the reactivation and pathogenesis of CMV infection and CMV disease. Polymorphisms of cytokine gene were found to be associated with the individual susceptibility and outcome of CMV infection. The major goal of preventing CMV infection is to reduce the incidence of CMV disease and the indirect effects associated with viral replication. Exploration of the role of cytokine gene polymorphisms is paramount for researchers and healthcare providers to improve health outcomes in patients especially with renal transplants and in patients with other disease conditions.

Key words: Cytokines; interferon gamma; gene polymorphism; cytomegalovirus; CMV infection; renal transplant recipients

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CYTOKINE GENE POLYMORPHISMS AND VIRAL INFECTIONS

An estimated 119,873 solid organ transplants were performed worldwide in 2014, while, 30,970 were performed in the United States alone in 2015.^[1] Among all solid organ transplants, renal transplants were the most common, followed by those of the liver, heart, lung, and others, including dual organ, pancreatic, and intestinal transplantation. Infections are a major cause of morbidity and mortality in renal transplant recipients and second leading cause of death in patients with allograft function. Twenty percent of hospital readmissions are due to infectious complications in the first year of post-renal transplant. In recent years, with the use of pre-transplant screening, immunization and antimicrobial therapy, to some extent such risk of infections can be minimized. The diagnosis of infections in renal transplant patients may be confounded because the infection does not manifest into its typical and sign and symptoms. Due to drug interactions and need of maintaining the immune suppression to avoid allograft rejection, treating infection becomes more complicated in renal transplant patients.

Many opportunistic pathogens have been reported in renal transplant recipients including bacterial and fungal organisms of special significance due to their increased incidence, greater virulence, or prototypic role. Many viruses are also associated with renal transplant that leads to opportunistic illness. These include Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and BK virus.

Cytomegalovirus (CMV) infection is the most common opportunistic infection that occurs in 8% of renal transplant recipients.^[2] The clinical presentation of CMV infection includes fever, malaise, myalgia, arthralgia, pneumonitis, and leukopenia. CMV infection remains mostly subclinical in healthy uncompromised patients, however, quickly turns into a lifelong latent infection. Donor sero-positivity, use of induction immune-suppression (T cell-depleting antibodies), simultaneous kidney-pancreas transplantation, donors of age >60

years, presence of allograft rejection, and concurrent infection from other viruses are the known risk factors for the development of CMV infection.^[3] The development and severity of CMV infection mostly depends on the interactions between virus's unique properties and the robustness of the host immune response.

Factors contributing to the development of CMV infection include individual's exposure to the virus amount and the virus's replication dynamics, and presence of other viral or bacterial infections. On the other hand, individual's ability to mount a full cell-mediated (T-cell) or humoral (B-cell) response is an important part of the host immune defense mechanisms. Cytokines play an important role in antiviral and inflammatory responses. The virus-host immune system interaction is controlled by the role of cytokines through balance between T-helper 1 lymphocytes (Th1); pro-inflammatory cytokines interferon gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), interleukin (IL)-2; and Th2 anti-inflammatory cytokines (IL-4, IL-5, IL-10, and IL-13).^[4] Cytokines also play an important role in the reactivation and pathogenesis of CMV infection and CMV disease. Polymorphisms of cytokine gene are associated with the individual susceptibility and outcome of CMV infection.^[5] CMV can lead to activation of nuclear factor-kB, a transcription factor involved in stimulating a broad array of genes, including those that may have a role in inflammatory responses and allograft outcomes.^[6] In renal transplant recipients, CMV infection conferred a significantly higher risk for nephropathy due to BK virus, whereas, cytokines were also found to be associated with allograft outcomes in renal transplant recipients.^[7]

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CMV infection can be prevented either through prophylaxis or by preemptive treatment. Both options were found effective for CMV disease prevention. However, there is no consensus on which is the best option, but prophylaxis is more favored in donor positive/recipient negative patients. Reducing the incidence of CMV disease and the indirect effects associated with viral replication is the major goal of preventing CMV infection.^[8] Intravenous ganciclovir, oral valganciclovir, and high doses of oral valganciclovir are considered the prophylactic treatment option for CMV infection in renal transplant recipients, whereas, valganciclovir is the preferred choice of drug for prophylaxis due to its efficacy and availability in oral form, although it is very expensive. Intravenous ganciclovir is the gold-standard drug for the treatment of CMV infection, whereas, there is limited evidence that oral valganciclovir is effective as much as that of intravenous ganciclovir.^[9]

Since, cytokine gene polymorphisms have shown to be involved in the susceptibility, clinical performance, and outcome in terms of CMV infection in renal transplant recipients, it is important for researchers to keep exploring the role of cytokine gene polymorphisms to inform healthcare providers about its possible role and impact on health outcomes especially in their renal transplant patients as well in patients with other disease conditions.

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