REVIEW ARTICLE

Tacrolimus-associated Pruritus: A Case Report and Review

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Abstract

The use of immunosuppressants following solid organ transplantation has become a general procedure nowadays. Various immunosuppressants have been used—among them tacrolimus, is a calcineurin inhibitor (CNI) and macrolide antibiotic has been chosen widely. But significant complaints associated with tacrolimus have been reported, for example, severe pruritus. As a result, physicians are required to substitute this one without compromising the intended therapeutic effect, minimizing adverse drug reactions. Everolimus becomes the best alternative, which is also a mammalian target of rapamycin (mTOR) inhibitor with a comparatively wide therapeutic index as compared to tacrolimus.

This present reporting is about the tacrolimus-associated pruritus which was severe and how the patient compliance has been ensured keeping in mind the other comorbidities.

Keywords: Everolimus, Pruritus, Solid organ transplantation, Tacrolimus.

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Introduction and Background

Solid organ transplantation (SOT) has transformed the survival and quality of life of patients with end-organ dysfunction. It includes a variety of solid organs—liver, kidney, pancreas, heart, and lung.[1] The patients with other comorbidities have no options for survival. Vast experiences, as well as scientifically signified experimental models, can provide the footing of the knowledge—how to deal with the critical immunologic concepts for transplantation, including the basis for allograft rejection and the development of immunosuppressive pathways.[2]

Tacrolimus is a calcineurin inhibitor (CNI) and macrolide antibiotic that is frequently used as an immunosuppressant following solid organ transplantation. The therapeutic window is narrow.[3,4] Tacrolimus inhibits the upstream signal of IL-2-mediated cell proliferation, and mTOR inhibitor blocks it downstream. CNIs, although a mainstay of immunosuppression after liver transplantation, is associated with long-term complications, such as nephrotoxicity and increased risk for hepatocellular carcinoma recurrence,[5–7] which results in different approaches to minimize chronic CNI exposure, for example, through the use of mammalian target of rapamycin (mTOR) inhibitor class of immunosuppressant. Everolimus is the only mTOR inhibitor approved worldwide for use in liver transplantation.[8]

Case Description

A 46-year-old male diabetic (type-2) patient underwent a liver transplant in the last week of January 2020 at a private hospital in New Delhi, India. The patient was hypertensive. The patient was receiving the following drugs as per the doses mentioned below:

- Basal bolus insulin (long-acting glargine insulin and rapid-acting insulin aspart),
- Tacrolimus 3 mg BD,
- Prednisolone 10 mg BD,
- Mycophenolate mofetil 250 mg OD,
- Amlodipine 10 mg,
- Ursodeoxycholic acid 300 mg BD.

Presently the patient reported that he had complaints of itching since March 2020. After consultation with a dermatologist, he was given conservative management of itchings like an anti-allergic tablet and emollient application—but this did not provide any relief to the patient. Besides, the blood glucose level was also fluctuating, and reported several instances of post-prandial hyperglycemia (approximately 350–400 mg/dL) with evening and night-time hypoglycemic episodes (40–70 mg/dL). The complaint of severe generalized itching all over the body, with localized skin swelling around the insulin administration site was reported in early June 2020.

Diagnosis and Outcome

The patient consultation with the clinical pharmacologist had been done via telemedicine due to the lockdown situation. The initial investigation pointing towards a dispensing error related to insulin dose and administration time. The patient was receiving glargine insulin three times a day instead of rapid-acting aspart insulin. The same has been rectified accordingly. But the complaint of itching persisted. Further investigation suggested that there was a possible drug interaction and the drug tacrolimus was found to be the causative agent. The patient was asked to check his renal function, liver function, and blood trough level of tacrolimus. It was evident from the reports that the blood level of tacrolimus was towards the higher range (14 mg/dL) with normal liver and renal function tests which indicates the correct assumption of the clinical pharmacologist. To resolve this

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problem, the suggestion of the clinical pharmacologist was to switch tacrolimus to everolimus, and subsequently, the patient had been also advised to consult with the liver transplantation physician.

Discussion and Conclusion

The problems associated with this case were of two types. One was the dispensing errors related to both long and rapid-acting insulins, which was promptly solved. The other problem of severe generalized itching was found to be solved with the discontinuation of tacrolimus and switching to everolimus which was also agreed by the liver transplanting doctor. The itching subsided slowly over a period of two weeks. The blood glucose level was well maintained (FPG (fasting plasma glucose) 112 mg/dL and PPPG (postprandial plasma glucose) 146 mg/dL, respectively).

The literature review also revealed that everolimus is structurally similar to tacrolimus. But it has a different mechanism of immunosuppression than tacrolimus. It exerts its antiproliferative and immunosuppressive activities by inhibiting the IL-2 receptor-mediated signal transduction pathway with no effect on calcineurin activity.[8] Clinically, mTOR inhibitors (used to treat dermatologic diseases) have been used in antirejection regimen in solid organ transplant as well as in anticancer therapy. It could potentially have versatile effects toward putative psoriatic pathologic pathways. For example, the mTOR inhibitor can reduce keratinocyte proliferation and neutrophilic infiltration in a dose-dependent manner.[7]

Pruritus and rash are already reported and well-known adverse reactions of tacrolimus. The US and European randomized clinical trial data also reveal that 36% and 15% of patients with liver transplants have been suffering from pruritus, respectively whereas for rashes it was reported as 24 and 10%, respectively.

Tacrolimus as a potentially neurotoxic drug and substituting it with a different immunosuppressant can prevent permanent damage and decrease the risk of severe adverse drug reactions for comorbid patients. Therefore using everolimus instead of tacrolimus can lead to a reduction of dose and finally producing less adverse reactions while achieving better therapeutic effects.

References

1. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21st century. Ann Transl Med 2018;6(20):409. DOI: 10.21037/atm.2018.09.68.
2. Rodrıguez-Peralvarez M, De la Mata M, Burroughs AK. Liver transplantation: immunosuppression and oncology. Curr Opin Organ Transplant 2014;19(3):253–260. DOI: 10.1097/MOT.0000000000000069.
3. Pennington CA, Park JM. Sublingual tacrolimus as an alternative to oral administration for solid organ transplant recipients. Am J Health Syst Pharm 2015;72(4):277–284. DOI: 10.2146/ajhp140322.
4. Farkas SA, Schnitzbauer AA, Kirchner G, et al. Calcineurin inhibitor minimization protocols in liver transplantation. Transpl Int 2009;22(1):49–60. DOI: 10.1111/j.1432-2277.2008.00796.x.
5. Mihatsch MJ, Kyo M, Morozumi K, et al. The side-effects of ciclosporine-A and tacrolimus. Clin Nephrol 1998;49(6):356–363.
6. Nankivell BJ, Borrow RJ, Fung CL, et al. Calcineurin inhibitor nephrotoxicity: longitudinal assessment by protocol histology. Transplantation 2004;78(4):557–565. DOI: 10.1097/01.tp.0000128636.70499.6e.
7. Wei KC, Lai PC. Combination of everolimus and tacrolimus: a potentially effective regimen for recalcitrant psoriasis. Dermatol Ther 2015;28(1):25–27. DOI: 10.1111/dth.12176.
8. Reitamo S, Spuls P, Sassolas B, et al. Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. Br J Dermatol 2001:145(3):438–445. DOI: 10.1046/j.1365-2133.2001.04376.x.