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An Insight about Possible Role of Imiquimod in Dermatology and Possible Benefit on Plane Warts: Review Article

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ABSTRACT

Background: Plane warts are smooth, flesh-colored papules that might be flat or raised slightly. Lesions can range in size from 1 mm to greater than 5 mm, and can number anywhere from a handful to the hundreds. The face, hands, and lower legs are frequent places for them to manifest. Scratching, shaving, and trauma can cause them to emerge in a linear pattern. Imiquimod enhances the immune system's reaction. Injecting imiquimod into a skin wound or ulcer triggers cytokine synthesis and activation of the innate and adaptive immune systems. This makes it an accessible alternative for the treatment of a wide range of dermatologic diseases, both benign and malignant.

Objective: Assessment of the possible role of imiquimod in dermatology and possible benefit on plane warts.

Methods: Research on Imiquimod, Skin cancer, and Genital warts was scoured through the databases PubMed, Google Scholar, and Science Direct. The authors also analysed references from related works, but only included the latest or most comprehensive study between October 2000 and January 2021. Documents written in languages other than English have been disqualified due to a lack of translation resources. Dissertations, conference abstracts, and oral presentations were not included since they do not constitute "important scientific discoveries".

Conclusion: Dermatologists have taken notice of imiquimod's recent rise to prominence as a useful immunomodulatory topical medication. However, the appropriate use and utilization of imiquimod in dermatology have been impeded by a lack of randomized controlled studies in the assessment of this potentially crucial medicine, as well as anecdotal evidence combined with varying treatment regimens.

Keywords: Imiquimod, Dermatology, Plane warts.

INTRODUCTION

Plane warts are smooth, flesh-colored papules that may be flat or slightly raised. They can be anywhere from 1 mm to greater than 5 mm in diameter, and there can be anywhere from a handful to hundreds of lesions. Common areas for their appearance are the face, hands, and lower legs. Scratching, shaving, or trauma can cause them to appear in a linear pattern [1].

Plane warts are a typical problem for young people. About 4.7% of elementary school students have warts, and the rate is slightly greater among students who live in rural areas and commute to school. [2, 3]. Despite being the rarest type of wart, 10% of the population or more is affected with plane warts [4], and tend to cluster together on a single person. Human papillomavirus types 3, 10, 28, and 29 commonly produce plane warts [5].

It is believed that 18% of all non-genital cases requiring medical attention are caused by verruca plana [6]. Frustration and discomfort are experienced by 51.7% of patients due to the lesions of verruca plana, which are resistant to therapy and frequently recur. About 38% of people with verruca plana report difficulties in social situations as a result of their condition [7]. Patients seeking therapy for verruca plana of the face often report significant cosmetic and social issues related to the condition [8].

Clinical Features:

In the clinic, plane warts look like slightly raised papules of pink, light brown, or light yellow-shaped like a polygon. Appear on the face, especially the forehead, the mouth, the backs of the hands, and the places where you've shaven. In this case, HPV testing is of no use. A shave biopsy can be used to confirm the diagnosis, but is typically unnecessary [9].

Because of their resistance to treatment, extended duration, and prevalence in aesthetically prominent regions, plane warts present a difficult therapeutic challenge [10]. Since severe treatments for plane warts might cause scarring, it's important to strike a balance between the benefits and risks of doing so. Although there are currently no controlled studies on the efficacy of this strategy, topical tretinoin is the therapy of choice in this situation. It's the same with light-based or laser-based treatments [11].

Non-pharmacologic:

Inflammation often precedes the regression of these lesions. Currently, there are no virus-specific treatments available for HPV [11].

Pharmacologic:

Based on results from five randomised, placebo-controlled studies, topical salicylic acid is among the most effective treatments for warts of all sorts. Legs are a more appropriate application area for salicylic acid than the face. Topical salicylic acid 17% is commonly used overnight, every night, until the warts disappear [12]. Another standard treatment is using a retinoic acid cream (0.025%, 0.05%, or 0.1%) to the affected areas before night. Applying it less frequently will result with a milder, finer scaling and erythema. We must take care to shield ourselves from the sun. Sometimes treatment takes a long time, even if it doesn't work [13].

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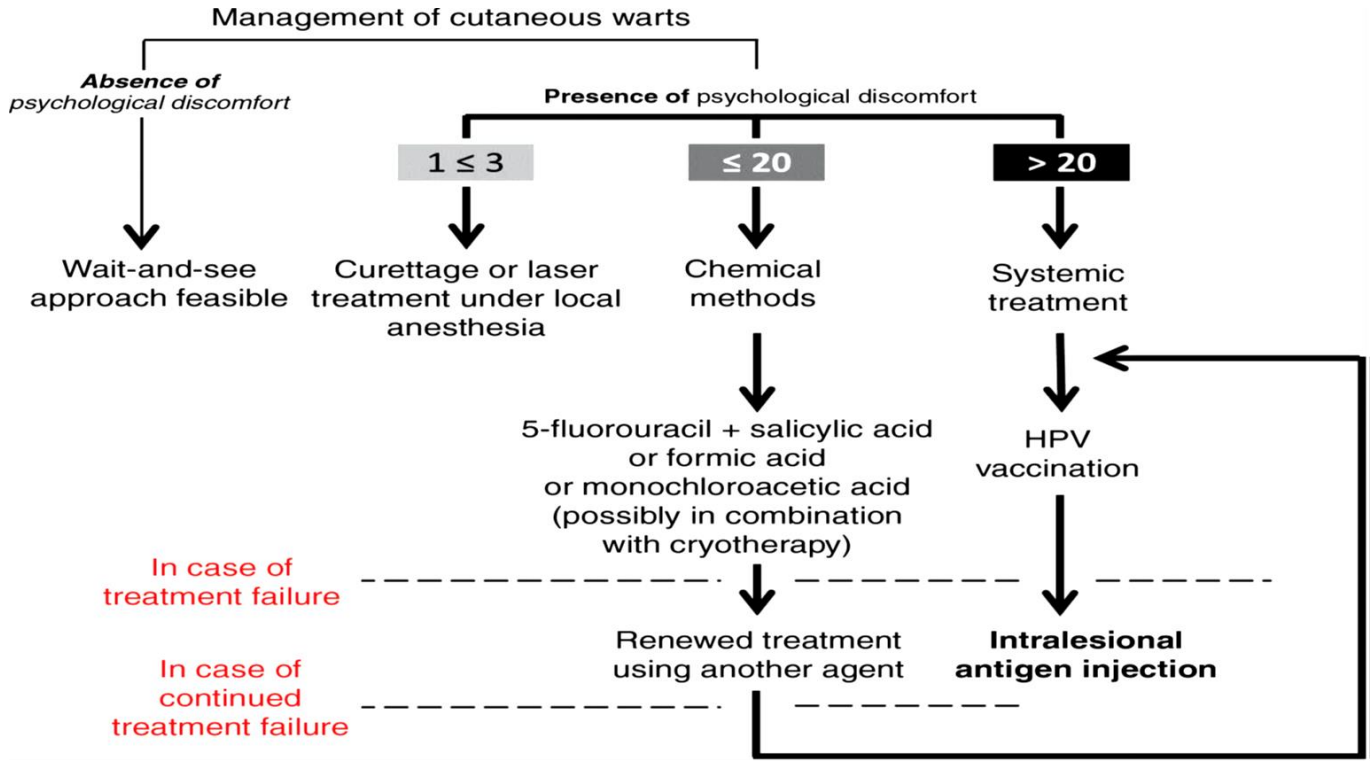

Figure (1): Management of extra-genital cutaneous warts [5].

Imiquimod:

Imiquimod enhances the immune system's reaction. The FDA gave its clearance to this drug so that it may be used on external genital and perianal warts. Then it was authorised again and again for use in treating actinic keratosis and superficial basal cell carcinoma. Both 5% and 3.75 % creams are sold commercially, albeit the lower concentration is more limited in availability. Injecting imiquimod into a skin wound or ulcer triggers cytokine synthesis and activation of the innate and adaptive immune systems. Because of this, it can be used to treat a wide range of dermatologic diseases, both benign and malignant. Imiquimod's actions include those of an antiviral, an anticancer, and immunomodulatory [14].

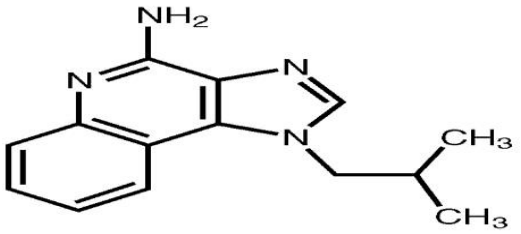

Figure (2): Imiquimod chemical structure [14].

Imiquimod's precise mode of action is not well understood. Studies on animals and humans, however, have shown that imiquimod boosts both the innate and acquired immune responses, making it a potent antiviral and anticancer agent. By increasing levels of interferon (IFN)-alpha, tumor necrosis factor (TNF), and interleukin (IL)-8, imiquimod stimulates the innate immune system. Immunomodulatory cytokines such as macrophage inflammatory protein, macrophage chemotactic protein-1, as well as granulocyte/macrophage colony-stimulating factor, were all produced in large quantities in response to imiquimod. Imiquimod, an agonist for Toll-like receptors (TLR)-7 and TLR-8, was shown to cause the production of these inflammatory cytokines by activating the master transcription factor, nuclear factor kappa B [14].

It has recently been shown that a specific type of dendritic cell called plasmacytoid dendritic cells (PDCs) contribute to the activity of imiquimod. PDCs are the principal source of locally synthesised type I IFNs, including IFN-a. Exposed to imiquimod, PDCs become activated, leading to activation of the TLR7/MyD88 signaling pathway w21, which leads to increased IFN-a production. To summarize, Toll-like receptor 7 (TLR7) on PDCs has a cytoplasmic component that interacts with MyD88 when imiquimod binds to it. Imiquimod-treated mice were protected from arbovirus, cytomegalovirus, and herpes simplex virus (HSV) [15]. This was mostly attributable to the fact that it caused IFN-a to be produced in both animals and people [16]. Increasing the migration of Langerhans cells from the epidermis to the draining lymph nodes is one way in which imiquimod stimulates adaptive immunity. By triggering the IL-12 receptor b2 subunit on T-helper (Th) type 1 cells, in addition to interferon (IFN) and other cytokines, imiquimod might indirectly stimulate the production of the cytokine, hence boosting acquired immunity. In addition, the presence of IL-12 triggers IFN-c production by Th1 cells. However, cytotoxic T cells and natural killer cells have been connected to IFN-c production [17].

There is conclusive evidence that imiquimod has anti-angiogenic effects owing to the upregulation of endogenous anti-angiogenic mediator and the generation of anti-angiogenic cytokines such interferon- (IFN-), interleukin-10 (IL-10), and interleukin-12 [18].

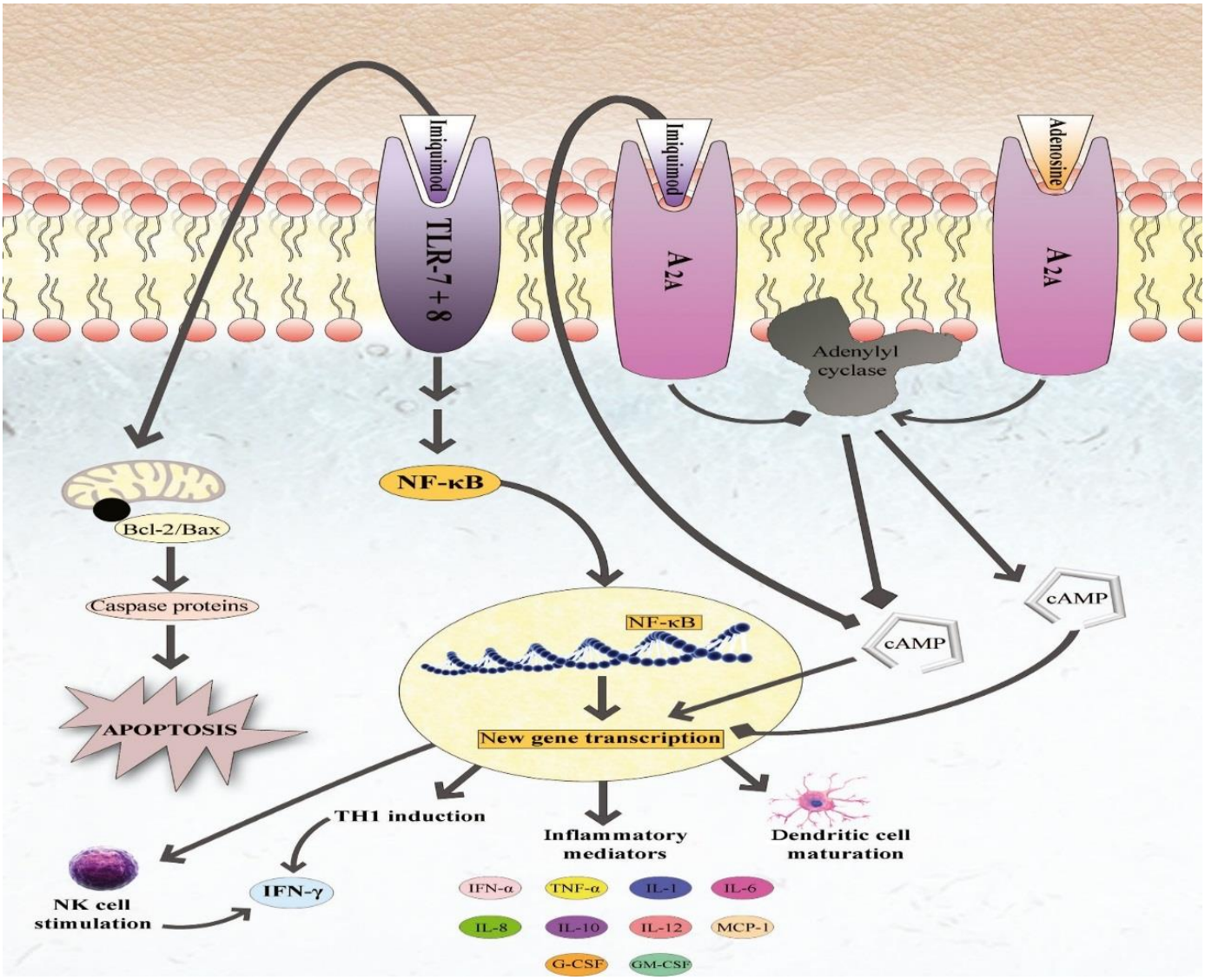

Figure (3): Topical imiquimod Mechanism of action [18].

Imiquimod indications in dermatology:

Numerous applications of imiquimod in cutaneous illnesses have been approved by the Food and Drug Administration. When originally tested, imiquimod was effective in treating anogenital warts. Later on, it was also authorized to treat superficial basal cell carcinomas and facial/scalp AKs**.** Most current first-line topical medicines for treating anogenital warts consider imiquimod. It has been shown that 50% of patients whose lesions were treated with imiquimod 5% cream three times weekly for up to 16 weeks saw a full resolution of their symptoms. Males have a slower clearance rate than females because the vulva is less keratinized and has more moisture than the penile shaft. The occurrence rate is between 13% and 19% [14]**.**

Use of imiquimod for warts other than those on the genitalia has less supporting data. There seems to be a significant drop in effectiveness. After applying a cream containing 5% imiquimod twice a day for an average of 22.34 weeks, 16 of 18 patients in a trial reported complete resolution of non-genital warts that are resistant to treatment [16]**.**

In a small sample size study that involved ten patients, it was found that nine of them with verruca valgaris showed good response and disappear of symptoms after use of imiquimod [19]**.**

Clinical improvement was shown in 33–50% of patients with immunosuppression, and 0% of patients showed complete clinical clearance, according to current data primarily targeted at evaluating the efficacy of imiquimod in the treatment of cutaneous non-genital warts [20]**.**

However, the number of studies that support the use of imiquimod as monotherapy or in combination therapy is so tiny that it cannot be effectively handled in clinical practice. The ideal combination of imiquimod and other therapeutic methods in non-genital warts management needs to be investigated, as does the efficacy of different doses and administration schedules of the drug**.** Some success with imiquimod has been reported in the treatment of epidermodysplasia verruciformis, a rare hereditary condition that raises the odds of contracting certain human papillomaviruses, which can lead to cancers of the skin. There has been some inconsistency

in the outcomes, with several evaluations showing either some progress or none [14].

In dermatology, imiquimod has been used to treat precancerous and cancerous skin lesions. Using imiquimod 5% cream for up to 8 weeks, or in tough instances up to 17 weeks, all six cases of actinic keratosis disappeared [20].

Basal cell naevus syndrome and several basal cell carcinomas on the scalp, have been treated with imiquimod in a number of small open trials or case reports. They appear to prove that topical use of imiquimod is helpful, particularly for individuals with numerous or challenging site illness. Two randomised open-label trials and one randomised double-blind pilot study evaluated the efficacy of imiquimod [21, 22].

Several studies showed that imiquimod, alone or in combination, is effective in treating resistant cutaneous warts. However, the sample sizes in these trials are tiny, and they were not randomised. Research into the efficiency of imiquimod, its appropriate dosing and administration, and its synergy with other treatment methods as paring, salicylic acid, and other invasive techniques, is warranted [20].

Problems with using imiquimod topically:

Many local and infrequently systemic adverse effects have been reported with imiquimod usage, particularly at larger dosages. Imiquimod's direct immunomodulatory impact on the skin involves activation of TLRs and the production of proinflammatory cytokines, which is why it causes skin irritation. Locally generated cytokines, including IFN-a, are thought to be responsible for the systemic adverse effects of Imiquimod, like psoriasis and pemphigus, by stimulating both innate (specifically PDCs) and adaptive immunity [14].

The majority of adverse effects manifest locally and include itching, burning, discomfort, soreness, peeling, erosions, and crusting. If used properly, just a localized quantity of the medicine should enter the bloodstream and go throughout the body. Headache, flu-like symptoms, lethargy, nausea, and musculoskeletal pain are some of the rare systemic adverse effects that have been recorded [23].

Contraindications:

Patients with autoimmune illness, as well as those with a known hypersensitivity to any of the chemicals in imiquimod, should not get this medication [24].

In plane warts:

Plane warts can be treated with imiquimod 5% cream, a costly topical immunomodulator. Local adverse effects such as erythema, irritation, edoema, and erosion have been reported, however systemic adverse effects are extremely uncommon [25]. The ointment is used thrice weekly to treat the lesions (every other day). The cream can be administered to the whole spot, not just the lesion. All non-occluded mucosal membranes can be treated, as well as any exterior HPV infection locations. If symptoms become too much to handle, treatment might be put on hold for a while. The very nonexistent scarring risk of imiquimod is a major benefit of this treatment. Although imiquimod 3.75% cream exists, there is no information regarding its efficacy against common or plane warts [26].

CONCLUSION

Dermatologists have taken notice of imiquimod's recent rise to prominence as a useful immunomodulatory topical medication. However, the appropriate use and utilization of imiquimod in dermatology have been impeded by a lack of randomized controlled studies in the assessment of this potentially crucial medicine, as well as anecdotal evidence combined with varying treatment regimens.

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REFERENCES

1. **Al-Hamamy H, Salman H, Abdulsattar N (2012):** Treatment of plane warts with a low-dose oral isotretinoin. ISRN Dermatol., 12: 163929. doi: 10.5402/2012/163929
2. **Abd-ElRaheem T, El-Tahlawy S, El Sherbiny N *et al.* (2019):** Prevalence and risk factors associated with cutaneous warts in Fayoum primary school children. Fayoum Univ Med J., 3: 24–28.
3. **Kasim K, Amer S, Mosaad M *et al.* (2013):** Some Epidemiologic Aspects of Common Warts in Rural Primary School Children. ISRN Epidemiol., 13: 1–6.
4. **Ntungo S, Malan M (2021):** Challenges in Managing Verruca Plana in a Resource Constrained Environment Complicated with Retroviral Disease: An Overview. Open Access J Biog Sci Res., 5: 1-6.
5. **Abeck D, Tetsch L, Lüftl M *et al.* (2019):** Extragenital cutaneous warts – clinical presentation, diagnosis and treatment. JDDG J Dtsch Dermatol Ges., 17: 613–634.
6. **Ghadgepatil S, Gupta S, Sharma Y (2016):** Clinicoepidemiological Study of Different Types of Warts. Dermatol Res Pract., 8: 1–4.
7. **Rodríguez-Cerdeira C, Sánchez-Blanco E (2011):** Glycolic Acid 15% Plus Salicylic Acid 2%. J Clin Aesthet Dermatol., 4 (9): 62–64.
8. **Zhang F (2018):** A novel cosmetic and clinically practicable laser immunotherapy for facial verruca plana: Intense pulsed light combined with BCG-PSN. Photodiagnosis Photodyn Ther., 22: 86–90.
9. **Sterling J (2014):** British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. Br J Dermatol., 171: 696–712.
10. **Mulhem E, Pinelis S (2011):** Treatment of Nongenital Cutaneous Warts. Am Fam Physician, 84 (3): 288-93.
11. **Maranda E, Lim V, Nguyen A *et al.* (2016):** Laser and light therapy for facial warts: a systematic review. J Eur Acad Dermatol Venereol., 30: 1700–1707.

12. **Dall'Oglio F, D'Amico V, Nasca M *et al.* (2012):** Treatment of Cutaneous Warts. Am J Clin Dermatol., 13: 73–96.
13. **Kwok C, Gibbs S, Bennett C *et al.* (2012):** Topical treatments for cutaneous warts. Cochrane Database Syst Rev., 9: CD001781. doi: 10.1002/14651858.CD001781.pub3.
14. **Hanna E, Abadi R, Abbas O (2016):** Imiquimod in dermatology: an overview. Int J Dermatol., 55 (8): 831-44.
15. **Angelopoulou A, Alexandris N, Konstantinou E *et al.* (2020):** Imiquimod - A toll like receptor 7 agonist - Is an ideal option for management of COVID 19. Environ Res., 188: 109858. doi: 10.1016/j.envres.2020.109858
16. **Gilson R, Nugent D, Bennett K *et al.* (2020):** Imiquimod versus podophyllotoxin, with and without human papillomavirus vaccine, for anogenital warts: the HIPvac factorial RCT. Health Technology Assessment (Winchester, England), 24 (47): 1–86.
17. **Yuan J, Ni G, Wang T *et al.* (2018):** Genital warts treatment: Beyond imiquimod. Human Vaccines & Immunotherapeutics, 14 (7): 1815–1819.
18. **Weber A, Zimmermann C, Mausberg A *et al.* (2013):** Induction of pro-inflammatory cytokine production in thymocytes by the immune response modifiers Imiquimod and Gardiquimod™. Int Immunopharmacol., 17: 427–431.
19. **Baker D, Ferris D, Martens M *et al.* (2011):** Imiquimod 3.75% Cream Applied Daily to Treat Anogenital Warts: Combined Results from Women in Two Randomized, Placebo-Controlled Studies. Infect Dis Obstet Gynecol., 11: 806105. doi: 10.1155/2011/806105
20. **Ahn C, Huang W (2014).** Imiquimod in the treatment of cutaneous warts: an evidence-based review. American Journal of Clinical Dermatology, 15 (5): 387–399.
21. **Hannuksela-Svahn A, Nordal E, Christensen O (2000):** Treatment of multiple basal cell carcinomas in the scalp with imiquimod 5% cream. Acta Derm Venereol (Stockh), 80: 381– 82.
22. **Kagy M, Amonette R (2000):** The use of imiquimod 5% cream for the treatment of superficial basal cell carcinomas in a basal cell naevus syndrome patient. Dermatol Surg., 26: 577– 8.
23. **Cantisani C, Lazic T, Richetta A *et al.* (2012):** Imiquimod 5% cream use in dermatology, side effects and recent patents," Recent Pat. Inflamm. Allergy Drug Discov., 6: 65–69.
24. **Whatling E, Balghari K, Powell B (2017):** Immune thrombocytopenic purpura: A rare side effect in a patient treated with Imiquimod for lentigo maligna. JPRAS Open, 13: 77–80.
25. **Hanna E, Abadi R, Abbas O (2016):** Imiquimod in dermatology: an overview. Int J Dermatol., 55: 831–844.
26. **Ahn C, Huang W (2014):** Imiquimod in the Treatment of Cutaneous Warts: An Evidence-Based Review. Am J Clin Dermatol., 15: 387–399.