

Neutropenia Related to Valacyclovir and Valganciclovir in 2 Renal Transplant Patients and Treatment With Granulocyte Colony Stimulating Factor: A Case Report

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Abstract

Objectives: Posttransplant leukopenia is frequently observed in renal transplant. Granulocyte colony-stimulating factor controls the production of functional neutrophils and their release into peripheral blood. Granulocyte colony-stimulating factor has been widely and frequently used for many conditions and disorders in the field of hematology and oncology.

Materials and Methods: We present the cases of valacyclovir-related and valganciclovir-related neutropenia in 2 renal transplant recipients.

Results: Both cases had renal transplants from live donors. The first one was an 18-year-old man. Laboratory investigations revealed his leukocyte count as $1.7 \times 10^9/L$. The patient was using mycophenolate mofetil, cyclosporine, and valganciclovir. Mycophenolate mofetil was stopped because he had neutropenia, and later, valganciclovir was also stopped because the neutropenia persisted. Because the neutropenia did not recover after we discontinued valganciclovir, the patient was administered granulocyte colony-stimulating factor. The neutrophil count increased to $2.2 \times 10^9/L$ (leucocyte count to $6.5 \times 10^9/L$) after 24 hours.

The second case was a 37-year-old man and was using mycophenolic acid, tacrolimus, and valacyclovir. Laboratory investigations revealed his leukocyte count to be $1.3 \times 10^9/L$. Mycophenolic acid and valganciclovir were stopped owing to

neutropenia. The patient was administered granulocyte colony-stimulating factor, and the neutrophil count increased to $3.8 \times 10^9/L$ (leucocyte count to $5.8 \times 10^9/L$). The kidney functions did not deteriorate in either patient, and the patients' kidney functions were similar to baseline levels 12 months after surgery.

Conclusions: We conclude that granulocyte colony-stimulating factor can be used safely and effectively in renal transplant patients.

Key words: *Kidney transplantation; Leukopenia; Cytomegalovirus prophylaxis; Filgrastim.*

Leukopenia is frequently observed in the setting of solid organ transplants. Leucopenia after renal transplants may result from several causative factors and is most-often related to antiviral and immunosuppressive agents used for the renal transplant (1). Granulocyte colony-stimulating factor is a glycoprotein that controls production of functional neutrophils and their release into peripheral blood. Granulocyte colony-stimulating factor has been widely and frequently used for many conditions and disorders in the field of hematology and oncology (2). In this paper, we present 2 patients with valacyclovir-related and valganciclovir-related neutropenia.

Case 1

An 18-year-old man had a renal transplant in September 2008 from a live donor. He was admitted to the nephrology clinic complaining of fatigue and loss of appetite 2 months after the transplant. The results of his physical examination were normal. Laboratory investigations revealed that his leukocyte count was $1.7 \times 10^9/L$ (0.15 polymorphonuclear leucocytes, 0.76 lymphocytes, and 0.09 monocytes in

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the peripheral smear), hemoglobin was 108 g/L, the number of thrombocytes was $294 \times 10^9/L$, C-reactive protein was 0.33 mg/L (normal range, 0-0.5 mg/L), glucose was 6.22 mmol/L (112 mg/dL), creatinine was $95.92 \mu\text{mol/L}$ (1.09 mg/dL), sodium was 136 mmol/L, potassium was 4.2 mmol/L, aspartate aminotransferase was 13 IU/L, alanine aminotransferase was 16 IU/L, albumin was 45 g/L, total protein was 69 g/L, and proteinuria was 100 mg/day. *Cytomegalovirus* DNA was negative in the serologic tests. The patient was using 2 g/day of mycophenolate mofetil, 375 mg/day of cyclosporine, and 900 mg/day of valganciclovir. Mycophenolate mofetil was stopped because he had neutropenia; and 2 days later, his valganciclovir was also stopped because his neutropenia persisted. The neutropenia did not recover after his valganciclovir was discontinued (white blood count and neutrophil counts did not increase beyond $1.9 \times 10^9/L$ and $0.1 \times 10^9/L$), and the patient was administered 5 $\mu\text{g/kg}$ granulocyte colony-stimulating factor once daily. The neutrophil count increased to $2.2 \times 10^9/L$ (leukocyte count to $6.5 \times 10^9/L$) after 24 hours. His creatinine was $105.6 \mu\text{mol/L}$ (1.2 mg/dL) and his proteinuria was 120 mg/day 12 months after the transplant.

Case 2

A 37-year-old man had a renal transplant in April 2008 from a live donor. The patient was admitted to our clinic complaining of fatigue and a burning sensation in his stomach 3 months after the transplant. The patient was using 720 mg/day mycophenolic acid, 2 mg/day tacrolimus, and 4.5 g/day valacyclovir. His physical examination was normal. Laboratory investigations revealed that his leukocyte count was $1.3 \times 10^9/L$ (0.1 polymorphonuclear leukocytes, 0.83 lymphocytes, 0.05 monocytes, and 0.02 eosinophils), hemoglobin was 130 g/L, thrombocytes were $151 \times 10^9/L$, blood sedimentation rate was 40 mm/h, C-reactive protein was 0.33 mg/L, glucose was 4.17 mmol/L (75 mg/dL), creatinine was $167.2 \mu\text{mol/L}$ (1.9 mg/dL), sodium was 147 mmol/L, potassium was 4.5 mmol/L, aspartate aminotransferase was 42 IU/L, alanine aminotransferase was 40 IU/L, albumin was 40 g/L, total protein was 64 g/L, and proteinuria was 80 mg/day. *Cytomegalovirus*-DNA was negative in the serologic tests. Mycophenolic acid was stopped owing to neutropenia, and

valacyclovir also was stopped 1 day later owing to persistent neutropenia. The patient was administered 5 $\mu\text{g/kg}$ granulocyte colony-stimulating factor because the neutropenia did not recover (white blood cell and neutrophil counts did not increase beyond $1.4 \times 10^9/L$ and $0.1 \times 10^9/L$). The neutropenia recovered after he had been given the third dose of the granulocyte colony-stimulating factor, and his neutrophil count increased to $3.8 \times 10^9/L$ (leukocyte count to $5.8 \times 10^9/L$). His creatinine level was $183.92 \mu\text{mol/L}$ (2.09 mg/dL), and proteinuria was 110 mg/day 12 months after the transplant.

Discussion

Cytomegalovirus is the most-frequent viral infectious agent after transplant. Valganciclovir and valacyclovir are used for treatment and prophylaxis of the cytomegalovirus infection (3, 4). Valacyclovir and valganciclovir have been reported to cause moderate, hematologic adverse effects (ie, leukopenia, neutropenia, thrombocytopenia, anemia, and pancytopenia) (5, 6). However, a severe bone marrow insufficiency was reported in a patient with recurrent kidney failure after a renal transplant after he was given a standard dosage of valganciclovir (7). Mycophenolate mofetil is an agent that decreases renal transplant rejection rate, and the bone marrow adverse effects increase when mycophenolate mofetil is used together with valacyclovir or valganciclovir (8, 9).

Many drugs are associated with neutropenia. Several pathogenic mechanisms for drug-induced neutropenia are postulated or supported by experimental evidence. These mechanisms include immune-mediated destruction of granulocytes or granulocytic precursors, dose-dependent inhibition of granulopoiesis, and direct, toxic effects on myeloid precursors on the marrow microenvironment (10, 11).

Granulocyte colony-stimulating factor is a 175 amino acid, highly purified, nonglycosylated protein produced by recombinant technology in a laboratory strain of *E. coli* by adding a gene expressing the granulocyte colony-stimulating factor (2). Granulocyte colony-stimulating factor is a hematopoietic growth factor that acts selectively on the cells of the neutrophil lineage. It induces neutrophil production, differentiation, and release from the bone marrow (12, 13). Although kidney functions deteriorated in a pediatric renal transplant

patient after being given granulocyte colony-stimulating factor for neutropenia (14), the neutropenia improved in another pediatric patient without any deterioration in renal functions (15). It has been reported that granulocyte colony-stimulating factor improves neutropenia in patients with neutropenia-related severe infections (16, 17). In our patients, neutropenia was related to the use of valacyclovir and valganciclovir; there was no evidence of an infection, and granulocyte colony-stimulating factor was used to treat persistent neutropenia despite discontinuation of antiviral agents. The neutropenia improved in both patients. Kidney functions did not deteriorate in either patient. Additionally, the patients' kidney functions were similar to the baseline levels 12 months after the transplant.

In conclusion, leukopenia/neutropenia after kidney transplant may be related to several factors. We conclude that granulocyte colony-stimulating factor is an effective treatment for treating neutropenia in renal transplant patients, and it does not precipitate or aggravate allograft rejection.

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