Indian J Hematol Blood Transfus (Oct-Dec 2019) 35(4):711–713
https://doi.org/10.1007/s12288-019-01113-w

SHORT COMMUNICATION

Tacrolimus Induced Diabetic Ketoacidosis Following Hematopoietic Stem Cell Transplantation

Sanjeev Kumar Sharma[1] · Divya Doval[1] · Vipin Khandelwal[1] · Meet Kumar[1] · Dharma Choudhary[1]

Received: 22 November 2018 / Accepted: 7 March 2019 / Published online: 15 March 2019

Abstract Risk of diabetes mellitus increases after solid organ and hematopoietic stem cell transplantation. Diabetic ketoacidosis has been reported after solid organ transplantation in patients receiving tacrolimus but has rarely been reported after stem cell transplantation. The major risk factors for diabetic ketoacidosis are immunosuppressive drugs used after transplantation. We report here three cases of allogenic stem cell transplant who developed diabetic ketoacidosis while on treatment with tacrolimus. The drug was stopped in all the cases and patients were treated with insulin therapy resulting in complete recovery from diabetic ketoacidosis.

Keywords Tacrolimus · Stem cell transplant · Diabetic ketoacidosis

Introduction

Tacrolimus is the commonly used immunosuppressive agent in solid organ transplant recipients and has been reported to cause diabetic ketoacidosis (DKA). New-onset diabetes mellitus after solid-organ transplant has been reported in 2% to 53% of patients receiving tacrolimus. There is scarcity of data on tacrolimus induced DKA in hematopoietic stem cell transplant patient (HSCT). With the increasing number of patients undergoing HSCT and with increasing use of tacrolimus in HSCT recipients, particularly in patients receiving haploidentical transplant, the risk of diabetes and DKA are likely to increase.

Case Studies

The study included retrospective analysis of all patients who underwent allogenic HSCT at the transplant centre. The study was approved by institutional review board and informed consent was taken from the patients. Out of 650 allogenic HSCT done between September 2010 to August 2018, 140 had received tacrolimus. Patients were on regular follow-up in the outpatient clinic and were undergoing routine evaluation with complete hemogram and liver and kidney function tests. Three patients (age 5–17 years) who underwent allogenic HSCT developed DKA after administration of tacrolimus (2.14%).

Materials and Methods

Two thalassemia major patients had received matched sibling allogenic HSCT and one aplastic anemia patient had undergone haploidentical HSCT. The conditioning regimens were as per disease and the protocol. The patients were on tacrolimus at the time when they presented to the hospital with vomiting and dehydration. All patients had high blood sugars and low arterial blood pH (metabolic acidosis) and urine was positive for ketones (Table 1). The other drugs patients were taking at that time were acyclovir, cotrimoxazole, ursodeoxycholic acid and folic acid.

✉ Sanjeev Kumar Sharma
sksanjeev13@yahoo.com

[1] Department of Hemato-Oncology and Bone Marrow Transplantation, BLK Superspeciality Hospital, New Delhi 110005, India

Table 1 Characteristic features of HSCT recipients who developed tacrolimus induced diabetic ketoacidosis

S. no.	Age/sex	Diagnosis	Condit-ioning	Neutrophil engraftment	GVHD prophylaxis	Reason for giving Tac	Days post SCT when DKA developed	Blood sugar (mg/dl)/pH/urine ketones	Tac levels[a]	Outcome	Comments
1	17y/M	TM	Bu/Cy/ATG	+ 17	CsA and Mtx	On day + 60, patient had liver GVHD, treated with steroids and CsA, after initial recovery bilirubin again started increasing so Tac substituted for CsA	+ 135	521/7.24/2+	5.0	Good	Tac changed to CsA[b]
2	15y/M	SAA	Flu/Cy/TBI	+ 14	PT Cy, Tac/MMF	As per protocol for haploidentical SCT	+ 112	484/7.18/3+	5.5	Good	Tac changed to CsA
3	5y/M	TM	Bu/Cy/ATG	+ 17	CsA and Mtx	Developed PRES on day + 30, CsA changed to Tac	+ 175	566/7.21/2+	14.0	Good	Tac changed to CsA[c]

Tac Tacrolimus, *CsA* cyclosporine, *PRES* Posterior reversible encephalopathy syndrome, *Bu* Busulfan, *Cy* Cyclophosphamide, *ATG* Anti thymocyte globulin, *Flu* Fludarabine, *TBI* Total body irradiation, *Mtx* Methotrexate, *MMF* Mycophenolic acid, *TM* Thalassemia major, *SAA* Severe aplastic anemia

[a]Trough Tac levels at presentation (ng/ml), [b]In case 1, CsA was restarted as his GVHD had recovered and Tac could not be given due to DKA; [c]In case 3, hypertension and CsA were supposed to cause PRES so CsA was changed to Tac but as patient developed DKA, CsA was reconsidered alongwith optimal control of hypertension and patient did not develop recurrent seizures later

Results

All three patients were found to have DKA at the time of presentation and the tacrolimus levels were within range (5–15 ng/ml) at that time. They were treated with intravenous saline along with insulin infusion and supportive care with which they recovered completely. The tacrolimus was stopped and the patients were started on cyclosporine. None of the patients had further episode of DKA on median followup of 6 months.

Discussion

Tacrolimus, a reversible calcineurin inhibitor, is one of the most commonly used immunosuppressive drugs for prevention or treatment of GVHD post HSCT [1, 2]. Tacrolimus has been reported to have superior immunosuppressive efficacy when compared with the cyclosporine A microemulsion [3]. This drug has diabetogenic potential and can cause DKA in renal transplant patients. The overall incidence of new-onset diabetes in renal transplant recipients receiving tacrolimus is 10% to 20% whereas in heart transplant recipients it is 19.6% [4, 5]. After HSCT, up to 30% of patients may have diabetes [6]. Although some of these cases resolve, the rate of diabetes and metabolic syndrome remains elevated in comparison with those in the nontransplant patient population during follow-up [7]. Tacrolimus induced DKA has rarely been reported post HSCT [8].

Tacrolimus has been found to induce mRNA transcription defect by binding of FK506 binding protein-12, leading to inhibition of calcineurin in β cells causing decreased insulin secretion [9]. Moreover, this defect is dependent on duration of exposure to tacrolimus. Both the insulin sensitivity and insulin secretion are decreased after tacrolimus [10]. The pathophysiology of diabetes after HSCT might differ to some extent from that in solid organ transplant because of use of conditioning regimens in the former and the need of lifelong immunosuppression in the latter. Tacrolimus is commonly used along with steroids, and this further increases the potential for developing diabetes [11]. One of our patients was on both steroids and tacrolimus whereas two patients were on tacrolimus only at the time when they developed DKA. If diabetes remains poorly controlled, a switch from tacrolimus to cyclosporine or substitution of an alternative immunosuppressive drug (e.g. mycophenolic acid) might be helpful because reducing the

dose of tacrolimus has not been found to be effective [12, 13]. We changed tacrolimus to cyclosporine in all of the patients and none of them developed DKA on follow-up. According to Naranjo adverse drug reactions probability scale [14], there was possibly tacrolimus induced DKA in these patients.

Conclusion

Tacrolimus is a known risk factor for the development for DKA in post transplant patients. It has been commonly reported with solid organs transplantation. The present cases highlight that DKA can possibly develop in stem cell transplant recipient patients on tacrolimus and that DKA can manifest even at its therapeutic plasma levels. The patients on tacrolimus should be monitored regularly for blood sugar levels and treatment involves substitution of tacrolimus with other immunosuppressants.

Acknowledgements We are thankful to Ms Bharti for collecting the data.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Fortune K, Couriel D (2009) Tacrolimus in hematopoietic stem cell transplantation. Expert Opin Drug Metab Toxicol 5(7):835–841
2. Koehler MT, Howrie D, Mirro J, Neudorf S et al (1995) FK506 (tacrolimus) in the treatment of steroid-resistant acute graft-versus-host disease in children undergoing bone marrow transplantation. Bone Marrow Transplant 15(6):895–899
3. Kramer BK, Montagnino G, Castillo D et al (2005) Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results. Nephrol Dial Transpl 20:968–973
4. Salvadori M, Bertoni E, Rosati A, Zanazzi M (2003) Post-transplant diabetes mellitus. J Nephrol 16(5):626–634
5. Greenspan LC, Gitelman SE, Leung MA et al (2002) Increased incidence in post-transplant diabetes mellitus in children: a case control analysis. Pediatr Nephrol 17:1–5
6. Traggiai C, Stanhope R, Nussey S, Leiper AD (2002) Diabetes mellitus after bone marrow transplantation during childhood. Med Pediatr Oncol 40:128–129
7. Griffith ML, Jagasia M, Jagasia SM (2010) Diabetes mellitus after hematopoietic stem cell transplantation. Endocr Pract 16(4):699–706
8. Solmaz S, Gökgöz Z, Gereklioğlu C et al (2017) Tacrolimus-induced diabetic ketoacidosis after allogeneic bone marrow transplant. Exp Clin Transpl 15(6):702–703
9. Ricordi C, Zeng Y, Alezandro R et al (1991) In vivo effect of FK506 on human pancreatic islets. Transplantation 52:519–522
10. Duijnhoven EM, Boots JM, Christiaans MH et al (2001) Influence of tacrolimus on glucose metabolism before and after renal transplantation: a prospective study. JASN 12:583–588
11. Jindal RM, Sidner RA, Milgrom ML (1997) Post-transplant diabetes mellitus. The role of immunosuppression. Drug Saf 16(4):242–257
12. Yoshida EM, Buczkowski AK, Sirrs SM, Elliott TG et al (2000) Post-transplant diabetic ketoacidosis—a possible consequence of immunosuppression with calcineurin inhibiting agents: a case series. Transpl Int 13:69–72
13. Montori VM, Basu A, Erwin PJ et al (2002) Posttransplantation diabetes: a systematic review of the literature. Diabetes Care 25(3):583–592
14. Naranjo CA, Busto U, Sellers EM et al (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239–245