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Calcineurin Inhibitors and Neutropenia: Is Cyclosporine Superior to Tacrolimus?

Authors' Contribution:
Study Design A
Data Collection B
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Data Interpretation D
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Patient: Female, 51
Final Diagnosis: Tacrolimus induced severe neutropenia
Symptoms: Abnormal lab values
Medication: —
Clinical Procedure: —
Specialty: Transplantology

Objective: Adverse events of drug therapy

Background: Renal Transplant recipients are at risk for developing neutropenia from a multitude of causes. The cause is often multifactorial, and reversal of the most common causes/insults is sometimes insufficient.

Case Report: We present the case of a renal transplant recipient who developed a prolonged course of post-transplant (PTx) neutropenia that resolved after switching from tacrolimus (tac) to cyclosporine (CsA).

Conclusions: Transplant recipients with persistent neutropenia, sometimes despite discontinuation of potential myelosuppressive agents like mycophenolic acid (MPA), valganciclovir, and sulfamethoxazole-trimethoprim (SMZ-TMP), and with introduction of granulocyte colony-stimulating factor (G-CSF), and ruling out alternative diagnoses, may benefit from changing from tac to CsA.

MeSH Keywords: Cyclosporine • Kidney Transplantation • Neutropenia • Tacrolimus

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Background

Renal transplant recipients (RTRs) are at risk of developing cytopenias.

The incidence of leucopenia in RTRs ranges from 10% to 55.5% and neutropenia ranges from 4.9% to 37.5% [1,2].

Many of the medications used for immunosuppression and infection prophylaxis can contribute to neutropenia. The major offenders include MPA and valganciclovir [3]. Other agents that can cause neutropenia are antithymocyte globulin (ATG), tac, sirolimus, everolimus, and SMZ-TMP. Neutropenia is a significant risk factor for infectious complications and can contribute to significant morbidity. This includes more bacterial infection, especially urinary tract infections and intra-abdominal infections. The severity of neutropenia is associated with the severity of infections [1].

Currently, there is no standard protocol for managing neutropenia in RTRs. Strategies utilized by transplant centers for its management includes reduction of dose or discontinuation of MPA, valganciclovir, or SMZ-TMP. G-CSF are often utilized in the setting of neutropenia to stimulate the production, maturation, and activation of neutrophils [4].

We present a case of an RTR in our institution with persistent neutropenia while on tac. The patient underwent several medication regimen modifications and received multiple treatments of G-CSF. The only change resulting in resolution of neutropenia was switching from tac to CsA.

Case Report

A 51-year-old African American woman with history of end-stage renal disease secondary to type 2 diabetes mellitus and hypertension received a deceased donor pediatric en bloc kidney transplant at our institution in December 2015. She was on peritoneal dialysis for 3 years prior to transplantation. She received a standard-criteria kidney and had immediate graft function.

For induction, the patient received 3 doses of ATG 100 mg (1.5 mg/kg) intravenously (IV) on post-operative days (POD) 0, 1, and 2. She also received methylprednisolone 250 mg IV on POD 0, followed by a steroid taper. Her maintenance immunosuppressive regimen consisted of mycophenolate mofetil (MMF) 1 g by mouth twice daily, prednisone taper, and tac with a target trough level of 10–12 mg/dL. The prophylaxis regimen consisted of SMZ-TMP 800/160 mg daily and valganciclovir 450 mg every 48-h prophylactic dose (adjusted for renal function) for *Pneumocystis jiroveci* pneumonia and Cytomegalovirus infections, respectively.

She was discharged home on POD 4 with a therapeutic trough on tac 1 mg twice daily, MMF 1000 mg twice daily, and prednisone, which would continue to be tapered to 5 mg daily. On the day of discharge, her serum creatinine was 2.2 mg/dL, absolute neutrophil count (ANC) was 3400/mm³, and the other lab results were within normal range.

Our patient's renal function continued to improve after discharge and tac was adjusted as necessary to target the goal trough of 8–10 mg/dL. On POD 46, during routine lab tests, she was noted for the first time to have neutropenia, with an ANC of 5700/mm³. The tac trough was 7.7ng/mL and the dose was increased from 13 mg to 17 mg twice daily. The MMF dose was reduced to 500 mg twice daily and the maintenance dose of prednisone was increased to 15 mg daily. SMZ-TMP was also discontinued at this time because of hyperkalemia, and was switched to inhaled pentamidine and ciprofloxacin for prophylaxis for PJP and UTI, respectively. She received G-CSF 300 mcg subcutaneous injection daily for 2 days. ANC improved to 1300/mm³. One week later, the ANC dropped further to 800/mm³, for which she received again G-CSF 300 mcg once, and valganciclovir was discontinued. Twelve weeks after the transplant, the patient's ANC improved to 1300/mm³ and her SMZ-TMP prophylaxis was subsequently resumed at this time. Valganciclovir 450 mg daily was resumed at week 14 after transplant because the neutropenia had resolved.

At 15 weeks after transplant, the patient was found to be severely neutropenic, with an ANC of 220/mm³. SMZ-TMP was switched to ciprofloxacin and inhaled pentamidine, valganciclovir was held, and the patient received G-CSF 300 mcg subcutaneously daily for 3 doses, followed by maintenance doses of G-CSF 300 mcg biweekly. MMF was discontinued completely at 19 weeks after transplant due to lack of resolution of neutropenia. Her goal tac trough level was reduced to 6–7 ng/dL due to tremors. At week 23, the patient reached her nadir ANC of 50/mm³ and was referred to Hematology. An infectious diseases workup, including CMV, BK virus, Epstein-Barr Virus, and parvovirus, came back negative.

The Hematology Department attributed her neutropenia to medication-induced myelosuppression. Thyroid-stimulating hormone levels, vitamin B12, and folate levels were checked and were in normal range. At 34 weeks after the transplant, the patient underwent a bone marrow biopsy, which showed hypocellular bone marrow for age with relative erythroid hyperplasia and myeloid suppression, but no overt evidence of dysplasia or increase in blasts. G-CSF was increased to 480 mcg daily for 3 doses, then weekly starting at week 35 PTx. At week 49, the Hematology Department increased G-CSF to 480 mcg twice a week.

Despite a multitude of interventions with no improvement in neutrophil count, on week 55, tac was switched to CsA 125 mg

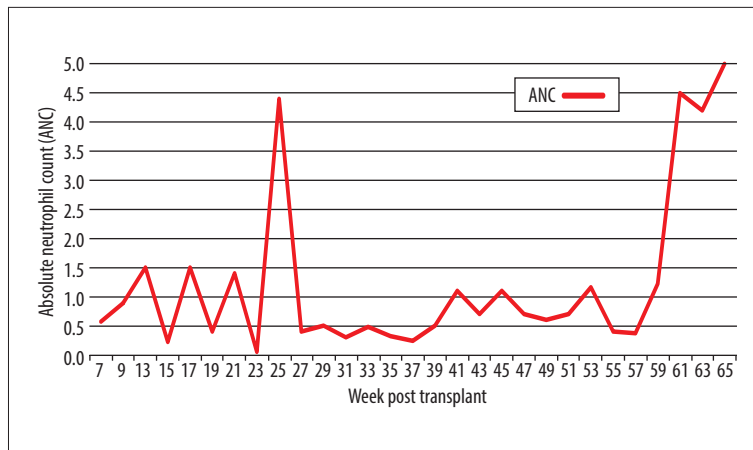


Figure 1. Absolute neutrophil count ranges from week 7 to week 65 after kidney transplant. X axis represents number of weeks after transplant; y axis represents absolute neutrophil counts (in 1000 per mm³).

Table 1. Review: Case reports in solid organ transplants (SOT) – reversal of neutropenia on switching tacrolimus to cyclosporine.

Case report reference	SOT	Patient age sex	Induction	Onset of neutropenia PTx	Time taken for resolution of neutropenia after FK-506 →CsA	Maintenance regimen
[6]	Liver	17-year-old F	Unclear	4 mo +Pancytopenia	1 month	Pred, CsA
[2]	Kidney 3 cases	63-year-old M	None	76 days	1 month	Pred, CsA, eventually MMF
		58-year-old F	None	79 days	~60 days	Pred, CsA, eventually MMF
		56-year-old M	None	85 days	unclear	Pred, CsA, eventually MMF
[7]	Heart	3-year-old M	Unclear	7 mo	1 month	Pred, CsA, eventually MMF
[8]	Kidney	42-year-old F	Thymo	50 days	2 days	Pred, CsA, eventually MMF

PTx – post transplant; FK 506 – tacrolimus; CsA – cyclosporine; mo – month; Pred – prednisone; MMF – mycophenolate mofetil; Thymo – thymoglobulin.

twice a day titrated to a goal trough of 150–200 ng/mL. She also received 4 doses of G-CSF 480 mcg weekly after the switch of calcineurin inhibitor therapy. G-CSF was subsequently discontinued because the neutrophil count started trending upward (Figure 1). One month after switching from tac to CsA, her ANC consistently remained above 1000/mm³. Ten weeks after discontinuation of tac, enteric-coated mycophenolate (EC-MPA) was started at 180 mg twice daily. Her ANC continued to remain steady and EC-MPA was increased to 360 mg twice daily 16 weeks after discontinuation of tac.

The patient is now at about 3.5 years after transplant, with stable renal function and on a maintenance immunosuppression regimen of cyclosporine, EC-MPA, and prednisone, with complete resolution of neutropenia.

Discussion

Immunosuppression and other medications used in RTR are associated with hematological adverse effects. Tac has some well-known hematological adverse effects, including anemia due to bone marrow suppression or hemolysis, leukopenia, and thrombocytopenia [5]. Sporadic cases of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, red cell aplasia, and generalized bone marrow suppression have also been noted. However, myelotoxicity resulting in neutropenia is an uncommon adverse effect of tac [5].

Neutropenia is known to result from 4 basic mechanisms: decreased neutrophil production, inefficient granulopoiesis, shift of circulating neutrophils to the vascular endothelium, and tissue pools and enhanced peripheral destruction [1].

The etiology of neutropenia in RTRs is often multifactorial, with contributory effects from bone marrow toxicity arising from medications, systemic infection, or post-transplant lymphoproliferative disease.

Neutropenia is more commonly associated with MPA, azathioprine, and valganciclovir.

There have been some case reports of neutropenia in solid-organ transplant recipients when tac has been used, and its resolution when switched to CsA (Table 1).

While the precise mechanism of myelotoxicity from FK 506 remains unclear, there have been some proposed mechanisms [2]:

1. Direct inhibition of myeloid cells via maturation arrest;
2. Effect on mononuclear accessory cells;
3. Interaction between various PTx medications (tac and MMF): Tac increases MPA bioavailability – the former does not inhibit enterohepatic recirculation of MPA, thus a second peak of MPA level is more pronounced in patients receiving both these drugs. Kidney recipients receiving MPA in combination with CsA have lower MPA plasma concentrations compared with recipients receiving MPA in combination with FK-506 [9] [10]. Patients receiving a combination of MPA and valganciclovir are also at higher risk of neutropenia [11];
4. Formation of autoantibodies against myeloid precursors or mature neutrophils.

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As in other case studies, while G-CSF administration decreased the duration of neutropenia, definite resolution of neutropenia occurred only when tac was substituted with CsA. Tac is superior to CsA [12]. The risk of rejection needs to be weighed against the benefits [13], and close monitoring of kidney functions is required after changes in post-transplant medication regimen.

Conclusions

Neutropenia is a common, multifactorial process in RTR. A systematic approach is required in ruling out infections, malignancy, and medication-induced adverse effects. Our case demonstrates the importance of accurately completing medication reconciliation, knowing the sequence and effects of changes in regimen, and being aware of the adverse effect profile of commonly used anti-rejection and prophylactic medications. After completing a stepwise approach to rule out all other potential causes of neutropenia, due diligence to medication reconciliation is needed. A change from tac to CsA in patients with refractory neutropenia is sometimes required.

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