

Newer Uses of Topical Imiquimod Therapy in Dermatology

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Date:	23 May, 2001
Venue:	Sheraton Hotel, Hong Kong
Speaker:	Prof. J. L. Jorizzo
Organizer:	HKSDV; Scientific Meeting

Imiquimod is a locally active immune response modifier, which stimulates natural killer cell activity and augments T-cell activities. Since its launch for the treatment of genital warts, newer uses have been described. Its mode of actions is summarized in Table 1.

Summary of phase I trials using topical imiquimod showed that the commonest side effects were local skin reactions. Undetected in serum or urine, it did not affect CD-4 counts or AIDS progression and less than one percent of patient had sensitization to imiquimod.

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| <ol style="list-style-type: none">1. Immune response modifier2. Up-regulates m-RNA for a number of cytokines: IFN-alpha, IFN-gamma, TNF-alpha, IL-6, IL-10 & IL-123. Increases cellular immunity4. Stimulates epidermal Langerhans' cell activity5. Enhances Langerhans' cell antigen presentation6. Promotes Langerhans' cell migration to local draining lymph node7. No direct effect on IL-2 or T cells8. No direct anti-viral activity in vitro9. Anti-viral and anti-tumor effects in vivo10. Significant reduction of human papillomavirus DNA |
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Table 1. Mode of Action of Imiquimod

Genital warts

Table 2 summarizes the results of the imiquimod 1004 trial, using topical imiquimod and vehicle three times per day for genital warts.

Table 2. Percentage of patients with total clearance of genital warts (Intention to treat analysis) (P<0.0001)

Patients	5% Imiquimod	Vehicle
All	50%	11%
Male	33%	5%
Female	72%	20%

Both imiquimod and vehicle groups had similar incidence of flu-like symptoms. For imiquimod the commonest site reactions included erythema, excoriations and erosions. No patient discontinued due to local skin reactions. The superior response rate seen in females was thought to be due to differences in the degree of wart keratinisation, earlier presentation to clinic and the natural occlusive effect of the female genitalia. The trial was performed in Caucasians with the majority of males having had circumcisions. The speaker described that the clearance rate in uncircumcised man reached 66%. This is of significance in Hong Kong as most Asian males are uncircumcised.

Common and plantar warts

The speaker favoured the use of combination therapy in treating stubborn common and plantar warts. After cryotherapy, 17% salicylic acid is applied at bedtime. This allows better penetration of imiquimod, which is applied in the morning after. For plantar warts, other destructive treatment including laser and curettage can be used in combination therapy.

Molluscum contagiosum

Combination therapy with topical intermittent cantharalin and imiquimod (once per day to three times per day) has been helpful especially in difficult cases.

Actinic keratosis and cheilitis

These can be treated with topical imiquimod three times per week for one to two months. An alternative approach is to use imiquimod for one to two weeks pre-

or post-cryotherapy. The speaker advocated a four-step approach for the management of patients with ultraviolet-induced keratoses:

1. Rule out ultraviolet-induced cutaneous malignancies;
2. Cryotherapy for hypertrophic actinic keratosis;
3. Topical imiquimod for earliest actinic keratosis; and
4. Cosmetic facial peels.

Bowen's disease

Bowen's disease can be treated by using topical imiquimod once daily for 16 weeks. In a small study of 16 patients, 15 completed the trial and 14 of which had complete clearance confirmed by biopsy.

Basal cell carcinoma

Studies are now in progress investigating the use of topical imiquimod to reduce the size of superficial and nodular basal cell carcinomas as part of combination therapy. Complete tumor clearance rate of up to 90% had been observed with daily or five times per week applications.

Herpes simplex

The use of topical imiquimod as a novel treatment of herpes simplex has been under investigation. Studies with guinea pigs suggested efficacy despite lack of direct anti-viral activity. Possible mechanism relates to recognition of herpes simplex virus by antigen presenting cells, induction of interferon-alpha and other cytokines, and enhancement of cell-mediated immunity. As imiquimod induces the production of T-memory cells, it is possible that its use may reduce herpes recurrence.

Alopecia areata

The pathogenesis of this non-scarring alopecia may involve cytotoxic T-cells. There were anecdotal reports showing favorable response using imiquimod three times per week.

Cutaneous T-cell lymphoma

The use of injections of interferon in the treatment of this T-helper cell cutaneous lymphoma had been established. Anecdotal success had been demonstrated using topical imiquimod three times per week.

Keloid

The role of surgery in the treatment of keloid has been limited by recurrence. Interferon injections at excision site have reduced recurrence after surgery but this is seldom used due to its cost. One recent study, yet to be published, had demonstrated the absence of recurrence six months after surgery when imiquimod was applied at excision site.

Other possible applications

Cell-mediated immunity is vital for immune surveillance of tumors and eradication of viral and fungal infections. As imiquimod stimulates cell-mediated immunity, its role in the management of these conditions is being explored. There were anecdotal successes using imiquimod for the treatment of tinea unguium, Bowen's disease and inoperable metastases from melanoma.

The question of whether increasing the frequency of imiquimod application could produce comparable results with combination therapy was raised. The speaker commented that he favored combination treatment for facilitation of imiquimod delivery. Regarding safety of imiquimod, he commented that he had used imiquimod in a four-month old for treatment of molluscum contagiosum with no adverse effects. Treatment of flat facial warts remains difficult. He favoured light freezing, topical salicylic acid and imiquimod.

Learning points:

According to the speaker, the clearance rate of genital wart by imiquimoid in uncircumcised man reached 66%. This is of significance in Hong Kong as most Asian males are uncircumcised.



Web sites of Dermatology & Venereology in Hong Kong

The homepage of the Hong Kong Society of Dermatology & Venereology
<http://www.medicine.org.hk/hksdv/>

Hong Kong Dermatology & Venereology Bulletin

(Official Publication of the Hong Kong Society of Dermatology & Venereology)
<http://www.medicine.org.hk/hksdv/bulletin.htm>

Hong Kong Dermatology & Venereology Bulletin

(Subscription site of Blackwell Science Ltd.)
<http://www.blacksci.co.uk/~cgilib/jnlpage.bin?Journal=hdv&File=hdv&Page=ed>

Handbook of Dermatology & Venereology

(Published by Social Hygiene Service, Department of Health)
<http://www.hkmj.org.hk/skin/>

CME Online (Dermatology)

(CME Programme accredited by the Hong Kong College of Family Physicians)
<http://www.medicine.org.hk/cme/>

The Homepage of the Asian Dermatological Association

<http://www.medicine.org.hk/ada/>

