Abstract

End-stage renal disease in the human immunodeficiency virus-positive population is increasing. Kidney transplant is the optimal therapy for this population rather than dialysis modalities if some criteria are met. These include undetectable plasma human immunodeficiency virus RNA, CD4 cell count over 200 cells/µL, and the absence of any AIDS-defining illness. Here, we describe the first living-donor kidney transplant in a human immunodeficiency virus-positive recipient in Turkey. The patient, a 52-year-old male diagnosed as human immunodeficiency virus positive, was on antiretroviral therapy, which consisted of 400 mg twice daily darunavir, 100 mg/day ritonavir, and 50 mg/day dolutegravir. He had been negative for human immunodeficiency virus RNA for the past 3 years. The patient developed renal insufficiency without any known cause and started hemodialysis. A living donor transplant from his son was performed, and the patient received ATG Fresenius-S (Neovii Biotech, Rapperswil, Switzerland) induction and a maintenance immunosuppression therapy consisting of methylprednisolone, mycophenolate mofetil, and tacrolimus. There were no incidences of delayed graft function or acute rejection. Because of tacrolimus and ritonavir interaction, tacrolimus trough levels were too high. With tacrolimus withdrawn, tacrolimus trough level decreased to detectable levels 2 weeks later. Antiretroviral therapy was continued on the same dosage. At month 4 posttransplant, the patient’s creatinine level was 1.01 mg/dL. At present, the patient has had no complications and no episodes of rejection. Kidney transplant is the most favorable replacement therapy for HIV-positive patients who are under controlled AIDS care with highly active antiretroviral therapy. However, drug interactions should be carefully evaluated.

Key words: HIV infection, Immunosuppression, Renal transplantation

Introduction

The introduction of highly active antiretroviral therapy has reduced the mortality and progression to acquired immunodeficiency syndrome (AIDS). However, end-stage renal disease can occur in patients who are human immunodeficiency virus (HIV) positive. A broad spectrum of diseases such as hypertension, diabetes mellitus, and glomerular diseases are the major causes of end-stage kidney disease. Human immunodeficiency virus-associated nephropathy is a specific glomerular collapsing sclerosing disease seen in HIV-positive patients. Whatever the cause, renal transplant is the optimal therapy for the HIV-positive population rather than dialysis modalities if some criteria are met. These criteria include undetectable plasma HIV RNA, CD4 cell count over 200 cells/µL, and the absence of any AIDS-defining illnesses. Over time, the best immunosuppression modalities have become better known for this population of patients. However, drug interactions are still important points with immunosuppression therapy. Delayed graft function (DGF) and acute rejection are the most important issues to be noted carefully during the early posttransplant period.

In Turkey, there are about 11988 HIV-infected patients. The number of patients needing renal replacement therapy in the HIV-positive population is unknown. The number of solid-organ transplants performed in 2012 was 3999, whereas there were 2905 kidney transplants. In 2015, 3204 kidney
transplants were performed in Turkey. Here, we describe the first living-donor kidney transplant in an HIV-positive recipient in Turkey.5,6

**Case Report**

A 52-year-old male patient was diagnosed as HIV positive 8 years previously. He was on antiretroviral therapy and was negative for HIV RNA for the past 3 years. The antiretroviral therapy consisted of 400 mg twice daily darunavir, 100 mg/day ritonavir, and 50 mg/day dolutegravir. The patient’s CD4 count was 457 cells/μL.

Over the past 2 years, the patient’s creatinine level was higher than 2 mg/dL; however, he did not have either proteinuria or hematuria. No biopsy was performed because of atrophic kidneys. His creatinine level progressed, and he had to start hemodialysis.

Two months after starting dialysis, the patient was considered for transplant. His blood pressure levels were about 130/80 mm Hg, and he was on amlodipine medication at 10 mg/day. The patient was assessed for other diseases, but no other diseases were found. He was negative for both class I and class II panel reactive antibody. His donor candidate was his 28-year-old son, and tissue typing revealed one haplotype match. CDC and flow cytometric crossmatch tests were negative. Further investigations revealed no opportunistic infections.

The transplant procedure was uneventful; there were no urinary or vascular surgical problems. ATG Fresenius-S (Neovii Biotech, Rapperswil, Switzerland) with 6 mg/kg cumulative dosage was administered for induction. The maintenance therapy consisted of prednisolone, mycophenolate mofetil, and tacrolimus. Valganciclovir and sulfamethoxazole/trimethoprim prophylaxis were started on postoperative day 1. The antiretroviral therapy was never interrupted. The patient was given tacrolimus at 0.1 mg/kg daily. On day 2, the tacrolimus trough level was 3.2 ng/mL, but the level increased to over 30 ng/mL, so tacrolimus was discontinued immediately. On day 3 posttransplant, the creatinine level was below 1 mg/dL and appeared to be stabilized. The potassium level remained steady at between 4.9 and 5.6 mEq/dL. The patient had hypertension, and a beta blocker was added. The patient also displayed tremor, but he was able to drink and write without assistance.

Although tacrolimus was stopped, trough levels continued to be over 30 ng/mL for about 2 weeks. Samples were studied in 2 different laboratories to rule out any errors, which used the high-performance liquid chromatography-enzyme-linked immunosorbent assay method to investigate tacrolimus trough levels. The 2 laboratories revealed similar levels of tacrolimus (over 30 ng/mL).

The patient had neither proteinuria nor hematuria, and the creatinine level was below 1 mg/dL. A biopsy was performed to rule out calcineurin inhibitor (CNI) toxicity or thrombotic microangiopathy (TMA) due to high tacrolimus level. There were no specific signs of any disease on biopsy. No microcalcification or TMA was found.

On day 12 posttransplant, the patient was discharged and followed at an outpatient clinic. The maintenance immunosuppression consisted of 1000 mg/day mycophenolate mofetil and 20 mg/day methylprednisolone until day 29. At that time, the tacrolimus level was 9.1 ng/mL, and tacrolimus at 0.5 mg/week was added. Tacrolimus levels stayed between 9 and 12 ng/mL. The patient’s HIV RNA was negative. Antiretroviral therapy was continued at the same dose levels. At month 5 posttransplant, the patient’s creatinine level was 1.01 mg/dL. Thus far, the patient has had no complications or rejection episodes.

**Discussion**

Here, we describe the first living-donor kidney transplant in an HIV-positive patient in our country. Kidney transplant is the most favorable replacement therapy for HIV-positive patients. The optimal therapy for both induction and maintenance immunosuppression has not yet been determined for this population. It is important to find the optimal dose to avoid rejection, infection, malignancy, and toxicity. This has been shown to be difficult while the patient is using other interacting antiretroviral agents.7

Increased incidence of DGF, which is defined as the need for dialysis after transplant, has been reported for HIV-positive patients, even with living donor transplants. Stock and associates reported DGF in 15% of living donor recipients and in 46% of deceased donor recipients.8,9 It is not well known whether HIV infection itself increases DGF incidence. Intraoperative surgical urinary or vascular com-
plications, hypotension, bleeding, and ischemia time are risk factors for HIV-positive patients, similar to the general population. In our patient, there were no intraoperative complications, and the donor was relatively young, so our patient had an immediate graft function and creatinine level regressed quickly.

A high incidence of acute rejection during the first year was previously reported in HIV-positive patients. Delayed graft function and inadequate immunosuppression are risk factors for acute rejection. Cyclosporine-based maintenance regimens were more pronounced with acute rejection versus that shown with tacrolimus. About 1 decade ago, low immunosuppression was used for patients who had HIV disease progression risk; however, today, with the highly active antiretroviral therapies, optimal immunosuppression and induction can be utilized.

Kidney allograft biopsy was performed with a suspicion of CNI toxicity or TMA as a result of the high tacrolimus level. However, no diagnostic findings for CNI toxicity or TMA were shown. There were also no findings for any acute rejections.

Although drug interactions are well defined, we had to struggle with finding the correct dosing for a long period. Tacrolimus trough level was 3.2 ng/mL at day 2 but was immediately over 30 ng/mL the next day. During patient follow-up, tacrolimus level increased and stayed over 30 ng/mL for 2 weeks. Protease inhibitors are strong inhibitors of CYP3A4. The doses of CNIs were recommended to be reduced up to 80% when used with protease inhibitors. Dramatic dose reductions of immunosuppressent drugs are often required to maintain target trough concentrations, such that some patients require only 1% to 2% of a typical dose of the immunosuppressive drug. Ritonavir-tacrolimus interactions are well-defined. With the inhibition of the CYP3A enzyme system, tacrolimus was recommended at 0.5 to 1 mg weekly to achieve a trough level of 8 to 12 ng/mL.

In conclusion, transplant is the best replacement therapy in HIV-positive end-stage kidney disease patients with controlled AIDS management under highly active antiretroviral therapy.

References