Choice of Immunosuppressants and the Risk of Warts in Renal Transplant Recipients

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Sir,

Graft-preserving immunosuppressive therapy is associated with many dermatological complications, as shown in renal transplant recipients (RTR) (1–7). Human papillomavirus (HPV) infection is one of the most frequently occurring infections (1–4, 6–8). The presence of HPV may augment the risk of skin cancer. A wide diversity of HPV types can be detected in biopsies from premalignant lesions and skin cancer of transplant recipients (9–10).

It is well known that therapy with cyclosporine and azathioprine leads to an increased risk of developing viral warts (3, 11, 12). However, the risk with the new immunosuppressive agents, such as mycophenolate mofetil, which are designed to provide immunosuppression with fewer side-effects, is unknown.

PATIENTS AND METHODS

A total of 328 unselected consecutive RTR patients were followed-up by the transplantation unit of Akdeniz University Faculty of Medicine, Antalya, Turkey, between 1979 and 2004, and were evaluated retrospectively. The ages of recipients at entry to the study ranged from 14 to 59 years (mean ± standard deviation (SD) 33.6 ± 10.8 years) and the sex distribution was 219 men (66.8%) and 109 women (33.2%).

For each patient the following data were recorded: age, sex, date of transplantation, graft survival time (GST), immunosuppressive regimens, date of clinical diagnosis and wart development time (WDT). The localization with respect to sun exposure and the types of warts were also noted.

GST and WDT were defined as the time from the date of transplantation to the study, and to the diagnosis of warts, respectively. For patients who died, GST was determined as the time between transplantation and death. The mean GST was 77.5 months (SD 64.9, range 4–292).

Patients were grouped according to the drugs they used after the transplantation. All of the RTR were taking prednisolone. Forty-eight patients were treated with prednisolone and azathioprine; 11 with prednisolone and mycophenolate mofetil; 105 with prednisolone, azathioprine and cyclosporine; 2 with prednisolone, azathioprine and tacrolimus; 69 with prednisolone, mycophenolate mofetil and cyclosporine; and 93 prednisolone, mycophenolate mofetil and tacrolimus. Azathioprine-based and mycophenolate mofetil-based therapies were used in 155 and 173 patients, respectively. The frequencies of warts according to the immunosuppressive regimes were determined.

The data were analysed using paired *t*-test and χ^2 test by using the SPSS statistical programme. *p*-values less than 0.05 were considered significant.

RESULTS

Thirty-eight of the 328 patients (11.9%) were found to have warts. The mean WDT was 61.4 months (SD

Table I. *Comparison of wart frequency in patients on different immunosuppressive regimens*

	Wart frequency *n* (%)	Total *n*	χ^2	*p*
All patients	38 (11.9)	328		
Prednisolone with:			1.20*	0.19
Azathioprine	9 (18.7)	48		
Mycophenolate mofetil	0 (0.0)	11		
Prednisolone + azathioprine with:			0.01*	0.90
Cyclosporine	23 (21.9)	105		
Tacrolimus	0 (0.0)	2		
Prednisolone + mycophenolate mofetil with:			2.68*	0.08
Cyclosporine	5 (7.2)	69		
Tacrolimus	1 (1.1)	93		
Prednisolone + azathioprine or prednisolone + mycophenolate mofetil with:			12.93*	0.0003
Cyclosporine	28 (16.1)	174		
Tacrolimus	1 (1.0)	95		
Prednisolone with:			18.18*	0.00002
Azathioprine + cyclosporine	23 (21.9)	105		
Mycophenolate mofetil + tacrolimus	1 (1.1)	93		
Prednisolone + cyclosporine with:			4.04*	0.044
Azathioprine	23 (21.9)	105		
Mycophenolate mofetil	5 (7.2)	69		
Prednisolone + cyclosporine or prednisolone + tacrolimus with:			21.21	0.000016
Azathioprine	23 (21.5)	107		
Mycophenolate mofetil	6 (3.7)	162		
Any combination with:			23.55	0.0000029
Azathioprine	32 (20.6)	155		
Mycophenolate mofetil	6 (3.5)	173		

*Yates corrected.

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35.4, range 1–152 months). Most of the warts were on exposed parts of the body, such as the hands, forearms and face. The 4 types of warts recognized in order of frequency were verruca vulgaris ($n = 35$), verruca plana ($n = 3$), verruca anogenitalis ($n = 3$) and, in one patient, epidermodysplasia verruciformis-like lesions. Four patients had a mixture of 2 clinical forms. Three patients with anogenital warts and one of 3 having verruca plana had common warts at the same time.

The frequency of warts in RTR receiving any azathioprine combination was significantly higher than those treated with mycophenolate mofetil (20.6% and 3.5%, respectively) ($p < 0.0001$). For details see Table I.

DISCUSSION

The incidence of viral warts in RTR varies from 8% to 55% depending on the patient's characteristics, the time since transplantation and immunosuppressive protocols (1–8). In our study, various types of warts were observed in 11.9% of the patients. As in other series, the distribution of warts was favoured by ultraviolet light and therefore located mainly on sun-exposed skin.

The specific role of immunosuppressive treatment as an additional risk factor for the development of warts has been debated only in a few studies. Prednisolone and azathioprine were the predominant immunosuppressants used in most transplant centres for many years. It has been shown that steroid therapy does not increase the risk of cutaneous warts (8, 12). Rudlinger et al. (8) investigated the effect of the dose of azathioprine on the prevalence of warts and concluded that the duration rather than the level of immunosuppression is important. Since the introduction of cyclosporine, most patients have received either a combination of cyclosporine and prednisolone or a triple therapy involving all 3 immunosuppressants. Viral warts have been found to be significantly more common in those on conventional prednisolone and azathioprine therapy (3, 7, 12). Barba et al. (6) have found that RTR receiving prednisolone + azathioprine or prednisolone + azathioprine + cyclosprine have an increased risk of developing viral warts than those receiving only prednisolone and cyclosporine.

According to our results, the patients receiving azathioprine therapy in any combination seem to have an increased risk of developing HPV infections. This can be explained by a longer follow-up time or that azathioprine itself is probably a more potent inducer of warts.

It is well known that Langerhans' cells play an essential role in cutaneous immunosurveillance; thus, inhibition of this cell population can predispose to infective conditions. The effects of these anti-proliferative agents on Langerhans' cells differentiation and maturation are still not clearly understood (13). Some studies showed that RTR have a significant reduction in the number of Langerhans' cells, and this change is more pronounced in patients receiving azathioprine and prednisolone than in those receiving cyclosporine and prednisolone (14, 15). In theory, Langerhans' cells may be altered by azathioprine which may facilitate HPV proliferation.

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