Acne in recipients of renal transplantation treated with sirolimus: Clinical, microbiologic, histologic, therapeutic, and pathogenic aspects

Emmanuel Mahé, MD,[a,b] Emmanuel Morelon, MD, PhD,[c,d] Sophie Lechaton,[c] Jean-Christophe Drappier, MD,[a] Yves de Prost, MD,[a] Henri Kreis, MD,[c] and Christine Bodemer, MD, PhD[a]

Paris and Lyon, France

We evaluated the clinical characteristics of sirolimus-induced acne in 80 recipients of renal transplantation. It developed in 36 of 48 (75%) men and 2 of 32 (6%) women. Lesion locations and clinical, bacteriologic, and histologic features differentiated sirolimus-induced acne from acne vulgaris, but therapeutic management was similar. The main limitation for this study was the absence of a control group without sirolimus. Epidermal growth factor inhibition by sirolimus is a plausible explanation for this acne. (J Am Acad Dermatol 2006;55:139-42.)

Sirolimus (Rapamune, Wyeth Pharmaceuticals, Paris, France) is an immunosuppressive drug licensed for renal transplantation. Because of its immunosuppressive properties, which differ from those of the calcineurin inhibitor, cyclosporine, and tacrolimus, and because it is not nephrotoxic, sirolimus is a suitable alternative to calcium inhibitors in organ transplantation.[1-8] Its immunosuppressive properties also have led to trials involving immune diseases.[9-11]

In the field of dermatology, the most prevalent side effects of sirolimus are pathologies of the pilosebaceous apparatus, chronic edemas, angioedemas, and mucous membrane involvement.[12-15] We recently reported the frequency of these cutaneous adverse events in recipients of renal transplantation taking sirolimus.[15]

This article describes in detail the acneiform complications of sirolimus among a series of 80 recipients of renal transplantation recently reported elsewhere.[15]

METHODS

Patients and clinical evaluation

In 2003, 80 consecutive recipients of renal transplantation taking sirolimus were examined (48 men and 32 women). The protocol for dermatologic evaluation was implemented by using a case report form created especially for the study and published previously.[15] The characteristics of these patients were described in detail in this publication.[15]

Acne was defined as the presence of follicular papules or pustules, comedones, or nodules in usual sebaceous areas. The treatments used for the acne were evaluated systematically. Nine bacteriologic and mycologic cultures of pustules were done for 6 patients, and skin biopsy specimen of inflammatory nodules for 5.

Statistical evaluation

The effect of the following nonparametric variables on the frequency of acne was evaluated with the use of Fisher exact test: sex, immunosuppressive and nonimmunosuppressive sirolimus-associated treatments, sirolimus switch, active smoking, associated skin diseases, and a history of severe acne vulgaris requiring systemic treatment or involving nodular acne or acne scars. The effects of 5 parametric variables were evaluated by the unpaired Student *t* test: age, duration of transplantation and of sirolimus ingestion, and sirolimus dosage and blood trough level. Differences were considered significant at P less than .05.

From the Departments of Dermatology[a] and Transplantation,[c] Necker-Enfants Malades University Hospital, Paris; the Department of Dermatology, Bichat-Claude Bernard University Hospital, Paris[b]; and the Department of Nephrology, Transplantation, and Clinical Immunology, Edouard Herriot University Hospital, Lyon.[d]

Funding sources: None.

Disclosure: Drs Morelon and Kreis are investigators in sirolimus trials conducted among recipients of renal transplantation.

Reprint requests: Emmanuel Mahé, MD, Service de Dermatologie, Hôpital Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France. E-mail: emmanuel.mahe@apr.aphp.fr.

0190-9622/$32.00

doi:10.1016/j.jaad.2005.11.1072

Table I. Clinical aspects of acne in 38 recipients of renal transplantation taking sirolimus-based therapy

Male/female sex, n	36/2*
Median period between introduction of sirolimus and appearance of acne, mo (range)	1 (0.1-34)†
Median no. of lesions (range)	22 (2-232)
Location of lesions, %	
Face	100
Cervical area	45
Anterior and/or lateral surfaces	24
Neck	37
Chest	68
Back	66
Shoulders, arm, forearm	32
Clinical features, %	
Appearance of the lesions	
Inflammatory papules/pustules/ inflammatory nodules	97/53/29
Closed comedones/open comedones/macrocomedones	21/5/5
General appearance of acne	
Inflammatory components alone	71
Noninflammatory components alone	0
Inflammatory and noninflammatory components	29
Painful lesions, %	29
Painful impressive nodular acne in cervical and facial areas, %	24
Scalp folliculitis, %	53*
Improvement in sun	4‡

*$P < .0001$.
†In 3 patients, previous acne was exacerbated after initiation of sirolimus.
‡Evolution in the sun was not evaluated, but 4 patients spontaneously declared that exposure to sun improved their lesions.

RESULTS

Frequency and clinical aspects of acne

Of 80 patients, 38 (45%) developed acne. It occurred in 36 of the 48 (75%) men and 2 of the 32 (6%) women ($P < .0001$). One woman had primary amenorrhea and the other postmenopausal amenorrhea. Neither patient had hormonal substitution. Sex was the only parameter that affected the frequency of acne. Among the men, acne was more frequent in patients with a history of severe acne vulgaris (6 of 36 in the group with acne vs none of 12 in the group without, P = not significant). There was no significant correlation between the daily dose of sirolimus, the blood trough level of sirolimus, and the development of acne; clinical aspects are given in Table I. Scalp folliculitis (papules, scabs, or pustules) was found in only patients with acne.

Microbiologic and histologic data

Of the 9 bacteriologic cultures, two were positive for *Staphylococcus epidermidis*, two for *Propionibacterium acnes*, and one for *Escherichia coli*. Fungal cultures were negative. Histologic examination of lesions disclosed unspecific folliculitis.

Treatments

Twenty-four patients were treated for acne. Nineteen received topical treatments (erythromycin, benzoyl peroxide, retinoid, metronidazole, or isoconazole) and 18 systemic treatments (doxycycline or isotretinoin). Topical treatments improved the acne in 10 of 19 (53%) patients. One patient treated his eruption with isoconazole spontaneously. Because this treatment was considered very effective, 6 other patients were treated with isoconazole, successfully in 3 of them.

Systemic treatments were considered to be helpful in 12 of 18 (67%) patients. Doxycycline (100 mg/d) was associated with topical treatments in 8 of 12 patients, and proved effective in 6 (50%) patients. In 6 patients, low-dose iosotretinoin (0.25 mg/kg/d, n = 2) or the usual dose (0.50 mg/kg/d, n = 4) produced dramatic improvement. However, two of them had to stop isotretinoin, respectively, because of severe dyslipidemia and diffuse edemas. The patient with severe diffuse edemas later resumed low-dose isotretinoin (0.25 mg/kg/d) with good tolerance and improved.

Evolution of acne after sirolimus discontinuation

Eight patients with acne had to stop sirolimus during the 6 months after the study. In two patients (one woman, one man), severe acne was responsible for sirolimus discontinuation because of social disability. After discontinuation (period of observation: 4-10 months), acne and scalp folliculitis disappeared in all the patients.

DISCUSSION

In previous sirolimus trials, the frequency of acne has been estimated at 15% to 25%.[3,7,9] We report here 80 recipients of renal transplantation taking sirolimus with an unusually high frequency of acne (45%), erupting soon after sirolimus initiation, mainly in men. Bacteriologic and histologic examinations suggest a nonspecific folliculitis. Topical therapies and doxycycline were effective in half the patients treated, whereas isotretinoin always was considered very effective. Isoconazole was effective in a few patients, probably by a nonspecific anti-inflammatory action.

Sirolimus seems to be the most likely cause of acne in our series and others for 3 reasons. First, such

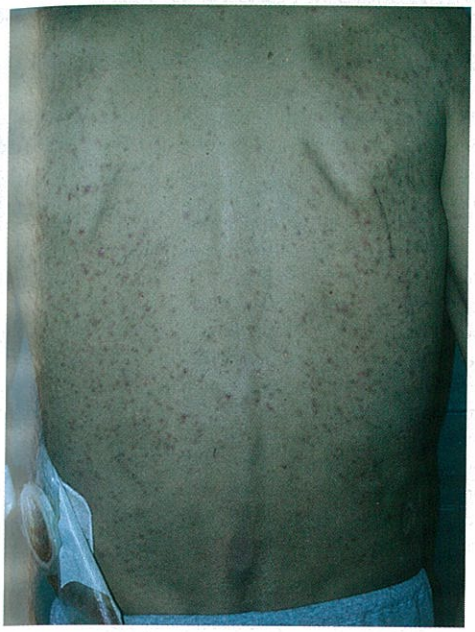

Fig 1. Severe diffuse acne of back in recipient of renal transplantation taking sirolimus-based therapy.

a high prevalence has never been reported with immunosuppressive therapies and, second, controlled trials have shown a higher prevalence in groups treated with sirolimus than in control groups.[3,9] Last, the complete regression of the eruption after the current discontinuation of sirolimus is highly suggestive of its responsibility for the pathogenesis of acne. The systematic, in-depth evaluation of our patients may explain the high frequency observed in this study. We think that the high frequency of acne in our study may be a result of high doses of sirolimus used in the protocols (12-20 ng/mL). We have not proven statistically that a dose effect exists, but only 4 patients received low-dose treatment (<10 ng/mL).

Clinically, sirolimus-induced acne differs from acne vulgaris. In our cases of sirolimus-induced acne, only inflammatory lesions were observed generally. Sebaceous areas were involved (Fig 1), but the lesions frequently extended to the forearms, internal surface of the arm, cervical area, and scalp. In at least a few patients, we observed severe unusual, painful, nodular, edematous lesions on the neck and face, suggesting a specific pathogenic role for sirolimus.

The role of sirolimus in the pathogenesis of acne may have many explanations including direct toxic effects on follicles or its chemical toxic modification of sebum. The most likely explanation is that sirolimus inhibits the epidermal growth factor (EGF) pathway, as is suggested by 3 lines of evidence. First, it has been demonstrated that sirolimus inhibits EGF action by inhibiting the mTOR pathway.[16] Second, anticancer therapies that inhibit specifically EGF (C225 antibody, gefitinib, and cetuximab) cause cutaneous toxicity, especially acne, and this toxicity is very similar to that caused by sirolimus as it induces ingrowing paronychia inflammation, aphthous ulceration, epistaxis, and xerosis.[15,17-20] Last, testosterone up-regulates EGF receptor synthesis, and sirolimus down-regulates testosterone synthesis.[21-23]Sirolimus might, therefore, induce acne because of its direct inhibition of EGF action (ie, the mTOR pathway) and do so predominantly in men because of the down-regulation of the EGF receptor by testosterone suppression.

In summary, acne is a frequent side effect of sirolimus in recipients of renal transplantation. Despite the efficacy of acne therapies in many patients, the eruption is sometimes severe and can lead to sirolimus discontinuation.

REFERENCES

1. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: a review of the evidence. Kidney Int 2001;59:3-16.
2. Groth CG, Backman L, Morales JM, Calne R, Kreis H, Lang P, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine; sirolimus European renal transplant study group. Transplantation 1999;67:1036-42.
3. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomized multicenter study: the Rapamune US study group. Lancet 2000;356:194-202.
4. MacDonald AS, Rapamune Global Study Group. 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.
5. Van Hooff JP, Squifflet JP, Wlodarczyk Z, Vanrenterghem Y, Paczek L. A prospective randomized multicenter study of tacrolimus in combination with sirolimus in renal-transplant recipients. Transplantation 2003;75:1934-9.
6. Morelon E, Kreis H. Sirolimus therapy without calcineurin inhibitors: Necker Hospital 8-year experience. Transplant Proc 2003;35(Suppl):S52-7.
7. MacDonald AS. Rapamycin in combination with cyclosporine or tacrolimus in liver, pancreas, and kidney transplantation. Transplant Proc 2003;35(Suppl):S201-8.
8. Kreis H, Oberbauer R, Campistol JM, Mathew T, Daloze P, Schena FP, et al. Long-term benefits with sirolimus-based therapy after early cyclosporine withdrawal. J Am Soc Nephrol 2004;15:809-17.
9. Reitamo S, Spuls P, Sassolas B, Lahfa M, Claudy A, Griffiths CE. 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;145:438-45.
10. Nadiminti U, Arbiser JL. Rapamycin (sirolimus) as a steroid-sparing agent in dermatomyositis. J Am Acad Dermatol 2005;52(Suppl):17-9.
11. Migita K, Eguchi K, Aoyagi T, Kawabe Y, Tsukada T, Aoyagi T, et al. The effects of the immunosuppressant rapamycin on the

growth of rheumatoid arthritis (RA) synovial fibroblasts. Clin Exp Immunol 1996;104:86-91.
12. Van Gelder T, ter Meulen CG, Hene R, Hene R, Weimar W, Hoitsma A. Oral ulcers in kidney transplant recipients treated with sirolimus and mycophenolate mofetil. Transplantation 2003;75:788-91.
13. Mohaupt MG, Vogt B, Frey FJ. Sirolimus-associated eyelid edema in kidney transplant recipients. Transplantation 2001;72:162-4.
14. Aboujaoude W, Milgrom ML, Govani MV. Lymphedema associated with sirolimus in renal transplant recipients. Transplantation 2004;77:1094-6.
15. Mahé E, Morelon E, Lechaton S, Le Quan Sang KH, Mansouri R, Ducasse MF, et al. Cutaneous adverse events in renal transplant recipients receiving sirolimus-based therapy. Transplantation 2005;79:476-82.
16. Nomura M, He Z, Koyama I, Ma WY, Miyamoto K, Dong Z. Involvement of the Akt/mTOR pathway on EGF-induced cell transformation. Mol Carcinog 2003;38:25-32.
17. Busam KJ, Capodieci P, Motzer R, Kiehn T, Phelan D, Halpern AC. Cutaneous side effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. Br J Dermatol 2001;144:1169-76.
18. Lee MW, Seo CW, Kim SW, Yang HJ, Lee HW, Choi JH. Cutaneous side effects in non-small cell lung cancer patients treated with Iressa (ZD1839), an inhibitor of epidermal growth factor. Acta Derm Venereol 2004;84:23-6.
19. Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD Jr, Morse D, et al. United States Food and Drug Administration drug approval summary: gefitinib (ZD1839; Iressa) tablets. Clin Cancer Res 2004;10:1212-8.
20. Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22:1201-8.
21. Noguchi S, Ohba Y, Oka T. Pretranslational enhancement of epidermal growth factor receptor by direct effect of testosterone in mouse liver. Endocrinology 1991;128:2141-8.
22. Fritsche L, Budde K, Dragun D, Einecke G, Diekmann F, Neumayer HH. Testosterone concentrations and sirolimus in male renal transplant patients. Am J Transplant 2004;4:130-1.
23. Tondolo V, Citterio F, Panocchia N, Nanni G, Castagneto M. Sirolimus impairs improvement of the gonadal function after renal transplantation. Am J Transplant 2005;5:197.