EXPERT OPINION

Immunotherapy in Dermatology

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Immunotherapy is a *type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection and other diseases*. Several cutaneous disorders occur as a result of an imbalance in the immunological pathway. The use of immunotherapy is well-established in malignancies and has a recognized role in the management of infections as well.[1,2]

Certain immunotherapies only target certain cells of the immune system while others affect the immune system in general. The immunotherapy can be of two types: **activation immunotherapy**, where immunity is induced or enhanced (used in infections, cancers) or a **suppression immunotherapy** where immunity is suppressed (used in autoimmune diseases). The different types of immunotherapy available today include cytokines, vaccines and some monoclonal antibodies.[2]

Topical immunotherapy has been used in the treatment of basal and squamous cell carcinoma, Bowen's disease, actinic keratosis, cutaneous T-cell lymphoma and primary and secondary malignant melanoma. Other conditions known to be treated successfully include lichen nitidus, nodular prurigo, vulval intraepithelial neoplasms, vulval paget's disease, condyloma accuminata, conjunctival squamous papillomata, atopic eczema and systemic lupus erythematosus.[3]

TOPICAL IMMUNOMODULATORS IN DERMATOLOGY

Topical immunomodulators are molecules which act by modifying the immune response locally when applied to the skin. They work by either **up-regulating (activating immune response/immunostimulation)** or **down-regulating (suppressing immune response/ immunosuppresion)** the immune response. Immunomodulators have been used in various dermatoses where the changes in the cutaneous immunology are central to their pathogenesis. They are categorized as steroidal and nonsteroidal immunomodulators.[4]

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The immunomodulator agents are classified as:[4]

Macrolactums

- Tacrolimus
- Pimecrolimus
- Sirolimus
- ABT-281
- Cyclosporine

Contact allergens

- Diphencyprone/Diphenylcyclopropenone (DPCP)
- Squaric acid dibutylester
- Dinitrochlorobenzene

Immunostimulators

- Imiquimod
- Resiquimod

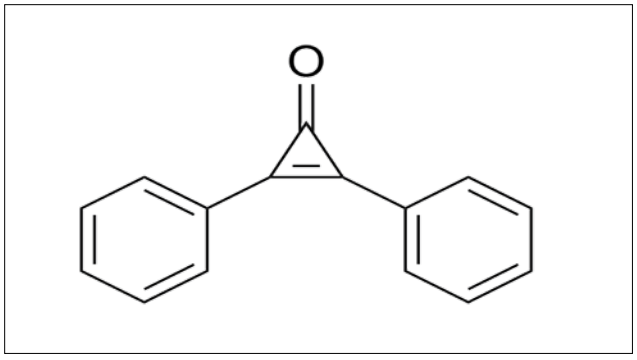
Miscellaneous agents

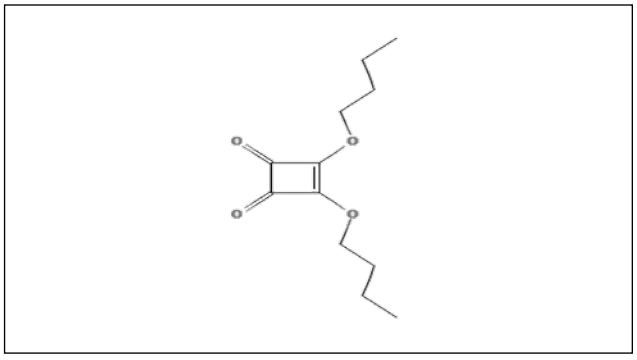
- Calcipotriol
- Anthralin
- Topical zinc
- Topical interferon
- Intralesional interferon
- Intralesional BCG.

Immunomodulators have emerged as the therapy of choice for several immune-mediated dermatoses such as atopic dermatitis, contact allergic dermatitis, alopecia areata, psoriasis, vitiligo, connective tissue disorders such as morphea and lupus erythematosus, disorders of keratinization and several benign and malignant skin tumors. The advantages associated with them include comparable efficacy, ease of application and greater safety when compared with their systemic counterparts. They can also be used for longer periods without aggressive monitoring.[4]

Diphencyprone or Diphenylcyclopropenone

It has been widely used as a topical treatment of alopecia areata and common warts. In alopecia areata, its use is based on antigenic competition theory, where the immune reaction to one antigen is proposed to





inhibit the development of immune response to other antigens. In the treatment of warts, the mechanism of action is not clear; however, it triggers a nonspecific cell-mediated immune response, triggering virus-infected cell lysis and death.[4]

Adverse effects include regional lymphadenopathy, eczema at treated site and impaired sleep. The less common side effects include fever and chills, fainting and flu-like symptoms. In female patients of childbearing age, pregnancy test should be negative before starting DPCP and a reliable contraception should be used by the patient throughout the treatment period. It is also recommended that it should not be used in children <15 years of age due to lack of long-term toxicity data.[4]

Squaric Acid Dibutylester

The mechanism of action of squaric acid dibutylester (SADBE) is similar to that of DPCP; however, long-term treatment of alopecia areata has the potential to lead to significant nonspecific suppression of delayed hypersensitivity reaction. Topical SADBE is used for the treatment of alopecia areata and warts.[4] Even though the side effects of SADBE are similar to DPCP, unlike DPCP, it is not mutagenic. It is not as stable as DPCP in acetone and requires refrigeration.[4]

Dinitrochlorobenzene

Dinitrochlorobenzene (DNCB) was the first topical sensitizer which was studied for use in the immunotherapy of alopecia areata and warts. It contains contaminants that have been shown to be mutagenic and carcinogenic in animal studies. Almost 40% of the drug is absorbed systemically. It has been largely replaced by DPCP and SADBE. It is used topically in the immunotherapy of alopecia areata and warts, skin cancers, melanoma, human immunodeficiency virus (HIV) infections and atopic dermatitis. Adverse effects include regional lymphadenopathy, eczema at treated site and impaired sleep. The less common side effects include fever and chills, fainting spells and flu-like symptoms.[4]

THE EVOLVING ROLE OF IMMUNOTHERAPY IN THE TREATMENT OF WARTS

Immunotherapy has become increasingly popular in the treatment of refractory cutaneous and genital warts including topical, intralesional and systemic agents. Even though there are no well-defined criteria on when immunotherapy should be tried in patient with warts, still the recent indications include recalcitrant warts, recurrent warts, extensive warts and difficult to treat areas (periungal and palmoplantar sites).[2]

There are many agents used for immunotherapy which show significant results in terms of safety and efficacy. Various agents used in the immunotherapy of warts are: topical agents (imiquimod, sinecatechins, Bacillus Calmette-Guérin [BCG]), intralesional agents (Mw vaccine, BCG vaccine, purified protein derivative [PPD], MMR vaccine, candidal extract, Trichophyton antigen, tuberculin, vitamin D_3, interferon α-2b) and systemic agents (such as zinc, cimetidine, levamisole, echinacea, propolis, human papillomavirus [HPV] vaccines).[2]

It is important to approach immunotherapy based on a patient-to-patient basis after considering factors such as disease burden, availability of medication, cost of therapy, potential side effects and immune status of the patient. Combined use of immunotherapy with other destructive modalities such as cryotherapy and radiofrequency ablation or concomitant use of multiple modalities of immunotherapy has been shown to enhance the treatment response.[2]

Immunotherapy can be administered in various ways for the treatment of warts, the simplest being topical application of certain inorganic molecules. These molecules elicit a contact hypersensitivity reaction with secondary activation of an immunological response, or

even topical applications of immune modulators like imiquimod and BCG vaccine.[5]

Use of immunotherapeutic agents in the treatment of recurrent warts (such as intradermal PPD) may be an effective, well-accepted and cost-effective treatment approach, especially in India where vaccination against tuberculosis is performed routinely and is mandatory. Various open studies and small randomized trials have also shown that immunomodulators are effective and devoid of major adverse effects. An additional advantage of the use of immunotherapy is that they have the potential to prevent recurrence of warts.[5]

TOPICAL IMMUNOTHERAPY IN ALOPECIA AREATA

Topical immunotherapy has been documented to be the best treatment for severe alopecia areata. DNCB, SADBE and DPCP are the contact allergens, which have been used for this purpose. While DNCB is mutagenic and is largely replaced by DPCP and SADBE, DPCP and SADBE are both nonmutagenic compounds. They are known to possess comparable efficacy and relapse rates. It has been seen that DPCP shows a response rate of 60% in severe alopecia areata to 17% in patients with alopecia totalis or universalis and shows about 88-100% high response rate in patients with patchy alopecia areata.[3]

REFERENCES

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4. Khandpur S, Sharma VK, Sumanth K. Topical immunomodulators in dermatology. J Postgrad Med. 2004;50(2):131-9.
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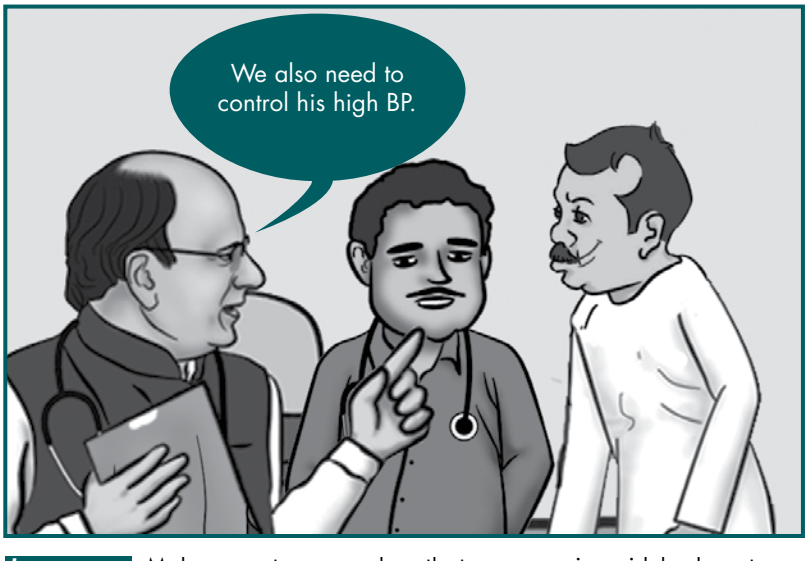
Make sure

DURING MEDICAL PRACTICE

SITUATION: A hypertensive patient with type 2 diabetes had high serum uric acid levels.



LESSON: Make sure to remember that serum uric acid had a strong association with levels of systolic and diastolic BP in type 2 diabetic patients. More attention to the serum uric acid level and treatment of hyperuricemia could halt the progress of diabetic nephropathy.

Iran J Kidney Dis. 2014;8(2):152-4.