REVIEW

Current and emerging treatment strategies for the treatment of actinic keratosis

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Abstract: Actinic keratoses are encountered by physicians worldwide on a daily basis. As these precancerous lesions can transform to skin carcinomas, it is important to understand the many available options to use as treatment. In recent years, new therapeutic options have emerged to treat this common condition. These treatments as well as a review of the literature of conventional therapies will be discussed.

Keywords: actinic keratoses, squamous cell carcinoma, 5-fluorouracil

General

Actinic keratoses or solar keratoses are among one of the most frequent diagnoses among dermatologists worldwide. The prevalence of actinic keratoses in Australia is estimated to be approximately 40%.[1] The risk of developing actinic keratoses is even higher in immunocompromised patients. This public health epidemic is similar in the United States where 60% of people over the age of 40 with predisposed risk factors such as chronic sun exposure, outdoor occupation, fair skin, light eye color, and frequent sunburns have at least one actinic keratosis.[2] Moreover, in 2002, it has been estimated that more than 8.2 million visits to physicians in the United States were related to actinic keratoses.[3] The estimated annual cost to treat actinic keratoses in the United States alone is approximately $900 million.[4]

The morphology of actinic keratoses can vary widely. The most common presentation is that of a pink scaly patch or plaque on an erythematous base. Even though actinic keratoses typically are a few millimeters in size, they can reach confluent patches of a few centimeters in diameter. Some other subtypes of actinic keratoses include: pigmented actinic keratoses, which present as hyperpigmented scaly patches; hyperkeratotic actinic keratoses, which present with a thick scale crust on an erythematous base; and lichenoid actinic keratoses, which clinically appear with more erythema surrounding the base of the lesion and histologically show a dense band-like inflammatory infiltrate. When actinic keratoses appear on the lip, they are referred to as actinic chelitis. They are characteristically found on the lower lip and can be present focally or encompass the majority of the lip.

Although these lesions can be found anywhere on the body, they are typically located on sun-exposed areas such as the face, neck, and extremities. It is thought the irradiation from the sun produces genetic mutations in keratinocytes as well as loss of tumor suppressor genes such as p53.[5] These changes coupled with suppression of the cutaneous immune response through inhibiting the ability of Langerhans cells

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119

to present antigen to helper TH1 lymphocytes result in the development of actinic keratoses.[6]

It is important for clinicians to recognize and effectively treat actinic keratoses given their potential to develop into squamous cell carcinomas as well as the belief of some that these lesions represent an early squamous cell carcinoma *in situ*. In a study of 169 people performed by the United States Department of Veteran Affairs, 65% of squamous cell carcinomas occurred from actinic keratoses.[7] This was further confirmed by Hurwitz et al who found 444 of 459 (97%) subjects had a contiguous actinic keratosis near the site of their squamous cell carcinoma.[8] Given the prevalence of actinic keratoses and the risk of subsequent development to squamous cell carcinoma, this review article will discuss the treatment options for physicians to consider when treating patients with this common condition. Both the number of lesions and the tolerability of the treatment need to be considered when choosing the appropriate regimen for patients.

Destructive measures

One of the most common forms of treatment for actinic keratoses is the use of cryosurgery with liquid nitrogen as the cryogen. Liquid nitrogen can be applied either via a cryospray, cryoprobe, or cotton tip. When liquid nitrogen makes contact with the skin, the temperature of the treated area is lowered to −50°C. The mechanism of action involves direct cellular freezing as well as vascular stasis occurring after thawing. The duration of the freezing time varies based upon the size and thickness of the particular lesion being treated. Thicker hyperkeratotic actinic keratoses can require up to 30 seconds of treatment where thin lesions are destroyed with a 5–7 second freeze time. To ensure eradication of the actinic keratosis, it is important to achieve a 2–4 mm margin of freeze around the target lesion. It has been estimated that cure rates of up to 98% occur in individual actinic keratoses following cryotherapy.[9] While the procedure is performed, patients experience mild pain, residual erythema, and crust formation. Blistering often develops which can last up to 3 weeks until the lesion is healed. The most notable long-term sequele is hypopigmentation, especially in darker complected individuals. A limitation of cryosurgery is the focus on discrete lesions and not on subclinical actinic keratoses, which occur in wide photodamaged areas. These subclinical lesions will continue to grow to form clinically apparent actinic keratoses and subsequent squamous cell carcinomas if left untreated.

The use of a curette, with or without electrosurgery, is also utilized to treat actinic keratoses. It has been estimated that curettage and cryosurgery account for approximately 78% of all treatments for actinic keratoses in the United States.[10] The method of curettage is particularly effective for the treatment of thicker, hypertrophic actinic keratoses as the curette mechanically scrapes away the atypical keratinocytes. If hemostasis is required after the procedure or if the physician wishes to further destroy the lesion, electrosurgery can be performed. In addition to the failure to treat actinic keratoses that are not yet clinically present, dyspigmentation, scarring, and rarely infection can arise. In the case of large hypertrophic, thick actinic keratoses, surgical excision can also be considered.

Another treatment modality is the use of medium-depth chemical peels with 35% trichloroacetic acid and Jessner's solution. This treatment allows a more widespread area of treatment with efficacy rates of up to 75% at 1 month.[11] The peel is generally well tolerated with desquamation and erythema lasting 10–14 days after the procedure. One limitation is that thick, hypertrophic actinic keratoses generally do not respond well.

The use of ablative lasers such as the carbon dioxide and erbium:yttrium-aluminum-garnet (erbium:YAG) laser have been shown to be effective in the treatment of actinic keratoses. Trimas et al found the carbon dioxide laser to be a safe and effective treatment in 14 patients treated with extensive actinic keratoses on the face and scalp.[12] Some limitations with the use of this laser are pain during the procedure and the potential for pigmentary changes. As an alternative, Wollina et al studied the erbium:YAG laser to treat actinic keratoses.[13] The erbium:YAG laser is 10 times more selective of water than the carbon dioxide laser, which results in less thermal damage and is generally considered less painful. The authors treated 29 patients and found a complete response in 89.7% of the patients studied with no residual actinic keratoses discovered in the treatment area at a follow-up examination at 3 months. These lasers are better suited for larger treatment areas instead of isolated lesions due to prolonged healing times.

5-Fluorouracil

Topical 5-fluorouracil is a pyrimidine analog which has been used in the treatment of actinic keratoses for more than 50 years since it was reported that intravenous fluorouracil led to resolution of numerous actinic keratoses.[14] The mechanism of action of fluorouracil involves its ability to interfere with the

synthesis of nucleic acids through its metabolite, 5-fluorode-oxyuridylic acid, which inhibits thymidylate synthase.[15] This inhibition is significant as thymidylate synthase catalyzes conversion of deoxyuridine 5-monophosphate to the DNA compound thymidine 5-monophosphate.[16] By interfering with DNA synthesis, 5-flourouracil clears actinic keratoses as these lesions have neoplastic keratinocytes that have a higher rate of DNA synthesis than normal skin.[15] Another proposed mechanism of action involves the incorporation of fluoroura-cil into RNA, which interferes with RNA synthesis.[16]

There are numerous methods of utilizing 5-fluorouracil in the treatment of actinic keratoses. The most traditional method is continuous use once to twice daily over a period of 2–3 weeks. This method is quite effective with a clearance rate of up to 75%.[17] A major limitation of using 5-fluorouracil without breaks is complaints of erythema, pruritus, and pain. Systemic toxicity is rare and generally limited to patients with a deficiency of dihydropyrimidine dehydrogenase, which is a key enzyme that degrades up to 90% of fluorouracil.[18] The troublesome local adverse effects often lead to premature discontinuation of the product or noncompliance which effects efficacy of clearance. The resulting noncompliance stresses the importance of physician education at the time of prescribing the product, either through verbal explanation or written handouts for the patient to review and decide if the treatment is appropriate for their lifestyle. As a result of the side-effect profile and consequent poor compliance, a study by Pearlman et al suggested a pulse-dosing regimen of 1–2 days per week over 6–8 weeks to decrease the adverse effects associated with 5-fluorouracil.[19] Although there were less adverse effects, this treatment paradigm led to decreased efficacy as a direct correlation was found between the total weekly dosage and effectiveness in eradicating actinic keratoses.[20] These findings were echoed by Jury et al who performed a randomized trial comparing 20 patients receiving either 5% 5-fluorouracil twice a day for 3 weeks versus 5% 5-fluorouracil twice daily for just 1 day a week over 12 weeks.[21] The authors found a statistically significant difference with improved efficacy in eradicating actinic keratoses with the group using 5% 5-fluorouracil twice a day for 3 weeks and concluded that although inflammation accounts for many of the adverse effects encountered by patients, it is likely necessary for improved treatment outcomes. Another approach to minimize the side-effect profile of 5-fluorouracil is through the use of a microsponge delivery system. This novel delivery system consists of porous microspheres that enable the gradual delivery of 5-fluorouracil on the epidermis and thereby minimize some of the local adverse effects.[22]

An attempt to elucidate the correct strength of 5-fluorouracil to see the best way to ensure efficacy while minimizing adverse effects has been studied by several authors. Simmonds et al performed a split-face, double blind investigator study with 16 patients applying 1% 5-fluorouracil cream to one side of their face and 5% cream to the other side of the face.[23] The authors found there was no difference in efficacy between the two concentrations with less adverse effects noted with the lower concentration. Based on this work, Loven et al studied the tolerability and efficacy of a 0.5% 5-flourouracil cream compared with 5% 5-fluorouracil cream in a similar split-face study.[24] Subjects in the study applied the 0.5% cream once a day and the 5% concentration twice a day for 4 weeks or to the point where treatment became intolerable. Although the 0.5% cream was applied only once a day, there was no statistically significant difference in reduction of actinic kera-toses between the two groups, with a higher patient preference towards the 0.5% 5-fluorouracil concentration due to the once daily application and more favorable adverse-effect profile with less erythema and pruritus being noted. As there were only 21 patients enrolled in the Loven study, the efficacy of 0.5% 5-fluorouracil cream was confirmed by Weiss et al in a larger study of 177 patients.[25] The authors performed a randomized, placebo-controlled, double-blind, multicenter study in which patients were divided into two groups and evaluated at 1, 2, or 4 weeks from the time of initiation of treatment. Statistically significant differences in reduction of actinic keratoses were seen with the once daily application of 0.5% 5-flouracil cream compared with placebo at each evaluation time, with a 78.5% reduction from baseline at week 1, a 83.6% reduction at week 2, and a 88.7% reduction at week 4. Interestingly, patients completing 4 weeks of therapy noted only a slight increase in erythema and irritation after week 2. Subjects reported a cessation of all adverse effects within 17 days of completing therapy. Given the once-daily application and less side effects compared with other concentrations, the use of 0.5% 5-flurouracil cream appears to be the most cost-effective choice of the three concentrations for physicians to use in their practices.

Diclofenac sodium

Diclofenac sodium is a nonsteroidal anti-inflammatory agent whose mechanism of action in the treatment of actinic keratoses involves its ability to inhibit cyclooxygenase (COX)-2.[26] The COX-2 enzyme is oversynthesized in actinic

keratoses and catalyzes the synthesis of prostaglandins. The resulting inhibition of COX-2 decreases the byproducts of arachidonic acid and thereby hinders tumor angiogenesis.[27]

An initial study by Rivers et al assessed the efficacy of diclofenac sodium in hyaluronic acid in a study of 27 patients.[28] At 1 month following the initial use of the medication, a complete response was found in 81% of the patients. The most common adverse effect was that of an irritant contact dermatitis at the site of treatment. As a result of these initial findings, a larger randomized, double-blind placebo controlled study was undertaken by Wolf et al.[29] In this study, 96 patients with at least five discrete actinic keratoses located on the face, scalp, arms, or hands were treated with either the inactive gel vehicle, hyaluronic acid, or diclofenac sodium in hyaluronic acid twice daily for 90 days. Each patient was evaluated 30 days after the completion of therapy, with 79% of patients reporting complete or partial clearance of actinic keratoses. Another study attempted to determine the appropriate length of time patients need to be treated with diclofenac sodium in hyaluronic acid.[30] One hundred and ninety-six patients were studied in both 30- and 60-day application periods. The investigators found a statistically significant better response with 60 days of treatment compared with 30 days.

A recent paper outlined a new way to consider the treatment of actinic keratoses by using diclofenac sodium in hyaluronic acid in the treatment of actinic keratoses after cryosurgery.[31] The goal of the study was to see if sequential therapy led to a higher overall cure rate than that seen with each individual therapy. In this study, 521 patients were randomized into two treatment arms: treatment with cryosurgery alone and cryosurgery followed by the application of diclofenac sodium 3% gel in 2.5% hyaluronic acid for 90 days. Lesion counts were obtained in target areas such as the forehead, scalp, and hands at baseline, and 45, 75, 105, and 135 days after cryosurgery. At day 135, 100% clearance in the target area was achieved in 64% of the subjects in the cryosurgery followed by diclofenac sodium 3% gel in 2.5% hyaluronic acid arm compared with 32% in subjects treated with cryosurgery alone. The average percent reduction in all target lesions over time for those subjects in the cryosurgery followed by diclofenac sodium 3% gel in 2.5% hyaluronic acid started with 69% at treatment day 45 reaching an 89% target lesion reduction at day 135, with the mean number of target lesions being reduced from 8.9 at baseline to 1.1 at the conclusion of the study. The authors concluded that a reason for the synergistic effect was that both clinically apparent actinic keratoses as well as subclinical lesions were treated by combining treatment modalities.

Imiquimod

Imiquimod 5% cream was initially approved by the US Food and Drug Administration in 1997 for the treatment of external genital and perianal human papillomavirus (HPV) infections. It subsequently gained approval for the use of nonhyperkeratotic, nonhypertrophic actinic keratoses in 2004, and subsequently superficial basal cell carcinomas in immunocompetent adults. The finding of HPV DNA in actinic keratoses is a reason why imiquimod is effective in treating both external genital and perianal warts as well as actinic keratoses.[32] Iftner et al found HPV DNA in 60.4% of actinic keratoses versus 4.7% in controls.[32]

Imiquimod is a member of the imidazoquinoline family, and there are several proposed mechanisms of action to explain the efficacy towards actinic keratoses. One such mechanism of action involves the ability to activate innate immune cells through the Toll-like receptor 7 pathway to increase cytokine production.[33] The Toll-like receptor 7 is one of 11 Toll-like receptors that allow the innate immune system to detect foreign pathogens.[34] Once the foreign pathogen is detected, Toll-like receptor 7 causes NF-κB to dissociate from its inhibitor and diffuse into the nucleus where it aids in gene transcription of tumor necrosis factor alpha, interleukins 1, 6, 8, and 12, and interferons alpha and gamma.[35] These cytokines increase the cell-mediated type 1 helper T cell response and consequent destruction of actinic keratoses. Additionally, imiquimod directly activates cytotoxic T lymphocytes and natural killer cells through activation of antigen-presenting Langerhans cells.[35] Lastly, imiquimod stimulates the proliferation of B cells and upregulates the receptors required in the p53 apoptotic pathway.[36] In contrast to 5-fluourouracil, which has to penetrate each individual actinic keratosis to be effective, imiquimod is not a cytotoxic agent, and the immune response elicited from this medication appears to extend deeper than the level of the medication's penetration.[6]

An initial study by Stockfleth et al investigated the use of a once daily application of 5% imiquimod cream 3 times a week for 6–8 weeks on six patients with actinic keratoses located on the scalp.[37] The authors found both clinical and histologic evidence of clearing of all of the actinic keratoses during the follow-up period which ranged from 3–12 months. Based upon these initial findings, Korman et al reviewed two larger Phase III randomized, double-blind, placebo-controlled, parallel-group,

multicenter studies with a total of 492 patients.[38] In the study, patients applied 5% imiquimod or vehicle cream once daily, three times per week for 16 weeks, to affected areas on the face or balding scalp and were evaluated 8 weeks after the last treatment. The median percentage reduction of baseline lesions was 86.6% for the imiquimod-treated group compared with 14.3% for the vehicle-treated group. Complete clearance rates of imiquimod-treated patients was statistically significantly higher than the vehicle-treated group, with a 48.3% rate noted in the imiquimod treatment arm. An interesting observation noted by Korman et al was an initial increase in the number of actinic keratoses when patients first used imiquimod. This occurrence has been hypothesized to be the result of subclinical lesions being uncovered as opposed to new lesions being created.[38] Adverse effects occurred in 73% of the subjects reviewed by Korman et al and commonly included erythema, scabbing, and flaking. The authors found that the patients which experienced a greater degree of these local adverse effects correlated with a greater chance of complete and partial clearance rates. In an attempt to reduce these adverse effects while still maintaining promising treatment results, two recent studies compared the efficacy and tolerability of imiquimod 3.75% cream and imiquimod 2.5% cream to investigate these lower doses of imiquimod.

The first study by Swanson et al was a randomized, placebo controlled trial of 479 patients placed into three groups: placebo, imiquimod 2.5% cream, and imiquimod 3.75% cream.[39] Each of these groups was treated cyclically for 2 weeks followed by a 2-week rest period and concluded with an additional 2-week treatment period. The patients then returned 8 weeks after completing their last 2-week cycle to determine the percentage of lesion reduction from baseline. The median reductions in lesion count were 25% for placebo, 71.8% for imiquimod 2.5% cream, and 81.8% for imiquimod 3.75%. Although these clearance rates were somewhat less than those found with imiquimod 5% cream, the study with these lower dosages of imiquimod treated a larger treatment area with more baseline lesions. With a greater area of treatment as well as more initial lesions, it is not surprising that the median reduction in lesion count was lower in the study of imiquimod 3.75% and 2.5%. Local skin reactions such as erythema, scabbing, pruritus, and erosions were most commonly reported in the treatment groups. Although these treatment-related adverse effects were 19.4% in the treatment group versus 2.5% in the placebo group, the placebo group actually had a slightly higher rate of study discontinuation at 1.9% versus 1.2%. The second study by

Hanke et al confirmed the aforementioned results, but the patients were treated an additional week with two 3-week cycles.[40] The median reductions in lesion count were 23.6% for placebo, 66.7% for imiquimod 2.5% cream, and 80.0% for imiquimod 3.75%. Given the comparable efficacy to the study by Swanson et al, patient compliance will be improved with the shorter treatment regimen of 2-week cycles.

Ingenol mebutate

Ingenol mebutate (ingenol-3-angelate, formerly PEP005) represents a new treatment for actinic keratoses. This novel agent is purified and extracted from the sap of the plant Euphorbia peplus and whose mechanism of action involves its ability to cause cellular necrosis through disruption of the plasma membrane and mitochondria.[41] Additionally, ingenol mebutate stimulates neutrophil-mediated and antibody-dependent cellular cytotoxicity to eradicate any residual diseased cells.[42]

An initial study by Siller et al investigated the safety and efficacy of ingenol mebutate in a randomized, double-blind, vehicle-controlled, multicenter study of 58 patients.[43] Patients received two total daily applications of either ingenol mebutate gel 0.0025%, 0.01%, or 0.05%, or placebo vehicle gel. The authors found the greatest efficacy with ingenol mebutate gel 0.05%, with a complete clinical clearance rate of 71%. The treatment was well tolerated with only local adverse effects of erythema, flaking, and crusting being reported. The results of this study were confirmed by Anderson et al with a larger sample size of 222 patients.[44] In this study, patients were randomized to receive either vehicle gel for 3 days, ingenol mebutate gel 0.025% for 3 days, or ingenol mebutate 0.05% for 2 or 3 days, with an 8-week follow-up period. The authors found the clinical responses to be dose dependent for all measures of efficacy with the most statistically significant rates of clearance occurring with the group receiving ingenol mebutate 0.05% for 3 days. This group had a partial clearance rate of at least 75% resolution of baseline lesions in 75.4% of patients and a complete clearance rate of 54.4%. An advantage of this treatment is the short 2–3 day course of therapy, which will help to improve compliance in patients who are not adherent to some of the aforementioned longer treatment regimens.

Photodynamic therapy

An emerging treatment for actinic keratoses is the use of topical 5-aminolevulinic acid (5-ALA) photodynamic therapy. After topical application, this photosensitizer

penetrates the stratum corneum and is absorbed by actinic keratoses, pilosebaceous units, and nonmelanoma skin cancer cells.[45] Once the prodrug 5-ALA is absorbed, it is converted into its active drug, protoporphyrin IX which can be detected in the epidermis four hours after application.[46] The active drug can then peakly absorb two different light wavelength sources: blue light (400–450 nm), known as the Soret band, and red light (640 nm). Once activated, reactive oxygen intermediates such as singlet oxygen are created that result in apoptosis and vascular endothelial damage.[47] The use of 5-ALA photodynamic therapy was approved by the US Food and Drug Administration for the treatment of nonhyperkeratotic actinic keratoses after a 14–18 hour incubation period followed by exposure to blue light for 16 minutes and 40 seconds.[45]

An initial study by Jeffes et al used a single treatment of 30% 5-ALA with activation from a 630 nm argon pumped dye laser for actinic keratoses on the face, scalp, trunk, and extremities.[48] The patients were evaluated 2 months following treatment with a 91% complete clearance rate on the face and scalp compared with a 45% rate of clearance on the trunk and extremities. The authors concluded that the treatment was more effective on thinner lesions and less likely to improve thick, hyperkeratotic actinic keratoses. The superior clearance rate for actinic keratoses on the face and scalp was confirmed by a randomized, placebo-controlled study of 243 patients by Piacquadio et al who evaluated 5-ALA photodynamic therapy versus placebo in the treatment of multiple actinic keratoses on the face and scalp.[49] The patients in both groups were evaluated following therapy at 24 hours, 1 week, 4 weeks, 8 weeks, and 12 weeks. At 8 weeks, 77% of patients receiving 5-ALA photodynamic therapy experienced 75% or more clearing of treated lesions versus 18% for placebo. In the study, the patients tolerated the 5-ALA photodynamic therapy well with the burning sensation during light treatment markedly decreasing within 24 hours of therapy and complaints of erythema and edema at the treated sites improving within 1–4 weeks after therapy.

5-ALA methylester is another photosensitizer that has been used in the treatment of actinic keratoses. It had been proposed that 5-ALA methylester may result in greater efficacy due to superior lipophilicity allowing enhanced penetration into atypical cells in comparison with 5-ALA. A study by Moloney and Collins investigated this question by comparing the two photosensitizers in 16 patients with extensive scalp actinic keratoses.[50] In the study, each photosensitizer was applied to either the left or right side of the scalp, thereby allowing for a direct comparison of the same

patient. The results of this double-blind, split-scalp study found a similar reduction in the number of actinic keratoses with no statistically significant difference found in the efficacy between the two photosensitizers. However, patients reported more pain, both during treatment and post-treatment, with 5-ALA in comparison with 5-ALA methylester. Another consideration in deciding between these two photosensitizers is cost, as 5-ALA methylester is more expensive than 5-ALA in many countries.

A study by Kurwa et al examined the effectiveness of topical 5-fluorouracil compared with 5-ALA photodynamic therapy.[51] In the study, 14 patients' right and left hands with actinic keratoses were randomized to receive either a 3-week course of 5-fluorouracil or 5-ALA photodynamic therapy. Lesion counts and tolerability were compared at weeks 1, 4, and 24 after initiation of treatment. The results of the study showed equal efficacy among the two treatments, without any statistically significant difference in clearance rates of actinic keratoses. However, 5-ALA photodynamic therapy did elicit a faster response and is a viable alternative for patients who have contact sensitivity to 5-fluorouracil or are noncompliant with the 5-fluorouracil treatment regimen.

Conclusion

Actinic keratoses are a common problem that physicians face on a daily basis. With the increased frequency of sun damage coupled with the aging of the population, the incidence of actinic keratoses will continue to rise. It is important to understand the various treatment options available to tailor therapy to each patient's needs. The number of actinic keratoses, the patient's tolerance to known side effects, and the amount of background photodamage in the treatment area are among factors that physicians need to consider. The treatments reviewed emphasize the importance to treat both individual actinic keratoses that are apparent as well as subclinical lesions that will later turn into precancerous lesions. With the well known transition of actinic keratoses to cancerous lesions, new therapies as well as the use of treatments in combination will become more prevalent.

Disclosure

The author reports no conflicts of interest in this work.

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