

1. Introduction: Immunotherapy for Dermatological Conditions

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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 cytomegalovirus, 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 IFN α 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 (AldaraTM) 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.

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