Imiquimod

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INTRODUCTION

Imiquimod, a heterocyclic imidazoquinoline amide, is an immune response modifying drug that has potent antiviral and antitumor activity.[1-2]

PHARMACOKINETICS[1]

Topical radiolabeled imiquimod has minimal systemic absorption. Less than 0.9% of the dose is excreted in the urine and feces.

MECHANISM OF ACTION[1,3]

Immunomodulator effects

It acts on both the major divisions of the immune system i.e., the innate and the acquired immune system by inducing the production of cytokines like IFN-γ, IFN-α and IL-12. These cytokines then stimulate T-helper Type 1 (Th 1) immune response. The production of T-helper Type 2 (Th-2) immune response is inhibited by imiquimod. Also there is upregulation of NK cell activity via induction of 2'5'oligoadenylate synthetase. Modulation of immune response controls tumors and creates an antiviral state which controls viruses. Imiquimod induces migration of Langerhans cells to regional lymph nodes and enhances the antigen presentation to naïve T cells.

INDICATIONS [TABLE 1]

Imiquimod was approved by the US Food and Drug Administration in 1997 for treating external genital and perianal warts and in 2004 for treating actinic keratoses and superficial basal cell carcinoma.

USES

Anogenital warts

Imiquimod is more efficacious in the treatment of anogenital warts than chemodestructive therapies such as podophyllin resin and trichloracetic acid.[1] Imiquimod causes less tissue damage than the destructive therapies and also has the benefit of self-application by the patient at home.[1] In a study of

Table 1: Indications of imiquimod

Viral warts[1,4]
External anogenital warts (condylomata acuminata)
Verruca vulgaris
Periungual warts
Plantar warts
Recalcitrant facial verruca plana
Warts in immunosuppressed individuals
Molluscum contagiosum[5]
Preneoplastic and neoplastic conditions
Actinic keratosis[6]
Superficial basal cell carcinoma (BCC) [7], nodular BCC[8]
Bowen's disease[9]
Invasive squamous cell carcinoma (SCC) [11]
Extramammary Paget's disease[11]
Lentigo maligna[12]
Metastatic melanoma[11]
Keratoacanthoma[11]
Mycosis fungoides[10]
Experimental indications
Morphea, [14] keloidal scarring, [1] porokeratosis of Mibelli, [1] stucco keratosis, [1] lip papillomatosis in immunodeficiency, [15] actinic cheilitis, [16] adult cutaneous Langerhans cell histiocytosis, [17] infantile hemangiomas, [18] cutaneous leishmaniasis, [19] recurrent genital herpes[20]

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108 patients, 51 patients received imiquimod and 57 patients received placebo. The patients on imiquimod showed a complete response rate of 40% and greater than 50% reduction in wart area was seen in 36.5%. Twenty-two per cent of patients cleared by four weeks of treatment and the remaining patients cleared within seven weeks. The recurrence rate was 19% which was lower than with other modalities.[2] Immunologic memory to HPV by imiquimod is probably responsible for the reduced rate of recurrence.[21] Imiquimod causes an increase in cellular immunity and gives long-term protection against recurrences or reinfection.[1]

Common warts

Imiquimod can be used in the treatment of cutaneous warts. Hengge *et al*. treated 50 patients with extragenital warts on the hands, feet and other locations using imiquimod 5% cream which was applied daily for five consecutive days per week over a 16-week period. A total clearance was seen in 30% of patients and > 50% reduction in wart size was seen in 26% of patients.

Molluscum contagiosum

Imiquimod is efficacious for molluscum contagiosum in both immunocompetent and immunocompromised individuals.

In an open-labeled study of 13 healthy children having molluscum contagiosum, 33% of subjects showed complete clearance at the end of four weeks of treatment.[5]

In another study by Hengge *et al*. 15 patients had mollusca which were evenly distributed on the extremities, face, disseminated and in the anogenital area. A total clearance was seen in 53% patients and >50% reduction in molluscum size was seen in 27%. The time interval for clearing of mollusca was 8-12 weeks. Recurrence developed in one patient who had new mollusca at treated locations ten weeks after achieving a complete remission. There was no systemic toxicity, however, some local adverse reactions occurred.[4]

Actinic keratoses

Imiquimod is effective in the treatment of actinic keratoses. The application of imiquimod topically (three times weekly for 12 weeks) in a study of histologically proven actinic keratoses cleared the lesions in 84% and partially cleared the lesions in 8% of patients. Two weeks after the last application of imiquimod clearance of lesions was histologically confirmed.[11] This interrupted therapy was also effective in the treatment of actinic keratosis.[6] In a regimen of cycled therapy for actinic keratoses, a four week therapeutic phase was followed by a four week imposed rest period. This had the advantage of reducing the adverse effects.

Superficial basal cell carcinoma[11]

A study of 35 patients with superficial basal cell carcinoma treated with imiquimod 5% cream, for a treatment period of 16 weeks or two weeks following clinical clearance of lesions revealed that there was clearance of superficial basal cell carcinoma in 100% of patients given the dose twice a day, once a day and three times a week. Clearance rates reduced when imiquimod 5% cream was given twice weekly (60%), once weekly (50%). In case of an acute localized reaction a treatment-free interval of one week was permitted.

Nodular basal cell carcinoma

Imiquimod is effective in nodular basal cell carcinoma but as compared to superficial basal cell carcinoma, it shows lesser efficacy.[11]

Squamous cell carcinoma *in situ* (Bowen's disease)

Imiquimod 5% cream was applied in 16 patients with single lesions of Bowen's disease for a period of 16 weeks. There was a complete histological clearance of the lesions in 93% of patients. During the six-month follow-up period, recurrences were absent.[11]

Invasive squamous cell carcinoma

Imiquimod was tried in invasive squamous cell carcinoma with encouraging results.[11]

Keloids[22]

Keloidal collagenase activity increases on application of imiquimod 5% cream due to increase in the levels of IFN-α. Keloidal collagen and glycosaminoglycan synthesis are reduced. Apoptosis is increased. This results in an antifibrotic and antikeloidal effect. Surgical therapy

of keloids is limited due to a high rate of recurrence which could be reduced by application of imiquimod. In a trial conducted on 12 patients, imiquimod was applied once daily for eight weeks at the site of surgical excision of the keloid. Minimal keloidal recurrences were seen following surgical excision.

CONTRAINDICATIONS

Ulcerations of the penis and vulva, sunburn, history of hypersensitivity to imiquimod or any of its ingredients. Relative contraindications include autoimmune disease, graft versus host disease, photosensitivity and immunosuppression.

DOSAGES AND ADMINISTRATION

It is important to counsel patients about the mode of application of imiquimod cream. Imiquimod 5% cream should be applied three times per week at bedtime. Imiquimod cream should be applied to external genital or perianal warts and should be rubbed in well and left on for six to ten hours. The cream should be removed from the area by washing with mild soap and water. The treatment should be continued until there is total clearance or for up to 16 weeks. In case of a severe local reaction, treatment may be discontinued and restarted later after local reaction settles down.

WARNINGS AND PRECAUTIONS

- Use of imiquimod cream should be avoided for urethral, intravaginal, cervical or intraanal warts.
- Sun exposure should be avoided due to heightened susceptibility to sunburn.
- Inflammatory conditions of skin may be aggravated.
- Barrier contraceptives like condoms and diaphragms may be weakened and hence sexual contact should be avoided while cream is on the skin.
- Likelihood of HPV transmission following application of imiquimod is unknown hence caution should be taken with sexual contact.
- The use of topical imiquimod cream is apparently safe in infants and older children[1,5,18,23] though the safety and efficacy is not established for patients less than 12 years of age.
- Lactation: There is minimal systemic absorption when the drug is applied topically. Excretion in milk is unknown.
- Imiquimod is pregnancy category B drug.

ADVERSE EFFECTS

Most frequent

Local reactions like erythema often occur (in 33-80%). Flu-like symptoms, fatigue, diarrhea, fever, skin blistering, erosion, excoriation, flaking, edema, paresthesia, pruritus, burning, tenderness, stinging, crusting, rash, superficial ulcer may occur.

Less frequent

Back pain, headache, myalgia, hyperkeratosis, rhinitis, severe erythema, vitiligo-like hypopigmentation,[24] and upper respiratory infection have been reported.

Rare

Alopecia, chills, diarrhea, dizziness, dyspepsia, fatigue, fever, lymphadenopathy, sinusitis, vomiting and angioedema have also been reported.[25]

Summary

In conclusion, imiquimod is the first member of a new class of immunomodulator drugs which modulate and upregulate the immune system. Imiquimod is currently FDA-approved only for the treatment of anogenital warts, actinic keratoses and superficial basal cell carcinoma, but there is promising evidence that imiquimod will have many more therapeutic applications in the future. Imiquimod has the added benefit of a self-application topical therapy which tends to be preferred by the patients, thus reducing the number of hospital visits to the risk-benefit ratio of imiquimod. Also in patients, who have failed to respond to other therapeutic modalities or who have had recurrence following standard therapy, or who are medically unfit for surgery, imiquimod may be beneficial. However a close follow up is mandatory.

Studies of imiquimod treating cutaneous malignancies have the drawback of absent long term follow up. The cure rates for imiquimod may be lower

when five year results are compared to standard treatments.[26] The paucity of data on the use of imiquimod in the Indian studies could be attributed to the relatively high cost of imiquimod, Resiquimod is a more potent and soluble analogue of imiquimod. The stimulation of Th1 cell-mediated immune response is similar to imiquimod. Resiquimod is active against genital herpes in the guinea pig model and has been successfully tried in recurrent genital herpes simplex infection.[22]

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