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Association of IL-15 and IP-10 Serum Levels with Cytomegalovirus Infection, CMV Viral Load and Cyclosporine Level after Kidney Transplantation

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Abstract

Background: Cytomegalovirus (CMV) infection is the most common complications following kidney transplantation. Natural killer (NK) cells demonstrated critical anti-viral role in controlling and elimination of CMV after transplantation. Interleukin-15 (IL-15) is a pleiotropic cytokine that promotes the activity of NK cells and strengthens the acquired immune system. Also, IP10 (CXCL10) is a chemotactic factor which regulates NK cell recruitment and antiviral immune response. We aimed to determine the correlation between the serum levels of IL-15 and IP-10 cytokines with CMV infection, CMV viral load, and cyclosporine as a major immunosuppressive treatment after transplantation.

Methods: Fifty-eight kidney transplant recipient patients without evidence of CMV virus disease before transplantation surgery were included in the study. From the day of transplant surgery, the patients were evaluated based on the presence of CMV Ag pp65, CMV viral load, serum levels of IL-15 & IP-10, Cyclosporine levels (C0 & C2), Glomerular Filtration Rate (GFR), and hematological & biochemical Index, up to 75 days.

Results: Comparison analysis of serum levels of IL-15 and IP-10 showed no significant association with CMV infection in kidney transplant recipients. In addition, CMV viral load and cyclosporine levels at C0 and C2 did not affect patients' IL-15 and IP-10 levels.

Conclusions: The levels of IP-10 and IL-15 cytokines are not affected with CMV infection, even if a viral infection occurs in the early days after transplantation or long afterwards. In addition, taking the different levels of cyclosporine did not affect the cytokines levels. Other mechanisms may play a role in maintaining the levels of these cytokines.

Keywords: Cytokine, Cytomegalovirus, IP-10, Interleukin-15, Transplantation.

Introduction

Cytomegalovirus (CMV) is a major cause of mortality and morbidity in immunodeficient patients and transplant recipients. CMV infection increases the relative risk of mortality in kidney transplant recipients from 2.5 to 2.9, and the prevalence of infection increases

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with age. More than 75% of transplant recipients are infected by CMV and almost 60% of the patients are infected with CMV within the first three months after transplant surgery (1, 2). CMV infection can lead to transplant rejection, also it is associated with diabetes and transplantation artery stenosis. In immunosuppressed patients, CMV can infect various organs and lead to functional impairment (3).

As the main cells in antiviral defense, both T cells and NK cell play the pivotal role in controlling and eliminating of the CMV (4). After transplantation, the activity of T cells is disrupted due to the use of immunosuppressive drugs, and as a result, adaptive antiviral immunity is impaired (5, 6). In contrast, NK cells undergo different treatment regimens and therefore convert to most important cell in the antiviral immune response to CMV (7, 8).

NK cells represent as an innate immune cell that comprise approximately 10% of peripheral blood lymphocytes (9). The major function of this cell, cytotoxicity, is the ability to recognize and kill tumor cells, virus-infected cell, damaged or non-self-cells that no express self- MHC class I molecules, without need to prior contact or reorganization. NK cell cytotoxicity is affected by various cytokines such as IL-12, IFN-γ and IL-15 which upregulate the CD69 receptor in NK cell that promote cytotoxic activity (10, 11). Interleukin-15 is a substantial cytokine for the survival and development of NK cells. Because of similar receptors and signal transduction, IL-15 exhibits shared function to IL-2, both of them stimulate the production of interferon (IFN) -γ (12, 13). IL-15 is secreted by mononuclear cells and macrophage in response to virus infections, then enhance the proliferation, cytokine secretion and cytotoxicity of NK and T cells (11, 14). Furthermore, interaction between IL-15 with IFN-αβ and IL-12 during the viral infection, is required to protective response of NK cell. Also, prescribing of IL-15 after transplantation has been effective in the reconstruction of NK-Cells (15).

IP-10 (CXCL10) is a chemotactic factor from the CXC category with the weight of 12 KD and 177 amino acids in its evolved form. IP-10 gene is located on the chromosome four and its expression can be induced by interferon gamma in stimulated APCs, neutrophil, endothelial, keratinocyte, fibroblast, mesenchymal, astrocyte, and dendritic cells. It regulates various biological processes including inflammation, recall of monocyte cells, NK-cells, B cells, and activated lymphocytes T by connecting to its receptor (CXCR3) (16-18). It also plays an important role in the absorption of Th1 cells. Th1 cells produce high levels of interferon with positive feedback for more IP-10 secretion. In addition, IP-10 has a negative effect on Th2 cytokine production and inflammation (19).

Regarding the relationship between IP-10 and hepatitis C, it has also been shown that low serum levels of IP-10 are associated with a reduction in the rate of virus replication, and better response to treatment with increased fibrosis and less inflammation in the liver (20). In transplant patients infected by CMV, elevated levels of IP-10 have been determined in several studies (21, 22). Furthermore, CMV infection increases morbidity of lung transplant recipients. It also promotes proliferation and response of Th-1, leading to upregulation of IP-10. After antiviral treatment, the level of IP-10 remains above the initial level (21).

Due to the administration of immunosuppressive drugs, cytomegalovirus causes infection and serious complications in transplant patients, and the severity of its complications is not only dose-dependent. In some patients, despite receiving a low dose of cyclosporine as an important immunosuppressive drug, high suppressive effects are observed. Pharmacokinetic examination revealed that cyclosporine concentration at 2 hours post-dose (C2) is the main time point in kidney (and some other organs) transplant patients to determine the immunosuppression levels. Also, C2 predicted nephrotoxicity and acute rejection episodes more efficient than trough levels (C0) (23). To evaluate the effect of CMV infection on the immune system and the outcome of transplantation, considering C2 and C0 level is recommended.

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The main aim of our study was to understand the effect of CMV and its viral load on serum levels of IP-10 and IL-15 in kidney transplant recipients. Also, to determine the effect of cyclosporine as an immunosuppressive treatment on these cytokines, relevant examinations were performed and analyzed.

Materials and Methods

We performed a cross-sectional study on the association of serum levels of cytokines (IL-15 and IP-10) with cytomegalovirus infection and CMV viral load in kidney transplant recipients.

Human Subjects

In this study, 58 kidney transplant recipients (male and female) were included from the beginning of transplant surgery without any evidence of CMV virus. This study started on September 1, 2017, on kidney transplant recipients who underwent surgery at Labbafinejad Hospital, Tehran, Iran. Patients were included if they were aged 16 years or older, CMV negative, waiting for their first transplant, their creatinine level was less than 3 mg / dL on the fourth day after transplantation. They received medications such as prednisolone, Cellcept or mycophenolate, and cyclosporine according to the transplantation protocol. Exclusion criteria included age under 16, waiting for a second transplant, presence of CMV, and hepatitis B or hepatitis C. Patients infected with the CMV virus after surgery, received medications such as monoclonal antibodies and the antiviral drug, ganciclovir.

Diagnosis of CMV and laboratory examination

Before transplantation surgery, the presence of CMV Ag pp65 was detected using CMV-Ag PP65 IQ-product immunofluorescence kit (Netherland). CMV viral load in a blood sample was determined by quantitative polymerase chain reaction (PCR) using a real star CMV PCR kit (Altona diagnostic, Germany).

Fifty-eight CMV negative patients were included. Serum concentration of cyclosporine, CMV Ag pp65, CMV viral load, creatinine concentration, levels of IL-15 & Ip-10 and CBC-Diff in blood samples were evaluated before transplantation surgery. Up to 75 days after surgery, CMV Ag was evaluated initially every week for up to one month and then every two weeks. Serum levels of IL-15 and IP-10 were also measured at day 75 after transplant surgery using ELISA (Human-IP-10 ELISA Kit, Abcam & Human IL-15 Elisa, eBioscience Inc). DNA was extracted from peripheral blood mononuclear cells (PBMC) (DNA extraction kit from Qiagen), then PCR was done using specific primer for CMV detection. The amount of GFR was also calculated based on MDRD formula. MDRD is one of the most common and valid methods to calculating GFR, which is calculated in this study through the following formula:

GFR, in, mL / min per 1.73 m^2 = 186.3 x SCr (exp [-1.154]) x
Age (exp [-0.203]) x (0.742 if female) x (1.21 if black)

Statistical Analysis

Statistical analyses were performed using the t test to comparing mean differences and Pearson regression to calculating the relationship between serum levels of cytokines (IL-15 and IP-10) with cytomegaly virus infection and viral load CMV. The statistical analyses were performed using SPSS version 22.

Results

Demographic characteristics of the kidney transplant Patients

Based on the inclusion and exclusion criteria, 58 eligible candidates for kidney transplant surgery in were enrolled from September 2017 to May 2018. Blood samples and initial clinical information of the participants were collected. Of the 58 participants, three died of major problems, while none of them showed evidence of infection or disease. Also, one patient developed hyperglycemia, kidney transplant failure (diagnosed by biopsy), and elevated creatinine levels after transplantation. Nine people refused to continue their cooperation due to personal reasons or the distance of their place of residence. Finally, 45 patients remained in all stages of the program. The demographic characteristics of the transplant patients are summarized in Table 1.

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Table 1. Demographic characteristics of the kidney transplant recipients.

Factor	Summary	
Total number of participants	N=45	
Average age (years)	16-69	
Patient's Gender	Female	13 (29%)
	Male	32 (71%)
Type of transplant donors	Living donor	33 (73.3%)
	Deceased donor	12 (26.7%)
CMV Ag (PP65)	Ag^+	19 (42%)
	Ag^-	26 (58%)
CMV Viral load	>2000 copy/ml	17 (%38)
	<2000 copy/ml	28 (62%)

The most common causes of kidney failure in this study were diabetes in 13 persons (28.8%), hypertension in 11 persons (24.4%), and nephrotic syndrome in 4 persons (8.8%). 11 patients had no specific cause for kidney failure before transplantation.

Patients' cytokine levels (IL-15 & IP-10) were not affected by viral cytomegalovirus infection

Based on whether the CMV test was positive or negative at the beginning and end of the study, patients were divided into two groups and their serum cytokine levels were compared.

All Patients were initially (before transplant surgery) CMV negative. Based on CMV infection after transplant surgery, they were divided into two groups including positive and negative CMV patients. Levels of both cytokines were assessed in participants during the study (comparison of levels at the beginning and end of the study). Compared to the start of the study, IL-15 levels increased in all patients, but it was greater in patients infected with CMV after surgery. IP-10 levels in CMV Ag positive patients decreased compared to the beginning of the study, while in CMV Ag negative did not change. The results are demonstrated in Table 2.

Table 2. Comparison of IL-15 and IP-10 levels of patients based on the positive or negative PP65 CMV Antigen.

Variable		CMV Ag pp65 (+)	CMV Ag pp65 (-)	p- value
		Mean±SD	Mean±SD	
IL-15 (pg/ml)	At the beginning of the study	12.6±2.9	13±2.1	0.8
	75 days after surgery	18.9±16.3	16.4±16.1	0.6
IP-10 (pg/ml)	At the beginning of the study	270.9±103.5	176.2±77.2	0.4
	75 days after surgery	218.2±77.9	178.8±66.2	0.7

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Table 3. Levels of IL-15 and IP-10 of patients based on CMV viral load in CMV Ag positive patients.

Variable		CMV viral load >2000 (copy/ml)	CMV viral load <2000 (copy/ml)	p- value
		Mean±SD	Mean±SD	
IL-15 (pg/ml)	Early in the study	12.6± 2.9	15.3±4.1	0.6
	75 days after surgery	18.9±16.3	16.4±16.1	0.6
IP-10 (pg/ml)	Early in the study	232.9±103.5	193.2+88.2	0.4
	75 days after surgery	301.2±115.9	163.8±55.2	0.7

CMV viral load has no effect on serum cytokine levels in kidney transplant patients

Patients who developed cytomegalovirus infection after surgery were assessed for viral load and divided into two groups of individuals with viral load above 2000 copies /ml (N= 17, 38%) and below 2000 copies/ml (N= 28, 62%). The results showed no statistically significant difference between the levels of IL-15 in both groups (according to viral load) in the early days of the study or at the end of the study. However, at the end of the study, the level of IL-15 in all patients was slightly higher than the beginning of the study (Not statically significant) (Table 3).

In patients with viral loads above 2000 copy/ml, higher levels of IP-10 were observed at both the beginning and end of the study. Furthermore, in patients with a viral load above 2000 copy/ml, IP-10 levels increased at the end of the study compared to the beginning of the study. However, this difference was not statistically significant (Table 3).

Cyclosporine levels (C0 and C2) did not show a significant relationship with serum levels of IL-15 and IP-10 in kidney transplant recipients

Cyclosporine as an important treatment in kidney transplant patients is carefully monitored, because in addition to suppressing the immune system to prevent transplant rejection, it has some side effects such as patients' weakness against viral infection and kidney toxicity. Pharmacokinetic studies have suggested that cyclosporine levels at 2 hours after dosing (C2) are the most important time to predict periods of acute rejection and renal toxicity and area under the concentration curve (AUC). To determine and understanding the effect and correlation of cyclosporine with the cytokine levels, we analyzed the relationship between the dose of cyclosporine and the levels of IP-10 and IL-15 in the serum of all participants. No significant relationship was observed between serum cyclosporine levels and cytokines (IP-10 and IL-15) (Table 4).

Table 4. Relationship between the serum levels of cyclosporine (C0 and C2) with blood levels of IL-15 and IP-10 in all patients.

Variable	C0		C2	
	Correlation coefficient	p-value	Correlation coefficient	P-value
IL-15	0.19	0.2	0.2	0.1
IP-10	- 0.12	0.4	- 0.19	0.2

Discussion

Due to the suppressed immune system, viral infections such as cytomegalovirus are common in transplant recipients. Immunosuppressive treatment is the main cause of weakness in the immune system in transplant recipients.

Viral infections in such conditions can lead to problems such as disruption in immune system and even transplant rejection (24). Therefore, understanding the changes that occur in the immune system caused by these viruses

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can be used as a tool to prevent transplant rejection and improve patients' health condition.

The results of the present study showed that cytomegalovirus infection is possible in the first month after transplant surgery. However, the risk of this infection is much higher in the second and third months after surgery. Also, there was no difference in the function of the transplanted kidney (GFR) until day 7, when people began to become infected. Furthermore, no differences were found in age and sex between these two groups (CMV positive and negative).

IL-15 and IP-10 are two cytokines involved in the activation of NK cells (25, 26). In this study, the relationship between IL-15 and IP-10 levels with CMV infection in kidney transplant recipients and manifestations of infection or transplant rejection was investigated from beginning the surgery to 75 days after that. There was no significant difference between IP-10 and IL-15 levels at the beginning of the study, when no participant was infected with CMV. After transplantation, IL-15 levels were increased in both groups. In addition, IP-10 levels in the group with CMV infection was reduced. However, none of these changes were significant. Furthermore, C0 and C2 level did not significant correlation or negative impact on the IP-10, IL-15 levels

IL-15, IP-10 and immunosuppressive drugs have major roles in the activation of NK cells (25, 26). NK cell has known and crucial role in transplant rejection and antiviral defense (27), so all factor that related with the function of this cells are remarkable in the studies in field of transplantation. Unlike some immunosuppressive drugs like as rapamycin (Rapa) and mycophenolic acid (MPA), cyclosporine has no effect on the cytotoxicity and phenotype of NK cell (balance between CD56 dim and CD56 bright NK cells) in the presence of IL-15 and IL-2 (28, 29). Due to preserving the anti-viral potency of NK cells, cyclosporine is desirable drug, but it may increase the risk of GVHD compared to otherdrugs.

However, Neudoerfl et al, showed that Cyclosporin is more associated with decreasing CD56 dim NK and CD56 bright NK in comparison with tacrolimus and MTOR inhibitor and MPA (7). The suppressive effect of cyclosporine on NK cells may be dose dependent (7). In addition, in lung transplant recipients, increasing the serum level of IP10 has been associated with acute cellular rejection (30). Similar to IP-10 , IL-15 have numerous effects on NK cells, it has been demonstrated that IL-15 increases the activity and number of NK cells (31), neutralize the inhibitory effect of cyclosporine on NK Cell (32), Increases CD69 on the surface of NKCs which is related with cytotoxic potency of NK cells (33). All these findings are related with anti-viral function of NK cells. However, in the present study, we have not found significant changing in the IP-10 or IL-15 followed by CMV infection and with CMV viral load. Furthermore, no significant correlation was observed between C0 and C2 of cyclosporine with the cytokine levels.

Other factors including genetics, cytokine and HLA polymorphisms, follow up-duration, and lifestyle of the patients after surgery were not evaluated in this study that can play crucial roles in the findings. It is also possible that cytomegalovirus infection does not affect cytokine levels but instead affects cells phenotype. Future studies are needed to explain the exact mechanism in immune regulation followed by immunosuppressive treatment and viral infection in transplant recipients. Also, the effect of other important immune cells (such as CTL or macrophages) in antiviral defense and transplantation should not be overlooked.

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