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Imiquimod in Dermatology

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Abstract

Imiquimod is a synthetic immune response modifier with potential antitumor and antiviral activity. Both direct and indirect activation of innate and acquired immune responses leads to its therapeutic effect in many dermatological conditions. Ease of self-administration by the patient, and good safety profile has increased the off-label usage of imiquimod for many dermatological conditions in recent years. Clinicians should be well aware of the rare cutaneous and systemic side effects of imiquimod before prescribing the medication. Patent should be informed and educated about proper method of application and the need for monitoring of severe local reactions and other rare side effects after starting the medicine. Regular follow up of the patient is important to identify the potential risks associated with the drug and to ensure safe and optimal treatment results.

Keywords: Imiquimod; Dermatology; Interleukin

Introduction

Imiquimod is a synthetic immune response modifier with potential antitumor and antiviral activity. Both direct and indirect activation of innate and acquired immune responses leads to its therapeutic effect in many dermatological conditions. The FDA approved indications of the drug include external genital and perianal warts, superficial basal cell carcinoma and actinic keratosis. As it is a relatively safe and well tolerated topical cream, it is recently used for many other dermatoses also.

Structure

Imiquimod (1-(2-methylpropyl)-1h-imidazo (4,5-c) quinolin-4-amine), also known as S-26308 or R-837, is an immune response modifier belonging to imidazoquinoline amine family [1] (Figure 1).

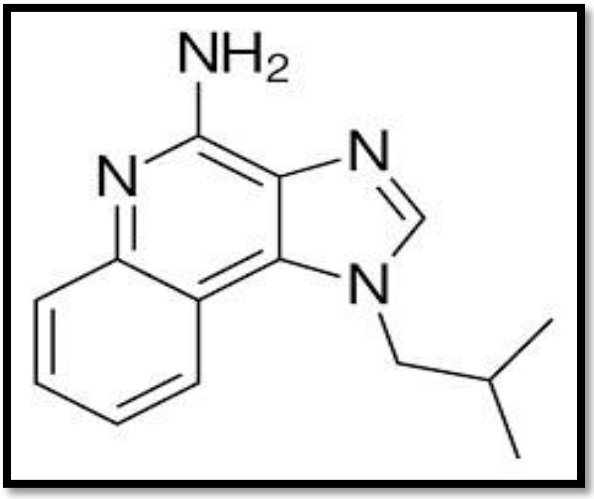

Figure 1: *Chemical structure of imiquimod.*

Mechanism of Action

Imiquimod's potential antitumor and antiviral action is by exerting multiple effects on different set of cells. Imiquimod directly or indirectly activate innate and acquired immune responses leading to identifying and killing of virus-infected cells or tumor cells [2].

Direct action is through toll like receptor dependent pathway and by induction of apoptosis. Imiquimod binds to cell surface receptors TLR-7 and TLR-8 on macrophages, monocytes and dendritic cells. This leads to nuclear factor kappa-B activation and causing increased local production of pro-inflammatory cytokines

such as tumor necrosis factor (TNF)-α, interferon (IFN)-α, interleukin-6,8 and 12, as well as chemokines including CCL2, CCL3, and CCL4. These cytokines along with enhancing the innate immune response, induce transformation of naive T cells to T helper (Th1) phenotype stimulating the secretion of IFN-γ thus indirectly leading to the enhancement of acquired immunity. In addition to the TLR dependent pathway, imiquimod has been shown to enhance inflammatory responses by interacting with adenosine receptors [2-7].

Imiquimod brings about apoptosis in tumor cells by activating the intrinsic pathway thereby activating the caspase family of proteases. In addition, the therapeutic role of imiquimod is partly due to its anti-angiogenic effect. This is by inducing the production of IFNs, interleukin-10, and interleukin-12 leading to the down regulation of some pro-angiogenic factors, vascular endothelial cell apoptosis, and the inhibition of vascular movement and invasion [8].

Pharmacokinetics

Systemic absorption is minimum after local application of the drug ant it depends on the area of application rather than amount applied. Peak plasma concentration varies between 0.1 and 3.5 ng/ml. Less than 0.9 % of the drug is excreted via renal and gastrointestinal system [9,10]. Imiquimod cream is available as 2.5%, 3.75% and 5%.

Uses/ Indications

FDA approved indications

These include external genital and perianal warts, superficial basal cell carcinoma and actinic keratosis

External anogenital warts

Before the introduction of imiquimod, external anogenital warts were mostly treated with physical removal methods like excision, electrocautery, cryotherapy or with application of caustic agents like trichloroacetic acid and podophyllin or by using intralesional interferon. These procedures had less compliance due to the need to attend clinic frequently, pain during procedure and chance of recurrence.

Imiquimod is FDA approved for the treatment of external anogenital warts in 1997 and is a relatively safe, reliable and self-administered drug and with low recurrence rate. Topical 5% imiquimod cream is applied three times per week overnight [for approximately 8 hours] for a maximum of 16 weeks or until warts have cleared. For 3.75% once daily overnight application for a maximum of 8 weeks or until complete clearance of warts is recommended [11-14].

Basal cell carcinoma

Basal cell carcinoma is the most common form of skin cancer and its worldwide incidence seems increasing. Although various treatment options are available for patients with low-risk basal-cell carcinoma, surgery is regarded as the gold standard treatment. Imiquimod 5 % cream is officially approved for treatment of biopsy confirmed superficial small (<2 cm) non-facial basal cell carcinoma. This include lesions on the trunk (excluding anogenital skin), neck, or extremities (excluding the hands and feet. The dosing schedule and treatment duration are not standardized. Factors such as the site, type of basal cell carcinoma and patient comfort is taken into account before deciding the regimen. The recommended schedule in the USA and Europe is 5 times a week for 6 weeks with success rate of 73-77% [15-19].

Though recommended for non- facial lesions less than 2 cm, giant facial basal cell carcinoma with complete clinical and histological clearance after imiquimod treatment is reported. Though Mohs surgery is the gold standard for BCC, in elderly with comorbidities who denies surgery imiquimod is a safe and effective alternative option [20,21].

Actinic keratosis

Actinic keratosis also known as solar keratosis, are benign intra-epithelial neoplasms mostly seen in fair-skinned older population with history chronic sun exposure. As these lesions have a potential to progress to invasive squamous cell carcinoma, early detection and treatment is pivotal. Studies have shown that imiquimod exerts its effect on the lesion and clinically invisible lesions in its vicinity at cellular level also. So it is considered as a field-directed treatment in patients with multiple, widespread lesions involving scalp and face. Imiquimod 5% cream applied thrice weekly for 16 weeks is safe and effective for the treatment of actinic keratosis [22-24].

Off Label Uses

Lately imiquimod is used commonly for the treatment of many other benign and malignant dermatological conditions. Successful use of imiquimod in treating molluscum contagiosum, non-genital viral warts, keloids, precancerous lesions like Bowen's disease, vulval intra-epithelial neoplasia, and actinic porokeratosis is reported in many clinical studies. Nodular basal cell caricnoma, lentigo maligna, extra-mammary Paget disease, Kaposi sarcoma and cutaneous T- cell lymphoma are a few malignant conditions for which use of imiquimod is studied and reported [2,25,26,27,45].

Adverse Effects

Imiquimod cream is known to be a safe and well tolerated drug. Adverse effects are mostly dose dependent local effects at application site and include pruritus, swelling, redness and pain, erosions, ulcerations, flaking and crusting. These are usually mild

reactions and subside after discontinuation of drug when the lesions resolve. Severe local reactions require stoppage of medication and physician consultation [2].

Infrequent cutaneous side effects reported include lichen planus and lichenoid reactions, irreversible vitiligo or vitiligo like pigment loss [29,30,31], psoriasis [32,33,34], erythema multiforme and Stevens Johnson syndrome [35,36], lupus erythematosus like reactions [37], pemphigus [38], pityriasis rubra pilaris [39], erosive pustular dermatosis of the scalp [40] and reversible hair loss [28]. The immune response modification and enhanced circulation of Th1 pro -inflammatory cytokines induced by imiquimod might be the trigger for this. Studies show that many such cases are related to the frequency and total doses of imiquimod applied and the degree of local reaction. So for the treatment of large areas low doses are recommended to avoid these complications. Most of these reported conditions resolved on stopping the medication or with appropriate treatment of the disease identified. This warrants early identification of these side effects to avoid further progression of the condition. Rare case reports of occurrence of skin tumors like epidermoid cyst [41], keratocanthoma [42], squamous cell carcinoma [43], melanoma at treatment site [44] further emphasize the need for proper patient education and monitoring while on imiquimod treatment.

Systemic side effects occur rarely and include headache, fatigue, myalgia, nausea and flu-like symptoms. Serious systemic reactions like severe myalgia and muscle weakness, postural hypotension, dizziness are also reported sporadically. Studies suggest that these may be caused by the locally produced cytokines spreading into the systemic circulation [46,47].

Contraindications

Hypersensitivity to imiquimod or any of its excipients, penile and vulvar ulceration. Caution is advised while using in patients with sunburn, immunosuppression, autoimmune disease, graft versus host disease [9].

Conclusion

Imiquimod cream is a well-accepted relatively safe drug used for a variety of benign and malignant dermatoses recently. Ease of self-administration by the patient, and good safety profile has increased the off-label usage of imiquimod for many dermatological conditions in recent years. Clinicians should be well aware of the rare cutaneous and systemic side effects of imiquimod before prescribing the medication. Patent should be informed and educated about proper method of application and the need for monitoring of severe local reactions and other rare side effects after starting the medicine. Regular follow up of the patient is important to identify the potential risks associated with the drug and to ensure safe and optimal treatment results.

References

1. National Center for Biotechnology Information. Imiquimod.
2. Bubna AK. Imiquimod - Its role in the treatment of cutaneous malignancies. Indian J Pharmacol. 2015; 47: 354-359.
3. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol. 2000; 43: 6-11.
4. Navi D, Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. Dermatol Online J. 2004; 10: 4.
5. Weber A, Zimmermann C, Mausberg AK, Kieseier BC, Hartung HP, Hofstetter HH. Induction of pro-inflammatory cytokine production in thymocytes by the immune response modifiers Imiquimod and Gardiquimod™. Int Immunopharmacol. 2013; 17: 427-431.
6. Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol. 2002; 3: 196-200.
7. Weeks CE, Gibson SJ. Induction of interferon and other cytokines by imiquimod and its hydroxylated metabolite R-842 in human blood cells in vitro. J Interferon Res. 1994; 14: 81-85.
8. Schön M, Bong AB, Drewniok C, Herz J, Geilen CC, Reifenberger J, et al. Tumor-selective induction of apoptosis and the small-molecule immune response modifier imiquimod. J Natl Cancer Inst. 2003; 95: 1138-1149.
9. Jobanputra KS, Rajpal AV, Nagpur NG. Imiquimod. Indian J Dermatol Venereol Leprol. 2006; 72: 466-469.
10. Kulp J, Levy S, Fein MC, Adams M, Furst J, Meng TC. Pharmacokinetics of imiquimod 3.75% cream applied daily for 3 weeks to actinic keratoses on the face and/or balding scalp. Arch Dermatol Res. 2010; 302: 539-544.
11. Edwards L, Ferenezy A, Eron L, Baker D, Owens ML, Fox TL, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol. 1998; 134: 25-30.
12. Buck HW, Fortier M, Knudsen J, Paavonen J. Imiquimod 5% cream in the treatment of anogenital warts in female patients. Int J Gyn Obs 2002; 77: 231-238.
13. Fife KH, Ferenczy A, Douglas JM Jr, Brown DR, Smith M, Owens ML, et al. Treatment of external genital warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. Sex Transm Dis. 2001; 28: 226-231.
14. Baker DA, Ferris DG, Martens MG, Fife KH, Tyring SK, Edwards L, et al. Imiquimod 3.75% cream applied daily to treat anogenital warts: combined results from women in two randomized, placebo-controlled studies. Infect Dis Obstet Gynecol. 2011; 2011: 806105.
15. Skerlev M, Čulav-Košćak I, Ljubojević Hadžavdić S, Sirotković-Skerlev M. Imiquimod. In: Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM. (eds) European Handbook of Dermatological Treatments. Springer, Berlin, Heidelberg. 2015.
16. Schulze HJ, Cribier B, Requena L, Reifenberger J, Ferrándiz C, Garcia Diez A, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from a randomized vehicle-controlled phase III study in Europe. Br J Dermatol. 2005; 152: 939-947.

17. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol. 2004; 50: 722-733.
18. Roozeboom MH, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: A systematic review and meta-analysis of randomized and nonrandomized trials. Br J Dermatol. 2012; 167: 733-756.
19. Clark CM, Furniss M, Mackay-Wiggan JM. Basal cell carcinoma: An evidence-based treatment update. Am J Clin Dermatol. 2014; 15: 197-216.
20. Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, Miller PS, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): A multicentre, non-inferiority, randomised controlled trial. Lancet Oncol. 2014; 15: 96-105.
21. Malhotra AK, Bansal A, Mridha AR, Khaitan BK, Verma KK. Superficial basal cell carcinoma on face treated with 5% imiquimod cream. Indian J Dermatol Venereol Leprol. 2006; 72: 373-375.
22. Topical imiquimod therapy for actinic keratosis: is long-term clearance a realistic benefit? J Clin Aesthet Dermatol. 2008; 1: 44-47.
23. Kopera D. Earliest stage treatment of actinic keratosis with imiquimod 3.75% cream: Two case reports-Perspective for non-melanoma skin cancer prevention. Dermatol Ther. 2020; 33: e13517.
24. Korman N, Moy R, Ling M. Dosing With 5% Imiquimod Cream 3 Times per Week for the Treatment of Actinic Keratosis: Results of Two Phase 3, Randomized, Double-blind, Parallel-Group, Vehicle-Controlled Trials. Arch Dermatol. 2005; 141: 467-473.
25. Ganjian S, Ourian AJ, Shamtoub G, Wu JJ, Murase JE. Off-label indications for imiquimod. Dermatol Online J. 2009; 15: 4.
26. David CV, Nguyen H, Goldenberg G. Imiquimod: a review of off-label clinical applications. J Drugs Dermatol. 2011; 10: 1300-1306.
27. Hyde MA, Hadley ML, Tristani-Firouzi P, Goldgar D, Bowen GM. A Randomized Trial of the Off-label Use of Imiquimod, 5%, Cream With vs Without Tazarotene, 0.1%, Gel for the Treatment of Lentigo Maligna, Followed by Conservative Staged Excisions. Arch Dermatol. 2012; 148: 592-596.
28. Zhang X, Xie Y, Wang L. Rare Cutaneous Side Effects of Imiquimod: A Review on Its Mechanisms, Diagnosis, and Management. Dermatol Ther (Heidelb). 2023; 13: 1909-1934.
29. Brown T, Zirvi M, Cotsarelis G, Gelfand JM. Vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts. J Am Acad Dermatol. 2005; 52: 715-716.
30. Wang HW, Miao F, Shi L, Lu T, Huang Z, Wang XL. Imiquimod-induced localized vitiligo in wife and lichen planus in husband. Chin Med J (Engl). 2013; 126: 2593.
31. Long FQ, Zhao LS, Qian YH. Vitiligo or vitiligo-like hypopigmentation associated with imiquimod treatment of condyloma acuminatum: not a casual event. Chin Med J (Engl). 2017; 130: 503-504.
32. Conrad C, Di Domizio J, Mylonas A, Belkhodja C, Demaria O, Navarini AA, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. Nat Commun. 2018; 9: 25.
33. Igari S, Ohtsuka M, Yamamoto T. Imiquimod-induced widespread psoriasiform eruptions. Eur J Dermatol. 2019; 29: 225-227.
34. Balak DM, Hajdarbegovic E. Drug-induced psoriasis: clinical perspectives. Psoriasis (Auckl). 2017; 7: 87-94.
35. Trayes KP, Love G, Studdiford JS. Erythema multiforme: recognition and management. Am Fam Physician. 2019; 100: 82-88.
36. Tedman A, Malla U, Vasanthakumar L, Buzacott K, Banney L. Stevens-Johnson syndrome due to topical imiquimod 5%. Aust J Gen Pract. 2020; 49: 662-664.
37. Maguiness SM, Farsani TT, Zedek DC, Berger TG. Imiquimod-induced subacute cutaneous lupus erythematosus-like changes. Cutis. 2015; 95: 349-351.
38. Moro F, Ciccone D, Fania L, Mariotti F, Salemme A, Rahimi S, et al. Case report: a rare case of imiquimod-induced atypical pemphigus vulgaris. Front Med (Lausanne). 2022; 9: 1054544.
39. Yang FC, Jessup C, Dahiya M, Reynolds R. Pityriasis rubra pilaris exacerbation with topical use of imiquimod. Int J Dermatol. 2008; 47: 1076-1078.
40. Giuffrida R, Borgia F, Cannavo SP. Two cases of erosive pustular dermatosis of the scalp occurring after topical 3.75% imiquimod for actinic keratoses. Dermatol Ther. 2019; 32: e12770.
41. Marty CL, Randle HW, Walsh JS. Eruptive epidermoid cysts resulting from treatment with imiquimod. Dermatol Surg. 2005; 31: 780-782.
42. Campalani E, Holden CA. Keratoacanthoma associated with the use of topical imiquimod. Clin Exp Dermatol. 2013; 38: 555-556.
43. Fernández-Vozmediano J., Armario-Hita J. Infiltrative squamous cell carcinoma on the scalp after treatment with 5% imiquimod cream. J Am Academy Dermatol. 2005; 52: 716-717.
44. Paul SP. Melanoma arising after imiquimod use. Case Rep Med. 2014; 2014: 267535.
45. Ventura F, Rocha J, Fernandes JC, Pardal F, Brito C. Topical imiquimod treatment of Lentigo Maligna. Case Reports Dermatol. 2009; 1: 78-81.
46. Pasadyn SR, Cain R. Topical Imiquimod Induces Severe Weakness and Myalgias after Three Applications: A Case Report. J Clin Aesthet Dermatol. 2019; 12: 58-59.
47. Saad S, Bobbak M, Housewright C. Acute exacerbation of myasthenia gravis with topical imiquimod use. Proc (Bayl Univ Med Cent). 2017; 30: 333.