Topical Imiquimod Therapy for Actinic Keratosis

Is Long-Term Clearance a Realistic Benefit?

by James Q. Del Rosso, DO, FAOCD

Topical imiquimod, available as a 5% cream, is approved by the United States Food and Drug Administration (FDA) for the treatment of actinic keratosis (AK), superficial basal cell carcinoma, and external genital warts.[1] Additionally, topical imiquimod has been reported to be effective for the treatment of selected cases of squamous cell carcinoma *in-situ*, nodular basal cell carcinoma, extramammary Paget's disease, lentigo maligna, molluscum contagiosum, and verruca plana.[2]

The mechanism of action of imiquimod, a toll-like receptor-7 agonist, is believed to be related to its ability to augment both the innate and acquired arms of immunologic response.[3–5] The result is immunologic cellular infiltration directed at the site of the target antigen (i.e., viral-infected cell, tumor) in the region where imiquimod is applied. The cellular infiltrate at the site is characterized by an increase in dendritic cells and natural killer cells, and a relative increase in CD4+ lymphocytes, along with an increase in local interferon (INF)-α and INF-gamma production.[3–5] Successful therapy with topical imiquimod requires antigen recognition followed by an intact and functional host immune response, as the drug itself has no direct cytotoxic or ablative activity. Ultimately, imiquimod serves to facilitate and amplify the immunologic response of the host.[3–5]

As imiquimod produces its activity through augmented antigen recognition and amplified cellular immunologic response, is it possible that immunologic memory may serve to reduce the development of recurrent or new AKs in the field treated with imiquimod? The significance of this question relates to the theoretical potential for imiquimod to produce prolonged benefit against the development of AKs and possibly subsequent squamous cell carcinoma.[2,5,6] As the development of invasive squamous cell carcinoma within or contiguous with an AK has been reported to occur in up to approximately 10 percent of lesions in immuno-competent patients, and in up to 40 percent of AKs in organ transplant recipients, long-term response is important from both medical and economic perspectives.[7–9]

What data are available on long-term response to treatment of AKs?

Despite the widespread nature of AK and implications regarding potential for progression to invasive squamous cell carcinoma, long-term data on prolonged clearance and recurrence after therapy is limited.[5]

Liquid nitrogen cryotherapy is a commonly employed ablative technique used for the treatment of individual AKs.[10] Response rates of AK to cryotherapy have been reported to range from 75 to 98%; however, controlled studies with long-term follow-up and/or histologic confirmation are lacking.[11,12] One year recurrence rates after cryotherapy have been noted to range from 1.2 to 12%.[13,14] The duration of liquid cryotherapy exposure (freeze time) correlates directly with both the clearance rate of AK and the risk of subsequent hypopigmentation.[15]

Topical 5-fluorouracil (5-FU) is a well-established, topical, FDA-approved therapy for AK.[16] Depending on the formulation, application once or twice daily is recommended for a usual duration of up to two weeks on the head region and up to four weeks on the upper extremities.[16–18] Although long-term data is limited, recurrence rates of up to 55 percent have been reported after treatment of AKs with topical 5-FU.[16–21]

Complete clearance rates reported with topical imiquimod therapy have ranged from 45 to 84%.[5,6,22,23] It is important to recognize that these reported cure rates are based on studies that have utilized a variety of regimens which incorporate varying application

frequencies (number of applications per week) and durations of therapy. Some studies have suggested that topical imiquimod may produce prolonged therapeutic benefit within the field of treatment.[5,6,24] In one study of patients treated with topical imiquimod applied three times per week for 12 weeks, the subsequent development of AKs within the treatment field was 10 percent within 12 months and 20 percent within 24 months after completion of the initial therapy.[24]

Topical diclofenac gel is another FDA-approved therapy for AK. The recommended regimen is twice daily application over a duration of three months. As with topical 5-FU and imiquimod, topical diclofenac may be used for the treatment of currently visible and/or palpable lesions and for field treatment of subclinical AKs. Long-term data are not currently available with topical diclofenac gel for AK.

Are comparative data available that evaluate both short-term and long-term efficacy with therapies used to treat AK?

A recently published randomized trial compared both clinical and histologic outcomes after treatment of AKs with either topical 5-FU, topical imiquimod, or cryotherapy.[25] Data on follow-up after 12 months was evaluated. In this study, 75 Caucasian subjects with a minimum of five and up to 10 AKs within an anatomic region of up to 50cm^2 on the head, neck, or décolleté were randomized to receive one of the following therapies:

- Liquid-nitrogen cryotherapy (n=25) for 20 to 40 seconds for each lesion using spray technique; a second session was completed for treated lesions that did not clear within two weeks
- Topical 5-FU cream (n=24) applied twice daily over a four-week duration; a rest period of up to one week was allowed in cases of marked acute inflammatory reaction
- Topical imiquimod 5% cream (n=26) was applied using a single sachet (0.25g) three times weekly at bedtime over a duration of four weeks, followed by four weeks off therapy (single cycle); a second treatment cycle was allowed if any lesion was persistent at the end of the first cycle (four weeks after active application); a rest period of up to one week was allowed in cases of marked acute inflammatory response.

Grids and photographs were used to keep track of the precise location of the initially treated AKs. Additionally, at baseline, a 4-mm punch biopsy specimen was obtained from a representative AK lesion within the treatment field in order to provide histologic assessment. Baseline characteristics of the treatment groups are depicted in Table 1.

End-of-therapy (EOT) was described as six weeks after the last cryotherapy application, four weeks after the last-applied dose of topical 5-FU, and eight weeks after the last-applied dose of topical imiquimod. For all subjects at EOT, another skin biopsy was performed from a cleared focus or, if present, from the most suspicious-appearing, persistent lesion.

The outcomes from this study are described in Table 2. At EOT, complete clinical clearance was observed in 68 percent of the subjects treated with cryotherapy, in 96 percent of subjects treated with topical 5-FU, and in 85 percent of those treated with topical imiquimod. Histologically confirmed clearance at EOT was observed in 32 percent of subjects treated with cryotherapy, 67 percent of those treated with topical 5-FU, and 73 percent of subjects treated with topical imiquimod.

At 12 months after EOT for each of the study arms, subjects were assessed to determine if initially treated AK lesions recurred. Complete clearance of initially treated lesions among subjects who were cleared at EOT was observed in 41 percent of cryotherapy subjects, 57 percent of subjects treated with topical 5-FU, and 86 percent of those treated with topical imiquimod. Among all subjects, including those not completely cleared at EOT, complete clearance of initially treated lesions was observed in 28 percent of cryotherapy subjects, 54 percent of subjects treated with topical 5-FU, and 73 percent of those treated with topical imiquimod.

As noted above, a benefit of topical therapy for AK, especially as compared to ablative therapies directed at treatment of individual lesions (such as cryotherapy), is treatment of subclinical AKs with field application. Importantly, sustained field clearance after 12 months was observed in four percent of cryotherapy subjects, 33 percent of subjects treated with topical 5-FU, and 73 percent of those treated with topical imiquimod.[25]

Are comparative data available that evaluate both short-term and long-term cosmetic outcomes with therapies used to treat AK?

The global cosmetic outcomes in the study comparing topical imiquimod, topical 5-FU, and cryotherapy were not significantly

different after completion of therapy.[25] However, after 12 months of follow-up, investigator assessments rated the cosmetic outcome as excellent in 81 percent of topical imiquimod-treated subjects, as compared to four percent in subjects treated with topical 5-FU or cryotherapy. Intergroup comparisons demonstrated statistically significant differences between each group ($P<0.002$). These results were essentially identical to the assessments of global cosmetic outcome reported by the study subjects.

Table 1. Patient Baseline Characteristics

	Imiquimod (n=26)	5-FU (n=24)	Cryosurgery (n=25)
Age (y), mean (SD)	70.8 (5.6)	70.4 (6.7)	72.1 (8.6)
Male, n (%)	22 (85)	19 (79)	20 (80)
AK lesions in field, mean (range)	7.9 (5-10)	8.3 (5-10)	7.9 (5-10)

Based on data from Krawtchenko et al. *Br J Dermatol* 2007;157(suppl. 2):34-40

Table 2. Study Results Summary

	Imiquimod (n=26)	5-FU (n=24)	Cryosurgery (n=25)	P-value
Clinical Clearance End of Treatment (EOT)	85%	96%	68%	p=.03
Histological Clearance End of Treatment (EOT)	73%	67%	32%	p=.03
Sustained Clearance of Cleared Lesions All subjects (12 Months)	73%	54%	28%	p<.01
Sustained Field Clearance All subjects (12 Months)	73%	33%	4%	p<.01
Cosmetic Outcome* ("excellent" rating)	81%	4%	4%	p<.0001

Based on data from Krawtchenko et al. *Br J Dermatol* 2007;157(suppl. 2):34-40
*Rating of "excellent" by investigators at 12 Months.

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