INTRODUCTION

Renal transplantation along with triple immunosuppression remains the gold standard treatment for end-stage renal disease. Renal transplant had gained importance as it prolongs the life of patients with kidney failure by replacing the diseased kidney with a new kidney from the donor. Renal transplant survival has increased mainly due to proper perioperative care as well treatment with antirejection drugs [1]. Triple immunosuppression causes various side effects such as nephrotoxicity, infections, new-onset diabetes after transplant, hypertension, weight gain, dyslipidemia, and neurotoxicities in various cases [2]. However, one of the major concerns among clinicians performing renal transplantation is patients developing hematological disorders usually due to infections or because of immunosuppressive drugs. Hence, we report a case of valganciclovir-induced thrombocytopenia in a postrenal transplant patient in a tertiary care hospital in southern India.

CASE REPORT

Informed consent was obtained from the patient. A 43-year-old post-cadaveric renal transplant on 11.11.2016, for Stage V chronic kidney disease due to adult polycystic kidney disease was put on triple immunosuppression with tacrolimus, mycophenolate mofetil (MMF), woxolone along with valganciclovir, and single strength cotrimoxazole for cytomegalovirus (CMV) prophylaxis. Induction therapy was also given with antithymocyte globulin in this patient. He was admitted with persistent leukopenia and transaminitis on 29.12.2016. On examination, his vitals were stable, no graft tenderness, no tremors, normal oral cavity, and no systemic findings. His lab reports showed normal renal function tests along with leukopenia and elevated transaminases levels. Hence, MMF, valganciclovir, and cotrimoxazole were stopped. CMV infection was suspected and patient was started on IV ganciclovir and IV hydration. In view of febrile neutropenia, he was started on IV teicoplanin and IV cefepime. His blood culture was sterile and PCR was negative for CMV. Hence, at this stage CMV was ruled out and cause of thrombocytopenia was found to be high-dose valganciclovir. Tacrolimus-induced thrombotic microangiopathy was also ruled because patient renal function test was normal. Others concomitant drugs causing thrombocytopenia was also ruled out. Hence, dose of valganciclovir was reduced to 450 mg twice daily and patient was asked to review in 4 days. On 09.01.2016, his platelet counts reverted to normal (Table 1). Thereby, it was proved valganciclovir was the cause for thrombocytopenia as de-challenge was done in our case by reducing the dose.

DISCUSSION

Blood disorders affecting renal transplant patients can be classified common and uncommon serious disorders. The former includes post-transplant erythrocytosis, post-transplant anemia and post-transplant cytopenias, and the latter includes thrombotic microangiopathies, hemophagocytic syndrome, therapy-related acute myeloid leukemia, and myelodysplasia. With a wide range of etiological factors playing a role in the development of blood disorders among renal transplant patient's infections and immunosuppressive treatment plays a major etiological role and remains a dreaded threat in development of life-threatening hematological complications [3]. Triple immunosuppression for prevention of graft versus host disease in renal transplant usually includes a calcineurin inhibitor either tacrolimus or cyclosporine, an antiproliferative agent like MMF or azathioprine and corticosteroids. As infections increase the chance of graft failure, usually prophylaxis is given with valganciclovir and cotrimoxazole [4].

Valganciclovir, an effective prodrug of ganciclovir is given orally and is effective as intravenous ganciclovir in the prophylaxis of CMV infection in solid organ transplant recipients. It helps in reducing the CMV resistance to drugs in transplant patients and it provides more systemic exposure of ganciclovir when compared to intravenous ganciclovir. Hence, valganciclovir is an effective alternative to other anti-CMV agents in solid organ transplant patients [5]. Valganciclovir is an L-valyl ester of ganciclovir and it is an orally acting prodrug. After being taken orally, it gets converted into active ganciclovir by cleavage by Esterases in the intestinal wall and liver. In CMV-infected ganciclovir undergoes phosphorylation to monophosphate form due to CMV-encoded UL97 protein kinase. Then, monophosphate form is converted to diphosphate and triphosphate forms by rapidly acting cellular kinases. Ganciclovir triphosphate inside the CMV-infected cell prevents DNA replication by competing with deoxyguanosine triphosphate which is a substrate for DNA polymerase. It also inhibits viral DNA replication by inhibiting DNA chain elongation [6]. It is known to cause various side effects which
Thrombocytopenia is defined as platelet counts <1.5 lakhs. Thrombocytopenia is a troublesome complication in renal transplant patient occurring usually after the 1st year following transplantation, but sometimes, it can occur even in the first 3 months. The major causes of thrombocytopenia in transplant setting include infections with CMV/EBV virus, folate/vitamin B12 deficiency, microangiopathies, bone marrow suppression with immunosuppressive agents, acute rejection episodes, and antiplatelet antibody therapy. Leukopenia and anemia usually overlaps thrombocytopenia in renal transplant settings. Drugs associated with thrombocytopenia includes calcineurin inhibitors such as tacrolimus causing thrombotic microangiopathy resulting in graft rejection, valganciclovir; ganciclovir; linezolid; antithymocyte globulin, and heparin [3]. In our case, valganciclovir, MMF and cotrimoxazole were stopped when patient first came with complaints of leukopenia and later ganciclovir intravenously was given for 1 week in view of prophylaxis for CMV/EBV/parvovirus infections along with antibiotics. Later as leukopenia reverted to normal with three doses of GM-CSF patient and bone marrow CMV/EBV/parvovirus was negative, patient was restarted with MMF and ganciclovir was changed to high-dose oral valganciclovir 900 mg twice daily awaiting CMV PCR reports to rule out any possibility of CMV infection. 2 days’ patient had drop in platelet counts and valganciclovir given in high dose was suspected to be the causative agent. Tacrolimus induced HUS was ruled out as renal function test was normal and other concomitant drugs causing thrombocytopenia were ruled out. CMV PCR report was negative ruling CMV as the cause of thrombocytopenia. Hence, the dose of valganciclovir was reduced to 450 mg twice daily and platelet counts came back to normal in 4 days.

Mechanism suspected here is direct bone marrow toxicity caused by high-dose valganciclovir and our case is similar to a case series in literature where four cases of bone marrow toxicity causing thrombocytopenia was reported with high-dose valganciclovir using 900 mg/day in post-transplant patients despite persistent renal failure [7]. Furthermore, literature evidence says incidence of thrombocytopenia with low dose valganciclovir as prophylaxis for CMV infections in post-transplant patients was 24% and almost 20% of patients discontinued valganciclovir due to thrombocytopenia [8].

Causality assessment was done using Naranjo’s scale [9] for establishing a causal relationship and a probable causal relationship was ascribed. Severity scale was done using Hartwig’s scale [10] and adverse reaction was found to be of mild severity, preventability assessment was done using Thornton’s scale [11] and adverse reaction was found to be not preventable (Table 2).

**CONCLUSION**

Valganciclovir being a very effective drug in the treatment as well prophylaxis of CMV infections in renal transplant recipients, possibility of thrombocytopenia when used in high dose should be kept in mind as evidence says even low-dose prophylaxis for long period’s causes thrombocytopenia. Furthermore, the renal function of the patient should be taken into consideration as valganciclovir is eliminated via the kidneys and poor renal function can have a very bad consequence on the patient resulting in grave toxicities. Hence, further prospective study can be done comparing the efficacy of high-dose valganciclovir versus low-dose valganciclovir in postrenal transplant patients and the effect of renal failure on the outcome of treatment.

**REFERENCES**

1. Dharmik DD, Modi KP, Patel AK, Chaudhary V. New onset of diabetes mellitus in Indian renal transplant recipient-a retrospective study. Int J Pharm Pharm Sci 2015;7(11):228-32.
2. Patel S, Patel BG, Gohel K. Incidences of-and risk factor for new onset diabetes after transplantation in live donor kidney transplantation: A prospective single centre study. Int J Pharm Pharm Sci 2016;8(2):230-3.
3. Yang Y, Yu B, Chen Y. Blood disorders typically associated with renal transplantation. Front Cell Dev Biol 2015;3:18.
4. Richardson AJ, Higgins RM, Ratcliffe PJ, Ting A, Marie J, Morris PJ. Triple therapy immunosuppression in cadaveric renal transplantation. Transpl Int 1990;3(1):26-31.
5. Cvetkovic RS, Wellington K. Valganciclovir: A review of its use in the management of CMV infection and disease in immunocompromised patients. Drugs 2005;65(6):595-78.
6. McGavin JK, Goa KL. Ganciclovir effect of renal failure on the outcome of treatment. Ann Pharmacother 2004;38(10):1323-30.
7. Ar MC, Ozbalak M, Tuzuner N, Bekoz H, Ozer O, Ugurlu K, et al. Severe bone marrow failure due to valganciclovir overdose after renal transplantation from cadaveric donors: Four consecutive cases. Transplant Proc 2009;41(5):1648-53.
8. Gabardi S, Magee CC, Baroletti SA, Powelson JA, Cina JL, Chandraker AK. Efficacy and safety of low-dose valganciclovir for prevention of cytomegalovirus disease in renal transplant recipients: A single-center, retrospective analysis. Pharmacotherapy 2004;24(10):1323-30.
9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-45.
10. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49(9):2229-32.
11. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27(6):538.