

Sirolimus-Based Immunosuppression for Treatment of Cutaneous Warts in Kidney Transplant Recipients

Shahrzad Shahidi,¹ Firouzeh Moeinzadeh,¹ Morteza Mohammadi,¹ Ali Gholamrezaei²

¹Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

²Poursina Hakim Research Institute, Isfahan, Iran

Keywords. human papillomavirus, kidney transplantation, sirolimus, viral infections, warts

Dermatological complications, especially skin infections, are very common following organ transplantation, and result in a lot of distress in the recipient. Herpes zoster, herpes simplex, and human papillomavirus infections are common infections in kidney transplant recipients, and therapeutic management is usually disappointing in immunosuppression state. We report here 2 cases of kidney transplant recipients who developed diffuse human papillomavirus-induced cutaneous warts with no response to conventional treatments. According to similar reports in organ transplant recipients, we modified the immunosuppressive regimen by converting to sirolimus, which led to a rapid relief from cutaneous warts in both patients. This evidence along with other case reports suggest that conversion to sirolimus may be considered as an effective strategy in cases of giant or multiple viral warts in kidney and perhaps other transplant recipients.

IJKD 2011;5:351-3
www.ijkd.org

INTRODUCTION

Nowadays, growing number of patients with end-stage renal disease (ESRD) can be treated with kidney transplantation. However, there is an increased risk of viral infections and nonmalignant or malignant skin lesions in immunosuppressed transplant recipients.¹ Cutaneous warts, caused by the human papillomavirus (HPV), are very common among these patients,² and they may progress to squamous cell carcinoma.³

Viral warts in immunocompromised patients are frequently recurring and current therapies are of limited efficacy. Some reports are available on the effectiveness of modulating immunosuppressive regimens in the treatment of viral warts in organ transplant recipients.^{4,5} New immunosuppressants such as sirolimus and everolimus, belonging to mammalian target-of-rapamycin (mTOR) inhibitors, have been successfully used in preventing organ rejection after transplantation.^{6,7} Using these agents has been associated with a significantly lower

risks of de novo malignancies and viral infections after kidney transplantation.^{7,8} Here, we reported the results of modifying the immunosuppressive regimen by converting cyclosporine to sirolimus in 2 kidney transplant recipients who suffered from severe refractory cutaneous warts.

CASE REPORT

Case 1

An 18-year-old woman with ESRD due to vesicoureteral reflux received a kidney allograft from a related living donor in 1998 and was on cyclosporine, 175 mg/d; prednisolone, 7.5 mg/d; and azathioprine, 50 mg/d, with changing dosages during the treatment period according to side effects. In 2000, she experienced multiple skin warts on her arms and hands (Figure 1) and was referred to a dermatologist. She received intensive topical therapies and cauterization. As no improvement was observed, cyclosporine was substituted by sirolimus, 2 mg/d, in 2008, which resulted in



Figure 1. Top, Warts in a kidney transplant recipients. Bottom, improvement of the warts after conversion of cyclosporine to sirolimus.

gradual disappearance of the warts until in less than 1 year (Figure 1).

Case 2

A 21-year-old man with ESRD due to systemic lupus erythematosus received a kidney allograft from an unrelated living donor in 2004. He was on cyclosporine, 250 mg/d; mycophenolate mofetil, 2 g/d; and prednisolone, 7.5 mg/d, with modifying dosages according to observed side effects, mostly diarrhea and vomiting. In 2006, the patient experienced multiple skin warts on his hands and fingers (Figure 2). He was referred to a dermatologist and received topical therapies and cauterization. Simultaneously, cyclosporine dose was reduced to 100 mg/d. Since the warts did not improve, cyclosporine was replaced with sirolimus, 2 mg/d, in 2008. Two months later, sirolimus dosage was decreased to 1 mg/d due to diarrhea and vomiting. The warts gradually disappeared within 3 months (Figure 2).



Figure 2. Top, Warts in a kidney transplant recipients. Bottom, improvement of the warts after conversion of cyclosporine to sirolimus.

DISCUSSION

The major immunosuppressive agents that are currently used in various combination regimens include corticosteroids, antimetabolites (azathioprine and mycophenolate mofetil), calcineurin inhibitors (cyclosporine and tacrolimus), and mTOR inhibitors (sirolimus and everolimus).⁷ Sirolimus, originally developed as an antifungal agent, was later found to have immunosuppressive and antiproliferative properties.⁹ Well-designed clinical trials on kidney transplant recipients showed that addition of sirolimus to cyclosporine and corticosteroid therapy reduced the occurrence and severity of acute rejection without increasing immunosuppressant-related complications (infections and malignancy).^{10,11} Evidence has shown lower risk of viral infections with receiving mTOR inhibitors versus calcineurin inhibitors.⁸ Also, the role of mTOR inhibitors in interfering with virus replication has recently been investigated.^{12,13}

Case reports are available on improvement of cutaneous warts after conversion of the immunosuppressive regimen from calcineurin inhibitors to mTOR inhibitors. In a kidney transplant recipient with widespread skin warts, Kostaki and colleagues replaced tacrolimus with sirolimus, which led to a significant regression of the lesions within about 5 months.⁴ Another report by Dharancy and colleagues on a liver transplant recipient showed regression of cutaneous warts after converting calcineurin inhibitors and mycophenolate mofetil to sirolimus monotherapy.⁵

The exact mechanism by which mTOR inhibitors can interfere with HPV replication is not clear. Evidence showed that mTOR pathway activation is essential for the replication of mammalian DNA viruses.¹⁴ The function of HPV E7 oncoprotein is essential for viral replication, and it is reported that the mTOR kinase inhibitor, rapamycin, decreases the level of E7 protein by blocking phosphorylation of the translation inhibitor, 4E-BP1.¹⁵ However, more direct investigation is needed to clarify this issue.

Current evidence suggest that conversion of the immunosuppressive regimen from calcineurin inhibitors to mTOR inhibitors (eg, sirolimus) can be helpful in the treatment of transplant recipients with severe skin warts. Further investigations are needed to prove these results and clarify the underlying mechanisms.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wisgerhof HC, Edelbroek JR, de Fijter JW, Feltkamp MC, Willemze R, Bouwes Bavinck JN. Trends of skin diseases in organ-transplant recipients transplanted between 1966 and 2006: a cohort study with follow-up between 1994 and 2006. *Br J Dermatol*. 162:390-6.
2. Iraj F, Kiani A, Shahidi S, Vahabi R. Histopathology of skin lesions with warty appearance in renal allograft recipients. *Am J Dermatopathol*. 2002;24:324-5.
3. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med*. 2003;348:1681-91.
4. Kostaki M, Venetz JP, Nseir G, et al. Giant warts in a kidney transplant patient: regression with sirolimus. *Br J Dermatol*. 162:1148-50.
5. Dharancy S, Catteau B, Mortier L, et al. Conversion to sirolimus: a useful strategy for recalcitrant cutaneous viral warts in liver transplant recipient. *Liver Transpl*. 2006;12:1883-7.
6. Mehrabi A, Fonouni H, Kashfi A, et al. The role and value of sirolimus administration in kidney and liver transplantation. *Clin Transplant*. 2006;20 Suppl 17:30-43.
7. Marcen R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. *Drugs*. 2009;69:2227-43.
8. Flechner SM, Goldfarb D, Modlin C, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. *Transplantation*. 2002;74:1070-6.
9. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc*. 2003;35:7S-14S.
10. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. *Lancet*. 2000;356:194-202.
11. MacDonald AS. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/ cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation*. 2001;71:271-80.
12. Di Benedetto F, Di Sandro S, De Ruvo N, et al. First report on a series of HIV patients undergoing rapamycin monotherapy after liver transplantation. *Transplantation*. 89:733-8.
13. Gallego R, Henriquez F, Oliva E, et al. Switching to sirolimus in renal transplant recipients with hepatitis C virus: a safe option. *Transplant Proc*. 2009;41:2334-6.
14. Buchkovich NJ, Yu Y, Zampieri CA, Alwine JC. The TORrid affairs of viruses: effects of mammalian DNA viruses on the PI3K-Akt-mTOR signalling pathway. *Nat Rev Microbiol*. 2008;6:266-75.
15. Oh KJ, Kalina A, Park NH, Bagchi S. Deregulation of eIF4E: 4E-BP1 in differentiated human papillomavirus-containing cells leads to high levels of expression of the E7 oncoprotein. *J Virol*. 2006;80:7079-88.

Corresponding to:

Firouzeh Moeinzadeh, MD

Isfahan Kidney Diseases Research Center, Noor Hospital,

Ostandari Ave, Isfahan, Iran

Tel: +98 913 133 8986

Fax: +98 311 668 7898

E-mail: fimoinzad@yahoo.com

Received October 2010

Revised February 2011

Accepted March 2011