Physician perceptions and experience of current treatment in actinic keratosis

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Abstract

Background  Topical therapy is important in the treatment of actinic keratosis (AK), a major risk factor for, and early development stage of, squamous cell carcinoma. Despite this, research addressing the limitations and challenges associated with topical field therapy in actinic keratosis is lacking.

Objectives  The aim of this study was to highlight the challenges associated with maximizing compliance in patients receiving topical AK therapy and to investigate real-world experience with currently available topical therapies including perceptions of adherence and persistence.

Methods  A 45-min online survey was developed and completed by physicians in eight countries. All had previously prescribed topical AK therapy and ≥1 other treatment. Physicians’ consensus was summarized as overall agreement/disagreement from ≥70% of respondents (≥60% for case-specific questions).

Results  More than 70% of the 427 respondents agreed that topical field therapy is essential and had concerns that lengthy treatments and local skin reactions caused non-adherence/persistence. More than 90% of physicians would preferentially prescribe the shortest duration treatment to such patients.

Conclusions  The research clarifies the challenges associated with prescribing topical AK therapy and highlights that short treatment duration and rapid clearance of skin reactions are key considerations for physicians. This provides a basis for the generation of recommendations for improving the real-world efficacy of topical therapy.

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Conflicts of interest

E Stockfleth – Speaker, Consultant, Advisory Board; Grants, Honoraria Meda, Leo Pharma and Almirall K Peris – Advisory Board; Honoraria (Leo Pharma, Roche, Meda). C Guillen – Advisory Board; Honoraria (Leo Pharma, Meda, Galderma, Almirall). R Cerio Speaker; Honoraria (Leo Pharma, Janssen, MSD/Pfizer). N Basset-Seguin – Consultant; Honoraria (Leo Pharma). P Foley – Advisory Board, Investigator, Speaker; Grants, Honoraria (Abbvie, Janssen, MSD, Pfizer) Advisory Board, Investigator; Honoraria (Amgen). Advisory Board, Consultant, Investigator, Speaker; Honoraria (Novartis). Consultant, Investigator, Speaker; Honoraria (Eli Lilly). Investigator; Honoraria (Celgene, BMS). Investigator, Consultant: Honoraria (Roche). Advisory Board, Investigator, Speaker; Honoraria (CSL, GSK). Advisory Board, Consultant, Speaker; Honoraria (Galderma). Advisory Board, Consultant, Investigator, Speaker; Honoraria (Leo Pharma). J Sanches – Advisory Board; Honoraria (Leo Pharma). A Culshaw – Consul-

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Introduction
Actinic keratosis (AK) is a dermatological disease characterized by visible clinical skin lesions which coexist with invisible (subclinical) lesions on areas of the skin exposed to cumulative UV radiation. Individuals with outdoor occupations and a fair complexion have a greater predisposition to AK. The incidence of AK has increased during recent years, particularly in regions with high UV indexes and this trend is still apparent. In 2006, the WHO estimated the number of AK patients worldwide to be 278 million.

Actinic keratosis is the biggest risk factor for squamous cell carcinoma (SCC) and represents an early stage in the development of it. It is therefore classified by some as in situ SCC. SCC is the second most common type of non-melanoma skin cancer and 40–80% of all invasive SCCs evolve from AK lesions. SCC is associated with a much higher patient and economic burden than AK. Since it is not possible to anticipate which lesions will progress, treating AK is of clinical and economic importance.

Current treatments target either specific lesions (lesion-directed) or the region where lesions are located (field-directed). Lesion-directed treatments, including physical modalities such as cryotherapy, laser, curettage and ablative treatments, are effective for clearing single lesions but do not target underlying actinic changes in the surrounding skin. Destructive procedures also have a high utilization cost.

Field-directed therapies, such as photodynamic therapy and patient-applied topical therapies, are advantageous over lesion-directed treatments as they target visible and non-visible lesions and are commonly used to treat multiple lesions on larger skin areas. Topical therapies are frequently prescribed as their ease of administration means that patients can apply these themselves, hence reducing health care utilization costs.

Topical treatment commonly causes local skin reactions (LSRs) including erythema, ulcers and crusting. It also has a longer treatment duration than lesion-directed treatments, often in the range of 4–16 weeks. This may impair the ability of patients to tolerate LSRs, reducing adherence (where the patient does not follow the recommended prescription in terms of dose taken or dosing frequency) and persistence (where the patient does not take the medication for the recommended time period), causing a reduction in real-world efficacy. There is a paucity of peer-reviewed research on the impact of adherence/persistence on real-world efficacy and ways of supporting patients to optimize adherence/persistence.

This questionnaire-based study investigated real-world experience of physicians with currently available topical therapies for AK. Assessments (via Likert scale) included the level of agreement with key statements concerning adherence and persistence and perceived links with efficacy for topical treatments, as well as the profiling of a recent patient who had experienced dissatisfaction with regard to the overall real-world efficacy of AK treatment. The blinded profiles of different treatments were also assessed. It aimed to characterize the difficulties associated with adherence and persistence and provide a basis for further research.

Method
A questionnaire was developed to understand physicians’ perceptions and clinical experience of topical treatment in AK. The content was informed by a targeted literature review that was conducted on PubMed Medline and the Cochrane Database to identify key papers reporting the impact of adherence and persistence on the effectiveness of topical treatments for AK. The following search criteria were used:

- (actinic OR solar OR senil$2) WITH (keratos$2 OR cheilitis)
- AND (compliance OR adherence OR persistence OR efficacy OR safety OR tolerability OR treatment OR intervention OR therapy OR 'treatment failure' OR 'treatment holiday' OR *QoL). The suffix $2 expanded the search to include two additional unspecified characters after the $ symbol.

Articles that reported on topical AK treatment and published since 1990 in English were selected. Relevant articles were reviewed to identify specific topics associated with the prescribing of topical therapy for AK. The findings were used to develop the questionnaire as a 45-min online survey.

The survey was refined by obtaining feedback from eight international experts with clinical and research experience in AK management, representing the target countries of Australia, Brazil, France, Germany, Italy, Spain, UK and the USA (also authors of this study). Two pilot surveys were also conducted with physicians in each country, with the physician completing the questionnaire independently and then participating in a follow-up telephone conversation with a member of the research team to provide feedback that was implemented through further refinements to the questionnaire.

A total of 537 physicians were recruited for screening. To be subsequently included in the study, physicians had to have been practicing for 2–30 years, have personal responsibility for AK treatment decisions, had treated AK with topical therapy and ≥1 other therapy, displayed a forward-thinking approach with
curiosity about AK (measured through a battery of attitudinal and behavioural statements) and not participated in AK market research in the previous 3 months. To fully assess physicians’ perceptions and clinical experience, the questionnaire included open-text, open numeric, precoded multiresponse and precoded single-response questions. Questions covered general perceptions of topical treatment and were also related to the last patient who experienced a suboptimal outcome. Respondents were stratified by primary and secondary care according to treatment practices in that country. An outline of the final survey is shown in Table 1.

Data analysis was performed using SPSS (v. 19, IBM; 2010, Armonk, NY, USA). Incomplete surveys were excluded from the analyses. Open-text responses were analysed by generating code frames and open numeric responses were analysed using standard descriptive analyses. Precoded multiresponse questions were analysed using frequency of response and precoded single-response questions were analysed using seven-point Likert scales that utilized three scale definitions: ‘strongly disagree/agree’, ‘not concerned/extremely concerned’ and ‘not realized/fully realized’. Scores of 1–3 indicated disagreement with the statement, scores of 5–7 indicated agreement and a score of 4 was defined as neutral.

Consensus gained on the issues assessed in the questionnaire was summarized as representing overall agreement or disagreement based on the category that had ≥70% of responses for theoretical questions, following similar published research in dermatology,25,26 or ≥60% of responses for questions relating to specific patient cases. A lower threshold for case-based questions was appropriate because these responses are made in the context of real-life influences which are not present in theoretical questioning.

Two-tailed t-tests were used to reach conclusions based on statistically significant differences between different statements and different categories of respondent (e.g. primary care physicians vs. specialists). All differences (including ones significant at ≥95%) are reported.

### Results

The key concept explored in the literature review was the extent to which patient non-adherence/persistence reduces real-world efficacy. Ten papers were identified that reported original research, treatment guidelines and expert opinion/discussion. Treatment guidelines provided an overview of treatment options and AK management6,27,28 and the only treatment algorithm retrieved highlighted the importance of patient involvement in treatment decisions to encourage adherence and persistence.22

From the 537 physicians recruited, 54 responses did not meet the screening criteria and a further 56 were incomplete when the study closed, leaving 427 questionnaires available for analysis (Table 2). The sample was stratified by the physicians’ geographical location and demographics including clinical specialty (Table 3) and patient sample (Table 4) to enable differences in therapy and prescribing between nations and clinical specialties to be identified.

### Table 1 Actinic keratosis. Overview of the design of the physician survey

| Topic                                                                 | Specific questions                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Physician workload and patient distribution                          | • Respondent demographics                                                           |
|                                                                     | • Overview of treatment practices                                                   |
| Perceptions, expectations and outcome of topical treatments (at a patient cohort level) | • Physician perceptions on overall importance of field and topical therapy         |
|                                                                     | • Specific factors relating to topical therapy                                      |
| Experience with topical treatments (with reference to a profiled patient) | • Physician level of perceived concerns prior to treating the most recent AK patient experiencing suboptimal real-world efficacy |
| Suitability of current and future treatment options (for profiled patients) | • Profile of treatment most appropriate for the physician’s most recent patient who had experienced suboptimal real-world efficacy from a choice of four (generic and trade name made anonymous):* 1. Topical gel applied daily 2–3 days (mild-moderate LSRs clearing after 4 weeks) 2. Cream applied daily for 2–3 days per week for 16 weeks (mild-moderate LSRs clearing after 18 weeks) 3. Topical gel applied twice daily for 10 weeks (mild-moderate LSRs clearing after 18 weeks) 4. Cream applied daily for 2 weeks followed by 2-week rest then once daily application for a further 2 weeks* (mild-moderate LSRs clearing after 14 weeks) |

*Responses were not sought from participants in the US due to the different launch statuses of products.

### Table 2 Actinic keratosis. Overview of questionnaire completion

|                        | USA  | Brazil | Australia | Germany | UK | Italy | France | Spain | Total |
|------------------------|------|--------|-----------|---------|----|-------|--------|-------|-------|
| Respondents            | 118  | 54     | 66        | 50      | 62 | 56    | 61     | 70    | 537   |
| Excluded at screening  | 33   | 0      | 3         | 0       | 5  | 5     | 2      | 2     | 54    |
| Incomplete responses   | 10   | 2      | 13        | 0       | 7  | 0     | 6      | 18    | 56    |
| Complete questionnaires| 75   | 52     | 50        | 50      | 50 | 50    | 50     | 50    | 427   |

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The questionnaire provided information around seven key themes. Regarding field and topical therapy, 80% of physicians agreed that field treatment is essential when treating the majority of AK patients and agreement was significantly higher among dermatologists compared to primary care physicians (mean score /SD = 5.6 /1.36 compared to 5.0 /1.68, P < 0.05).

There was also 76% overall agreement that topical therapy is the best field therapy.

There was 85% consensus among physicians that shorter treatment durations would improve adherence and persistence and this was supported by the mean score of 6.2 ± 0.99 (Fig. 1). There was also 87% agreement that topical treatments can target subclinical lesions (mean score = 6.0 ± 1.13 compared to 5.6 ± 1.21, P < 0.05). Both groups of physicians strongly associated non-persistence and non-adherence with a lack of efficacy, with overall agreement levels of 77% and 74% respectively (Fig. 1).

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**Table 3** Actinic keratosis. Respondent demographics and clinical practice

|                  | USA | Brazil | Australia | Germany | UK | Italy | France | Spain | Total |
|------------------|-----|--------|-----------|---------|----|-------|--------|-------|-------|
| Dermatologist    | 75  | 52     | 20        | 50      | 15 | 50    | 50     | 35    | 347   |
| Primary care     | –   | –      | 30        | –       | 35 | –     | –      | 15    | 80    |
| Total respondents| 75  | 52     | 50        | 50      | 50 | 50    | 50     | 50    | 427   |
| Type of practice |     |        |           |         |    |       |        |       |       |
| Hospital only    | –   | –      | –         | 18      | 14 | 21    | 34     | 5     | 92    |
| Office only      | 58  | 27     | 34        | 31      | 31 | 3     | 3      | 20    | 207   |
| Hospital and office | 17 | 25     | 16        | 1       | 5  | 26    | 13     | 25    | 128   |
| Type of hospital |     |        |           |         |    |       |        |       |       |
| Teaching         | 10  | 11     | 13        | 17      | 15 | 16    | 30     | 18    | 130   |
| General          | 4   | 8      | 1         | 2       | 4  | 30    | 16     | 10    | 75    |
| Private          | 3   | 6      | 2         | –       | –  | 1     | 1      | 2     | 15    |
| Dermatology practised | | | | | | | | | |
| Medical/surgical | 53  | 3      | 47        | 36      | 45 | 36    | 44     | 42    | 306   |
| Cosmetic         | –   | –      | –         | 2       | –  | 1     | –      | 1     | 4     |
| Both             | 22  | 49     | 3         | 12      | 5  | 13    | 6      | 7     | 117   |

**Table 4** Actinic keratosis. Respondent patient sample

|                  | USA | Brazil† | Australia | Germany | UK | Italy‡ | France | Spain | Mean |
|------------------|-----|---------|-----------|---------|----|--------|--------|-------|------|
| Average number of patients per month (all) | 582 | 367     | 371       | 502     | 163| 211    | 310    | 396   | 363† |
| Average number AK patients per month | 173 | 65      | 159       | 84      | 30 | 28     | 53     | 76    | 84‡  |
| Treatment methods |     |         |           |         |    |        |        |       |      |
| Topical | 75  | 52     | 50        | 50      | 50 | 50     | 50     | 50    | 41   |
| Photodynamic | 55  | 18     | 24        | 45      | 15 | 41     | 40     | 32    | 34   |
| Curettage | 57  | 44     | 37        | 46      | 36 | 25     | 22     | 41    | 39   |
| Dermabrasion | 12  | 18     | 3         | 27      | 14 | 31     | 3      | 21    | 16   |
| Cryotherapy | 75  | 42     | 50        | 35      | 47 | 34     | 50     | 45    | 47   |
| Surgery | 41  | 40     | 30        | 47      | 29 | 21     | 40     | 35    | 35   |
| Laser | 17  | 27     | 7         | 35      | 3  | 1      | 11     | 9     | 14   |
| Cryopeeling | 14  | 24     | 8         | 14      | 4  | 7      | 2      | 9     | 10   |

 Patients receiving topical treatment (%)*

|                   | USA | Brazil† | Australia | Germany | UK | Italy‡ | France | Spain | Mean |
|-------------------|-----|---------|-----------|---------|----|--------|--------|-------|------|
| 5-fluorouracil    | 19  | 45      | 25        | 12      | 26 | –      | 17     | 8     | 19   |
| Imiquimod 5%      | 12  | 17      | 9         | 19      | 9  | –      | 24     | 28    | 15   |
| Imiquimod 3.75%*  | 11  | –       | –         | –       | –  | –      | –      | 1     |      |
| Diclofenac 3%†    | 8   | –       | 6         | 39      | 33 | –      | 10     | 18    | 14   |
| Ingenol mebutate†* | 7  | –       | –         | –       | –  | –      | –      | 1     |      |
| None              | 43  | 38      | 61        | 30      | 32 | 24     | 49     | 46    | 40   |

*Imiquimod 3.75% and ingenol mebutate were only shown in the US.
†In Brazil, diclofenac was not given as a response option.
‡In Italy, data were only requested on the number of patients receiving/not receiving a topical treatment.
#These values denote the average number of patients per month per country among the countries studied.
The survey also showed that ≥70% of physicians had specific concerns about adherence/persistence being negatively influenced by long treatment durations (mean score 5.1 ± 1.41), severe LSRs (mean score 5.0 ± 1.54), long-lasting LSRs (mean scores 4.9 ± 1.46) and low patient tolerability to adverse effects of treatment (mean score 5.0 ± 1.55) (Fig. 2).
Physician perceptions on topical AK treatment

Figure 3 Actinic keratosis. Mean rank for physicians’ concerns prior to prescribing topical treatment for actinic keratosis in relation to the most recent patient in whom real-world efficacy was unsatisfactory (measured on a 1–7 Likert scale where scores of 1–3 = disagree/not concerned, 4 = neutral and 5–7 = agree/concerned) ± standard deviation (n = 427, % relates to proportion of respondents selecting each numbered response).

Figure 4 Actinic keratosis. Mean rank for the extent to which physicians’ concerns prior to prescribing topical treatment for actinic keratosis were realized during treatment in relation to the most recent patient in whom real-world efficacy was unsatisfactory (measured on a 1–7 Likert scale where scores of 1–3 = not realized, 4 = partly realized and 5–7 = fully realized) ± standard deviation (n = 427, % relates to proportion of respondents selecting each numbered response).
Based on the recall of the most recent patient with AK who experienced suboptimal real-world efficacy, >60% of respondents had pretreatment concerns relating to the negative effects of treatment tolerability, severity and duration of LSRs and long overall treatment durations on adherence and persistence (Fig. 3). Concerns regarding efficacy in terms of lesion reduction/complete clearance and ease of administration (whether patients can self-administer treatment) became completely/almost completely apparent in ≥60% of cases. Before treatment, only 58% and 33% of physicians had concerns regarding lesion reduction/complete clearance and ease of administration respectively (Fig. 4).

Of the four treatment profiles presented to physicians in the survey (Table 1), the one most likely to be prescribed conformed to profile 1 (Fig. 5). This profile, in comparison to the others, was characterized by the shortest treatment duration and skin reactions which clear most rapidly (Profile 1 in Table 1). Physicians were also asked to state what percentage of their

Figure 5  Actinic keratosis. Physicians’ ranking of four treatment profiles for actinic keratosis according to the perceived probability of a patient completing the treatment course (1st = greatest chance of patient completing the treatment; greatest preference for prescribing, 4th = lowest chance of patient completing the treatment; lowest preference for prescribing). See Table 1 for profile definitions. Responses were not obtained from participants in the US due to the different launch statuses of products.

Figure 6  Actinic keratosis. Percentage of AK patient sample that physicians would prescribe a shorter treatment to if one was available (stratified by country). Responses were not obtained from participants in the US.
patients they would prescribe a short-duration treatment to. The results were stratified by country and ranged from 54% (Italy) to 81% (Brazil) (Fig. 6).

Discussion

The presented study provides insight into the opinions of a large sample of AK-treating physicians on issues affecting adherence and persistence when prescribing topical therapy. The findings emphasize the importance of topical field therapy to the treatment algorithm for AK, as previously suggested with physicians’ agreeing that topical field therapy is the most beneficial form of field therapy. One perceived advantage of topical field therapy over lesion-directed therapy is its ability to target subclinical lesions and 87% of physicians’ agreed with this, highlighting the importance of this factor. The higher level of agreement amongst dermatologists compared to primary care physicians for both factors indicates that dermatologists associate topical therapy with a greater level of importance.

Physicians were most concerned generally about long treatment durations, severe and long-lasting LSRs and poor patient tolerability negatively affecting adherence and persistence. When considering the most recent patient treated, these concerns were partly realized during treatment and concerns regarding efficacy in terms of lesion reduction/complete clearance and ease of administration reached consensus. This implies that more factors adversely affect real-world efficacy than anticipated by the responding physicians prior to commencing therapy. It may also represent a decline in real-world efficacy parallel to treatment duration. Our findings agree with a recent review which also acknowledged treatment duration, patient compliance, severe LSRs and suboptimal patient satisfaction as issues when prescribing topical AK therapy.

Our study revealed 85% consensus among physicians that reducing the duration of treatment would improve adherence/persistence. This would correspond to a greater likelihood of patients completing the prescribed treatment. The likelihood of therapy being complete prior to the emergence of LSRs would also be greater, reducing the implications of patients’ negative perceptions of LSRs on treatment adherence/persistence. Any LSRs that do occur would also be in closer proximity to the completion of treatment, incentivizing patients to complete the prescribed therapy.

There was a 70% consensus among physicians that prolonged LSRs are a cause of non-adherence/persistence. As LSRs are treatment related, their duration tends to correlate with the duration of the therapy, so a corresponding shortening in the duration of treatment-emergent LSRs would also be observed with shorter therapies.

In theory it may be possible to perform short treatment breaks (1–3 days) and to use moisturizing and emollient creams during the day to reduce or prevent LSRs. These strategies, however, have not been studied closely in clinical trials. The impact on efficacy of reducing drug concentration and/or treatment duration, and using topical corticosteroids to reduce LSR has also not been studied.

The concept that shorter treatment with only minimal LSRs would improve real-world efficacy is supported by other research. A patient-reported outcomes study involving patients receiving photodynamic field therapy indicated that patients prefer treatments with equal effectiveness but better cosmetic outcomes and shorter recovery time. It is possible that the shorter recovery time actuated patients’ perceptions of improved cosmetic outcome, supporting the concept that treatments of shorter duration will make patients more amenable to therapy by reducing the duration of LSRs and hence the recovery time. It has also been recognized that patients’ willingness to pay is influenced by their perceptions of the cosmetic result, a further indication of the benefit of developing treatments that reduce the severity and duration of LSRs.

There is limited published evidence on the real-world impact of non-adherence and non-persistence. To our knowledge, this is the largest study to evaluate physicians’ perceptions of topical AK treatment. The large sample size and stringent inclusion criteria support the validity of the current results. Results were analysed from 427 physicians recruited from eight different countries who all had personal involvement in the delivery of topical therapy for AK. The respondent sample represented European and non-European countries. The stringent criteria for a physician to be eligible to participate ensured that participants had appropriate experience and involvement in the treatment of AK to be able to provide valid responses and also prevented propensity from participation in previous market research from influencing the results.

The main limitation of the study was imposed by physicians answering on behalf of patients as their perceptions of patients’ attitudes to AK therapy may not be the same as direct patient-reported outcomes. The actual factors reducing patients’ adherence/persistence may be different from factors perceived by their physicians. This may include the patient’s ability to afford the medication, especially in countries such as the US. However, as physicians are the first point of contact for their AK patients in relation to the condition and its treatment, they are in a good position to impartially evaluate factors affecting clinical outcomes. The use of a physician survey as opposed to a patient survey therefore helps to overcome any bias or skewing of responses that may occur if patients were surveyed directly. For instance, patients may be reluctant to admit to an investigator that they are struggling to comply with a prescribed treatment regimen.

Our results indicate that outcomes in topical AK field therapy are affected by the treatment duration and the occurrence of LSRs. Further validation of the findings with dermatology experts would reinforce the observed trends. It would be useful...
to identify whether experts’ consensus matches physicians’ consensus and to use the consolidated findings to generate recommendations for improved patient adherence/compliance which would translate into improved clinical outcomes. Research investigating the type of patient outcomes that are influenced by shorter treatments and the extent to which they are influenced is also lacking. Future research should concentrate on identifying patient-reported outcomes for other AK field therapies and investigate the direct effect of shorter treatments on patient outcomes. This would also help prescribing to be tailored to the particular needs and tolerability of each patient, as suggested previously.6,22

In conclusion, although physicians consider topical field therapy to be an essential component of AK treatment, their concerns about limitations with current topical AK therapies reducing clinical efficacy were justified in real-world clinical examples. This research highlights how these concerns could be addressed by developing new topical therapies with equal efficacy but a shorter duration, which would be expected to increase adherence and persistence, improve clinical outcomes and reduce the long-term economic and patient burden of AK.

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