

## Review

**A consensus approach to improving patient adherence and persistence with topical treatment for actinic keratosis**

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**Abstract**

**Background** Topical therapy is important in the treatment of actinic keratosis, but guidance for improving adherence/persistence during topical therapy is still lacking.

**Objectives** To utilize expert consensus to generate a list of recommendations to improve real-world efficacy when prescribing topical therapy for actinic keratosis.

**Methods** An expert panel of eight dermatologists was convened to generate recommendations based on facilitated discussion and consensus generation using a modified Delphi session. The recommendations were ratified with the expert panel.

**Results** Facilitated discussion generated 31 issues within five themes, which were prioritized using expert voting. Consensus was achieved on the importance of short and simple treatment regimens for maximizing patient compliance, physician awareness of the progression of actinic keratosis to squamous cell carcinoma, provision of appropriate patient information, and the use of effective communication strategies to educate physicians about actinic keratosis. Based on these key findings, eight recommendations were generated.

**Conclusions** The recommendations will assist physicians when prescribing topical actinic keratosis therapy. Further research should focus on the types of patient outcomes that are influenced by the characteristics of topical field therapy.

**Introduction**

Actinic keratosis (AK) is a characteristic skin lesion present on areas exposed to prolonged ultraviolet radiation.<sup>1</sup> Some experts have classified it as *in-situ* squamous cell carcinoma (SCC).<sup>2,3</sup> It is the biggest risk factor for and early stage of SCC,<sup>4-7</sup> and the majority of cases of cutaneous SCC arise from AK.<sup>8</sup> SCC is the second most common type of non-melanoma skin cancer<sup>9-11</sup> and is associated with a higher economic and patient burden than AK alone.<sup>12,13</sup> As it is not currently possible to predict which AK lesions will develop into SCC,<sup>14,15</sup> early treatment of AK is recommended.

Currently available treatment modalities for AK can be broadly grouped into two categories. Lesion-directed treatments, including cryotherapy and curettage,<sup>10</sup> target single lesions but do not reverse underlying actinic changes in the surrounding skin. Field-directed therapies, including topical therapies and photodynamic therapy, target visible and non-visible lesions<sup>14</sup> and are commonly used to treat multiple lesions over a larger skin area. However, topical therapies have long treatment durations, typically up to 16 weeks and local skin reactions (LSRs) including erythema, ulcerations, and crusting<sup>16</sup> are common. The long treatment duration may reduce the ability of patients to tolerate LSRs, contributing to poor adherence (where the patient does not follow the prescribed dosage or frequency)

and persistence (where the patient does not follow the treatment schedule for the prescribed duration).

Actinic keratosis is also now regarded as a chronic disease,<sup>17</sup> and chronicity reduces adherence/persistence as long-term therapy increases the opportunity for patients not to comply. Clinical outcomes are greatly influenced by patients' attitudes towards therapy, so there is a need for patients to be appropriately supported while receiving topical therapy. Current treatment guidelines advocate patient involvement in the treatment choice,<sup>14</sup> patient education,<sup>18</sup> and consideration of patient preferences<sup>14</sup> but do not suggest further strategies to support a successful treatment outcome.

Consensus studies with experts have been acknowledged as an appropriate way to inform clinical decision making and develop supporting strategies.<sup>19</sup> The Delphi approach unites experts to discuss and make progress on complex issues based on consensus opinion<sup>20</sup> and has previously been applied successfully to produce therapeutic recommendations in dermatology in the areas of psoriasis<sup>21–23</sup> and epidermolysis bullosa.<sup>24</sup> This study convened a modified Delphi approach to generate consensus on factors constraining the real-world efficacy of topical AK therapy and make recommendations for the future development of AK care strategies.

## Methods

We conducted an expert session in London in September 2012, using a modified Delphi approach. Eight international experts representing Australia, Brazil, France, Germany, Italy, Spain, the UK, and USA were invited based on their clinical and research experience in AK and their background in AK care. The session was conducted via a bespoke web-based platform that allowed real-time ideation, categorization, and prioritization (voting) of topics discussed.

The session commenced with an open discussion of the challenges faced when prescribing topical therapy for AK. Stimulus to discussion included the findings from previously conducted research into the perceptions of AK-treating physicians on topical therapy.<sup>25</sup> The topics on which physicians had reached consensus were summarized into key themes, and the level of expert agreement on these themes was assessed using a seven-point Likert scale, where a score of 1 = strongly disagree and a score of 7 = strongly agree.

During the expert session, discussion of the key issues was monitored to identify topics for further exploration. Facilitators categorized the topics generating consensus into themes and issues that were then shared with the participants to confirm that they accurately represented the issues discussed. Issues within themes and emerging critical issues were prioritized using Likert scales, as used in previous consensus studies in dermatology.<sup>20,21,23,24</sup> Our experts ranked issues using a

six-point Likert scale (1 = least important, 6 = most important). For issues where it was more appropriate to assess the level of agreement, a seven-point Likert scale was used to evaluate expert opinions (1 = strongly disagree, 7 = strongly agree). For both scales, a mean score of  $\geq 5$  was deemed to represent a consensus agreement among our experts. The issues generating consensus were then explored further within the group and developed into recommendations.

This approach used techniques and characteristics of the classic Delphi panel: expert involvement, structured flow of information to experts, controlled feedback from experts, and selective anonymity through an iterative approach.<sup>26</sup> Modification through real-time controlled feedback allowed "live" clarification of responses and queries for both facilitators and panelists.

The bespoke web-based platform generated descriptive data, including mean scores, statistical distribution, and standard deviation to aid interpretations.

## Results

Seven of the eight invited experts attended the modified Delphi session. The findings from the previous physician research<sup>25</sup> were presented, and the statements that had received  $\geq 70\%$  agreement from physicians were grouped into three key concepts (Table 1). Our experts' agreement with these findings was 97–100%, forming the basis for the next stage. The concepts were further explored, and ways of overcoming the challenges were evaluated in facilitated discussion, which generated 31 items ranked under five themes (Tables 2 and 3).

The eight issues that generated the highest level of consensus (highlighted in italics in Tables 2 and 3) were then explored further within the group and developed into eight specific recommendations.

### **Recommendation 1: Increase physician awareness of the potential risks of squamous cell carcinoma and the progression of actinic keratosis to squamous cell carcinoma**

There was strong agreement that the risk of progression of AK to SCC is a key message to convey to physicians. Our panel agreed that an improved understanding of the link between AK and SCC has resulted in AK being increasingly perceived as a chronic disease rather than merely a cosmetic concern, fundamentally underpinning the importance of early and effective intervention. Experts agreed that interest in AK has increased, exemplified by the inclusion of AK content in scientific communications and a greater number of healthcare professionals seeking advice on AK, but awareness on the risk of progression of AK to SCC was deemed to be lacking. Our group suggested that successful activities to embed knowledge

among the physician community would include the linking of specific educational programs and accreditations to professional credentials and thought that the provision of free examinations for skin cancer in the primary care community, with referral to specialists as appropriate, would help.

**Recommendation 2: Develop topical treatments with shorter treatment durations but equal clinical efficacy**

There was strong consensus among experts that adherence and persistence to therapy was reduced by treatments with long durations. The corresponding theory that increased use of shorter treatments would simultaneously enhance efficacy was spontaneously generated and supported by the panel. The rationale was that shorter treatment durations would reduce the opportunity for non-adherence/persistence and therapy would be complete before local skin reactions develop sufficiently to cause discontinuation.

**Recommendation 3: Address physician concerns around the impact of topical treatment on quality of life through treatments employing a shorter duration**

Our group agreed that LSRs associated with prolonged treatment durations diminish patients' quality of life. Our

experts surmised that more favorable treatment durations would reduce the time that patients endure LSRs, improving their quality of life in a multitude of ways.

**Recommendation 4: Physician concerns around completion of full courses of treatment should be addressed through treatments with shorter durations**

The members of our group highlighted their concerns about non-completion of prescribed topical treatments. There was strong support for addressing this concern through treatments with reduced durations as experts expected this to make patients more likely to adhere to, and persist with, the prescribed treatment course. Our group suggested that patient perceptions of the severity of the LSRs might guide adherence/persistence regardless of treatment duration, further supporting the use of rapidly acting treatments that are complete before LSRs are elicited.

**Recommendation 5: Treatment regimens should be simple as this may increase levels of adherence and persistence (and subsequent clinical outcomes)**

Our group identified treatment simplicity as having a positive influence on patient adherence/persistence. A

**Table 1** Level of expert agreement on the key findings of previous perceptual research<sup>2,5</sup> (summarized by consolidating topics with agreement above a predefined 70% threshold)  $\pm$  SD

Statement	Response <sup>a</sup>	N	SD	Mean	Key finding	Expert consensus	SD	Mean expert rank <sup>b</sup>
<i>Related to general perceptions</i>								
Field therapy is essential when treating the vast majority of patients with AK	80%	427	1.44	5.5	Field therapy, including topical treatment, is an integral part of the treatment algorithm	100%	0.00	7
Topical therapy is the best type of field therapy	76%	427	1.31	5.3				
Combined statement about perceptions of AK	81%	427	1.40	5.7	Current topical treatments generate notable perceptual and clinical concerns	97%	0.08	6.71
Combined concern about topical therapy when prescribing	72%	427	1.50	5.0				
<i>Related to the last patient with AK treated for whom treatment was unsatisfactory</i>								
Combined concerns expressed about topical therapy when prescribing	(64%)	427	1.58	4.68				
Combined realization of concerns expressed about topical therapy	(49%)	427	1.68	4.35				
Physicians ranking a treatment profile with shortest duration as the most likely to be completed	91%	352	0.62	1.2	A treatment profile showing a shorter treatment duration is preferred by physicians	100%	0.00	7

<sup>a</sup>Mean ranking by experts using the above scale.

<sup>b</sup>Percentage of responses ranked 5–7 on a seven-point Likert scale, where 1–3 = strongly disagree, 4 = neutral, and 5–7 = strongly agree.

Brackets denote <70% agreement.

AK, actinic keratosis.

**Table 2** Mean rank for the issues generated during the Delphi consensus generation (1 = least important; 6 = most important) ± SD

Theme and component issues	Mean	SD
Theme: Lack of physician awareness of, and the significance of, AK being a chronic disease		
<i>Physicians should be made aware of the risk of progression to SCC from AK<sup>a</sup></i>	5.88	0.06
Physicians need to know that the disease is caused by chronic exposure to the sun and ultraviolet protection is critical	3.38	0.20
Physicians should be made aware that stem cells are damaged and therefore it is a chronic disease	3.38	0.28
AKs untreated as a result of physician lack of awareness can influence cosmetic and appearance related outcomes	2.88	0.19
Although physician awareness is low there is the potential for positive outcomes if awareness is raised	2.88	0.24
If not treated properly, AKs run the risk of becoming hypertrophic	2.63	0.26
Theme: Tactics important for communication to patients around treatment expectations		
<i>Photographs should be easily available to physicians for them to share with patients to manage expectations around treatment<sup>a</sup></i>	5.13	0.27
<i>Clearer information (including statistics) on the disease, different treatments, their efficacy, local skin reactions, and precancerous risk should be available<sup>a</sup></i>	5.00	0.16
Quality prepared information on what to expect from treatment, in particular local skin reactions, would reassure patients	4.63	0.27
Better information on risks of non-completion (i.e., increased risk of SCC) of treatment courses would improve adherence/persistence	4.38	0.30
External support for patients (e.g. patient groups/forum/hotline) would be beneficial	3.25	0.19
Nurses have an important role in the treatment process including managing expectations	3.25	0.31
More intelligent use of social media should be employed to communicate better with physicians	2.38	0.21
Theme: Suitable modes of communication to patients and physicians		
<i>Verbal communication via talks, presentations and conferences is important<sup>a</sup></i>	5.00	0.28
Courses at specialized centers should be offered to support physicians to learn more about AK	4.50	0.22
Publications in academic journals represent a useful vehicle to engage with physicians	3.88	0.18
Visibility of information is important for patients so leaflets/posters etc. in surgeries would support communication	3.13	0.21
Direct advertising to consumers would represent a valuable mode of communication	2.75	0.23
Website or social media outlets represent more innovative engagement and should be advocated	1.75	0.18
Theme: How to encourage adherence and persistence in patients		
<i>Shorter duration treatments (with no reduction in clinical efficacy) would encourage adherence and persistence and thus real-world efficacy<sup>a</sup></i>	5.13	0.15
<i>Simple treatment regimens encourage adherence/persistence and better outcomes<sup>a,b</sup></i>	4.50	0.22
Positive reinforcement of the beneficial outcomes of appropriate administration of treatment	4.13	0.27
Communicating the potential for progression to invasive SCC will help encourage adherence and persistence	3.00	0.20
Prevention via sunscreen is as important as treatment	2.13	0.18
Data demonstrating evidence of reduced recurrence of AKs and reduced risk of progression to AK will be important	2.13	0.21

<sup>a</sup>Issue achieved expert consensus (mean score  $\geq 5$ ).

<sup>b</sup>Although not a consensus-level score, expert discussion revealed this to be an important issue, and experts agreed to include it as a recommendation.

AK, actinic keratosis; SCC, squamous cell carcinoma.

simple regimen is also easy for physicians to explain and for patients to understand. The group postulated that increased patient understanding of the treatment would translate into an improved engagement with the therapy. A simple treatment regimen may also encourage wider prescribing, increasing the proportion of patients with AK who are receiving active therapy.

**Recommendation 6: Modes of communication to physicians around actinic keratosis as a disease and its treatment should be varied and include talks, presentations, and conferences**

Our group favored communication to physicians through talks, presentations, and conferences, and concurred that analogies would help to explain to physicians the potential for AK to progress to SCC.

**Recommendation 7: Clear communication of treatment expectations to patients through the availability and use of photographs**

Our discussion highlighted the diversity in the type and grade of LSRs. Experts concurred that patients can still be disturbed by their appearance, although physicians can attempt to reassure patients that these are normal during topical therapy and indicate efficacy. Our panel favored use of photographs, stating that if patients are prepared to experience LSRs and have realistic expectations on their severity, they would be more likely to comply with the treatment regimen. They also thought that photographs would help patients to prepare for more serious LSRs and highlight how patients would appear in the future if their AK was allowed to progress, encouraging them further to adopt a more positive approach to

**Table 3** Mean rank for the issues generated during Delphi consensus generation that were evaluated using a Lickert scale (1 = strongly disagree; 7 = strongly agree) ± SD

Theme and component issues	Distribution							Mean	SD
	1	2	3	4	5	6	7		
<b>Addressing physician concerns around patient adherence/persistence through shorter treatment durations</b>	0	0	0	0	0	1	6	6.86	0.06
<i>Patients more likely to complete full course of treatment if they are shorter<sup>a</sup></i>	0	0	0	0	0	1	2	4	0.12
<i>Shorter treatment durations (and associated increases in real-world efficacy of treatment) have a direct impact on quality of life (return to work, social benefits etc.)<sup>b</sup></i>	0	0	0	0	0	1	2	4	0.12
A shorter and thus simpler regimen is suitable for greater range of patients (e.g. elderly patients)	0	0	0	0	0	2	2	3	0.14
More patients can be seen and treated as a result of shorter treatment durations	0	0	1	0	2	2	2	5.57	0.22
Patients may make fewer visits to physicians as therapies are complete and do not need additional explanation/reassurance	0	0	0	2	2	1	2	5.43	0.20
Treatment costs less and thus increases accessibility to treatment and adherence/persistence with treatment	1	0	0	0	2	3	1	5.14	0.30

<sup>a</sup>All issues generated a consensus level score in this theme; therefore, only the top two (in italics) were prioritized for further in-depth discussion to formulate recommendations.

treatment. The experts, however, noted that using photos in isolation might cause patient trepidation and adversely affect compliance. They recommended accompanying imagery with verbal explanations and suggested the use of post-therapy imagery would highlight regression of LSRs and demonstrate response to therapy.

**Recommendation 8: Patients should be provided with clear information on actinic keratosis and its treatments to help manage expectations of treatment**

Our group stated that clear information on the disease and treatments helps to manage patients’ expectations of treatment, supplementing visual imagery. Other quoted means of promoting patient adherence/persistence included establishing patient information hotlines and providing regular access to nurses. Looking comparatively across countries, the consensus was that informative resources could be shared between countries.

**Discussion**

Although topical therapy is an important component of an AK treatment plan, this study highlights the challenges of maximizing the real-world efficacy of this approach. Our experts supported the consensus of physicians treating AK on the importance of field therapy in its management. The strong agreement between practicing physicians and expert dermatologists suggests that both practitioners share the same issues and concerns when prescribing topical AK therapy. Treatment duration, patient adherence, severe LSRs, suboptimal patient satisfaction, and expense have already been acknowledged as issues when prescribing topical AK therapy.<sup>7</sup>

Use of an expert panel confers two advantages. The first is that findings can be translated into recommendations rapidly, unlike clinical research, which often has a significant delay. The second is that recommendations can be simultaneously ratified with the expert panel. In this study, issues emerging during discussions were utilized to develop recommendations, which were validated with the panel to suggest new directions in topical AK therapy to improve clinical efficacy.

Our experts agreed that the introduction of topical field therapies with shorter and simpler regimens would improve overall clinical outcomes by promoting adherence and persistence. They also agreed that the correspondingly shorter duration of LSRs would improve patients’ quality of life, supporting the suggestion that reduced drug exposure reduces the incidence of adverse events.<sup>15</sup> Previous research has also found that patients have a greater preference for treatments with equal efficacy to others but a better cosmetic result,<sup>27</sup> and the willingness of patients to pay is also influenced by their perceptions of cosmetic

results,<sup>13</sup> providing further support for developing treatments with improved cosmetic outcomes.

This study also demonstrates how expert consensus can be used to generate complementing strategies for future AK treatment guidelines. Recommendations were also generated based on the importance of effective patient management, including the provision of clear information on AK. Our experts strongly advocated the use of photographs to explain to patients the role of topical field therapy in suppressing disease progression and to manage their expectations on its characteristics. Patient education in AK and use of digital photography to monitor the progress of lesions has also been advocated in another dermatological consensus study.<sup>24</sup> The particular importance of educating patients on protection from ultraviolet light, self-examination, and detection of early lesions has been recognized,<sup>15</sup> and this advice should be incorporated into educational strategies for patients. The expert panel additionally recommended providing information to patients on different treatments, their efficacy, LSRs, and the risk of AK developing into SCC. This could be achieved by providing information and support to patients through patient support groups, websites, or patient meetings. Our experts did not feel that patient adherence/persistence would benefit as much from statistical data relating to the reduced recurrence of AKs and risk of progression.

Our expert panel concurred that AK is being increasingly perceived as a disease but thought that awareness of the risk of AK progressing into SCC is still lacking. Physicians' awareness of this therefore needs to increase, supporting the finding of another consensus study<sup>28</sup> that concluded the main treatment goal is to promote a good overall outlook by minimizing the risk of progression of AK to SCC. Developing physicians' knowledge of the potential for SCC to develop would provide them with the necessary background to promote and manage a successful treatment strategy that maximizes adherence and persistence. We recommend using a variety of modes of communication to raise physicians' awareness of AK, its treatment and the risk of progression, including scientific events and initiatives in the primary care community, such as free skin examinations, to nurture physicians' understanding of AK. Use of social media and direct advertising to inform physicians was not thought to be as appropriate.

To our knowledge, this is the first attempt to use expert consensus to propose recommendations for improving the real world efficacy of topical AK field therapy. The effectiveness of the Delphi approach for producing recommendations for new therapeutic directions has already been shown for psoriasis<sup>21–23</sup> and epidermolysis bullosa.<sup>24</sup> This research provides a balanced consensus that encompasses both physician and patient perspectives, providing a

sound basis on which to argue for new directions in topical AK treatment.

Seven experts participated in the Delphi session. Although this is similar to the samples used in the preliminary stage of the Delphi process in existing studies,<sup>21,23,24</sup> this figure is lower than the preferred number for a Delphi session, and much higher samples were used in the latter stages of previously published research.<sup>21,24</sup> Therefore we acknowledge that the low total number of participants may contribute to potential bias. Although a minimum of 10 experts is more usual, the size of the Delphi panel has not been shown to have an adverse impact on the validity of the results.<sup>20</sup> Delphi panel sample sizes have ranged from 5 to 2865 experts,<sup>20</sup> and a similar study using an expert Delphi panel to develop treatment recommendations for scalp psoriasis sought input from seven experts.<sup>21</sup> The real-time application and relevance of the Delphi process has also been demonstrated.<sup>23</sup> We therefore consider the consensus generated to be representative of the expert sample it is intending to portray.

To further improve the management of patients with AK, it would be useful for future research to identify the specific patient outcomes that are influenced by the characteristics of topical field therapy and how they are affected. It would also be beneficial to elucidate the channels that are most effective for communicating with patients and to investigate how patients' understanding of the information received when treatment is initiated affects their attitudes to therapy. Furthering our understanding in this way would help the results of our consensus research on AK to be conveyed into vastly improved clinical outcomes by adding to the recommendations of this study and enabling treatment strategies to be individually tailored to each patient. The importance of personalized therapy to an effective treatment algorithm has already been highlighted.<sup>14,15</sup>

In summary, our study provides expert confirmation of the perception that current topical AK treatment is hindered by unsatisfactory real world efficacy. Our experts believe that real world efficacy could be vastly improved by shorter treatments coupled with effective patient management. We therefore recommend focusing future research and development in AK on the development of topical field therapies with shorter treatment durations and simpler regimens that are not only clinically effective but also effective in the real world with good patient-reported outcomes.

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