

Imiquimod 5% Cream: A Review of Its Safety and Efficacy in the Management of Superficial Basal Cell Carcinoma

Lance E. Davis, Katherine Fiala and David F. Butler

Department of Dermatology, Scott and White Clinic, Texas A&M College of Medicine, Temple, Texas.

Email: dfbutler@swmail.sw.org

Abstract: Imiquimod 5% cream (Aldara) was approved by the Food and Drug Administration for the treatment of non-facial superficial basal cell carcinomas (sBCC) in 2004 and has become one of the most commonly used topical treatments for this variant of basal cell carcinoma. Application of the cream once a day, 5 days per week for 6 weeks has demonstrated a clinical and histological cure rate approximating 80% for non-facial sBCCs. Erythema, erosions, and crusting are common local adverse events; but systemic side effects are much less common. The clinical use of imiquimod for nodular or facial basal cell carcinomas, particularly on the nose, has not been as successful. Cure rates range from 42%–76%, depending on the frequency and duration of use. Several reports have described the usefulness of imiquimod cream as an adjunctive therapy of basal cell carcinomas when combined with a surgical modality. However, most of these “adjunctive” studies were neither blinded nor controlled. We review the safety and efficacy of imiquimod 5% cream in the treatment of sBCC, report on its effectiveness in the treatment of nodular and facial basal cell carcinomas, and comment on its role as an adjunctive therapy.

Keywords: imiquimod 5% cream, Aldara, superficial basal cell carcinomas



Introduction

Basal cell carcinoma (BCC) is the most common skin cancer in the world. It is estimated that approximately 1 million new BCC tumors are diagnosed each year in the US, with incidence increasing worldwide by up to 10% per year. While rarely life-threatening and with a low metastatic potential, BCC can be locally aggressive, tissue destructive, and disfiguring. BCCs of the head and neck can be particularly disfiguring, and, in general, may be more treatment resistant. Basal cell carcinoma accounts for 75% of all skin cancers. The most common subtypes are superficial and nodular; but morpheaform, cystic, and pigmented variants have been well described. Consequently, the development of new therapeutic strategies and treatment methods for the removal of BCC is crucial in combating this growing problem. Numerous treatment options for BCCs are available, including: curettage and electrodesiccation, simple excision, Mohs micrographic surgery, cryotherapy, laser ablation, radiation therapy, photodynamic therapy and intralesional therapy (interferon and 5-fluorouracil). Imiquimod 5% cream and 5-fluorouracil cream are the only two FDA-approved topical therapies for sBCC.

History

Imiquimod (Aldara, Graceway Pharmaceuticals, Bristol, TN), a synthetic imidazoquinoline which acts as a toll-like receptor agonist, was initially approved for the treatment of condyloma acuminatum (genital warts) in 1997.¹ It later received FDA approval in 2004 for the treatment of actinic keratosis and non-facial superficial BCCs.¹ The safety of imiquimod during pregnancy remains uncertain; thus, imiquimod carries an FDA pregnancy C classification.

Imiquimod cream is indicated for the topical treatment of biopsy-confirmed, primary sBCC in immunocompetent adults, with a maximum tumor diameter of 2 centimeters. Tumors located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), can be treated topically when surgical methods are medically less appropriate; and patient follow-up can be reasonably assured. Currently, imiquimod is available only as a cream at a concentration of 5% and is dispensed in 12 or 24 small “sachet” packets. For sBCCs, standard treatment consists of application of the cream 5 times per week for 6 weeks. The medication is

normally applied at bedtime so that the cream may be left in place for 8–10 hours.

Mechanism of Action

While the mechanism of action of imiquimod is not completely understood, studies suggest imiquimod may exert its antitumor activity via a targeted immune response. Imiquimod is an immunological adjuvant. Agonist activity at toll-like receptor (TLR)-7 results in a cascade of events that begins with reprogramming gene expression through the movement of a transcription factor called nuclear factor kappa B (NF- κ B) to the nucleus.² Next is the induction of various cytokines, including but not limited to, interferon alpha, interferon gamma, tumor necrosis factor (TNF)-alpha, interleukin 12, and interleukin 1 alpha. Imiquimod further enhances professional antigen presenting cells (APCs) antigen presentation to T cells. A Th1 weighted cellular immune response ensues.² Imiquimod bridges both the innate and adaptive immune responses.

Imiquimod modulates the innate immune system by stimulation of mononuclear cell infiltration into BCC tissue. Normally, BCC tissue is relatively devoid of a cell-mediated immune response subsequent to the typical absence of tumor cell expression of adhesion molecules, preventing binding of immune cells. Tumor clearance via apoptosis may result from a rapid and immense increase in peritumoral and intratumoral infiltrating cells following imiquimod administration.³ Infiltrate density in excised superficial BCC tissue accounted for less than 5% of all cells in 4 of 6 patients with non-recurrent, primary tumors prior to imiquimod therapy.³ Infiltrate density increased to >50% in 5 of 6 patients following treatment with imiquimod 5% cream 5 times per week for a maximum of 6 weeks.³ Thus, an increase in infiltrate density, as demonstrated by comparison of excised superficial BCCs by conventional surgery both with and without imiquimod therapy may account for tumor eradication. This enhanced infiltrate may be in part due to enhanced endothelial expression of intercellular adhesion molecule-1 (ICAM-1) following imiquimod therapy.³

Absence of tumor-infiltrating cells in basal cell carcinoma has been attributed to lack of expression of adhesion molecules, such as ICAM-1, on tumor cells, thus preventing binding of immune cells.⁴ ICAM-1 is



up-regulated by a number of inflammatory mediators, such as IL-1, TNF-alpha, and IFN-gamma. Previous studies reveal little to no expression of ICAM-1 on BCC cells; however, ICAM-1 expression by dermal endothelial cells is more robust in areas of peritumoral inflammatory infiltrate compared with normal skin.⁴ Following imiquimod treatment, ICAM-1 is strongly enhanced on dermal endothelial cells with no affect in ICAM-1 expression of tumor cells. This suggests that imiquimod-induced enhancement of ICAM-1 expression on endothelial cells may play a role in recruitment of a peritumoral inflammatory infiltrate⁴ and possibly underscore one of its multifaceted mechanisms of action.

It is now well-known that imiquimod is an agonist of TLR 7. Agonist action results in a subsequent upregulation of mRNA expression of various cytokines and chemokines, including TNF-alpha, interleukin 12, and interferon-alpha. Such agonist activity may also account for upregulation of macrophages and natural killer cells important in regression of BCC tissue. It has been suggested that stimulation of TLRs results in the activation of a signaling cascade dependent upon the protein MyD88 which subsequently acts in concert with TLR to recruit protein kinases and transcription factors, ultimately resulting in the stimulation of NF-kB.⁵ In a non-randomized, open-label, vehicle-controlled study in 12 patients, imiquimod 5% cream was applied 5 times per week on week-nights only, up to a maximum of ten applications.⁶ Of the 12 excised BCCs, 6 of 12 patients showed natural killer cells accounting for approximately 25% of the infiltrate, and were often located in close apposition to BCC cells.⁶

Toll-like receptor (TLR)-7 is an intracellular TLR expressed on membranes of endosomes, recognizing nucleosides and nucleotides from intracellular pathogens. Synthetic agonists of TLR7 include guanine nucleoside analogues, stabilized immune modulatory RNA, as well as imidoazoquinoline-based compounds.² Activation of pattern recognition receptors like TLR with appropriate agonists induces a sophisticated defense machinery involving the innate immune system.² Thus, targeting TLR pathways represents a cleverly devised and promising therapeutic strategy. At present, imiquimod is the most frequently used TLR7 ligand in clinical practice, approved for the treatment of external genital warts, pre-cancerous skin lesions

such as AKs and superficial basal cell carcinoma.² Subsequent to topical application, this TLR7 agonist induces increased production of interferon-alpha, interleukin-12, TNF-alpha and a Th1 prone immune response.² Additionally, imiquimod enlists and recruits myeloid and plasmacytoid dendritic cell subtypes and cytotoxic T cells, increasing the capacity of antigen-presenting cells to induce reactive T cells.

Not only does imiquimod serve a role in up-regulation of the body's immune function and surveillance, but also induces apoptosis in BCC cells. In a randomized, double-blind, vehicle-controlled trial in 30 patients, with primary BCCs, 24 patients applied imiquimod 5% cream either 5 (n = 12) or 3 (n = 12) times per week.⁷ The apoptotic index significantly increased from 0.57% at day 0 to 1.54% at day 15 in the 5 times weekly group, and from 0.51% to 1.77% in the 3 times weekly group (both $P < 0.05$ vs. baseline).⁷ Apoptosis is induced by either upregulation or down-regulation of genes involved in apoptotic signaling. Following topical imiquimod exposure, expression of bcl-2, an anti-apoptotic protein, is decreased in BCC cells; however, expression of CD95-receptor (FasR), a receptor not normally expressed on BCC cells but necessary for apoptosis, is increased following therapy. In 24 patients who applied imiquimod 5% cream 5 or 3 times weekly, bcl-2 expression significantly decreased from 88.7% to 61.4% ($P = 0.01$).⁷

In vitro studies have shown imiquimod to induce down-regulation of genes involved in oncogenesis, including Patched, GL11, and GL13 involved in the pathogenesis of BCC.⁸ Furthermore, opioid growth factor receptor gene was increased in patients with BCC following imiquimod treatment.⁸ This upregulation may be imiquimod or IFN-alpha induced, and preliminary evidence points to an antiproliferative effect on basal cell carcinoma cell lines.⁸

Adverse Events

Application site reactions, mainly mild to moderate in intensity, are the most common adverse events. These include itching, pain, erythema, tenderness, erosions, crusting, hyperpigmentation, hypopigmentation and alopecia. Systemic absorption is minimal, and significant systemic adverse events are rare, but may include nausea, fatigue, headache, or myalgia.⁹ These flu-like symptoms are attributed to the local



production of interferon, are transient and reversible, and have rarely been associated with discontinuation or patient dropout in clinical trials. Rare cutaneous adverse events such as erythema multiforme, Stevens-Johnson syndrome and lupus erythematosus have been reported. Exacerbation of immunological disorders such as atopic dermatitis, psoriasis and spondyloarthritis have also occurred.¹⁰ Severe local reactions with widespread erosions and severe crusting with ultimate good outcome and cosmetic results occur in a very small percentage of patients.¹¹ Individual case reports of vitiligo-like depigmentation and pemphigus-like lesions can be found in the literature as well.^{12,13}

Management of severe local reactions may include emollients, careful observation, and/or topical corticosteroids. Severe crusting usually resolves within 2–3 weeks of discontinuation of therapy. Treatment of more severe reactions such as erythema multiforme or Stevens-Johnson, albeit rare, may require discontinuation of the medication and appropriate supportive care.

Treatment of Superficial BCCs

Basal cell carcinomas (BCCs) represent the most common cutaneous malignancy, with an estimated lifetime risk of 30% in Caucasian populations. Annually, there are approximately 1 million reported cases; likely, another 1 million cases go unreported. This tumor most commonly affects the nose, accounting for 25% to 30% of all primary BCCs. Interestingly, local tumor invasiveness often characterizes nasal BCCs, and routine excision frequently results in positive margins. BCCs in extranasal facial sites, scalp, and anterior chest are notably less aggressive. While treatment guidelines recommend surgical excision as the primary treatment option, the number of BCCs, extent, and location may pose limitations to this treatment modality.

The effectiveness of topical imiquimod 5% cream in treating superficial BCC (sBCC) has been shown in randomized, double-blind, vehicle-controlled clinical trials. Histologically confirmed clearance rates were 79% to 87% for imiquimod-treated and only 2% to 19% for placebo-treated sBCC.¹⁴ In a study of sBCC treated with imiquimod 5% cream 5 times per week for 6 weeks, the initial clearance rate at 12 weeks post-treatment was reported to be 90.3%, and the

long-term (5-year) sustained clinical clearance rate was 80.9% in those patients who achieved initial clearance.¹⁵ Of note, all recurrences in this study occurred within 12 months of long-term follow-up. This data supports the clinical assessment of initial response as strongly predictive of a longer-term outcome in patients. A single noncomparative trial of 143 patients showed a relapse rate of 21% at 2 years, indirectly indicating a higher relapse rate than alternative treatments for basal cell carcinoma,¹⁶ albeit still on par with comparative treatments such as electrodesiccation and curettage. The strength of this single noncomparative study is uncertain.

Literature review performed by Karve et al in 2008 revealed composite sBCC clearance rates in large randomized trials (combined histological and clinical assessments) ranged from 75% to 80.8% among patient using imiquimod 5 times per week and 73% to 87.1% among patients using imiquimod 7 times per week.^{17,18} Of note, treatment periods were either 6 weeks or 12 weeks. Studies evaluating increasing frequency of application, as often as twice daily, have been performed, yielding quantitatively higher histological clearance rates, as high as 100% in some small study subgroups.¹⁷ However, further study is warranted to assess for doses beyond FDA approval for sBCC (5 times per week for a full 6 weeks to a biopsy-confirmed superficial basal cell carcinoma measuring 2.0 cm or less in greatest diameter).

Treatment of Other BCCs Nodular BCC

Imiquimod has found a potential role in the treatment and/or debulking of basal cell carcinomas of the nodular type. A trial designed to evaluate the effects of imiquimod 5% cream applied 3 times per week for 8 or 12 weeks for treatment of nodular BCC, reported complete clinical clearance in 78%; however, 17% of the patients with clinical clearance had pathological evidence of residual disease.¹⁹ Clearance based on clinical appearance alone does not accurately reflect the presence or absence of disease, as evidenced by biopsy-proven residual tumor in nearly 1 in 5 patients with nodular BCC treated with imiquimod. The authors indicated that an excisional test-of-cure biopsy of the nodular BCC should be employed in all such cases.¹⁹



However, in another report, dosing 7 times per week was observed to be more effective than less frequent dosing, including 3 times per week dosing, with 71%–76% histological clearance observed for nodular BCC.²⁰

Other BCC subtypes

At the time of writing, no relevant studies have reported the use of 5% topical imiquimod therapy in pigmented, morpheaform, cystic, or micronodular BCCs.

Use as an Adjunctive Therapy for Nodular BCCs

Imiquimod has been investigated as an adjunctive modality in the treatment of BCCs, primarily of the nodular type. Curettage and electrodesiccation (C&D) is a widely used method to treat nodular BCC. However, residual tumor is present immediately after this procedure in approximately 20 to 40% of patient cases.²¹

Combining imiquimod with a surgical procedure has been proposed to reduce the chance of recurrence and the risk of post-surgical scarring. In one study, a 96% clearance rate at an average of 36 months of follow-up with a favorable cosmetic outcome was reported for BCCs (61% nodular, 13% infiltrative, 13% mixed, 7% superficial, and 7% recurrent) treated with imiquimod following curettage.²² When imiquimod was used following curettage without electrodesiccation, zero percent of BCCs had clinical recurrences.²² Superior cosmetic results were obtained compared to curettage with electrodesiccation or surgical removal of the BCCs in all patients.

A prospective, randomized, double-blind study by Butler et al included 31 patients with primary nasal nodular BCCs to investigate the effect of imiquimod 5% cream applied nightly under occlusion for 6 weeks before Mohs surgery. This study failed to show a difference in the number of Mohs stages, defect sizes, or costs between the treatment group and vehicle group.²³ Imiquimod 5% cream was not helpful as an adjunctive treatment for nodular, nasal BCCs before surgery, although the study was limited by its small sample size. Nasal BCCs, particularly nodular BCCs, may be more resistant to imiquimod therapy.

A study evaluating the efficacy of once-daily application of imiquimod 5% cream 5 times per

week for 6 weeks on 17 nodular non-facial basal cell carcinoma lesions after initial treatment of curettage without electrodesiccation revealed 100% histological clearance upon post-treatment excision.²⁴

Another similar study of 34 lesions revealed 32 of 34 treated lesions (94%) were histologically clear of basal cell carcinoma.²⁵ Fourteen of 17 patients rated the cosmetic outcome of treatment as excellent or good.

An additional study was performed to investigate the frequency of residual tumor following the combination regimen of daily imiquimod 5% cream applied for one month with C&D versus C&D alone.²¹ Twenty patients were randomized to the imiquimod (n = 10) or vehicle (n = 10) treatment arms. After 8 weeks, the proportion of patients with residual tumor was substantially decreased with imiquimod (10%) compared with vehicle (40%). In summary, imiquimod 5% cream once daily for 1 month as adjunctive therapy after three cycles of C&D substantially reduced the frequency of residual tumor and improved cosmetic outcome compared to C&D alone.²¹

Summary

Imiquimod 5% cream (Aldara) has established its niche in the treatment of non-facial superficial basal cell carcinomas. Local adverse events, while common, are well tolerated especially when compared to the surgical alternative. Its role in the treatment of nodular basal cell carcinomas is not clear since many studies lack histological verification of tumor eradication. Imiquimod was not successful as an adjunctive therapy in addition to Mohs surgery and by itself demonstrated a relatively low rate of clearance of nodular BCCs on the nose. It may merit consideration as an adjunctive therapy in combination with a less aggressive surgical therapy such as curettage and electrodesiccation.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest.

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