

Topical Therapy for Actinic Keratoses: Current and Evolving Therapies

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Abstract: Actinic keratoses (AKs) are evolving malignant cutaneous neoplasms. They are also known as solar keratosis, squamous cell carcinoma in situ—solar keratotic type, or keratinocytic intraepidermal neoplasia. Actinic keratoses can be treated by two general methods: by physical/destructive methods and with topical therapies. This article will review current and evolving topical therapeutic options for AKs. Several topical treatment options have been shown to offer some significant benefit in the alleviation of these lesions. The therapies include 5-fluorouracil, imiquimod, diclofenac, colchicine and retinoids.

Actinic keratoses (AKs), also known as solar keratoses or senile keratoses, are the most common neoplastic skin lesions detected on Fitzpatrick skin type I or II individuals. These lesions are the third most common reason a patient visits a dermatologist [1]. AKs were first described in the literature during 1898 by Dubreuilh at the third International Congress of Dermatology [2].

They appear as papules in a vast spectrum of sizes, shapes, colors and other characteristics. Their size and shape can range from a well circumscribed single millimeter papule to an irregular shaped lesion that can span several centimeters. These neoplasms can be flesh colored, red, or pigmented and can also scale or become hyperkeratotic.

They can occur anywhere the skin is exposed to chronic sun radiation. The most common sites where the lesions can be found are the face, ears, scalp, neck, forearms, and hands. Chronic repetitive UV exposure results in repetitive cycles of DNA damage. Eventually, the repetitive cycles of damage and repair spawn a significant unrecoverable error. The DNA lesion most likely responsible for these neoplasms is/are the P53 and/or *ras* proto-oncogene mutation [3]. Multiple studies have shown the P53 mutation is present in 53% of AKs and 69% to 90% of squamous cell carcinomas (SCCs) [3,4].

The Australian population has the highest prevalence of these lesions, approximately 40% [5]. In the United States, a population study examining AK prevalence vs. sun exposure revealed prevalence ranging from 23.3% to 36.7% and 18.6% to 34.1% for men and women, with low and high UV exposure, respectively [6].

An individual's current AK population is a dynamic balance between the appearance of new lesions and the spontaneous resolution of a percentage of the existing ones. Annual rates of incidence and resolution have been demonstrated to be as high as 48% and 26%, respectively

[7]. Further, the current literature reflects that 60% to 99% of all SCC arise from AKs. Subsequently, the overall annual incidence of an AK to SCC transformation is 0.075% to 0.096% [8]. When this data is extrapolated out, the 10-year incidents for developing a SCC for a patient afflicted with an average AK burden is 10.2% [9]. To combat this very common lesion a host of topical preparations have been examined and are reviewed here. They include 5-fluorouracil, imiquimod, diclofenac, colchicine and retinoids. (Table 1) [A PubMed search was performed to identify studies of these medications in the treatment of actinic keratoses. All relevant case series and clinical trials will be discussed.](#)

5-FLUOROURACIL

Topical 5-fluorouracil has been a mainstay of the treatment for AKs for many years and, as a result, has been the focus of a multitude of studies (Table 2). The main mechanism of action is well understood and entails the topical formulation undergoing ribosylation and phosphorylation after entering cells, resembling a natural nucleotide. Fluorouracil then binds to thymidylate synthase, using the cofactor 5,10-methylene tetrahydrofolate. As a result, thymidylate synthase is inhibited and cannot convert deoxyuridine nucleotides to thymidine nucleotides. The depletion of thymidine leads to reduced synthesis of DNA [10]. This agent acts selectively to cause cell death in the actinic lesions and not in the normal skin. It is not clear whether normal cells simply absorb less fluorouracil than AK cells or whether the absorption is the same in both without producing equal effects on both cell types [11-13].

Among the earlier studies of 5-fluorouracil in the treatment of actinic keratoses is a double blind investigation comparing a 1% to a 5% formulation by Simmonds [14], in which sixteen patients applied a 1% cream to one side of the face and a 5% cream to the other side and were evaluated at seven day intervals. Results indicated that for half of the patients, when both sides were equally affected at the start of the treatment, both creams produced equal results [14]. While the most common fluorouracil cream formulations utilized have been the 1% and 5% versions, a relatively new 0.5% formulation has recently garnered much attention [15].

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Table 1. Topical Formulations for AK Treatment

Product	Status	Company	Brand Name	Available Strengths
5-FU	FDA Approved	Dermik	Carac Cream	0.5%
		ICN	Efudex Cream	5%
			Efudex Topical Solution	2%, 5%
		Allergan	Fluoroplex Topical Cream	1%
			Fluoroplex Topical Solution	1%
Imiquimod	FDA Approved	3M	Aldara Cream	5%
Diclofenac Na	FDA Approved	Bioglan	Soleraze Gel	3%
Colchicine	Off label	n/a	n/a	0.5%, 1%
Tretinoin	Off label	Bertek	Avita Cream	0.025%
		Ortho Dermatological	Renova Retin-A cream	0.02%, 0.05% 0.025, 0.05, 0.1
			Generic	tretinoin

Table 2. Summary of 5-FU Topical Studies

Authors/Year	Number of Patients	Treatment	Results	Most Common Adverse Events
Simmonds – [1973] ¹⁴	16	5-FU 1% to the right side of the face and 5% to the left side of the face twice daily for 14-29 days.	No difference in treatment time or degree of efficacy for either the 1% or 5% fluorouracil topical cream.	Most patients experienced mild erythema.
Levy <i>et al.</i> – [2001] ^{15,16}	21	5-FU 0.5% once daily or 5% twice daily for up to 28 days.	Plasma concentrations of fluorouracil were detectable in 3 of 10 patients treated with 0.5% 5-FU and 9 of 10 treated with 5% 5-FU.	Facial irritation was evident with both formulations but reached a plateau during treatment with 0.5% fluorouracil.
Loven <i>et al.</i> – [2002] ¹⁷	21	5-FU 0.5% once daily and 5% twice daily to opposite sides of the face for 4 weeks.	0.5%- lesion reduction from 11.3 to 2.5, 5%- 10.3 to 4.2. Patients preferred 0.5% [P=0.003].	All 21 patients experienced facial irritation, the most common being erythema, erosion, and dryness.
Weiss <i>et al.</i> – [2002] ¹⁸	177	5-FU 0.5% or vehicle once daily for 1, 2, or 4 weeks.	A mean lesion decrease to 3.0 following four weeks of treatment compared to 13.7 following vehicle.	77.5%-81.6% in each treatment group experienced mild to moderate facial irritation with majority showing dryness [58%] and erythema [73%].

Levy *et al.* [15] performed an *in vitro* study involving the penetration of three fluorouracil 0.5% creams (formulations A, B, and C) employing a Microsponge delivery system and one commercially available fluorouracil 5% cream administered every three hours for twenty-four hours on full-thickness human cadaver skin. The three 0.5% creams differed in the method of incorporating fluorouracil within the vehicle base, and a preservative was present only in formulation A. The total absorption was defined as the sum of the amount of cumulative flux through the skin over twenty-four hours and the amount retained in the skin at twenty-four hours. The findings indicate that the flux through the skin of the fluorouracil 5% formulation was twenty to forty times greater than that of the fluorouracil

0.5% formulation. A higher percentage of absorbed fluorouracil was retained in the skin after twenty-four hours with the 0.5% formulations (86%-92%) than with the 5% formulation (54%), (P<0.001) [15].

Another study by the same group employing a different methodology, systemic exposure, was evaluated *via* plasma and urine fluorouracil concentrations following topical administration of fluorouracil to patients with a minimum of three AKs [16]. The patients were randomized to receive 1-g doses of either fluorouracil 0.5% cream or fluorouracil 5% cream. Treatment regimens were consistent with prescribing regimens- once daily for the fluorouracil 0.5% cream and twice daily for the fluorouracil 5% cream for up to twenty-eight days. After determining the pharmacokinetics, it was

found that measurable fluorouracil plasma concentrations were identified in three patients treated with the 0.5% cream than in nine patients treated with the 5% cream [16].

Loven *et al.* [17] investigated the efficacy and tolerability of the fluorouracil 0.5% cream as compared with the fluorouracil 5% cream in a single-blind study. Patients with a balanced number of AKs on each side of the face were treated with the 0.5% cream on one half of the face once daily and the 5% cream on the other side of the face twice daily for four weeks, or to the point that treatment became intolerable. Both the total clearance of AKs and the incidence of any adverse event were not found to be significantly different between the two groups. However, the majority of patients in the study preferred the 0.5% cream to the 5% cream ($P=0.003$) secondary to the once-daily treatment schedule, less irritation and ease of product application [17].

In a similar study examining the efficacy of 0.5% fluorouracil in a randomized, double-blind, vehicle-controlled trial, Weiss *et al.* [18] reported a significant reduction in the number of AKs with the 0.5% cream. Treatment duration consisted of one, two, or four weeks with a percent reduction in the number of AKs from baseline of 78.5%, 83.6%, and 88.7%, respectively, ($P<0.001$). Total lesion clearance occurred in 26.3%, 19.5%, 47.5%, and 3.4% of patients in the one, two, and four week fluorouracil and vehicle groups, respectively. Facial irritation was experienced by patients in the one-week and two-week groups and appeared to increase during the entire treatment period. The patients in the four-week group noted only a slight increase in irritation beyond the second week. Irritation returned to baseline levels fifteen to seventeen days after completing therapy, regardless of the duration of application [18]. Further supporting that the use of the 0.5% formulation of topical fluorouracil cream may be more cost-effective is a study comparing the two other formulations (5% and 1%) conducted by Gupta [19]. The results suggest that fluorouracil 0.5% cream maybe be more cost-effective compared with the higher concentrations in a

patient with multiple AKs, most likely due to the once-daily regimen [19].

In all the studies reviewed, the most common reported side effects from treatment were mild to moderate facial irritation associated with erythema, dryness, and burning. Few serious adverse events have been reported with topical fluorouracil use and include allergic contact dermatitis [20] and a single case of inflammatory colitis following topical application of a 5% formulation for a basal cell carcinoma of the scalp [21]. This individual had a severe deficiency of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in fluorouracil breakdown. It is thought that this is the only case of a life-threatening toxicity in a patient receiving topical 5-fluorouracil [21].

Imiquimod

Another medication currently used to treat AKs is imiquimod. This drug has been approved by the FDA as a therapy of external genital warts [22]. However, there are an increasing number of case reports and reviews that show the efficacy of topically applied imiquimod in off-label conditions such as molluscum contagiosum, basal and squamous cell carcinoma, Bowen's disease, human papillomavirus infections, vulvar intraepithelial neoplasms, and actinic keratosis (Table 3) [23-28].

Imiquimod is as an immunomodulator. Application of the drug results in increased levels of IFN- α , IFN- β , IFN- γ , and TNF- α in lesional tissues. Further, keratinocytes exposed to imiquimod release increased levels of IFN- α , IL-6, and IL-8. These and other cytokines activate and sensitize the local cellular immune system, including, but not limited to, natural killer and cytotoxic T-cells. The cascade results in a localized immune response against the abnormal cells in the application area [24-27].

Salasche *et al.* [29] conducted a twenty-five patient open-label trial using three times per week application of imiquimod 5%. The therapeutic regimen consisted of four

Table 3. Summary of Imiquimod Topical Studies

Authors/Year	Number of Patients	Treatment	Results	Most Common Adverse Events
Stockfleth <i>et al.</i> – [2001] ³¹	6	Imiquimod 5% applied 2 to 3 times a week for a maximum of 8 weeks.	All patients experienced a complete clearing	Pruritis and Erythema were the only reported adverse effects overall the medication was well tolerated.
Persaud <i>et al.</i> – [2002] ³⁰	22	Imiquimod 5% applied to the patients body 3x a week for a maximum of 8 weeks	A mean 3.9 lesion decrease per patient	82% - mild to moderate erythema pruritis and or scabbing
Salasche <i>et al.</i> – [2002] ²⁹	25	Imiquimod 5% applied to sites 3x a week for a max of three 4-week cycles	82% of the treatment sites were cleared	Some patients had mild to moderate irritation. Five patients experienced severe medication reactions.
Stockfleth <i>et al.</i> – [2002] ³²	36	Imiquimod 5% applied 3 times a week for a maximum of 12 weeks.	21 patients experienced a complete clearing	All patients experienced mild to severe reactions. The five most common reactions were erythema, scabbing, erosions, flaking and ulcerations.

weeks of treatment followed by a one month resting period. No more than an additional two cycles of treatment were given if total clearing did not occur by the end of the first rest period. At the end of the first cycle, fifteen of the thirty-three study areas were devoid of any lesions. After the second cycle, an additional twelve sites were cleared. Only one patient underwent a third cycle of treatment resulting in a 75% clearance of their study areas. Overall, 82% of the treated sites were cleared using this therapy. Some patients experienced a mild to moderate local irritation which was well tolerated without complication. However, there were five patients that reported severe medication reactions all of which occurred during the first cycle. These reactions followed an intense and early response to therapy [29].

Persaud *et al.* [30] conducted a twenty-two patient study applying imiquimod 5% cream to half of each patient's body three times a week for a maximum of eight weeks. The treatment period was followed by an eight-week monitoring period. The seventeen patients who completed the study had mean AK reduction on the imiquimod side of 3.9 per subject as compared to a 0.5 lesion reduction on the vehicle side, ($P < 0.005$). Eighty-two percent of the patients experienced either mild or moderate erythema, pruritis and/or scabbing as a result of treatment. Further, twelve patients required a one or two rest periods followed by a reduction in application frequency in order to complete the study [30].

Stockfleth *et al.* [31] conducted a six patient study examining the efficacy of imiquimod 5% applied two to three times a week for six to eight weeks. Upon completion of the treatment period all the patients were clinically and histologically cleared of all the AKs in their test area(s). Patients were followed for a maximum of twelve months and had no recurrence of disease in their treated area(s). All the patients decreased their dosage from three times a week to two times a week for more than half of their individual treatment period secondary to the inflammatory response provoked by the medication. The treatment was well tolerated with only mild to moderate pruritis and erythema reported [31].

In another study Stockfleth *et al.* [32] treated thirty-six patients with imiquimod 5% three times a week for a maximum of twelve weeks. By the fourteenth week of the study twenty-one of the twenty-five patients treated with imiquimod experienced complete clinical and histological clearance of their study area(s). Further, the fifteen patients that maintained a three times per week application protocol all experienced total clearance of their study area(s). These results were found to be significant upon comparison to the clearance rate of the control group, ($P < 0.001$). During the treatment period every patient using imiquimod experienced some type of mild to severe adverse reaction. The five most common occurrences were; erythema, scabbing, erosions, flaking and ulcerations [32]. A phase III trial evaluating imiquimod in the treatment of AKs has recently been completed.

Diclofenac

Diclofenac, an NSAID, has also been evaluated in the treatment of AKs (Table 4). Currently, this drug's mechanism of action with respect to the treatment of

precancerous lesions is not clearly understood. However, there are current research efforts exploring the theory that diclofenac's clinical effect occurs through the inhibition of the cyclooxygenase enzymes. Inhibition of cyclooxygenase decreases the down stream by-products of arachidonic acid metabolism. Some of these by-products control overall immuno-surveillance, the inhibition of apoptosis, and up-regulation of the invasive ability of tumor cells [33-36].

Rivers *et al.* [37] performed a twenty-nine subject open labeled study using diclofenac 3% in 2.5% hyaluronan gel applied twice daily to one or more target lesions. The AKs were treated until they resolved or they had been treated for one hundred and eighty days. The twenty-seven patients that completed the study had treatment times ranging between thirty-three and one hundred and seventy-six days. At the thirty-day post-treatment exam, 81% of the patients had complete resolution of the target lesions [37].

Wolf *et al.* [38] examined the efficacy and safety of diclofenac 3% 2.5% hyaluronan gel in one hundred and twenty subjects. During the first three months of this study the patients applied the cream to the target area twice a day. Follow-up evaluations occurred one month after the treatment period had been completed. At this point 50% of the treatment patients and 20% percent of the placebo patients experienced total clearance of the target AKs present at the initiation of the study. Further, 47% of the treatment patients had totally clear treatment areas while only 19% of the placebo patients experienced total clearance. The difference seen between the number of treated and placebo patients that achieved these response levels were significant in both instances, ($P < 0.001$) [38].

A second study conducted by Rivers *et al.* [39] conducted a one hundred and ninety-six subject study that examined both thirty and sixty day application periods of diclofenac 3% 2.5% hyaluronan gel. At the conclusion of the study period significant improvement was only reported in the sixty day regimen group. A comparative examination of that group and their match controls showed that 33% of these treatment patients experienced clearance of their initial lesions while only 10% of the matched control patients achieved clearance, ($P < 0.05$). Further, 31% of the treatment patients were devoid of any AKs in the treatment area as compared to only 8% of the matched control group, ($P < 0.05$). Comparative analysis of the thirty day treatment group and their matched controls showed no significant therapeutic benefit to treating AKs with such a short course of diclofenac [39].

In contrast to the other studies presented here, McEwan *et al.* [40] conducted a one hundred and thirty person study evaluating diclofenac 3% applied twice daily for one hundred and eighty days. Analysis of their data showed no significant benefit using diclofenac on AKs. Further, their data did show that local reactions occurred at significantly higher rate in the therapy group, ($P = 0.0002$) [40].

The most common reported side effects using this treatment included pruritus, application site reactions, dry skin, rash, and erythema. However, the vast majority of these events were classified as mild to moderate and most resolved of their own accord. All hematological studies that were

Table 4. Summary of Diclofenac and Colchicine Topical Studies

Diclofenac				
Authors/Year	Number of Patients	Treatment	Results	Most Common Adverse Events
Rivers <i>et al.</i> – [1997] ³⁷	29	Diclofenac 3% applied 2x daily for maximum 180 days	81% had complete resolution 1 month after therapy	72% mild-moderate skin irritation
McEwan <i>et al.</i> – [1997] ⁴⁰	130	Diclofenac 3% applied 2x daily for 180 days	No benefit was shown	Local reactions
Wolf <i>et al.</i> – [2001] ³⁸	120	Diclofenac 3% applied 2x daily for 3 months	50% of the treated patients cleared	96% mild- moderate Pruritis, site reactions, dry skin, erythema
Rivers <i>et al.</i> – [2002] ³⁹	195	Diclofenac 3% applied 2x daily for 30 or 60 days	33% of the 60 day treated patients cleared	mild-moderate pruritis, rash, dry skin, application site reaction
Colchicine				
Authors/Year	Number of Patients	Treatment	Results	Most Common Adverse Events
Grimaire <i>et al.</i> – [2000] ⁵³	20	Colchicine 1% applied 2x daily for 10 days	70% of the patients cleared by 60 days	No systemic side effects reported
Akar <i>et al.</i> – [2001] ⁵⁴	16	Colchicine 0.5% or 1% applied 2x daily for up to 3 10-day cycles	Total clearance occurred in 7/8 of the 0.5% patients and 6/8 of the 1.0% patients	No systemic side effects reported

conducted on these patients were found to be within normal limits [37-40].

Colchicine

The next topical treatment is the alkaloid plant extract, colchicine. This medicine is most widely known for its usage as a treatment of gout. The chemical was described in the first century and was first applied as a treatment of gout in 1793. It was not until 1968 that Marshall described its usefulness as a treatment for AKs [41]. Subsequently, several studies have examined colchicine's therapeutic efficacy on these lesions (Table 4).

Colchicine is a yellow, UV sensitive, water soluble powder [42]. When instilled into living systems, colchicine disrupts the polymerization of tubulin and subsequently arrests microtubule formation [43]. This results in various effects including the arrest of mitosis and a decrease in the chemotactic and phagocytic ability of leukocytes. Other leukocyte studies revealed that colchicine suppressed white cell function by increasing cyclic adenosine monophosphate and prostaglandin E production as well as stabilizing the cell's lysosomal bodies. All these effects result in a functional down-regulation of the affected leukocytes [44-48]. In addition to the aforementioned effects, colchicine also enhances collagenase production and decreases the production, release, and/or expression of collagen, II-1, immunoglobulin, histamine, and surface antigens [49-52].

In 2000, Grimaire *et al.* [53] conducted a twenty person study examining topical application of colchicine 1% to forehead AKs twice a day for ten days. By the tenth day, a significant localized inflammatory response arose on the

lesions in the treated area. Patients described the reaction as a sunburn-like feeling that occurred one to three days after the treatment began. This was followed by the development of a pustular reaction that subsequently intensified until the treatment was discontinued. At the thirty-day follow-up, the AK crusts on six of the treatment patients had resolved. Additionally, two of these patients experienced complete clearance of their disease state. Subsequently, five additional treatment patients cleared their AKs by the sixty day follow up, resulting in a complete clearance in seven of the ten treatment patients [53].

Akar *et al.* [54] examined the efficacy and safety of the 0.5% and 1% colchicine cream applied twice daily. In the sixteen patient study subjects were randomly separated into the 0.5% or the 1% treatment group. Most of the patients were treated with a single ten day course of the medication while a few received a second course of colchicine. The overall lesion reduction seen in the two groups was 77.7% and 73.9% for the 0.5% and 1% groups, respectively. Further, total target AK clearing occurred in seven of the eight in the 0.5% group and six of the eight in the 1.0% group, showing that both concentrations are equally efficacious [54].

Regular blood exams showed that none of the patients had any systemic absorption. Further there were no observed or reported systemic side effects seen in these patients [53,54].

Retinoids

Retinoids demonstrate potent antiproliferative and differentiation-inducing effects and have thus been shown to

improve the manifestations of skin photodamage. More recently, epidemiological and biochemical studies have indicated cancers originating from the epithelium may be associated with a relative deficiency of retinal [55,56]. This line of thinking has been extended to actinic keratoses since as early as 1962. During that year Stuttgen [57] was the first to employ vitamin A acid alone for the treatment of AKs in three cases. Subsequently, Bollag and Ott [58] reported four to six patients treated with three to six weeks of tretinoin 0.1% therapy. The patients experienced greater than a 50% reduction in AKs of the forearms and hands. Further, three patients treated with tretinoin 0.3% experienced similar levels of AK reduction. Modest progress has been made since these earlier reports (Table 5) [58].

Kligman *et al.* [59] performed a multi-center, double blind study including 1265 patients who were treated for histologically confirmed AK with tretinoin 0.05%, tretinoin 0.1%, or vehicle only, for periods up to fifteen months. They found the most effective treatment for reducing AKs to be tretinoin 0.1% applied twice daily [P<.001]. An excellent

response was observed in 73% of tretinoin-treated patients, compared with only 40% of the vehicle patients [59]. In a similar large study, topical tretinoin 0.05% cream applied once or twice daily was found to significantly decrease the number and size of facial AKs by approximately 50% after six to fifteen months [60].

With respect to topical isotretinoin, Alirezai *et al.* [61] conducted a one hundred patient randomized, double-blind, placebo-controlled, parallel-group study examining the efficacy of the twice daily applications of the 0.1% cream as compared to the vehicle. The patients applied these creams for twenty four weeks to their face, scalp, and upper extremities and were assessed every four weeks. It was determined that the reduction in number of facial actinic keratoses at the end of treatment period was greater for patients who applied isotretinoin [3.9 ± 0.6 , i.e. 66% of patients with a reduction >30%] as compared to placebo [1.7 ± 0.5 , i.e. 45% of patients with a reduction >30%] (P=0.001). No significant treatment benefit was seen for lesions on the scalp or upper extremities [61].

Table 5. Summary of Tretinoin Topical Studies

Authors/Year	Number of Patients	Treatment	Results	Most Common Adverse Events
Bollag <i>et al.</i> – [1975] ⁵⁸	6	Tretinoin 0.1% twice daily for 3-6 weeks.	Greater than 50% reduction in AKs of the forearms and hands.	n/a
Kligman <i>et al.</i> – [1991] ⁵⁹	1265	Tretinoin 0.05%, .1% or vehicle only twice daily for up to 15 months	The greatest reduction of lesions was seen after treatment with .1% twice daily [P<.001]	n/a
Alirezai <i>et al.</i> – [1994] ⁶¹	100	Isotretinoin 0.1% cream or vehicle twice daily for 24 weeks to face, scalp, and upper extremities	66% of patients achieved a reduction of lesions >30% after being treated with isotretinoin compared with 45% of those treated with vehicle.	Signs of local irritation were common in both treatment groups, but more frequent with isotretinoin.
Moglia <i>et al.</i> – [1996] ⁶²	18	Retinoid Fenretinide applied topically twice daily for 3 months.	Complete regression of lesions in 56% and partial regression in 44% of cases	No local or distant adverse effects
Misiewicz <i>et al.</i> – [1991] ⁶³	25	Ro 14-9706 and tretinoin 0.05% twice daily for 16 weeks to opposite sides of the face.	Mean percent decrease in the number of AKs was 37.8% for areas treated with Ro-14-9706 and 30.3% for areas treated with tretinoin [P<0.01]	Local inflammation was slight or absent in most patients and tretinoin caused severe erythema in 50% and severe scaling in 23% of patients.
Moriarty <i>et al.</i> – [1982] ⁶⁴	50	Oral etretinate for 4 months	84% of patients versus only 5% of placebo group had a complete or partial response.	Dryness of mouth and lips, desquamation, rash/pruritis
Bercovitch <i>et al.</i> – [1987] ⁶⁵	19	5-FU 5% cream on each arm twice daily followed by nightly application of tretinoin 0.05% to one arm and an control to the other.	Tretinoin-treated arms had 3.4 ± 2.6 lesions following treatment compared to 4.2 ± 2.5 lesions in the control arm [P<0.04].	Twelve patients experienced more irritation on the side treated with tretinoin than the control, while two patients reported severe irritation at distant sites.

Similarly, Moglia *et al.* [62] treated eighteen patients with facial actinic keratoses with the retinoid fenretinide (4-HPR) topically twice-daily for three months. Following this treatment period, complete regression was observed in 56% of the patients. Further, partial regression of the lesions was observed in an additional 44% of cases. Eight patients relapsed within three months of ending therapy. Additionally, only two patients [11%] showed complete regression six months later. No adverse effects were observed. It was also found that baseline plasma retinol levels were lower than in healthy subjects which suggests that reduced retinol levels might be involved in the pathology of AKs [62].

In a double-blind, randomized, within-patient comparative study, the efficacy and tolerability of Ro 14-9706 (an arotinoid methyl sulfone) in the treatment of AKs was compared with that of tretinoin [63]. A total of twenty-five patients with more than three lesions on each side of the face were involved in the study. The patients applied each agent twice daily for sixteen weeks as a 0.05% cream to opposite sides of the face. The mean percent decrease in the number of actinic keratoses was assessed before and at weekly intervals during the treatment period. The mean percent decrease in the number of actinic keratoses was 37.8% for areas treated with Ro 14-9706 and 30.3% for areas treated with tretinoin. These decreases were significantly different from baseline ($P < 0.01$), but not from each other. There was an associated severe erythema in 50% and severe scaling in 23% of patients whereas Ro 14-9706 was better tolerated with only a slight or absent inflammation [63].

Studies have also examined the efficacy of high-dose systemic etretinate for the treatment of AKs. Moriarty *et al.* [64] conducted a double-blind crossover study of fifty patients with AKs who were treated with a four month course of oral etretinate. They concluded that 84 % of patients who completed treatment with etretinate versus only 5% of the placebo group had a complete or partial response. Unfortunately, the systemic toxicity of retinoids discourages its use for long term treatment at high doses [64].

Retinoids have also been shown to enhance the effectiveness of 5-fluorouracil. In a randomized double-blind controlled study by Bercovitch, [65] nineteen patients applied 5-fluorouracil 5% cream to AKs on each arm twice daily, followed by nightly application of tretinoin 0.05% cream to one arm, and a control cream (Eucerin) to the other arm until discomfort precluded further applications. After three months, the tretinoin-treated arms had 3.4 ± 2.6 AKs following treatment versus 15.7 ± 6.1 AK before treatment. In contrast, the control arm had 4.2 ± 2.5 lesions following therapy compare to 15.3 ± 6.9 AKs before therapy ($P < 0.04$) [65]. Sander *et al.* [66] found similar results as to a synergistic effect in the treatment of disseminated actinic keratoses on photodamaged skin when low-dose isotretinoin and topical fluorouracil are combined. As with etretinate mentioned above, such combination treatment regimens have limited usage secondary to such side effects as pain, irritation, and bleeding. These symptoms were the extent of the adverse effects seen in treatment with retinoids for AK in the majority of cases reviewed [66].

CONCLUSION

While the diagnosis of actinic keratosis affects countless individuals, research efforts have revealed an encouraging array of topical and semi-invasive treatment options. The plethora of choices allow the dermatologist and patient to select a therapy that specifically suits their needs by balancing both therapeutic and aesthetic outcomes in a way that is in accord with the patient's lifestyle. With the relative ease of administration and minimal incidence of severe adverse effects, the benefit of the topical treatments currently available to treat AKs is easily visualized. More importantly, these novel and standard treatments allow dermatologists to alleviate the apprehension and inconvenience in the lives of patients burdened by these lesions.

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