Topical Therapy for Actinic Keratoses, II: Diclofenac, Colchicine, and Retinoids

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GOAL

To examine the validity of diclofenac, colchicine, and retinoids in the topical treatment of actinic keratosis (AK)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the mechanisms of action of diclofenac, colchicine, and retinoids.
2. Explain the efficacy and side-effect profiles of diclofenac, colchicine, and retinoids.
3. Examine the studies of diclofenac, colchicine, and retinoids in the treatment of AK.

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Actinic keratoses (AKs) are evolving, malignant cutaneous neoplasms. AKs can be treated with physical or destructive methods and by topical therapies. This article is the second in a 2-part series of current topical therapeutic options for AKs and discusses topical diclofenac, colchicine, and retinoids. The first part focused on topical 5-fluorouracil and imiquimod.

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Actinic keratoses (AKs) are the most common neoplastic skin lesions detected in individuals with Fitzpatrick skin type I or II. AKs 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 irregularly shaped lesion that can span several centimeters. These neoplasms

Table 1.

Topical Formulations for AK Treatment*

Product	Status	Company	Brand Name	Available Strengths, %
Diclofenac	FDA approved	Bioglan Pharmaceuticals	Solaraze™ gel	3
Colchicine	Off label	N/A	Cream	0.5, 1
Tretinoin	Off label	Bertek Pharmaceuticals, Inc.	Avita® cream	0.025
		Ortho Dermatological	Renova®	0.02, 0.05
			Retin-A® cream	0.025, 0.05, 0.1
		Generic	tretinoin	0.025, 0.05, 0.1

*FDA indicates US Food and Drug Administration.

can be flesh colored, red, or pigmented and also can scale or become hyperkeratotic. The most common sites for these lesions are the face, ears, scalp, neck, forearms, and hands. Chronic, repetitive UV exposure results in repetitive cycles of DNA damage. Eventually, these cycles of damage and repair spawn a significant unrecoverable error.

To combat this very common lesion, a host of topical preparations has been investigated. Therapies include 5-fluorouracil, imiquimod, diclofenac, colchicine and retinoids. This second part of a 2-part review focuses on topical diclofenac, colchicine, and retinoids (Table 1).

Diclofenac

Diclofenac, a nonsteroidal anti-inflammatory drug, also has been evaluated for the treatment of AKs (Table 2).[1-4] Currently, this drug's mechanism of action in the treatment of these 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, which decrease the downstream by-products of arachidonic acid metabolism. Some of these by-products control overall immunosurveillance, the inhibition of apoptosis, and up-regulation of the invasive ability of tumor cells.[7-10]

Rivers and McLean[1] conducted a 29-patient, open-label study using 3% diclofenac in 2.5% hyaluronic acid gel applied twice daily to 1 or more target lesions. The AKs were treated until they resolved or until they had been treated for 180 days. The 27 patients that completed the study had treatment times ranging from 33 to 176 days. At the 30-day posttreatment examination, 22 of the 27 patients (81%) had complete resolution of the target lesions. Generally, the preparation was well tolerated, though in 7 of the original patients (24%), an irritant-type contact dermatitis confined to the treatment site developed.[1]

Wolf et al[2] examined the efficacy and safety of 3% diclofenac in 2.5% hyaluronan gel in 120 subjects. During the first 3 months of this study, patients applied the cream to the target area twice a day. Follow-up evaluations occurred one month after the treatment period had been completed. Then, 50% of treatment patients and 20% of placebo patients experienced total clearance of target AKs present at the initiation of the study. Further, 47% of treatment patients had total clearance, while only 19% of placebo patients experienced total clearance. The difference between the number of treatment patients and placebo patients who achieved these response levels was significant in both instances ($P<.001$). Both treatments were well tolerated, with most adverse events related to the skin.[2]

Rivers et al[3] conducted a second study, in which 195 patients were evaluated in both 30- and 60-day application periods of 3% diclofenac in 2.5% hyaluronan gel and placebo. It was concluded that

Table 2.

Summary of Topical Diclofenac and Colchicine Studies*

Diclofenac Study	No. of Patients	Treatment	Results	Most Common Adverse Events
Rivers and McLean, 1997[1]	29	3% diclofenac BID for maximum of 180 days	22 of 27 evaluable patients (81%) had complete resolution one month posttreatment	21 of 29 patients experienced mild to moderate skin irritation
Wolf et al, 2001[2]	120	3% diclofenac BID for 3 months	50% of treatment patients had total clearance	96% experienced mild to moderate pruritus, application site reactions, dry skin, erythema
Rivers et al, 2002[3]	195	3% diclofenac BID for 30 or 60 days	33% of treatment patients in the 60-day regimen had total clearance	Mild to moderate pruritus, rash, dry skin, application site reaction
McEwan and Smith, 1997[4]	130	3% diclofenac BID for 180 days	No benefit was shown	Local reactions
Colchicine Study				
Grimaitre et al, 2000[5]	20	1% colchicine BID for 10 days	7 of 10 treatment patients had complete clearance by the 60-day follow-up	No systemic side effects reported
Akar et al, 2001[6]	16	0.5% or 1% colchicine BID for up to two 10-day cycles	Total clearance occurred in 7/8 of patients treated with 0.5% colchicine and in 6/8 of patients treated with 1% colchicine	No systemic side effects reported

*BID indicates twice a day.

significant improvement was reported only in the 60-day regimen group. A comparative examination of that group and the matched control group showed that 33% of treatment patients experienced clearance of their initial lesions, while only 10% of the matched control patients achieved clearance ($P<.05$). Further, 31% of treatment patients were devoid of any AKs in the treated area compared with only 8% in the matched control group ($P<.05$). Comparative analysis of the 30-day treatment group and the matched control group showed no significant therapeutic benefit to treating AKs with such a short course of diclofenac. Both treatments were generally well tolerated, and the incidence of the most common adverse events was similar between groups.[3]

In contrast to the other studies, McEwan and Smith[4] reported on a 130-patient study that evaluated 3% diclofenac applied twice daily for 180 days. Data analysis showed no significant benefit using diclofenac for the treatment of AKs. Further, data showed that local reactions occurred at a significantly higher rate in the treatment group ($P=.0002$).[4]

Among all the studies, the most commonly reported side effects using diclofenac included pruritus, application site reactions, dry skin, rash, and erythema. However, most of these events were

classified as mild to moderate and most resolved on their own. All results of hematologic studies conducted on these patients were within reference range.[1-4]

Colchicine

Colchicine, an alkaloid plant extract, is most widely known for the treatment of gout. The chemical was described in the first century and was first used as a treatment of gout in 1793. It was not until 1968 that Marshall[11] described its usefulness in the treatment of AKs. Reported here are the 2 most current studies examining colchicine's therapeutic efficacy on these precancerous lesions (Table 2).

Colchicine is a yellow, UV-sensitive, water-soluble powder[12] that when instilled into living systems, disrupts the polymerization of tubulin and subsequently arrests microtubule formation.[13] 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.[14-18] In addition, colchicine enhances collagenase production and decreases the production, release, and/or expression of collagen, IL-1, immunoglobulin, histamine, and surface antigens.[19-22]

In 2000, Grimaitre et al[5] conducted a 20-patient study examining the topical application of 1% colchicine to forehead AKs twice a day for 10 days. By the tenth day, a significant, localized inflammatory response appeared on the treated lesions. Patients described the reaction as a sunburnlike feeling that occurred 1 to 3 days after the treatment began, followed by the development of a pustular reaction that subsequently intensified until treatment was discontinued. At the 30-day follow-up, the AK crusts on 6 of the treatment patients had resolved. In addition, 2 of these patients experienced complete clearance. Subsequently, 5 additional treatment patients were cleared of their AKs by the 60-day follow-up, resulting in complete clearance in 7 of the 10 treatment patients.[5]

Akar et al[6] examined the efficacy and safety of the 0.5% and 1% colchicine cream applied twice daily in a 16-patient study. Subjects were separated randomly into either the 0.5% treatment group or the 1% treatment group. Most patients were treated with a single 10-day course of the medication, while a few received a second course of colchicine. The overall lesion reduction seen in the 2 groups was 77.7% and 73.9% for the 0.5% and 1% concentrations, respectively. Further, total target AK clearing occurred in 7 of the 8 patients in the 0.5% group and in 6 of the 8 patients in the 1% group, showing that both concentrations are equally efficacious.[6]

Regular blood examinations showed that none of the patients in these 2 studies had any systemic absorption. Further, there were no observed or reported systemic side effects in these patients.[5,6]

Retinoids

Retinoids demonstrate potent antiproliferative and differentiation-inducing effects and thus improve the manifestations of skin photodamage. Recently, epidemiologic and biochemical studies have indicated that cancers originating from the epithelium may be associated with a relative deficiency of retinal.[23,24] This reasoning was extended to AKs as early as 1962. At that time, von Stuttgen[25] was the first to use vitamin-A acid alone for the treatment of AKs in 3 cases. Subsequently, Bollag and Ott[26] examined 4 to 6 patients treated with 0.1% tretinoin for 3 to 6 weeks. The patients experienced greater than a 50% reduction in AKs of the forearms and hands. Further, 3 patients treated with 0.3% tretinoin experienced similar levels of AK reduction.[26] Modest progress has been made since these earlier reports (Table 3).

Kligman and Thorne[27] performed a multicenter, double-blind study on 1265 patients who were treated twice daily for histologically confirmed AK with 0.05% tretinoin, 0.1% tretinoin, or vehicle only, for up to 15 months. They found that the most effective treatment for reducing AKs was 0.1% tretinoin applied twice daily ($P<.001$). An excellent response was observed in 73% of tretinoin-treated patients compared with only 40% of vehicle patients.[27] In a similar large study, topical 0.05% tretinoin cream applied once or twice daily significantly decreased the number and size of facial AKs—by approximately 50% after 6 to 15 months.[33]

Alirezai et al[28] conducted a 100-patient, randomized, double-blind, placebo-controlled, parallel-group study examining the efficacy of twice-daily applications of the topical 0.1% isotretinoin cream compared with vehicle. Patients applied these creams for 24 weeks to their face, scalp, and upper extremities and were assessed every 4 weeks. The reduction in the number of facial AKs at the end of treatment was greater for patients who applied isotretinoin (3.9 ± 0.6, ie, 66% of patients with a reduction >30%) compared with placebo (1.7 ± 0.5, ie, 45% of patients with a reduction >30%)($P=.001$). No significant treatment benefit was seen for lesions on the scalp or upper extremities.[28]

Table 3.

Summary of Retinoid Studies*

Study	No. of Patients	Treatment	Results	Most Common Adverse Events
Bollag and Ott, 1975[26]	6	0.1% tretinoin BID for 3–6 weeks	>50% reduction in AKs of the forearms and hands	N/A
Kligman and Thorne, 1991[27]	1265	0.05% or 0.1% tretinoin or vehicle BID for up to 15 months	Greatest reduction of lesions seen posttreatment with 0.1% tretinoin BID ($P<.001$)	N/A
Alirezai et al, 1994[28]	100	0.1% isotretinoin or vehicle BID for 24 weeks to face, scalp, and upper extremities	66% of patients achieved a reduction of lesions >30% posttreatment with isotretinoin compared with 45% of patients treated with vehicle	Signs of local irritation were common in both treatment groups but more frequent with isotretinoin
Moglia et al, 1996[29]	18	Retinoid fenretinide BID for 3 months	Complete regression of lesions in 10 patients (56%) and partial regression in 8 patients (44%)	No local or distant adverse effects
Misiewicz et al, 1991[30]	26	Ro 14-9706 and 0.05% tretinoin BID for 16 weeks to opposite sides of the face	Mean percentage decrease in the number of AKs was 37.8% for areas treated with Ro 14-9706 and 30.3% for areas treated with tretinoin ($P<.01$)	Local inflammation was slight or absent in most patients treated with Ro 14-9706, whereas tretinoin caused severe erythema in 13 patients (50%) and severe scaling in 6 patients (23%)
Moriarty et al, 1982[31]	50	Oral etretinate for 4 months	37/44 (84%) of patients in etretinate group versus only 2/42 (5%) in placebo group had complete or partial response	Dryness of mouth and lips, desquamation, rash/pruritus
Bercovitch, 1987[32]	19	5% fluorouracil BID on each arm, followed by nightly application of 0.05% tretinoin to one arm and control cream to the other arm	Tretinoin-treated arms had 3.4±2.6 AKs after treatment compared with 4.2±2.5 lesions in the control arm ($P<.04$)	12 patients experienced more irritation on the side treated with tretinoin than the control, while 2 patients reported severe irritation at distant sites

*BID indicates twice a day.

Similarly, Moglia et al[29] treated 18 patients with facial AKs with topical retinoid fenretinide, 4-HPR (N-[4-hydroxyphenyl]retinamide), twice daily for 3 months. Following this treatment period, complete regression of the lesions was observed in 56% (10) of patients. Further, partial regression was observed in an additional 44% (8) of patients. Eight patients (44%) relapsed within 3 months after treatment. In addition, only 2 patients (11%) showed complete regression 6 months later. No adverse effects were observed. Also, it was found that baseline plasma retinol levels were lower than in healthy subjects, which suggest that reduced retinol levels might be involved in the pathology of AKs.[29]

In a double-blind, randomized, within-patient comparative study, the efficacy and tolerability of Ro 14-9706 (an arotinoid methyl sulfone) for the treatment of AKs were compared with those of tretinoin.[30] Twenty-six patients with more than 3 lesions on each side of the face were included in the study. Patients applied each agent twice daily for 16 weeks as a 0.05% cream to opposite sides of their face. The mean percentage decrease in the number of AKs was assessed before treatment and at weekly intervals during the treatment period. The mean percentage decrease in the number of AKs 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 ($P<.01$) but not from each other. There was an associated severe erythema in 50% (13) of patients treated with tretinoin and severe scaling in 23% (6), whereas Ro 14-9706 was better tolerated, with only a slight or absent inflammation.[30]

Studies also have examined the efficacy of high-dose systemic etretinate for the treatment of AKs. Moriarty et al[31] conducted a double-blind crossover study of 50 patients with AKs who were treated with a 4-month course of oral etretinate. They concluded that 37 of the 44 patients (84%) who completed treatment with etretinate versus only 2 out of 42 patients (5%) in the placebo group had a complete or partial response. Unfortunately, the systemic toxicity of retinoids discourages their use for long-term treatment at high doses.[31]

Retinoids also enhance the effectiveness of 5-fluorouracil. In a randomized, double-blind controlled study by Bercovitch,[32] 19 patients applied 5% fluorouracil cream to AKs on each arm twice daily, followed by nightly application of 0.05% tretinoin cream to one arm and a control cream to the other arm, until discomfort precluded further applications. Three months after treatment, the tretinoin-treated arms had 3.4±2.6 AKs versus 15.7±6.1 AKs before treatment. In contrast, the control arm had 4.2±2.5 lesions after treatment compared with 15.3±6.9 AKs before treatment ($P<.04$).[32] Similar results were found by Sander et al[34] as to a synergistic effect in the treatment of disseminated AKs on photodamaged skin when low-dose isotretinoin and topical 5-fluorouracil are combined. As with etretinate, such combination treatment regimens have limited usage secondary to such side effects as pain, irritation, and bleeding. These symptoms were the extent of adverse effects seen in treatment with retinoids for AK in the majority of cases reviewed.[34]

Conclusion

While countless individuals are diagnosed with AKs, research efforts have revealed an encouraging array of topical and semi-invasive treatment options that allow the dermatologist and patient to select a therapy that specifically suits the patient's needs by balancing both therapeutic and aesthetic outcomes in accordance with the patient's lifestyle. Topical treatments currently available to treat AKs offer the benefits of relative ease of administration and minimal incidence of severe adverse effects. More important, these novel and standard treatments allow dermatologists to alleviate the apprehension and inconvenience experienced by patients affected by these lesions.

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