Taylor & Francis
healthsciences

5. Imiquimod 5% Cream for the Treatment of Cutaneous Lesions in Immunocompromised Patients

RICHARD JOHNSON and EGGERT STOCKFLETH

INTRODUCTION

Diseases that compromise the immune system can either be acquired, e.g. human immunodeficiency virus (HIV), or the result of a treatment that suppresses the individual's immune system, e.g. after organ transplantation. On a global scale approximately 45 million individuals are immunosuppressed and of this total, 40 million are infected with HIV. In the United States of America (USA) the number of people with HIV is thought to be between 700,000 to 900,000, whilst the number of organ transplant patients approximates 100,000 with 20,000 new transplant operations every year. In 2001, the number of new infections of HIV recorded in sub-Saharan Africa was 3.5 million, 45,000 in USA and about 35,000 in Western Europe, whilst the number of new-borns infected with HIV disease was around 800,000.

TREATMENT OF SKIN LESIONS WITH IMIQUIMOD 5% CREAM IN HIV-INFECTED PATIENTS

HIV causes disease by infecting lymphocytes and destroying critical regulatory and effector cells of the immune system. Helper T cells (CD4), which initiate and co-ordinate cell-mediated and humoral immunity are progressively destroyed. As the CD4 count falls, the patient becomes susceptible to an increasing number of opportunistic infections and cancers (1). Neoplastic conditions observed within this group of immuno-compromised individuals include non-Hodgkin's lymphoma and cervical and anal intraepithelial neoplasia. In addition, HIV-infected patients have increased frequency of Burkitt's lymphoma, Epstein–Barr-virus-negative large cell lymphoma and Merkel cell carcinoma (2, 3). Tumors in HIV-infected patients are characterized by aggressive clinical behavior, more advanced stage lesions and shortened survival (3). Cutaneous viral infections most commonly observed in this group of patients include facial herpes (herpes simplex virus-1 (HSV-1), genital herpes (HSV-2), herpes zoster (varicellisa zoster virus (VZV)), oral hairy leukoplakia (Esptein-Barr virus), Kaposi's sarcoma (HHV-8), plantar warts (HPV-1) and facial and flat warts (1). These cutaneous infections are problematic as they cause both physical annoyance and cosmetic embarrassment.

The therapeutic options encompass three different methods of treatment. The first takes the form of treating the HIV disease itself irrespective of the patient's immune status e.g. treatment of VZV with systemic acyclovir or famcyclovir or the use of interlesional interferons (IFNs) (1, 4, 5). Alternatively, the HIV can be directly targeted through highly active anti-retroviral therapy (HAART) (6). The third treatment option involves restoring the patient's immune defenses, irrespective of the patient's viral load (1). This treatment option has only recently become available, following the use of systemically administered interleukin-2 to stimulate the production of CD4 cells. Alternative approaches take the form of topically applied creams that penetrate the skin, which help by either restoring or stimulating defenses against cutaneous viral diseases at the site of application (1).

It is now understood that an effective cell-mediated immune response is required for the control of viral skin diseases. The cells that play a role in this immune response are Langerhans' cells. These cells identify and process viral antigens and recruit CD4+ lymphocytes and macrophages for the local immune response (7). Dysfunction or absence of these cells prevents normal functioning of the T helper (Th) cells resulting in compromised local immune surveillance (8). This may be avoided through a new treatment option, which has demonstrated potent antiviral and antitumor activities in both animals and humans (9, 10). Imiquimod is an immune response modifier that stimulates the local immune system and has been proposed as a therapeutic alternative for the treatment of viral skin lesions in HIV-infected patients. Its indirect antiviral and anti-tumor activities (*in vivo*) stem from its stimulatory effect on the innate and cell-mediated immune response through the activation of local cytokines, including IFNα, interleukins (1, 6, 8, 10 and 12), and tumor necrosis factor α (9, 10). These in turn stimulate production of the Th1 immune response, enhancing acquired cellular immunity. Imiquimod 5% cream (Aldara™) is indicated for the topical treatment of external genital and perianal warts and recommended via guidelines in the USA, Australia, Latin America and Europe (9–14). The properties of imiquimod are fundamental for its clinical effect (15, 16) and are discussed in more depth by Professor Chosidow and Professor Dummer in this supplement.

Imiquimod's therapeutic benefits have been extensively studied and well documented for the treatment of cutaneous viral infections and skin cancers (17–21). In

contrast to traditional cutaneous therapies e.g. trichloro-acetic acid, electrocautery, laser or surgical excision, imiquimod therapy for genital warts is associated with minimal scarring and lower rates of recurrence (18, 22, 23). These studies have been conducted in otherwise healthy individuals; however, the use of imiquimod for treating dermatological conditions in HIV-infected patients has not been thoroughly addressed. Recently, in a randomized, double-blind, safety study, Gilson et al. (24) investigated the effect of imiquimod for the treatment of external anogenital warts in HIV-infected patients. Although the results did not demonstrate a significant difference between the effect of imiquimod 5% cream and vehicle in the total number of patients with clinical clearance in their baseline warts (imiquimod 11% versus vehicle 6%) (24), a greater proportion of imiquimod-treated patients experienced a 50% or greater reduction in baseline warts. These results suggested that imiquimod 5% cream might have clinical utility in treating external anogenital warts in some HIV-infected patients. As the patient population in this study was not receiving HAART, further studies are necessitated to examine the efficacy of imiquimod in HIV-infected patients who are receiving HAART.

Imiquimod has also been shown to be effective in obtaining complete clinical clearance of facial molluscum contagiosum (MC) in a severely immunocompromised HIV-positive patient who demonstrated a persistently low CD4 cell count and high viral load (7). At present very few clinical trials have been conducted with imiquimod for the treatment of MC in HIV-infected patients. However, the findings to date suggest that treatment of several viral dermatological conditions with imiquimod is promising.

USE OF IMIQUIMOD FOR THE TREATMENT OF SKIN LESIONS IN ORGAN TRANSPLANT RECIPIENTS

Another group of patients who have a higher risk of cutaneous infections and malignancies are those who are immunosuppressed following organ transplant operations. Globally, an estimated one million patients have benefited from organ transplantation, demonstrating an impressive survival rate of 20-25 years (25). Currently 140,000 organ transplant recipients are alive in the USA and 22,953 solid organ transplantations were performed in 2000 (26).

The long-term success of organ transplantation depends on the prevention of allograft rejection (25). This has been achieved through better immunosuppressive regimens e.g. prednisolone, azathioprine, cyclosporine and a new generation of agents, tacrolimus and mycophenolic acid (25). However, these immunosuppressive agents not only impair the patient's reactivity to the graft but also to infectious organisms, thereby making them more susceptible to opportunistic pathogens. Organ

transplant recipients by virtue of their immunosuppressive regimens are predisposed to epithelial malignancies and infections (25). For example, organ transplant recipients have a three- to four-fold greater risk than the general population in developing cutaneous cancers (27, 28). This increased prevalence is due to two distinct mechanisms. Firstly, the agents used in transplantation may be directly carcinogenic and secondly, chronic immunosuppression resulting from post-transplant immunosuppressive regimens creates a state in which immune surveillance and eradication of pre-cancerous changes are impaired (26). These mechanisms increase the transplant recipient's susceptibility to risk factors associated with cutaneous malignancies. Bearing in mind that 80% of all cutaneous carcinomas are located on sun-exposed skin areas, exposure to sunlight is a risk factor. Other documented risk factors include oncogenic viruses e.g. human herpes virus type 8 and Epstein Barr virus which are implicated in Kaposi's sarcoma and non-Hodgkin's lymphoma, respectively (29, 30). An additional risk factor is human papillomavirus (HPV) infection. In 1995, Jong-Tieben et al. (31) showed that 85% of all skin tumors observed in renal transplant recipients originated from HPV infection. In addition to this, HPV also causes non-malignant skin lesions that include anogenital, plantar and palmar warts (32).

The most common types of post-transplantation neoplasms are skin cancer, lymphoma, lung cancer, Kaposi's and other sarcoma and cancer of the cervix and inner genitalia (33, 34). With regard to skin cancer, organ transplant patients have been documented to have a greater than 200 and 250 times increased risk of developing squamous cell carcinoma (SCC) and actinic keratosis (AK), than non-immunosuppressed patients, respectively. In addition, the prevalence of AK increases to between 40% and 60% within 20 years post-transplantation (35). In contrast, the risk of basal cell carcinoma (BCC) is not as pronounced, with a 10–15 times increased risk compared to that observed in the general population (35). Post-transplant skin cancers are more prevalent within countries with a predominantly white population, inevitably causing morbidity and even mortality (26).

Recently we have investigated the prevalence of HPV and two tumor suppressor genes, p53 and p60, in cutaneous neoplasms within both organ transplanted patients and non-grafted, non-immunosuppressed patients (Professor Stockfleth, personal communication). These tumor suppressor genes have been identified as the most frequently mutated genes in a range of human cancers (36, 37) including skin cancer (38). Upon investigating the prevalence of HPV DNA in SCC, we observed a higher incidence of HPV DNA in the transplanted population than in the non-immunosuppressed patients. In addition, these lesions contained higher

levels of positive mutated p53, thereby suggesting a correlation between the presence of HPV and p53 expression. The presence of mutated p53 could be used as a positive tumor marker for the detection of cutaneous malignancies within organ transplant recipients. The first step in the management of skin cancers takes the form of prevention; however, in the case of immunosuppressed individuals this option is not always feasible. An alternative step may take the form of a prophylactic vaccination. We are currently identifying the types of HPV commonly implicated in skin lesions of transplant patients in the hope of developing a specific vaccine to immunize pre-transplant patients to HPV-related skin lesions.

Stimulation of the local immune response may also be a viable treatment option for these patients. The immune response modifying properties of imiquimod are particularly beneficial for immunosuppressed patients, as they induce activation of the immune response at the site of application alone, with no reported effect on the systemic system. However, to date few studies have been published demonstrating the use of imiquimod for treating cutaneous lesions in transplant patients. The first documented study by Smith et al. (39), investigated the treatment of Bowen's disease with a combination of imiquimod 5% cream and 5-fluorouracil 5% gel, a topical chemotherapeutic agent. The sampled population of five renal transplant patients were on chronic immunosuppressive chemotherapy regimens to prevent rejection of their transplants. The results demonstrated total clearance of the area of Bowen's disease after treatment with imiquimod. This study suggested that local cytokines induced by imiquimod may have beneficial effects in treating Bowen's disease within organ transplant recipients (39). In addition to these findings we have recently demonstrated the successful treatment of multiple AKs with imiquimod 5% cream in organ transplant recipients (40). Four transplant patients with histories of multiple SCC and extensive AKs were treated with imiquimod 5% cream, three times a week, for a total of 12 weeks. All AK lesions in three of the patients were clinically and histologically clear, whilst 80% clearance was reported in the fourth patient. The only side effects observed were mild erythema, edema and erosion. No effect on systemic immunity or on the graft was observed. During the course of treatment with imiquimod, immunosuppressive therapy continued unchanged (40). To confirm the validity of imiquimod for the treatment of AK in organ transplant patients we are planning to conduct a vehicle-controlled study, to determine its efficacy and safety.

The documented use of imiquimod for treating viral conditions such as external genital warts in otherwise healthy individuals (17, 41) and HIV-infected patients (42), led to a study conducted by Gayed (43) who investigated the effect of topical imiquimod cream for

the treatment of recalcitrant perianal warts in renal transplant patients. The results showed that imiquimod was both safe and effective in clearing these lesions in immunocompromised, renal transplant recipients. Patients experienced mild side effects of localized erythema, a natural consequence of pro-inflammatory cytokine induction that is well documented with imiquimod use (22, 41). In addition to these documented benefits of imiquimod, we have successfully demonstrated the treatment of HPV6-associated warts in a double lung transplant patient (Professor Stockfleth, personal communication). The patient developed the cutaneous infection approximately four months after transplantation. He was instructed to topically apply imiquimod 5% cream three times a week at the site of the lesion. Following just 8 to 10 applications, a marked decrease in the size of the warts occurred, accompanied by mild erythema. After 10 weeks of treatment, total clearance of the lesion was observed. During a two year follow-up, he experienced no recurrence of his warts.

CONCLUSION

The number of immunocompromised patients, whether acquired through HIV infection or following organ transplantation, is increasing worldwide. Not only does this pose a problem for the individual; it has health, economic and social implications. One problem takes the form of opportunistic infections such as HPV-associated warts, as well as cutaneous malignancies (e.g. SCC or BCC), which cause both discomfort and embarrassment to the patient. However, the mode of action of imiquimod to stimulate innate and cell-mediated immunity has resulted in increased interest in this therapy option for the treatment of cutaneous infections and malignancies in this patient population. Although research is slowly emerging on its potential use for treating skin lesions within immunosuppressed patients, further clinical studies are required to assess the safety and efficacy of imiquimod for the treatment of dermatological conditions commonly observed in immunocompromised patients.

REFERENCES

1. Conant MA. Immunomodulatory therapy in the management of viral infections in patients with HIV infection. J Am Acad Dermatol 2000; 43: S27–S30.
2. Schulz TF, Boshoff CH, Weiss RA. HIV infection and neoplasia. Lancet 1996; 348: 587–591.
3. An KP, Ratner D. Merkel cell carcinoma in the setting in HIV infection. J Am Acad Dermatol 2001; 45: 309–312.
4. Meadows KP, Tyring SK, Pavia AT, Rallis TM. Resolution of recalcitrant molluscum contagiosum virus lesions in human immunodeficiency virus-infected patients with cidofovir. Arch Dermatol 1997; 133: 987–990.
5. Syed TA, Cheema KM, Khayyami M, Ahmad SA, Ahmad S, Ahmad TA. Human leukocyte interferon-alpha versus podophyllotoxin in cream for the treatment of

genital warts in males. A placebo-controlled, double-blind, comparative study. Dermatology 1995; 191: 129–132.

6. Ochsendorf FR, Schofer H, Runne U, Milbradt R. Therapy of oral hairy leukoplakia with acyclovir. Hautarzt 1988; 39: 736–738.

7. Strauss RM, Doyle EL, Mohsem AH, Green ST. Successful treatment of molluscum contagiosum with topical imiquimod in a severely immuno-compromised HIV-positive patient. Int J STD AIDS 2001; 12: 264–266.

8. Cruz PD, Bergstresser PR. Antigen processing and presentation by epidermal Langerhans' cells: introduction of immunity or unresponsiveness. Dermatol Clin 1990; 9: 633–647.

9. Miller RL, Gerster JF, Owens ML. Imiquimod applied topically: a novel immune response modifier and new class of drug. Int J Immunopharmacol 1999; 21: 1–14.

10. Sauder DN. Immunomodulatory and pharmacological properties of imiquimod. J Am Acad Dermatol 2000; 43: S6–11.

11. Centers for Disease Control & Prevention (CDC). 2002 Guidelines for treatment of sexually transmitted diseases. Mortality & Morbidity Weekly Report (MMWR) 2002; 51(RR 6): 53–56.

12. Professional Advisory Board (PAB) of the Australia and New Zealand HPV Project, Guidelines for the medical management of genital HPV and/or genital warts in Australia and New Zealand. 2002; 1–22.

13. Tatti SS, Belardi G, Marini MA, Eiriz A, Chase LA, Ojeda J, et al. Consenso en la metodologia diagnostica y terpeutica para las verrugas anogenitales. Rev Obst Ginecol Latino-americanas 2001; 59: 1–16.

14. von Krogh G, Lacey CJ, Gross G, Barrasso R, Schneider A. European course on HPV associated pathology: guidelines for primary care physicians for the diagnosis and management of anogenital warts. Sex Trans Infect 2000; 76: 162–168.

15. Suzuki H, Wang B, Shivji GM. Imiquimod, a topical immune response modifier, induces migration of Langerhans cells. J Invest Dermatol 2000; 114: 135–141.

16. Pehoushek J, Smith KJ. Imiquimod and 5% flurouracil therapy for anal and perianal squamous cell carcinoma in situ in an HIV-1- positive male. Arch Dermatol 2001; 137: 14–16.

17. Berman B. Imiquimod: a new immune response modifier for the treatment of external genital warts and other diseases in dermatology. Int J Dermatol 2001; 41: 7–11.

18. Buck HW, Fortier M, Knudsen J, Paavonen J. Imiquimod 5% cream in the treatment of anogenital warts in female patients. Int J Gynaecol Obs 2002; 77: 231–238.

19. Tyring SK. A randomised, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. J Infect Dis 1998; 178: 551–555.

20. Beutner KR, Geisse JR, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999; 41: 1002–1007.

21. Schroeder TL, Sengelmann RD. Squamous cell carcinoma in situ of the penis successfully treated with imiquimod 5% cream. J Am Acad Dermatol 2002; 46: 545–548.

22. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998; 134: 25–30.

23. Garland SM, Sellors JW, Wikstrom A, Peterson CS, Aranda C, Aractingi S, et al. Imiquimod 5% cream is a safe and effective self-applied treatment for anogenital warts: results of an open-label multicentre Phase IIIB trial. Int J STD AIDS 2001; 12: 722–729.

24. Gilson RJ, Shupack JL, Friedman-Kien AE, Conant MA, Weber JN, Nayagam AT, et al. A randomised, controlled safety study using imiquimod for the topical treatment of anogenital warts in HIV-infected patients. Imiquimod study group. AIDS 1999; 13: 2397–2404.

25. Stockfleth E, Ulrich C, Meyer T, Christophers E. Epithelial malignancies in organ transplant patients: a clinical presentation and new methods of treatment. Recent Results Cancer Res 2002; 160: 251–258.

26. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis and management. J Am Acad Dermatol 2002; 47: 1–17.

27. Shell AG. Development of malignancy following renal transplantation in Australia and New Zealand. Transplant Proc 1992; 24: 1275–1279.

28. Penn I. Occurrence of cancers in immunosuppressed organ transplant recipients. Clin Transplant 1998; 147–158.

29. Andreoni M, Goletti D, Pezzotti P, Pozzetto A, Monini P, Sarmati L. Prevalence, incidence and correlates of HHV-8/ KSHV infection and Kaposi's sarcoma in renal and liver transplant recipients. J Infect 2001; 43: 195–199.

30. Hsieh WS, Lemas MV, Ambinder RF. The biology of Epstein-Barr virus in post-transplant lymphoproliferative disease. Transplant Infect Disease 1999; 1: 204–212.

31. de Jong-Tieben LM, Berkhout RJ, Smits HL, Bouwes Bavinck JN, Vermeer BJ, van der Woude FJ, et al. High frequency of detection of epidermodysplasia verruciformis-associated human papillomavirus DNA in biopsies from malignant and premalignanat skin lesions from renal transplant recipients. J Invest Dermatol 1995; 105: 367–371.

32. Bouwes-Bavinck JN, Felthkarmp M, Struijk L, ter Scheggett J. Human papillomavirus and skin cancer risk in organ transplant recipients. J Invest Dermatol 2001; 6(Suppl): 207–211.

33. Penn I. Post-transplant malignancy: the role of immunosuppression. Drug Safety 2000; 23: 101–113.

34. Penn I. Cancers in renal transplant recipients. Ad Renal Replacement Ther 2000; 7: 147–156.

35. Boyd AS, Stasko T, Cameron GS, Russel M, King LE. Histologic features of actinic keratoses in solid organ transplant recipients and healthy controls. J Am Acad Dermatol 2001; 45: 217–221.

36. Lai H, Lin L, Nadji M, Lai S, Trapido E, Meng L. Mutations in the p53 tumor suppressor gene and early onset breast cancer. Cancer Biol Ther 2002; 1: 31–36.

37. Crowe DL, Hacia JG, Hsieh CL, Sinha UK, Rice H. Molecular pathology of head and neck cancer. Histol Histopathol 2002; 17: 909–914.

38. McGregor JM, Harwood CA, Brooks L, Fisher SA, Kelly DA, O'nions J. Relationship between p53 codon 72 polymorphism and susceptibility to sunburn and skin cancer. J Invest Dermatol 2002; 119: 84–90.

39. Smith KJ, Germain M, Skelton H. Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% 5-fluorouracil therapy. Dermatol Surg 2001; 27: 561–564.

40. Ulrich C, Busch J, Christophers E, Sterry W, Stockfleth E. Successful treatment of multiple actinic keratoses with imiquimod 5% in organ transplant patients. Poster presented at the 20th World Congress of Dermatology, 2002; Paris, France.

41. Beutner KR, Spruance SL, Houghman AJ, Fox TL, Owens ML, Douglas JM. Treatment of genital warts with an immune-response modifier (imiquimod). J Am Acad Dermatol 1998; 38: 230–239.

42. Saiag P, Bourgault-Villada I, Pavlovic M, Roudier-Pujol C. Efficacy of imiquimod on external anogenital warts in

HIV-infected patients previously treated by highly active antiretroviral therapy. AIDS 2002; 16: 1438–1440.
43. Gayed SL. Topical imiquimod cream 5% for resistant perianal warts in renal transplant patients. Int J STD AIDS 2002; 13: 349–351.

QUESTIONS AND ANSWERS

Question: *Do you have any experience in treating skin lesions within other immunosuppressed groups of patients, for example those with autoimmune disease?*

Professor Stockfleth: Within my group we have demonstrated the use of imiquimod in single-case studies, primarily within HIV-infected patients. My colleague Professor Hengge has published the use of imiquimod for treating common warts and molluscum contagiosum in otherwise healthy patients and in difficult-to-treat patient populations. In addition, I have demonstrated its success in treating skin lesions in HIV-infected patients with CD4 counts as low as 50.