CHAPTER 18

IMIQUIMOD

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INTRODUCTION

Imiquimod, an imidazoquinoline (1-(2 methylpropyl)-1 H-imidazo [4,5c] quinolin-4 amine), is a new synthetic immune response modifier that activates innate and adaptive immune system through activation of toll like receptor (TLR) 7 and 8. It has antiviral, antitumor and immunregulatuar actions via the induction, synthesis and release of cytokines such as interferon (IFN) alpha, interleukin (IL)-6, IFN-gamma, tumor necrosis factor-alpha (TNF-α) and activates and enhances the migration of Langerhans cells, stimulation of the natural killer (NK) cells and secretion of nitric oxide from macrophages.[1-6] The action mechanism of imiquimod was shown in Figure 1.[4] It was approved in 1997 by the US Food and Drug Administration (FDA) for topical treatment of actinic keratosis (AK) on the head and neck, superficial basal cell carcinomas and anogenital warts.[1, 4, 7, 8]

DOSAGES AND USES

It is commercially available as a 5% cream.[1] Imiquimod 5% cream is only suitable for topical use. It is usually used once a day for 3-5 days a week and left on the skin for about 8 hours. Treatment should continue until the complete disappearance of lesions, or up to 16 weeks. It should be applied just before bedtime. After 8 hours, the area washed with mild soap and water.[2,4]

SIDE EFFECTS AND CONTRAINDICATIONS

The most common side effects with imiquimod cream are skin reactions at the treatment site including; redness, swelling, a sore, blister, or ulcer, skin peeling, scabbing and crusting, itching, burning and changes in skin color.[1,2,4,5] Generally, the cosmetic outcome is good, but pigmentary changes may occur. Although photocontact allergy and phototoxicity has naot been shown, sun protection are recommended. Conjuctivitis and keratitis may occur in the treatment of periocular lesions. Rarely, the onset of other dermatological disorders, such as psoriasis, pemphigus foliaceus, angioedema and vitiligo may occur.[2,4]

Systemic absorption of imiquimod 5% cream is minimal.[1,2,5,9] Systemic side effects such as fatique, fever and chills, arthralgias, myalgias, nausea, and diarrhea may rarely occur in patients, especially when the treatment area is large.[1,2,4,5,9] In the study that evaluated the safety and efficacy of imiquimod, a total of 58 adult patients with AK applied imiquimod cream three times a week up to 16 weeks. Patients were assessed after the first and last of treatment, as well as biweekly. Imiquimod and its metabolities were measured in the serum and urine. In the urine of all subjects, less than 0.6% of the applied doses were recovered. Serum imiquimod levels were detected very low.[9]

Conraindications of imiquimod are not known.[1] Animal studies did not show any evidence of teratogenicity or fetotoxicity.[2] There are no adequate and well-controlled studies for the use of imiquimod in pregnant and breastfeeding women. It is not known if imiquimod cream passes into breast milk. Imiquimod 5% cream is classified as pregnancy category B.[1,4]

Indications

Imiquimod 5% cream is used for several skin conditions such as AK,[2,7,10-17] external and perianal warts,[2,18-22] molloscum contagiosum (MC),[2,23-26] superficial basal cell carcinoma,[2,3,7,27-29] discoid lupus erythematosus [(30)], Bowen's disease,[2,7,17,31,32] extramammary Paget's disease,[7,33] erytroplasia of Queyrat,[7] lentigo maligna,[7,34,35] herpes genitalis[36] morphea,[37] porokeratosis,[38] Kaposi sarcoma[39] and keloids scars.[40]

a.Actinic keratosis (AK): AK lesions represent part of a disease continuum which can progress from initial subclinical disease into invasive squamous cell carcinoma. The visible and invisible lesions coexist in the field of sun-exposed skin area in the same patient.[7,9,13,14,16]

Imiquimod is the one of the new treatment options in the treatment of AK.[4,7,9,10,13,14,17] It is generally applied to the lesions three or two times a week for 6-8 weeks.[4,10,17] In a vehicle-controlled clinical study that assessed the safety and efficacy of imiquimod in 22 patients with actinic keratosis, it was detected a significant reduction in the average number of lesions after 8 weeks.[15] In another study, 6 patients used imiquimod 5% cream to lesions three times a week for a maximum of 12 weeks, or until the lesions had resolved. Lesions were clinically resolved in over 80% of patients. The clinical improve-

ment was confirmed with histolopathological examination in patients.[13] In both studies, similar side effects including erythema, itching and scabbing were observed as well.[13,15] The low recurrence rates were observed in animal and clinical studies with imiqumod.[14]

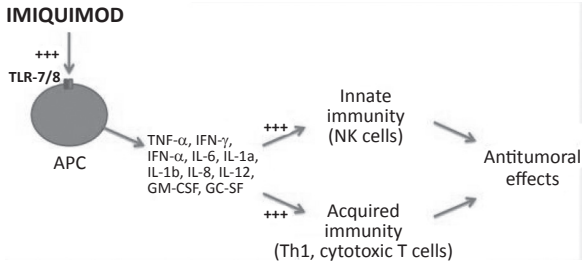


Figure 1: The action mechanism of imiquimod. APC: Antigen presenting cell, GC-SF: Granulocyte colony stimulating factor, GM-CSF: Granulocyte-macrophage colony stimulating factor, IFN: Interferon, IL: Interleukin, TLR: Toll Like receptor, TNF: Tumor necrosis foctor [(4)].

In addition, sub-clinical AK lesions may become apparent in the treatment area during the treatment with imiquimod. Therefore, imiquimod has a potential role in the detection of lesions at subclinical stage and in the prophylaxis of squamous cell carcinoma.[2,14,16]

b. Cutaneous viral diseases:

1.Warts: Imiquimod 5% cream was first approved as a topical cream for the treatment of genital warts by United States FDA in 1997. It has been shown to possess an excellent safety profile and be effective in the treatment of anogenital warts. It is generally applied to the lesions three times a week for 6-8 weeks.[19-22] In the randomized, placebo-controlled trial evaluating the efficacy of imiquimod in anogenital warts, imiquimod was applied once daily 3 times per week for 16 weeks. Complete clearance rate was observed in 50% of patient treated with topical imiquimod 5% cream and 11% patient in the placebo vehicle cream group. There was also a notable disparity between the response of women and men to imiquimod, thought to be due to higher keratinization in male genitalia than in female.[41]

Beside its established use in anogenital warts, there are case reports and studies suggesting the effectiveness of imiquimod 5% cream, either alone or as combination therapy, in the treatment of recalcitrant cutaneous warts. However, these studies are limited in number.[8]

Imiquimod has been demonstrated fewer efficacies for recalcitrant cutaneous warts in immunocompramised patients. In a case series of adult organ transplant recipients and iatrogenically immunosuppressed individuals with verruca vulgaris, patients applied imiquimod once nightly 3 times per week. Clearance was seen in only 1 of 12 patients after 10 weeks and partial clearance in 5 of 12 patients. It was observed in this case series that those immunosuppressed patients did not respond to imiquimod therapy.[42] In addition, anogenital warts treatment with imiquimod in pregnancy seems to be promising and not compromise a good pregnancy outcome.[22, 43]

2. Molloscum contagiosum (MC): Imiquimod 5% cream was found effective and safe on the treatment of MC in children. Since it is painless and offers better cosmetic results, imiquimod can be preferred treatment in children, especially with numerous small lesions [(23,24,26)]. Whereas, imiquimod was found ineffective in clearing of MC in two randomized controlled trials.[44]

c. Superficial basal cell carcinoma (SBCC):

Imiquimod has been approved as a new topical treatment for adults with small SBCC, when surgery is less favorable.[4,7,28,45] Imiquimod inhibits angiogenesis and rapidly increases peritumoral infiltration of NK cells and cytotoxic T-cells resulting in apoptosis of basal cell carcinoma cells.[3,4,28,35] It acts by blocking directly the Hedgehog pathway activation in basal cell carcinoma.[45] In a study, imiquimod was applied five or seven times per week or vehicle for 6 weeks in patients with SBCC lesions. The composite clearance rates at 12 weeks post treatment were 75%, 73% and 2%, respectively. In the long-term efficacy of imiquimod 5% cream following application five times per week for 6 weeks, a clinical clearance rate was reported as 90% at the initial 12 week post treatment examination. The rate of clinical clearance at the 1-year follow-up was 84%.[28] Topical application of imiquimod 5% cream was detected to be effective in the treatment of multiple basal cell carcinomas in xeroderma pigmentosum.[29]

In recent years, it has been reported that imiquimod 5% cream is also a useful alternative treatment for nodular basal cell carcinoma, especially for lesions <10 mm. In addition, it has a significant neoadjuvant effect on lesions >10 mm.[46]

Conclusion

Imiquimod is a topically active immunomodulatory agent for the treatment of some viral and non-viral conditions such as AK, anogenital warts, molloscum contagiosum and SBCC. It has been shown to be a safe and effective in the treatment of those cutaneous disorders. It is also rarely used in several skin diseases such as discoid lupus erythematosus, extramammary Paget's disease, morphea, herpes genitalis, Kaposi sarcoma and keloids scars. However, further studies are needed to determine the efficacy of imiquimod, dose frequency and application and optimal combination with other therapeutic measures.

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