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REVIEW

Pharmacotherapy of Basal Cell Carcinoma, Anogenital Warts, and Actinic Keratoses: Focus on Topical Imiquimod

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Abstract: Imiquimod, an imidazoquinoline compound, has been widely-recognized for its ability to induce both innate and adaptive immune responses. Topical imiquimod has been approved for the treatment of actinic keratoses (AK), external genital warts (EGW), and superficial basal cell carcinoma (BCC). There are reports of many successful off-label uses as well. The pharmacology and mechanisms of action, safety, efficacy, and adverse effects with regards to differing concentrations and dosing regimens are discussed in depth in this chapter. Field-directed therapies for AK along with non-surgical treatments for BCC are rapidly-evolving, with increasing numbers of studies providing evidence-based rationale for their use in management.

Keywords: imiquimod, basal cell carcinoma, anogenital warts, actinic keratoses

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Introduction

Imiquimod, an imidazoquinoline compound, is a low-molecular weight immune response modifier with the ability to upregulate the natural anti-tumor and anti-viral response in cells. Topical imiquimod, a chemotherapeutic agent that modifies the immune response, has been FDA approved at a concentration of 5% for the treatment of actinic keratosis (AK) and external genital warts (EGW) since February 27, 1997, and for treatment of superficial basal cell carcinoma (sBCC) since July 15, 2004. Recently in March 2010, the FDA approved a 3.75% formulation of imiquimod for the treatment of actinic keratoses. There is also evidence that imiquimod has an unmasking effect on subclinical, non-visible lesions, adding to the arsenal of treatment options dermatologists have for often-undiagnosed lesions of the skin.[1] Off-label uses for imiquimod include treatment of molluscum contagiosum, vulvar intraepithelial neoplasia, difficult-to-treat verruca, and lentigo maligna, among others (Table 1).[2] For an exhaustive list of off-label indications for imiquimod, an excellent review by Ganjian et al in 2009 is available.[3]

Imiquimod is marketed in a 5% cream form as Aldara™, and as 3.75% cream form as Zyclara™, both by Graceway Pharmaceuticals. In Japan, a 5% cream form is available as Beselna™ by Mochida Pharmaceutical Company. In September 2010, Fougera® and Perrigo were given FDA approval to manufacture and market a generic imiquimod 5% cream; however, it should be noted that the solvent that the active ingredient is diluted into is different from that of Graceway, who also have a generic imiquimod 5% cream available. A study by Harrison et al found differences in the release rates of imiquimod between the innovator and generic compounds in vitro.[4] Due to differences in the composition of the vehicles, there may be differences in the efficacy and safety between these generically available compounds as well. To answer this question, a nationwide, multi-center, double-blind, vehicle-controlled trial comparing a generic imiquimod 5% cream to Aldara™ for the treatment of actinic keratoses on the face or scalp for 16 weeks is currently underway.[5]

Clinically, both resolution of tumor and excellent cosmesis have been achieved using topical imiquimod

Table 1. Off Label uses of imiquimod.

Condition	Comments
Lentigo maligna	Several studies with high complete clearance rates and low recurrence at 1–2 years
Cutaneous melanoma metastases	Little evidence; mostly case reports
Bowen's disease (SCC in situ)	Multiple studies and case reports of complete clearance and low recurrence at 6–31 months (longest reported follow-up); 10 cases used with sulindac 200 mg to good effect
Vulvar intraepithelial neoplasia	Several studies with partial clearance rates ranging from 24%–100%; many reports lack reporting of recurrence rates
Bowenoid papulosis	Few case reports, all reporting 100% complete clearance and no recurrence at 12–18 mos.
SCC	Few case reports, all reporting 100% complete clearance with no recurrence at 3–18 mos.
Cutaneous T-cell lymphoma	Few reports, partial clearance rates ranging from 25%–100%; no recurrence reported at 8–10 mos.
Mycosis fungoides	Few reports with complete clearance ranging from 75%–100%; 33% recurrence seen in longest follow-up of 2 years
Molluscum contagiosum	Several studies with partial clearance ranging from 54%–92% and complete clearance ranging from 8%–100%; no recurrence reported at 3–6 mos.
Leishmaniasis	Couple of studies with complete clearance rates of 50%; 90% without recurrence at 6 mos.
Porokeratosis of Mibelli	Several case reports with 100% complete clearance and no recurrence at 1–2 years
Infantile hemangioma	Few studies with complete clearance ranging from 75%–100%; recurrences reported as 0%–30% at 4–7 mos.
Xeroderma pigmentosum	Several case reports with 100% complete clearance rates and 0% recurrence at 6–8 mos.

for both large sBCC as well as squamous cell carcinoma (SCC) in-situ. Focal recurrences can occur, with rates differing depending upon lesion treated and patients' compliance with treatment regimen; however, these lesions are often resolved with surgical excision.

There are risks and adverse events that have been associated with the use of imiquimod, and these will be discussed within the appropriate sections of this chapter. The most common adverse effects experienced by patients include local erythema, edema, scabbing/crusting, scaling, erosion, and weeping or exudate. Most reactions are considered mild to moderate.[6]

With the 2010 FDA approval of the new drug application for 3.75% imiquimod for the treatment of actinic keratoses, and with the recent availability of a generic imiquimod 5% cream, there is little doubt that even more clinical applications for this immune modifier will continue to emerge in the near future.

Imiquimod Overview

Imiquimod (1-(2-methylpropyl)-lH-imidazo[4,5- c] quinolin-4-amine) has a structural formula indicative of a novel compound (Fig. 1).[7]

Mechanism of action

Imiquimod has potent antiviral and antitumor activity in animal models; however, it does not exhibit direct antiviral or antiproliferative activity in cell culture systems. Imiquimod is the first of a new class of drugs emerging in the treatment of a wide variety of dermatologic disorders. An immune response modifier, imiquimod indirectly acts to enhance the body's natural ability to heal through the induction of innate and cell mediated pathways (Fig. 2). Stimulation of these immune pathways leads to the synthesis and release of cytokines, mostly interferon-α (IFN-α), tumor necrosis factor-α (TNF-α), and interleukins (IL-1, IL-6, IL-8, and IL-12).[8]

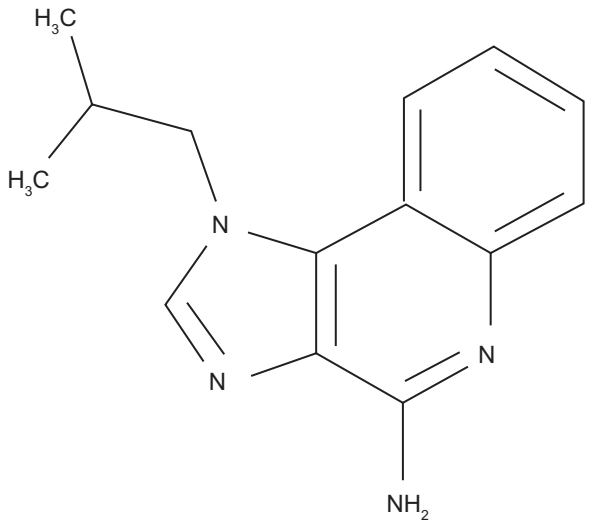

Figure 1. Chemical structure of imiquimod.

The cytokine-producing cells include monocytes, macrophages, and toll-like receptor 7 (TLR7)-bearing plasmacytoid dendritic cells.[9] Activity of natural killer cells, macrophages, B lymphocytes, and Langerhans cells is also enhanced significantly.[10] Imiquimod is able to indirectly stimulate production of the T-helper type-1 (Th1) cytokine IFN-γ in mouse splenic cultures, bone marrow cultures, and human peripheral blood mononuclear cell cultures.[11] However, imiquimod does not stimulate T cells to divide or cause direct induction of T-cell cytokines such as IL-2, IL-4, or IL-5. IFN-α can induce the IL-12 receptor β2 subunit on Th1 cells, which can then respond to IL-12 and produce IFN-γ.[11] Thus, Th1 cells may be a major source of IFN-γ. Cytotoxic T-cells are responsible for killing virus-infected and tumor cells, and these cytotoxic T cells and natural killer cells may also produce IFN-γ following stimulation by imiquimod.

Imiquimod also induces memory, which can aid in the prevention of future recurrence. The proposed mechanism for this is via activation of natural killer cells (NK cells), macrophages, B lymphocytes, and Langerhans cells, which subsequently migrate through the lymphatic system to activate the adaptive immune system.[11]

New research has shown that imiquimod's anti-proliferative effect is totally independent of immune system activation or function. Imiquimod exerts its effect by increasing levels of the opioid growth factor receptor (OGFr). Blocking OGFr function with siRNA technology resulted in loss of any antiproliferative effect of imiquimod.[12]

Metabolism

With topical application, imiquimod has a half-life of approximately 30 hours. With subcutaneous application, the half-life is 2 hours. Systemic absorption of topically applied imiquimod appears to be minimal.[13]

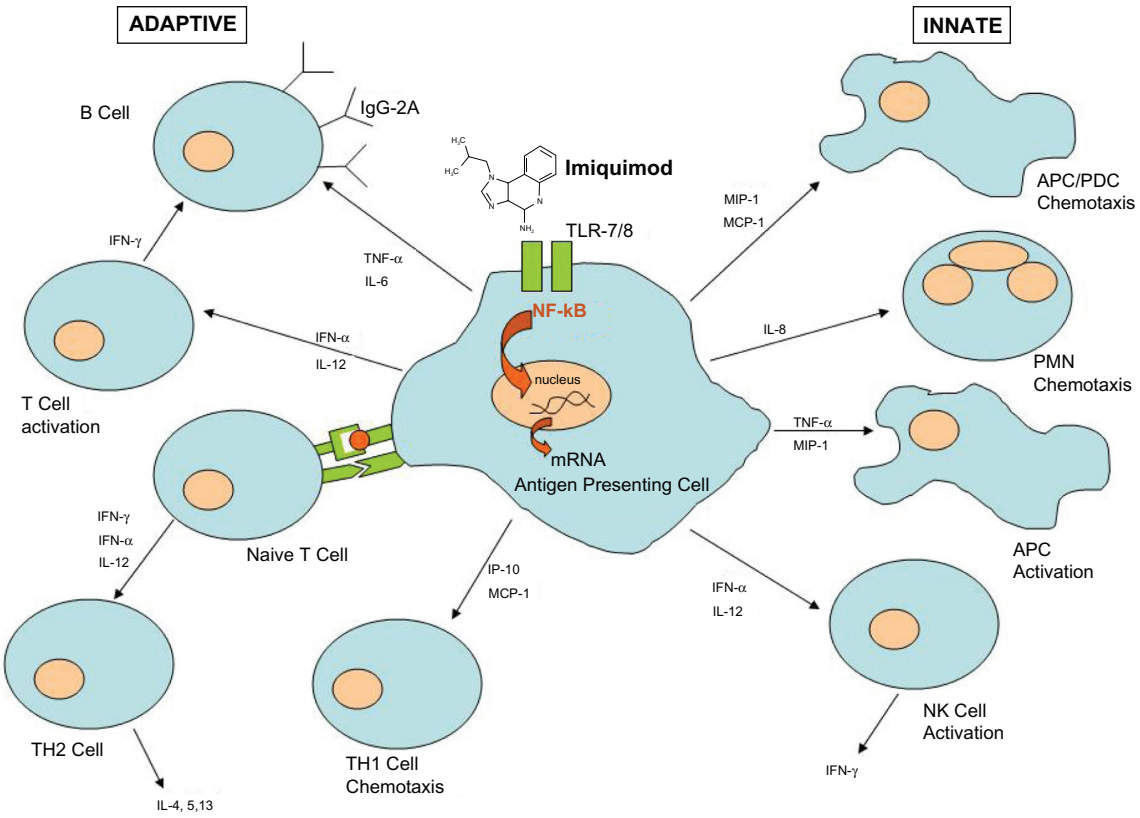

Figure 2. Mechanism of action of immune modification of imiquimod on TLR 7/8-bearing cells.

Pharmacokinetic profile

Minimal systemic absorption of imiquimod through intact skin occurs during treatment with topically applied imiquimod 5% cream. Clinical studies showed no quantifiable concentrations of imiquimod or metabolites in serum, and <0.9% of a single 5-mg dose was excreted in urine and feces.[6] No radioactivity was detected in serum.[14]

Adverse effects

Imiquimod 5% cream is generally well tolerated. The most common adverse events occur at the application site and are mild to moderate in intensity. Discomfort has been reported by patients receiving imiquimod 5% cream during clinical trials, and in most of these trials, less than 2% discontinued therapy because of adverse events. The most common application-site reactions reported at least once were itching, burning, pain, and soreness.

Treatment with imiquimod 5% cream is also associated with local skin reactions, the most common of which, in female patients, were erythema, erosion, excoriation/flaking, edema, ulceration, and induration at the application site. Erythema is characteristic of a local immune response.

Safety

Imiquimod is listed as a Category C drug for use in pregnancy, meaning that animal studies have shown an adverse effect and there are no adequate studies in pregnant women, or that no animal studies have been conducted. Consequently, use of imiquimod is contraindicated during pregnancy, and women of child-bearing potential who are prescribed imiquimod are also counselled regarding the importance of contraception, since teratogenic effects are currently unknown.[6,7]

Appropriate studies on the relationship of age to the effects of topical imiquimod for actinic keratosis or skin cancer have not been performed in the pediatric population. Safety and efficacy have not been established. On December 13, 2006, the FDA granted pediatric exclusivity to Aldara™. Between approval and November 2008, Aldara™ prescriptions in the pediatric population (ages 0–16 years) accounted for approximately 21% of total dispensed

Table 2. Imiquimod formulations and dosing regimens for the treatment of AK.

Imiquimod formulation	Dosing regimen	Comments
5% cream/topical	2 times per week for up to 16 weeks	Treatment of clinically typical, nonhyperkeratotic, nonhypertrophic AKs on the face or scalp in immunocompetent adults. Restricted to an area of skin totaling 25 cm^2
3.75% cream/topical	Daily use for 2 weeks, followed by 2 weeks of non-treatment, followed by 2 weeks of daily use for a total of 6 weeks	Treatment of clinically typical, visible, or palpable AKs on the full face or balding scalp

Aldara™ prescriptions, mostly for viral warts and molluscum contagiosum.[15]

Actinic Keratosis

Actinic keratoses (AKs) are small, rough, scaly erythematous papules most commonly found in sun-exposed areas of the body and are considered to be pre-malignant, with an approximate 2.6% and 1.6% risk of developing into either squamous cell or basal cell carcinoma, respectively, in 4 years.[16,17] These numbers may sound insignificant; however, consider a patient with numerous AKs, for whom these numbers are multiplied exponentially throughout his years of life. Furthermore, greater than 97% of the 459 SCCs examined histologically by Hurwitz et al had arisen from or formed in close proximity to AKs.[18] Most practicing dermatologists today recommend treatment,[19] particularly for a patient with multiple clinical and subclinical lesions in an anatomical area, known as field cancerization.[20] This therapy is referred to as field-directed therapy, a concept for which treatment options are rapidly-evolving.[21] In contrast to lesion-directed therapy, which uses a destructive modality (ie, cryosurgery with liquid nitrogen) to damage atypical cells and often surrounding normal tissue, these field-directed therapies utilize topical medical creams and lotions to target AKs as well as subclinical lesions in the surrounding skin. Examples of such field-directed therapies include 5-fluorouracil, 3% diclofenac in 2.5% hyaluronan gel, delta amino levulinic acid solution followed by photodynamic therapy, medium-depth chemical peels, and imiquimod.

Imiquimod 5% cream was the first approved formulation (Aldara™) for the treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults. The recommended dosage is 2 times per week for up to 16 weeks. Recently, the FDA approved a 3.75% cream formulation (Zyclara™), determining it to be safe and effective for the treatment of clinically typical, visible or palpable AKs. The new treatment can be used on large areas of skin, including the full face or balding scalp on a shorter, 6-week dosing cycle. While both concentrations are FDA-approved for the treatment of AKs, Zyclara™ is indicated for daily use for two weeks, followed by two weeks of non-treatment, followed by two weeks of daily treatment for a total of 6 weeks. In contrast, Aldara™ is not approved for daily dosing (Table 2). Also, the 3.75% concentration may be used on the full face or balding scalp (up to 200 square centimeters), while the 5% concentration is restricted to an area of skin totalling 25 square centimeters. The safety of the use of imiquimod 5% cream in areas larger than 25 square centimeters has not been established.[6]

In 2000, a double-blind randomized pilot study[22] examined 41 patients with AKs who applyied either imiquimod in differing doses or a vehicle cream to three target lesions for up to 16 weeks, with clinical resolution of all target lesions. Stockfleth and colleagues reported 6 cases in which complete histological clearance of AKs was obtained in patients treated with imiquimod 5% cream thrice weekly for 6–8 weeks.[23] A Phase II study evaluated imiquimod in 22 patients with AKs and demonstrated a significant reduction in the number of AKs after 16 weeks compared to vehicle control.[24] It was found that offering patients a rest period by introducing a "cycle therapy" dosing regimen decreased untoward local effects without compromising clearance rates, resulting in increased patient compliance.[1] Further clinical studies for imiquimod 5% cream were done by Stockfleth et al in 2002 demonstrating 84% complete clinical clearance in AKs treated with imiquimod 5%

Table 3. Clinical data on the efficacy and safety of imiquimod for the treatment of AK.

Study first author, Year of publication, [Number of patients]	Trial	Frequency/duration of treatment	Clearance rate (P = partial; C = complete; N = no response)	Adverse reactions
Jorizzo 2010[31] [247]	Multicenter, randomized, double-blind, placebo controlled	Subjects with ≥10 AKs on face underwent cryosurgery to 5–14 lesions; subjects with ≥5 lesions remaining were randomized to either 3.75% imiquimod or placebo daily for 2 wks, no treatment for 2 wks, then daily for 2 wks	cryo/3.75% imiquimod = 59.5% (C); cryo/placebo = 29.8% (C)	Local erythema; one subject in each arm experienced a fatal cardiac arrest (considered unrelated to treatment)
Hanke 2010[30] [490]	Randomized, placebo controlled	Imiquimod 2.5% or 3.75% daily for two 3 wk cycles, separated by 3 wks	Placebo = 5.5% (C), 12.8% (P); imiquimod 2.5% = 25.0% (C), 42.7% (P); imiquimod 3.75% = 34.0% (C), 53.7% (P)	Application site pruritus, irritation, and pain were dose-dependent, but only 7 discontinuations (1 placebo, 2 imiquimod 2.5%; 4 imiquimod 3.75%)
Swanson 2010[33] [479]	Randomized, placebo controlled	Imiquimod 2.5% or 3.75% daily for two 2 wk cycles, separated by 2 wks	Placebo = 6.3% (C), 22.6% (P); imiquimod 2.5% = 30.6% (C), 48.1% (P); imiquimod 3.75% = 35.6% (C), 59.4% (P)	25% developed severe erythema
Del Rosso 2009[26] [551]	Multicenter, randomized	Imiquimod 5% cream 2x/wk for 16 wks	36.4% (C), 68.6% (P)	<4% discontinued treatment due to adverse events such as local erythema
Krawtchenko 2007[32] [75]	Randomized	3 treatment groups: cryosurgery (1 or 2 courses); topical 5-FU 2x/day for 4 wks; topical imiquimod 5% cream 3x/wk for 4 wks (1 or 2 courses)	Initial clearance rates: cryo = 68%, 5-FU = 96%, imiquimod = 85%; sustained clearance 1 year: cryo = 28%, 5-FU = 54%, imiquimod = 73%	One patient refused a second course of imiquimod due to local reactions; no serious adverse event occurred during treatment
Persaud 2002[24] [17]	Phase II, randomized, vehicle controlled	Imiquimod 5% cream vs. vehicle 3x/wk for 8 wks or until total clearance	Measured reduction in average number of lesions: for vehicle = 8.1 (pre) to 7.6 (post); for imiquimod = 10.1 (pre) to 6.2 (post)	Mild-moderate erythema, pruritus, scabbing
Stockfleth 2002[25] [36]	Randomized, double-blind, vehicle controlled	Imiquimod 5% cream vs. vehicle 3x/wk for a maximum of 12 wks	Imiquimod 5% = 84% (C), 8% (P)	Local erythema

cream thrice weekly for a maximum of 12 weeks.[25] Del Rosso and colleagues found that multiple courses of imiquimod 5% over 16 weeks resulted in an 80% reduction in the number of AKs and was well tolerated by subjects.[26] Complete clearance was achieved in 36.4% of subjects, and partial clearance in 68.6%. Fewer than 4% of participants discontinued treatment due to adverse events.

With regards to patient tolerance and satisfaction, when comparing imiquimod 5% to other therapies for

Table 4. Clinical data on the efficacy and safety of imiquimod for the treatment of EGW.

Study first author, Year of publication, [Number of patients]	Trial	Frequency/ duration of treatment	Complete clearance rate	Recurrence rate	Adverse reactions
Beutner 1998 (Feb)[38] [108]	Phase II	24 hour application 3 days/wk for 8 wks	40% for imiquimod 5% cream vs. 0% for vehicle	19% at 10 weeks	Not reported (NR)
Beutner 1998 (Apr)[97] [279]	Phase III, multicenter, randomized, double-blind, placebo controlled	8 hour application daily for 16 weeks or until totally clear	71% for imiquimod 5% cream vs. 16% for imiquimod 1% cream vs. 4% for vehicle	19% for imiquimod 5% cream; 17% for imiquimod 1% cream; 0% for vehicle	Local erythema
Edwards 1998[39] [311]	Phase III, multicenter, randomized, double-blind, placebo controlled	8 hour application 3 days/wk for 16 weeks or until totally clear	50% for imiquimod 5% cream vs. 21% for imiquimod 1% cream vs. 11% for vehicle	13% for imiquimod 5% cream; 0% for imiquimod 1% cream; 10% for vehicle	Local erythema
Conant 1998[46] [100]	Multicenter, double-blind, vehicle controlled	3x/wk for 16 weeks or until totally clear	11% for imiquimod 5% vs. 6% for vehicle		Mild erythema
Garland 2001[42] [943]	Phase IIIB open-label multicenter	3x/wk for up to 16 weeks; additional 16 weeks extended treatment if necessary	47.8% for imiquimod 5% initial treatment period; 53.3% for extended treatment weeks	8.8% and 23% at 3- and 6-month follow-ups, respectively	Local erythema in 67% of patients
Carrasco 2002[44] [60]	Retrospective chart review	20 patients had surgical removal alone; 20 patients had imiquimod 5% cream 3x/wk for 16 weeks; 20 patients had imiquimod 5% cream 3x/wk for 16 weeks then surgical excision of residual warts	100% for all treatment modalities (basis for selection)	65% for surgical removal (average time to recurrence 5 mo.); 15% for imiquimod monotherapy (avg. time to recurrence 17 mo.); 20% for imiquimod + surgical excision (avg. time to recurrence 19 mo.)	NR
Saiag 2009[51] [50]	Open-label, noncomparative study	3x/wk for up to 16 weeks	32%	0% at 3 mo.	Local skin reactions such as erythema (22%) or ulceration (12%)
Ferris 2010[52] [981]	2 identical Phase III studies	Up to 250 mg of cream per dose was applied once daily for up to 8 weeks or until complete clearance of all (baseline and new) warts	22.1% for imiquimod 2.5%; 28.3% for imiquimod 3.75%; 9.4% for placebo	40.5% for imiquimod 2.5%; 30.4% for imiquimod 3.75%; 7.7% for placebo at 12 weeks follow-up	15.0% on imiquimod 2.5% and 16.3% on imiquimod 3.75% experienced severe local skin reactions

AKs such as photodynamic therapy (PDT) with methyl aminolevulinate (MAL PDT), Serra-Guillen and colleagues found that both treatments are well-tolerated by patients, with no significant difference in tolerance found with regards to patient sex, race, sun-exposure time, or hair color.[27] There was a higher percentage of patients reporting "very satisfied" with treatment for MAL PDT compared to imiquimod (93% vs. 62%, $P = 0.004$); however, most patients reported that they would continue the same treatment. Economic studies have demonstrated that imiquimod may be the more cost-effective choice compared to MAL PDT.[28]

The safety and efficacy of imiquimod 3.75% have been assessed in two clinical trials.[29,30] In the trial by Swanson et al 479 subjects were randomized to use either placebo, imiquimod 2.5% or 3.75%. Subjects were observed to have reduction in mean lesion number of 25% for placebo, 72% for imiquimod 2.5%, and 82% for imiquimod 3.75%, which were all significantly different rates ($P < 0.001$ for each active vs. placebo; $P = 0.048$ for 2.5% vs. 3.75%).[29] Complete clearance was noted in greater than 33% of imiquimod-treated subjects versus 6% for placebo, after a treatment regimen of daily application to the entire face or balding scalp for two, 2-week cycles, separated by a 2 week period of no treatment. Moreover, compliance rates were greater than 90%, with no subject withdrawing due to severe erythema, which developed in approximately 25% of subjects and was the most commonly-observed adverse effect of treatment.[29] Efficacy was assessed eight weeks after the last dose. Interestingly, the subjects in the treatment group had increases in the number of lesions from baseline during treatment; however, complete clearance rates reflect treatment of both visible or palpable and new lesions revealed during treatment.

Recent clinical studies have revealed that, when coupled with 3.75% imiquimod cream, the efficacy of cryosurgery is greatly increased. Compared to cryosurgery alone, patients also treated with imiquimod cream experienced twice the complete clearance rates (29.8% vs. 59.5%).[31] The efficacy was assessed through 26 weeks of follow-up. In comparison studies of topical imiquimod 5%, topical 5-fluorouracil (5-FU), or cryosurgery, clearance rates at 12 months follow-up were 73%, 33%, and 4%, respectively.[32] The imiquimod group also reported superior cosmetic outcomes. Results from these studies are summarized in Table 3.

The most commonly reported side effects of topical imiquimod treatment for AK are localized skin erythema (25%), scabbing or crusting (14%), ulceration (11%), and flaking, scaling, or dryness (8%).[33] Most patients do experience some degree of discomfort as a result of the inflammatory response induced during standard imiquimod treatment courses; however, by cycling treatment weeks with off-treatment weeks, these side effects can be minimized while still achieving satisfactory clearance rates (Fig. 3). The pharmacokinetics of imiquimod 3.75% cream and metabolites were assessed by Kulp and colleagues,[34] who characterized serum markers in 19 subjects applying two packets (18.75 mg total) once daily for 21 days to a treatment area on the face or balding scalp of approximately 200 square

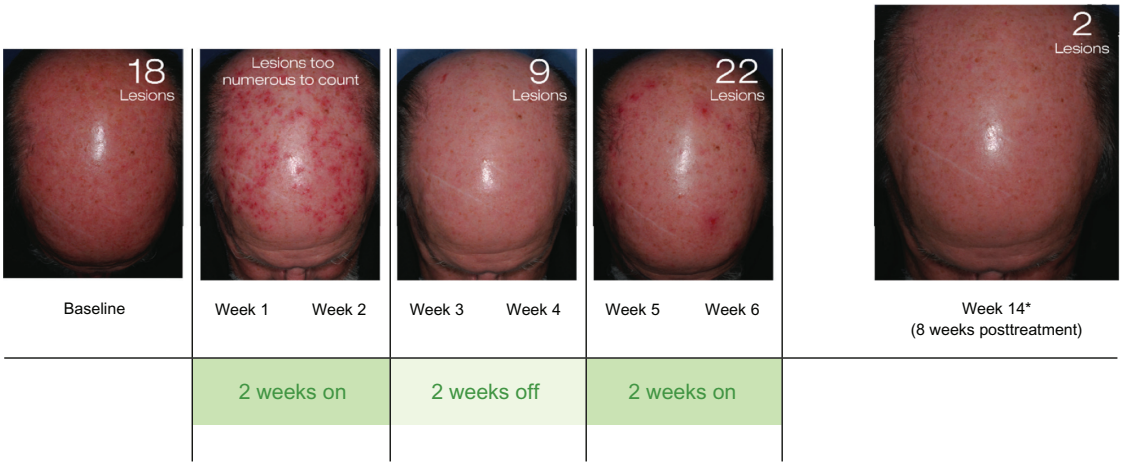

Figure 3. Typical patient response during standard course of treatment of AKs with imiquimod 3.75% cream.
*Results depicted represent a single patient. Overall median lesion count at 14 weeks posttreatment was 2. Results may vary.

centimeters. Researchers took serum samples from patients at baseline, and prior to application on days 7, 14, and 21. Steady state concentration was achieved by day 14, and after 21 days, the max serum imiquimod mean concentration was 0.323 mg/mL with a half-life of approximately 29 hours. Researchers concluded that systemic imiquimod exposure was low after daily application of two packets of imiquimod 3.75% cream for 21 days.[34]

Patient preference rates comparing 5% and 3.75% regimens have not yet been studied; however, the fact that the total treatment time is reduced from 16 weeks to 6 weeks with the 3.75% confers a significant advantage in terms of patient compliance. As treatment for AK, imiquimod will continue to have a significant place in therapy. Imiquimod is unique in its ability to effectively treat existing lesions as well as to unmask subclinical lesions that may have otherwise gone untreated. With the lower concentration and a shorter dosing cycle now available, 3.75% imiquimod cream has become the gold standard in the treatment of AK over larger skin areas. A general consensus guideline regarding the treatment of AKs remains to be updated. Physicians must take into account many factors when choosing a treatment modality for their patient with AKs, including age, patient preference, number and location of lesions, anticipated sun exposure, expense, and anticipated compliance, among others.[19] Prevention remains the most important message to convey to patients, emphasizing avoidance of sun and artificial sources of ultraviolet light along with use of sun block, frequent self-examinations, and annual skin examinations with a professional.[35]

External Anogenital Warts

External genital warts (EGW), also known as condylomata acuminata, are highly-contagious sexually-transmitted papules caused by several strains of human papillomavirus (HPV), particularly HPV 6 and 11. It is estimated that 10%–20% of the sexually-active adult population in the United States is infected with HPV, while approximately 1% manifest clinical symptoms.[36] The prevalence of EGW in the American population is estimated to be 15%, with an annual incidence of 1 million new cases, two-thirds of which are diagnosed in women.[36] Effective treatment is important due to the high oncogenic risk associated with infection of certain HPV strains, as well as the psychological trauma associated with the clinical manifestations of genital warts.[37]

One of the first approved applications for imiquimod was for treatment of external genital warts (perianal warts/condyloma acuminata) in patients 12 years or older. The recommended dosage is 3 times per week until cleared (for a maximum of 16 weeks).

The immune response modifier imiquimod 5% cream is approved as a patient-applied therapy for EGW. A Phase II study of 108 patients comparing imiquimod 5% cream to vehicle thrice weekly for 8 weeks found 40% wart clearance compared to 0%, respectively.[38] 81% of the imiquimod-treated patients remained condyloma-free after 10 weeks follow-up. In a randomized, vehicle-controlled trial, treatment with imiquimod 5% cream thrice weekly for up to 16 weeks resulted in complete clearance in 50% of patients, with a significant clearance rate disparity with regards to gender: 72% of females experienced clearance while only 33% of males did.[39] It has been postulated that this disparity is due to the most common lesion locations, with higher keratinization on the shaft of the penis compared to the vulva.[40] A study of uncircumcised males in Europe was done which observed clearance rates of 62% when using the same dosing schedule.[41] This difference in efficacy may be due to the fact that the first study was done in America, where males tend to be circumcised; non-circumcision may be associated with a lower degree of keratinization and may also offer an occlusive benefit.

An international Phase III trial involving 943 patients demonstrated the efficacy of imiquimod 5% cream thrice weekly for 16 weeks for the treatment of EGW, with a 47.8% effective clearance rate.[42] If complete clearance was not achieved in the initial 16 week period, an additional 16 week period was extended, resulting in clearance of 52/151 patients. The overall clearance rate was 53.3%, with a median time to clearance of 8.8 weeks. Clearance rates for females and males were 75.5% and 56.9%, respectively, as expected from previously reported studies.[42]

Studies have compared imiquimod to ablative or destructive therapies such as electrocautery, cryosurgery, surgery, CO2- and Nd:YAG-laser vaporization, or caustic agents such as podophyllotoxin and trichloracetic acid, which are often associated with high recurrence rates due to failure to completely

eliminate the HPV-infected cells surrounding the visible lesions.[43] Monotherapy with imiquimod was found to be superior to destructive therapy with a lower rate of relapse; monotherapy with imiquimod was not inferior to combination treatment of imiquimod with destructive therapy.[43] Recurrence rates have been demonstrated to be lower in patients treated with imiquimod monotherapy (15%–20%) compared to surgical monotherapy (65%) at 17 and 5 month follow-up, respectively.[44]

A meta-analysis of over 10 years of clinical data was performed to ascertain the optimal dosing regimen of imiquimod 5% cream for EGW.[45] It was concluded that the best scheduling frequency is three times per week for 16 weeks as opposed to daily treatment, when balancing efficacy and occurrence of adverse skin reactions.[45]

There have been several studies demonstrating the efficacy of imiquimod in patients infected with human immunodeficiency virus (HIV), a population in whom rates of EGW are higher than their immunocompetent cohorts.[46–51] Safety and efficacy of imiquimod in immunocompromised patients with EGW was studied by Conant et al.[46] Successful treatment was defined as achieving a >50% reduction in wart area, which occurred in 38% of patients treated with imiquimod versus 14% for vehicle, a statistically significant difference.[46] An open-label study of EGW in HIV-positive patients concurrently treated with highly active antiretroviral therapy (HAART) and imiquimod 5% cream demonstrated a total clearance of EGW of 50% in successfully-treated patients.[51] In patients not successfully treated with HAART (as defined by total CD4+ cell counts <200 cells/mm^3), clearance rates were lower. These studies suggest that T-cell responses are important factors in the clearance of EGW. Imiquimod is an effective and safe treatment for use in patients with HIV-positive status.

Recently, the FDA accepted a new drug application for imiquimod 3.75% cream to be used for 8 weeks for the treatment of EGW. Data presented by Ferris et al at the Human Papillomavirus (HPV) Conference in Montreal, Canada in July 2010 demonstrated that both imiquimod 3.75% and 2.5% creams were effective in treating EGW when applied once daily for up to 8 weeks.[52] In 981 subjects aged 12 years or older with 2–30 EGWs, complete clearance was achieved in 28.3% of the group randomized to receive imiquimod 3.75% cream and in 22.1% of the group receiving imiquimod 2.5% cream, compared to only 9.4% of the placebo group, with statistically significant differences between both treatment groups compared to each other and to placebo using intent-to-treat analysis. The researchers noted that clearance rates were greater for females than males (36.6% versus 18.6%), a finding that is congruent with current literature on imiquimod 5% cream for EGW. In patients who achieved complete initial clearance at 8 weeks post-treatment, this clearance was sustained at the 12 week follow-up time point, with rates of clearance of 69.6% for imiquimod 3.75%, 59.5% for imiquimod 2.5%, and 92.3% for placebo, respectively.[52] Imiquimod 3.75% concentration is efficacious and offers a potentially safer profile and more manageable treatment regimen over the current 5% concentration. Results from these studies are summarized in Table 4.

Imiquimod is not a cure for genital or perianal warts, and new warts may develop during treatment.[6] The goal of treatment for EGW is resolution of visible lesions, rather than eradication of the HPV infection. It is recommended that female patients take special precautions when applying topical imiquimod cream in the genital area, as use on the vaginal opening is considered internal and is not recommended, due to risk of edema and resulting difficulty in urination. For these same reasons, sexual contact of any kind should be avoided while the active treatment is on the skin, even if condoms or diaphragms are used, because the imiquimod cream may damage latex.[6] Although it is currently not known whether imiquimod cream reduces the transmission of genital or perianal warts, it is certain that treatment results in lower recurrence rates of EGW in these patients.[53] Patient preference should guide treatment, according to the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease Treatment Guidelines of 2006.[54] Due to the convenience, minimal pain, and autonomy associated with self-administration, treatment of EGW with imiquimod cream is preferred by patients over other more painful, physician-administered ablative and destructive options.[55]

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common type of skin cancer, affecting approximately 800,000 persons in the United States each year.[56] Usually occurring on sun-exposed areas such as the face, chest,

arms, and back, BCCs can be locally destructive and physically disfiguring, although metastasis is rare. In 2004, the FDA approved the use of imiquimod for treatment of biopsy confirmed primary superficial BCC (sBCC) on the body, arms, legs, and neck, but not the face, in immunocompetent adults when surgery is not recommended. The recommended dosage is 5 times per week for up to 6 weeks. The FDA also urges regular follow-up appointments to ensure complete clearance of the lesion. Treatment for other subtypes of BCC is considered off-label.

The scientific rationale for treatment of BCCs with imiquimod has been reviewed by Berman.[57] Normally, cell death receptors such as the FasReceptor (FasR) are not expressed in BCC, thereby allowing these cells to evade apoptosis via the FasR-Fas ligand interaction. Imiquimod is able to modify the host immune system locally to induce expression of FasR in BCC cells, resulting ultimately in apoptosis.[58]

There is controversy over whether clearance rates may be confounded by the presence of mixed-histologic subtype BCCs; it is a common practice of dermatopathologists to label tumors based on 50% or greater composition of one particular subtype.[59] These mixed tumors may be labelled and treated as superficial BCCs, when they are actually comprised of other, more resistant subtypes. Thus, the requirement for strict follow-up is further imposed.

Although Mohs surgery achieves 99% cure rates in studies at 12 weeks follow-up compared to 77% for imiquimod,[60] imiquimod often offers the advantage of improved cosmetic outcomes.[61] The elderly are a population of patients in whom surgery is often contraindicated for one reason or another. With the incidence of BCC increasing with age, imiquimod provides an excellent alternative to surgical treatment in these patients. A study of 97 patients over the age of 65 years with BCC was done in which patients were treated three times weekly with imiquimod 5% cream for 6 weeks. After 10 weeks, the percentage of patients remaining in the tumor free interval was 67%, and after 1 year follow-up was 49.5%.[62]

The initial study of topical imiquimod 5% cream for BCC was a double-blind, randomized pilot trial of 35 patients who received one of five dosing regimens or placebo over 16 weeks.[63] Histologic clearance was ascertained in 83% of patients treated for 6 weeks with imiquimod versus 9% of patients treated with vehicle only. Optimal dosing regimens were investigated by Marks et al in a trial involving 99 patients with sBCC.[64] Patients whose lesions were treated with imiquimod 5% cream twice every day experienced 100% histological clearance, once every day experienced 87.9% clearance, twice daily 3 times per week experienced 73.3% clearance, and once daily 3 times per week experienced 69.7% clearance.[64] Adverse local skin reactions were mild to moderate and were also dose-related.

Although not FDA approved for nodular BCC, imiquimod has been used with varying degrees of success for this entity, with clearance rates ranging from 60%–100%.[65–68] Bianchi et al observed clearance in 11 out of 13 lesions treated daily for 10–18 weeks,[67] while Vidal and colleagues observed a 74% clearance at 2 years follow-up in lesions treated 3–5 times weekly for 5–8 weeks.[68] The use of occlusion does not result in statistically higher clearance rates for either superficial or nodular BCCs.[66]

A Phase III trial in multiple centers in Europe established the safety and efficacy of imiquimod 5% cream in the treatment of sBCC.[69] 166 subjects with at least one histologically-confirmed sBCC were randomized to imiquimod or vehicle cream application once daily for 6 weeks. After 12 weeks follow-up post-treatment, 80% histological clearance was demonstrated in the imiquimod group compared to 6% in the vehicle group.[69] Lacanubba et al conducted a six-week study on 99 patients with sBCC treated with imiquimod.[70] Success rates of 100%, 88%, 73%, and 70% were found for twice daily, once daily, 6 times weekly, and 3 times weekly application, respectively.[70] A regimen of 5 versus 7 applications per week for 6 weeks found no significant difference in clearance rates (73% vs. 75%, respectively);[60] thus, a dosage of 5 times per week is recommended to minimize treatment-related adverse side effects.

A low-frequency regime of imiquimod was evaluated whereby 82 patients with sBCC were treated with imiquimod 5% creams thrice weekly for 4 weeks. Patients experienced clinical clearance rates of 89% and 85% at 1 and 2 years follow-up, respectively.[71] Recently, the results of a prospective 5-year Phase III study on sustained clearance rates of sBCC treated once daily for 6 weeks with imiquimod 5% cream were reported.[72] The initial clearance rate 12 weeks post-treatment was 94%, with 85.4% of these subjects

remaining clinically clear at 60 months follow-up. Although 20/169 tumors recurred, most (70%) of these recurred within the first 24 months of follow-up.[72] Researchers found that participants with hyperpigmentation and skin surface abnormalities resolved compared to baseline, with slight worsening of hypopigmentation. These results are promising for long-term sustained clearance of sBCCs treated with imiquimod.

The SINS trial, a Phase III trial comparing excisional surgery with imiquimod 5% cream for the treatment of nodular and superficial BCCs, is currently underway.[73] Researchers aim to evaluate several endpoints at 3 years follow-up, including recurrence rates, time to recurrence, cosmesis after treatment, pain, and cost-effectiveness.

When used as adjunctive therapy before Mohs micrographic surgery, cryosurgery, or other conventional surgical therapies, imiquimod 5% cream has demonstrated varying degrees of efficacy.[74,75] In a randomized, double-blind vehicle-controlled study, there was no difference found in subjects who applied imiquimod 5% cream nightly under occlusion for 6 weeks prior to Mohs surgery.[74] The use of imiquimod prior to surgical excision was criticized by Moehrle and colleagues,[76] who protest that the use of these topical destructive treatments may cause false-negative results with subsequent surgery due to sparing of tumor islands.

Although the clearance rates for BCCs treated with surgical excision are higher, the cost-effectiveness of imiquimod and other non-invasive procedures such as PDT were found to be superior with regards to total, direct, and indirect medical costs.[77]

Several adverse events have been reported with the use of imiquimod, including pigmentary changes, superficial scarring, alopecia,[78] and rare induction of other dermatologic disorders such as pemphigus foliaceus,[79,80] aphthous ulcers,[81] vitiligo,[82–84] angioedema,[85] and eruptive epidermoid cysts.[86] Reports of induction of psoriasis associated with imiquimod have also been made. Most of these have been in patients with a prior history of psoriasis,[87–90] but there have been cases of de novo occurrence.[91]

Strict follow-up visits to ensure successful clearance of the BCC must be emphasized with the patient upon prescribing imiquimod. A consensus on whether or not follow-up biopsies are necessary to ensure complete eradication has not been reached;[92] however, studies have revealed that skin biopsies have proven residual BCC in 66% of patients who clinically appear tumor-free.[93,94] The standard of care for BCCs remains to be surgical excision;[95] in patients for whom this is not an option, imiquimod with proper follow-up is an appropriate alternative for treating superficial BCCs. Other non-surgical therapeutic options for the treatment of BCC include radiation therapy, PDT with 5-aminolevulinic acid, laser treatment using carbon dioxide or erbium YAG laser, and 5-fluorouracil (the only other FDA-approved topical medication for superficial BCC).

Conclusions

In just over a decade since its approval by the FDA, imiquimod 5% cream has proven to be a unique and effective monotherapy for the treatment of actinic keratoses, external anogenital warts, and superficial basal cell carcinomas. Its ability to elicit an immune response at various levels enhances the efficacy of other treatment modalities when used in combination, as mentioned previously.[96]

Pharmacotherapy of actinic keratoses, external anogenital warts, and superficial basal cell carcinomas with imiquimod has been proven an effective strategy by many clinical studies mentioned within this text. The safety, efficacy, and patient satisfaction rates are such that this medication has become one of the main choices for treatment of these and other skin conditions by many dermatologists today. Its place in therapy has been solidified by the many conclusive clinical trials and positive patient experiences.

Present off-label uses of imiquimod in dermatological practices across the globe, as well as in clinical studies currently underway, will certainly contribute to the consensus that imiquimod and similar compounds will continue to be utilized for an even wider array of clinical diseases in the future.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere.

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