Published in final edited form as:

Br J Dermatol. 2007 December ; 157(Suppl 2): 25–31. doi:10.1111/j.1365-2133.2007.08269.x.

Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients

C. Ulrich^{*}, J. Bichel[†], S. Euvrard[‡], B. Guidi^{**}, C.M. Proby[§], P.C.M. van de Kerkhof[¶], P. Amerio^{**}, J. Rønnevig^{††}, H.B. Slade^{‡‡}, and E. Stockfleth^{*}

^{*}Clinic for Dermatology of the Charité, Charité Hospital, Campus Mitte, Charité-Platz 1, 10117-Berlin, Germany [†]3M Medica, Neuss, Germany [‡]Service de Dermatologie, Hôpital Edouard Herriot, Lyon, France [§]Centre for Cutaneous Research, Barts and The London School of Medicine and Dentistry, London, U.K. [¶]Department of Dermatology, University Hospital Nijmegen, Nijmegen, The Netherlands ^{**}Istituto di Clinica Dermatologica Policlinico, Universitario A. Gemelli, Rome, Italy ^{††}Department of Dermatology, The National Hospital, Oslo, Norway ^{‡‡}DFB Pharmaceuticals, Fort Worth, TX, U.S.A.

Summary

Objective—In this study the safety and efficacy of imiquimod 5% cream for the treatments of actinic keratoses in kidney, heart and liver transplant recipients is evaluated.

Background—Growing populations of organ transplant recipients face increased risk of developing actinic keratosis (AK) and skin cancer secondary to continuous systemic immunosuppressive therapy. Imiquimod 5% cream is an effective option for the treatment of AK, but the safety of topical immune stimulation in immunocompromised patients has not been widely evaluated.

Methods—A total of 43 patients in six European transplant centres applied two sachets of topical imiquimod or vehicle cream three times per week to a 100 cm² field. Dosing continued for 16 weeks regardless of lesion clearance. Patients were assessed for safety variables that included adverse events, local skin reactions, laboratory results, vital signs, dosage of immunosuppressive medication and indication of graft rejection. A blinded independent expert committee was responsible for safety monitoring and final safety assessment.

Results—No graft rejections or trends for a deterioration of graft function were detected. No meaningful trends were observed in laboratory results. Among patients randomized to imiquimod, the complete clearance rate was 62.1% (18/29); for vehicle patients, the complete clearance rate was 0% (0/14). Clinical clearance was confirmed histologically in all cases.

© 2007 British Association of Dermatologists

Correspondence, Claas Ulrich. E-mail:claas.ulrich@charite.de.

Conflicts of interest

ES acts as a consultant to Meda Pharma. JB is an employee of 3M. SE has been a consultant to 3M and has received honorarium for a clinical study. CU is a member of the speaker bureau of MEDA and 3M. All other authors declare no conflict of interest.

Conclusions—Imiquimod appears to be a safe alternative for the treatment of multiple actinic keratoses in patients with solid organ transplants. Efficacy was within the range previously observed in nontransplanted populations.

Keywords

actinic keratoses; imiquimod; organ transplant recipients; safety study

Transplantation has been the treatment of choice for more than one million patients worldwide with end stage organ disease. Improvements in patient selection, donor organ collection, surgical procedures and highly effective immunosuppressive treatment regimens have enhanced patient survival and have resulted in increasing numbers of transplants being performed.

While graft survival has almost doubled over the past 20 years,¹ the attendant requirement for chronic immunosuppression creates a significant risk of malignancy. The most frequently seen cutaneous cancers after transplantation, among white populations, are squamous cell carcinomas (SCC), their preinvasive form actinic keratoses, and basal cell carcinomas (BCC).²⁻⁴

Actinic keratosis are the clinically detectable lesions equivalent to spots or regions of dysplastic keratinocytes which, when confluent to a whole area, are defined as 'field cancerization'.⁵ The incidence of AK is significantly higher in transplant recipients compared with age matched controls, implying impaired immune elimination of previously damaged keratinocytes.^{6,7} These areas of 'field dysplasia' account for much of the skin cancer related morbidity and mortality in organ transplant recipients (OTR) and, in recent years, have become the key target of most dermatological initiatives to reduce the skin cancer burden in OTR.

Imiquimod is one of the first described members of a novel class of Toll-like receptor 7 agonists which serve as immune response modifiers with the ability to stimulate the innate and acquired cellular immune system.⁸ Imiquimod 5% cream is effective in the treatment of AK in immunocompetent patients, as evidenced in multiple randomized controlled clinical trials,^{9,10} and recurrence of lesions is found to be low in patients who achieve clearance.¹¹ Reports of imiquimod treatment of individual cases and small, non placebo-controlled case series, suggest that efficacy is similar in transplant recipients with BCC or even invasive SCC.¹²⁻¹⁴ A single placebo-controlled study in renal transplant recipients (RTR) found imiquimod to be safe when treating acral areas of field cancerization.¹⁵

The report here describes a multicentre, placebo-controlled safety and efficacy study for the use of imiquimod 5% cream to treat AK in heart, kidney and liver transplant recipients. The purpose of this study was to provide physicians with an estimate of the safety margin seen with topically applied imiquimod, for the treatment of multiple AKs in systemically immunocompromised patients, as well as to evaluate its efficacy.

Methods

Study design

The primary objective of this study was to compare imiquimod 5% cream and vehicle cream with respect to safety assessments in graft recipients (specifically, whether a patient had a rejection and its relatedness to study drug). Safety of the graft was monitored by an independent and blinded safety committee. A secondary objective was to compare complete and partial AK clearance rates between the imiquimod and vehicle groups.

Patients with one of three organ transplant types (kidney, liver, heart) were randomized 2 : 1 (active : vehicle) in this vehicle-controlled, double-blind, parallel group design. Patients applied study medication three times per week for 16 weeks to a defined treatment area of 100 cm². Evaluations were made 8 weeks after cessation of dosing. The total duration of patient participation in this study was a maximum of 28 weeks.

Patients

Patients were eligible for enrolment if they had received a kidney, liver, or heart transplant more than 3 years prior to inclusion into the study, with stable status of the transplanted graft in the 12 months prior to entering the study, and who had 4-10 clinically typical AK lesions in a contiguous 100 cm² area on the face, forehead, or balding scalp. Criteria for determining the stability of grafts were specific to each transplant type. Immunosuppressive therapy must have been stable within the previous 6 months before enrolment, with an expectation that the therapy would remain stable for 7 months of study participation.

Patients were ineligible if they had evidence of unstable cardiovascular, immunological, haematological, hepatic, neurological, renal, endocrine, collagen-vascular, gastrointestinal abnormalities or disease, persistent hepatitis B and/or C infections, had used steroids up to 3 days before enrolment, or had used any prophylactic antibody in the first 6 months after transplantation. Patients could not have invasive malignant tumours of the skin within the treatment area 6 months before enrolling in the study or any evidence of systemic cancer. Patients could not have received any systemic cancer chemotherapy or radiation therapy within 6 months of study treatment initiation nor have received other systemic treatments, including retinoids, interferons or investigational drugs within 4 weeks of study initiation. Vitamin A usage > 15 000 units per day was also excluded.

Study procedures

This study was conducted in compliance with all applicable US and EU regulations. Ethical Committee review and approval was obtained for each study centre, and all patients provided written informed consent. The study was conducted at six transplant clinics in Europe.

Eligibility was determined at the prestudy visit, at which time a 3-4 mm punch biopsy of a lesion was performed to confirm the presence of AK in the treatment area. All eligible patients returned to the clinic 2-4 weeks following the prestudy visit for treatment initiation. Baseline data were collected, and the patients were randomized to study drug. Patients returned to clinic for evaluations throughout the treatment period (weeks 1, 2, 3, 5, 7, 9, 12 and 16) and post-treatment (weeks 19 and 24).

Patients applied 500 mg (two full sachets) of imiquimod 5% cream, or vehicle cream, to the treatment area on three nonconsecutive days per week for 16 weeks. Each dose was applied at approximately the same time of day. Study cream remained on the treatment area for at least 8 h, after which patients washed the treatment area with mild soap and water. Treatment continued for a full 16 weeks regardless of clinical evidence of lesion clearance.

Efficacy evaluations

At the treatment week 7, 12, and 16 visits and 3- and 8-week post-treatment visits, a clinical count was made of the number of visible AK lesions in the treatment area. Histologic verification of AK at the week 8 post-treatment visit was obtained through a 3-4 mm punch biopsy of a lesion mapped at the initiation visit.

Safety evaluations

Safety variables included transplant rejection status, laboratory results, adverse events, local skin reactions, vital signs measurements, and the dosage of immunosuppressive medications.

Serum levels of immunosuppressive medication were monitored for all patients. All patients were monitored for changes in haematology and serum chemistry, specifically: levels of serum creatinine, C-reactive protein, and proteinuria were monitored for RTR; levels of gamma glutamyl-transpeptidase, glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase, and bilirubin were monitored for liver transplant recipients; heart transplant recipients were monitored specifically for GOT and GPT, white cell blood count, serum creatinine, haemoglobin, and signs of heart failure.

Three transplant physicians comprised a blinded, independent safety committee to monitor for any signs of graft rejection in each transplant group. The safety committee routinely reviewed patient's data to determine the safety status of the patient and the graft.

At the week 8 post-treatment visit (week 24), investigators assessed the skin quality of the treatment area with regard to skin surface, hyperpigmentation, hypopigmentation, the degree of scarring, and any atrophy. Local skin reactions, which included erythema, oedema, erosion/ulceration, scabbing/crusting, weeping/exudate, vesicles, and flaking/scaling/dryness, were assessed by the investigator at all study visits.

Statistical analysis

Sample size for the study was based on the assumption that 0-1 spontaneous rejection events might be expected to occur in 45 patients observed over the length of the study. All safety and efficacy analyses were performed on the intent-to-treat population which included all randomized patients. Descriptive statistics were used to summarize the safety variables for transplant rejection status, local skin reactions, adverse events, laboratory values and skin quality and the efficacy variables for complete and partial clearance rates by transplant type and treatment. The complete clearance rate was the proportion of patients at the 8-week post-treatment visit that had no histological evidence of AK at the target lesion and no clinically visible lesions in the remainder of the treatment area. The partial clearance rate was the proportion of patients at the 8-week post-treatment visit who obtained at least 75% reduction in the number of lesions counted at baseline in the treatment area. No formal statistical comparisons between transplant types or treatment groups were made.

Results

Patient disposition

Among 61 patients screened at six centres, 43 were eligible and were randomized to imiquimod (29) or vehicle (14). Major reasons for ineligibility were not meeting the inclusion/exclusion criteria (9), abnormal lab values (7), personal (1) and other (1). A Total of 34/43 (79%) of the patients completed the 16 weeks treatment phase and presented for the post-treatment evaluation. Two additional subjects did not complete 16 weeks of treatment but did attend the post-treatment evaluation (Fig. 1). Patient demographics are shown in Table 1.

Safety

During this study, eight patients (five imiquimod; three vehicle) reported 11 serious adverse events (SAEs). None of the SAEs were related to transplant rejection nor considered related to study drug. Three patients discontinued due to adverse events [two imiquimod patients (severe depression and melanoma in the treatment area) and 1 vehicle patient (acetabulum

fracture)]. None of these AEs were considered related to study drug. The acetabulum fracture resulted in the only death during the study. Possibly or probably related AEs in the imiquimod patients included application site reaction (5/29), fatigue (1/29), headache (1/29), diarrhoea (1/29), nausea (1/29), rash (1/29), skin disorder (1/29), and leucopenia (1/29). The most commonly reported adverse event was application site reaction. Local skin reactions in the treatment area, including erythema and erosion, were usually mild to moderate although some subjects did experience severe LSRs [most commonly severe erythema: six (30%) of subjects in the kidney imiquimod group]. Wound healing after therapy was very good and led to excellent and cosmetically appealing results. No wound infections were observed.

No patient in either the imiquimod group or the vehicle group experienced transplant rejection. No substantial adjustments to immunosuppressive regimens were made during the study. No meaningful trends were observed in laboratory results for creatinine, transaminases and C-reactive protein or other laboratory markers. As expected, transitory fluctuations in laboratory levels were observed but were not medically significant. One vehicle patient (liver transplant) experienced elevated transaminases and CRP. These levels remained elevated through week 9 at which point the patient was discontinued. The investigator considered these lab values to be clinically significant although the safety monitoring board did not consider these changes diagnostic for graft rejection.

Efficacy

Both complete and partial clearance rates in the imiquimod treated patients were high. No vehicle-treated patients achieved complete (100%) or partial clearance (75%) of AKs. Clearance rates are shown in Figures 2 and 3. The clinical assessment of AK lesion clearance was verified by histology in all cases which confirmed the clinical diagnosis to be a reliable tool for efficacy evaluation.

Overall clearance rates for individual AK lesions (Table 2), for patients who applied imiquimod, were 73.7% vs. (–) 99.1% for vehicle patients, showing a large increase in the overall lesion count from baseline for patients assigned to vehicle.

Discussion

Unlike immunocompetent patients, immunosuppressed patients have a highly accelerated rate of AK development and progression. Systemic immunosuppressive therapies either directly or indirectly interfere with the innate and adaptive immune responses. Imiquimod's ability to enhance adaptive and innate immune responses is the basis of its antiviral and antitumor activities. This specific mode of action, therefore, was thought to be particularly helpful in patients with acquired or therapeutically induced immune deficiency, like transplant patients.

Imiquimod has previously been evaluated in uncontrolled studies or case series for the treatment of AK and other diseases in OTR with good success.^{14,16–20} In contrast to these studies, this is a vehicle-controlled, randomized study that evaluated imiquimod in a variety of transplant patients with AK and explored a substantial margin of safety by requiring two full sachets of drug to be applied to 100 cm² 3×/week for 16 weeks. A similar vehicle-controlled, randomized study by Brown evaluated renal transplant patients with a similar dosing schedule but applied only a single sachet.¹⁵

Altogether, 500 mg of imiquimod cream appeared to have no systemic immunostimulatory effects on transplant organs. Although this study included only small numbers of liver, heart and kidney grafted patients, data from this study and the study by Brown, suggest that

imiquimod treatment does not have adverse effects on grafted organs in systemically immunosuppressed organ transplanted patients.

Imiquimod patients developed typical erythematous reactions that were restricted to the area of application. Additionally, local side effects consisted of mild scabbing and crusting and mild to moderate erosion. Compared to immunocompetent patients, the local skin reaction profile seemed to be similar in intensity but slightly protracted in our graft recipients.^{15,17,20}

With respect to efficacy, imiquimod patients experienced significant reduction in AK lesion counts, with most patients experiencing clearance of at least 75% of AKs in the treatment area. Conversely, vehicle treated patients showed a considerable progression of disease. The baseline number of lesions doubled within the period of study participation. Considering the demonstrable progression of AKs under immunosuppression, complete clearance of lesions in more than 60% of patients and partial clearance in nearly 80% of patients is impressive in this population. In addition, the histological assessment of the post-treatment biopsy showed in all cases that clinical clearance corresponded with the histological evaluation. With respect to the high rate of AK progression to invasive squamous cell carcinoma¹⁹ and subsequent metastasis in graft recipients, this finding is relevant from a safety perspective because it confirms an actual cure of lesions also in deeper parts of the epidermis. This may also have an implication for recurrence rates as it could be assumed that recurrences arise when neoplastic cells remain in the epidermis after treatment. In case of clinical cure, these neoplastic cells could not be detected by histology in any observed cases from this study.

Management strategies that counteract the effects of systemic immunosuppression via the induction of a locally restricted, tumour specific immune response are a useful addition to the therapeutic portfolio available. In conclusion, imiquimod 5% cream appears to be an effective and well tolerated therapy to treat areas of AK in systemically immunocompromised OTR.

New diseases, and to a certain extent also the side effects of otherwise life-saving new generations of drugs like immunosuppressive therapies, require new therapeutic concepts. Education, primary prevention, early intervention and close follow-up by specialized, multidisciplinary teams are cornerstones of any initiative to lessen the burden of skin cancers in OTR.⁴

Acknowledgments

Data safety monitoring for transplant rejection was performed by Drs A. Costard-Jäckle, H. Kraemer-Hansen, and G. Leimenstoll (Christian-Albrechts-University, Kiel, Germany). Thanks to Mark A. Tomai (3M Pharmaceuticals) for review and advice on this manuscript, to Scott Mc Rae for statistical support and to Leslie Charles (3M Pharmaceuticals) for assistance with manuscript preparation.

This study was supported by 3M Pharmaceuticals. H.B. Slade and J. Bichel were employees of 3M Pharmaceuticals at the time of this study. E. Stockfleth has received research funding and consultancy fees, and was a member of the speaker bureau for 3M.

References

1. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med*. 2000; 342:605–12. [PubMed: 10699159]
2. Sheil AG, Disney AP, Mathew TG, et al. Malignancy following renal transplantation. *Transplant Proc*. 1992; 24:1946–7. [PubMed: 1412921]
3. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant*. 2004; 4:905–13. [PubMed: 15147424]

4. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol.* 2002; 47:1–17. [PubMed: 12077575]
5. Hitt R, Echarri MJ. Molecular biology in head and neck cancer. *Clin Transl Oncol.* 2006; 8:776–9. [PubMed: 17134964]
6. Boyle J, MacKie RM, Briggs JD, et al. Cancer, warts, and sunshine in renal transplant patients. A case-control study. *Lancet.* 1984; 1:702–5. [PubMed: 6143041]
7. Parrish JA. Immunosuppression, skin cancer, and ultraviolet A radiation. *N Engl J Med.* 2005; 353:2712–13. [PubMed: 16371639]
8. Hengge UR, Ruzicka T. Topical immunomodulation in dermatology: potential of toll-like receptor agonists. *Dermatol Surg.* 2004; 30:1101–12. [PubMed: 15274700]
9. Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. *Br J Dermatol.* 2007; 157:133–41. [PubMed: 17501955]
10. Jorizzo J, Dinehart S, Matheson R, et al. Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. *J Am Acad Dermatol.* 2007; 57:265–8. [PubMed: 17512087]
11. Stockfleth E, Christophers E, Benninghoff B, Sterry W. Low incidence of new actinic keratoses after topical 5% imiquimod cream treatment: a long-term follow-up study. *Arch Dermatol.* 2004; 140:1542. [PubMed: 15611446]
12. Vidal D, Matias-Guiu X, Alomar A. Open study of the efficacy and mechanism of action of topical imiquimod in basal cell carcinoma. *Clin Exp Dermatol.* 2004; 29:518–25. [PubMed: 15347339]
13. Hausteil UF, Paasch U. Aggressive undifferentiated squamous cell carcinoma in an immunosuppressed patient after kidney transplantation. *J Dtsch Dermatol Ges.* 2005; 3:44–6. [PubMed: 16353749]
14. Prinz BM, Hafner J, Dummer R, et al. Treatment of Bowen's disease with imiquimod 5% cream in transplant recipients. *Transplantation.* 2004; 77:790–1. [PubMed: 15021851]
15. Brown VL, Atkins CL, Ghali L, et al. Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial. *Arch Dermatol.* 2005; 141:985–93. [PubMed: 16103328]
16. Harwood CA, Perrett CM, Brown VL, et al. Imiquimod cream 5% for recalcitrant cutaneous warts in immunosuppressed individuals. *Br J Dermatol.* 2005; 152:122–9. [PubMed: 15656812]
17. Gayed SL. Topical imiquimod cream 5% for resistant perianal warts in a renal transplant patient. *Int J STD AIDS.* 2002; 13:501–3. [PubMed: 12171672]
18. Schmook T, Nindl I, Ulrich C, et al. Viral warts in organ transplant recipients: new aspects in therapy. *Br J Dermatol.* 2003; 149:20–4. [PubMed: 14616341]
19. Euvrad S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med.* 2003; 24:1681–91. [PubMed: 12711744]
20. Ulrich C, Busch JO, Meyer T, et al. Successful treatment of multiple actinic keratoses in organ transplant patients with topical 5% imiquimod: a report of six cases. *Br J Dermatol.* 2006; 155:451–4. [PubMed: 16882188]

Fig 1.
Study flow diagram.

Fig 2.
Complete clearance rates by transplant group.

Fig 3.
Partial clearance rates by transplant group.

Table 1

Patient disposition

Variable	Liver		Kidney		Heart	
	IMIQ, n = 2	Vehicle, n = 2	IMIQ, n = 20	Vehicle, n = 10	IMIQ, n = 7	Vehicle, n = 2
Sex						
Female	0 (0)	0 (0)	4 (20)	1 (10)	0 (0)	0 (0)
Male	2 (100)	2 (100)	16 (80)	9 (90)	7 (100)	2 (100)
Age (years)						
Mean $\pm$ SD	65.5 $\pm$ 4.95	65.0 $\pm$ 1.41	62.2 $\pm$ 8.16	60.7 $\pm$ 10.53	63.0 $\pm$ 9.18	63.0 $\pm$ 5.66
Range	62-69	64-66	37-76	42-74	45-70	59-67
Race white	2 (100)	2 (100)	20 (100)	10 (100)	7 (100)	2 (100)
Treatment area location						
Face	0 (0)	2 (100)	17 (85)	5 (50)	9 (71)	2 (100)
Scalp	2 (100)	0 (0)	3 (15)	5 (50)	2 (29)	0 (0)

Values within parentheses are percentages.

Table 2

Clearance of individual AK lesions by treatment group

	Liver		Kidney		Heart	
	Imiquimod	Vehicle	Imiquimod	Vehicle	Imiquimod	Vehicle
Individual lesion clearance	17/17 (100%)	-25/15 (-167%)	88/125 (70%)	-55/88 (-63%)	32/44 (73%)	-32/10 (-320%)

A negative number indicates an increase in lesions compared to baseline. Number of subjects analysed in each treatment group includes only those with baseline and 8-week post-treatment counts.