Acta Derm Venereol 2003; Suppl. 214: 5–7
DOI: 10.1080/03658340310011870

Taylor & Francis
healthsciences

1. Introduction: Immunotherapy for Dermatological Conditions

DARRELL RIGEL and BRIAN BERMAN

Over the last few decades we have observed that modification of the immune response is a successful methodology for treating a broad scope of dermatological conditions. The range of immunomodulators that is currently available is split into two categories: those that up-regulate the immune response and those that suppress it.

The response of the immune system is key in the protection against infection and other harmful environmental attacks. The first line of defense is innate immunity, which protects against pathogens. The innate response includes those mechanisms that are already present and can be activated immediately, such as non-specific resistance by the skin. If micro-organisms do penetrate the outer layer of the skin, or a mucous membrane, they will encounter phagocytic white blood cells or natural cytotoxic cells which will destroy them. Other protective mechanisms include the complement system that consists of a group of blood proteins that act to eliminate the invading microorganisms.

The immune system also mounts a specific response to pathogens defined as the acquired (humoral or cell-mediated) immune response. Humoral immunity involves the production of antibodies by B-lymphocytes, which circulate in the blood, plasma and other extracellular fluids and bind specifically to the antigen that induced them. Binding of antibody to antigen prevents access to host cells, enabling phagocytic cells to ingest them or activating the complement system.

Also there is cell-mediated immunity, which is particularly important in the defense against viruses and possibly cancer cells. This response depends on direct interactions between T lymphocytes and cells bearing the antigen the T cells recognize, such as virus-infected cells and tumor cells. However, cytotoxic T lymphocytes also require the assistance of T-helper cells, which can be divided into T-helper 1 (Th-1) cells and T-helper 2 (Th-2) cells, each producing a distinct profile of cytokines. Th-1 cells secrete cytokines, including interferon (IFN) γ, and result in the activation of macrophages whereas Th-2 cells help B cells produce antibodies.

The combination of the innate and cell-mediated immunity acts to eliminate viral infections and tumors, and in the majority of cases this takes place successfully so that the host is unaware of the attack. Even for those viral or oncological conditions that do develop, the immune system often has the capacity to eliminate either the virus or the tumor, and it has been reported that spontaneous regression of one viral condition, genital warts, occurs in 10–30% of patients (1). This regression is considered to result from an active cell-mediated immune response (1). Furthermore, spontaneous regression of cutaneous tumors such as basal cell carcinoma (BCC) also occurs relatively frequently (approximately 20%) and is thought to be associated with a cell-mediated immune response (2–4).

The importance of the immune system is further exemplified by those patients whose system is not working adequately, e.g. in patients who are immunocompromised due to immunosuppressive medication received following organ transplantation. These patients tend to experience an increased incidence of viral infections such as those that are caused by cytomegalo virus, herpes simplex virus, varicella zoster virus, Epstein-Barr virus and hepatitis B and C viruses (5). This patient group also has a significantly higher risk of developing different types of malignancies, in particular, cutaneous tumors (5). It is now well recognized that renal grafted patients have an increased risk of non-melanoma skin cancer (NMSC), predominantly squamous cell carcinoma (SCC). As studies have shown that the likelihood of developing skin cancer increases with the number of years of immunosuppression (6), the importance of a functioning immune system in eliminating these malignancies is clearly demonstrated.

As the immune response is a crucial factor in the etiology of these viral conditions and cutaneous malignancies, it is logical to presume that methods that stimulate or mimic this response may be effective treatment options. One type of immunotherapy that has been used for a number of viral and oncological conditions is T-cell cytokines such as IFN and interleukins (ILs). Interferon has successfully treated a range of viral conditions such as cutaneous warts and hepatitis B and C (7–11). Cutaneous malignancies, including BCC and Bowen's disease, have also been resolved with intra-lesional and peri-lesional injections of the cytokines IFNα and IL-2 (12–17). Cytokines, however, are not routinely used as treatment options for NMSC as the efficacy does not approach that achieved with surgery. In addition, administration can be time consuming and costly, and many patients experience flu-like symptoms as side effects.

The successful treatment of several viral and oncological conditions with T-cell cytokines, and the role of the cell-mediated immune system in their spontaneous regression, highlights the potential for

methods that stimulate the innate and cell-mediated immune response to be successful treatment options in these conditions. This hypothesis has become a reality with a family of imidazoquinolines that are immune response modifiers. The first member in this family is imiquimod, a molecule that possesses both antiviral and antitumor activity *in vivo* (18, 19). Imiquimod 5% cream (Aldara™) is currently a recommended first-line treatment option for external genital and perianal warts (20, 21). Imiquimod has been successfully used for the treatment of a range of viral and oncological conditions and several small-scale trials and case studies have been published on the use of imiquimod for the treatment of non-genital warts and other viral conditions such as molluscum contagiosum in both immunocompetent and immunosuppressed patients (22–28). These will be discussed in more detail in this supplement. Initial studies have also highlighted the potential of imiquimod for the treatment of cutaneous malignancies such as BCC and actinic keratosis (29–37), which also are discussed further in this supplement. It will be interesting to see the potential of imiquimod in the large-scale studies that are ongoing for actinic keratosis and BCC.

REFERENCES

1. Coleman N, Birley HD, Renton AM, Hanna NF, Ryait BK, Byrne M, et al. Immunological events in regressing genital warts. Am J Clin Pathol 1994; 102: 768–774.
2. Curson C, Weedon D. Spontaneous regression in basal cell carcinomas. J Cutan Pathol 1979; 6: 432–437.
3. Hunt MJ, Halliday GM, Weedon D, Cooke BE, Barnetson RS. Regression in basal cell carcinoma: an immunohistochemical analysis. Br J Dermatol 1994; 130: 1–8.
4. Halliday GM, Patel A, Hunt MJ, Tefany FJ, Barnetson RS. Spontaneous regression of human melanoma/nonmelanoma skin cancer: association with infiltrating CD4+ T cells. World J Surg 1995; 19: 352–358.
5. Stockfleth E, Ulrich C, Meyer T, Arndt R, Christophers E. Skin diseases following organ transplantation: risk factors and new therapeutic approaches. Trans Proc 2001; 33: 1848–1853.
6. Bouwes Bavinck JN, Hardie DR, Green A, Cutmore S, MacNaught A, O'Sullivan B, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. Transplantation 1996; 61: 715–721.
7. Monsonego J, Cessot G, Ince SE, Galazka AR, Abdul-Ahad AK. Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. Genitourin Med 1996; 72: 111–114.
8. Bornstein J, Pascal B, Zarfati D, Goldshmid N, Abramovici H. Recombinant human interferon-beta for condylomata acuminata: a randomized, double-blind, placebo-controlled study of intralesional therapy. Int J Std AIDS 1997; 8: 614–621.
9. Dinsmore W, Jordan J, O'Mahony C, Harris JR, McMillan A, Radcliffe KW, et al. Recombinant human interferon-beta in the treatment of condylomata acuminata. Int J Std AIDS 1997; 8: 622–628.
10. Sharieff KA, Duncan D, Younossi Z. Advances in treatment of chronic hepatitis C: 'pegylated' interferons. Cleve Clin J Med 2002; 69: 155–159.
11. Liaw YF. Management of patients with chronic hepatitis B. J Gastroenterol Hepatol 2002; 17: 406–408.
12. Chimenti S, Peris K, Di Cristofaro S, Fargnoli MC, Torlone G. Use of recombinant interferon alfa-2b in the treatment of basal cell carcinoma. Dermatology 1995; 190: 214–217.
13. Kaplan B, Moy RL. Effect of perilesional injections of PEG-interleukin-2 on basal cell carcinoma. Dermatol Surg 2000; 26: 1037–1040.
14. Ikic D, Padovan I, Pipic N, Knezevic M, Djakovic N, Rode B, et al. Basal cell carcinoma treated with interferon. Int J Dermatol 1991; 30: 734–737.
15. Alpsoy E, Yilmaz E, Basaran E, Yazar S. Comparison of the effects of intralesional interferon alfa-2a, 2b and the combination of 2a and 2b in the treatment of basal cell carcinoma. J Dermatol 1996; 23: 394–396.
16. Dogan B, Harmanyeri Y, Baloglu H, Oztek I. Intralesional alfa-2a interferon therapy for basal cell carcinoma. Cancer Lett 1995; 91: 215–219.
17. Kowalzick L, Mensing H, Weyer U, Kimmig W, Brzoska J. Bowenoid actinic keratosis: therapy with intralesional injection of recombinant beta-interferon. Hautarzt 1992; 43: 373–375.
18. Harrison C, Jenski L, Voychehovski T, Bernstein D. Modification of immunological responses and clinical disease during topical R-837 treatment of genital HSV 2 infection. Antiviral Res 1988; 10: 209–223.
19. Sidky YA, Borden EC, Weeks CE, Reiter MJ, Hatcher JF, Bryan GT. Inhibition of murine tumour growth by an interferon inducing imidazoquinolinamine. Cancer Res 1992; 52: 3528–3533.
20. Centre for Disease Control & Prevention (CDC). 2002 Sexually Transmitted Diseases Treatment Guidelines Mortality & Morbidity Weekly Report (MMWR) 2002; 51(RR6): 53–56.
21. 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 Transm Inf 2000; 76: 162–168.
22. Buckley R, Smith K. Topical imiquimod therapy for chronic giant molluscum contagiosum in a patient with advanced human immunodeficiency virus 1 disease. Arch Dermatol 1999; 135: 1167–1169.
23. Hengge UR, Esser S, Schultewolter T, Behrendt C, Meyer T, Stockfleth E, Goos M. Self–administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. Br J Dermatol 2000; 143: 1026–1031.
24. Schwab RA, Elston DM. Topical imiquimod for recalcitrant facial flat warts. Cutis 2000; 43: 555–556.
25. Cutler K, Kagen MH, Don PC, McAleer P, Weinberg JM. Treatment of facial verrucae with topical imiquimod cream in a patient with human immunodeficiency syndrome. Acta Derm Venereol 2000; 80: 134–135.
26. Weisshaar E, Gollnick H. Potentiating effect of imiquimod in the treatment of verrucae vulgares in immunocompromised patients. Acta Derm Venereol 2000; 80: 306–307.
27. Liota E, Smith KJ, Buckley R, Menon P, Skelton H. Imiquimod therapy for molluscum contagiosum. J Cut Med Surgery 2000; 4: 76–81.
28. Brown CW, O'Donoghue M, Moore R, Tharp M. Recalcitrant molluscum contagiosum in an HIV afflicted male treated successfully with topical imiquimod. Cutis 2000; 65: 363–366.

29. Beutner KR, Geisse JR, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999; 41: 1002 – 1007.
30. Marks R, Gebauer K, Shumack S, Amies M, Bryden J, Fox TL, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. J Am Acad Dermatol 2001; 44: 807 – 813.
31. Stockfleth E, Ulrich C, Salasche SJ, Christophers E. A randomised, double-blind, vehicle controlled study to assess imiquimod 5% cream for the treatment of multiple actinic keratoses. Arch Dermatol 2002; 138: 1498 – 1502.
32. Persaud AN, Shamuelova E, Lou W, Lebwohl M. Clinical effect of imiquimod 5% cream in the treatment of actinic keratosis. J Am Acad Dermatol 2002; 47: 553 – 556.
33. Geisse JK, Rich P, Pandya A, Gross K, Andres K, Ginkel A, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. J Am Acad Dermatol 2002; 47: 390 – 398.
34. Salasche SJ, Levine N, Morrison L. Cycle therapy of actinic keratoses of the face and scalp with 5% topical imiquimod cream: an open label trial. J Am Acad Dermatol 2002; 47: 571 – 577.
35. Shumack S, Robinson J, Kossard S, Golitz L, Greenway H, Schroeter A, et al. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma. Arch Dermatol 2002; 138: 1165 – 1171.
36. Sterry W, Ruzicka T, Herrera E, Takwale A, Bichel J, Andres K, Ding L. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomised studies comparing low-frequency dosing with and without occlusion. Br J Dermatol 2002; 147: 1227 – 1236.