European Dermatology Forum

Guideline for the Treatment of Actinic Keratosis

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Evidence and consensus based (S3) Guidelines for the Treatment of

Actinic Keratosis

International League of Dermatological Societies (ILDS) in cooperation with the European Dermatology Forum (EDF)

Short Version

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Conflicts of interest have been declared at various points of the guidelines development process. The declarations of interests of each author are published together with the methods and results report of the guideline, available at JEADV DOI: 10.1111/jdv.13179.

Introduction

The primary goal of these evidence- and consensus-based guidelines for the treatment of actinic keratosis (AK) was the development of treatment recommendations appropriate for different subgroups of patients presenting with AK. This was subject to a systematic literature review and a formalized consensus conference including the members of the guidelines' expert panel. Target groups include all health care professionals involved in the assessment and treatment of patients with AK, primarily dermatologists, histopathologists and general practitioners (GP).

Along with a clearance of AK lesions and prevention of their recurrence, the provision of evidence-based treatment algorithms intends to decrease the percentage of patients with progression from AK to invasive squamous cell carcinoma (SCC). To take frequent clinical situations into account, different patient subgroups were defined, according to the severity of the disease and the medical history of the patients.

A secondary aim of these guidelines is the implementation of knowledge relating to the clinical background of AK, including recommendations for the histopathological definition, diagnosis and the assessment of patients presenting with AK.

Supporting material (long version), is available as online supplement. Furthermore, a methods report, results report and declarations of interest of the guideline development group members have been published at JEADV DOI: 10.1111/jdv.13179. Recommendations and definitions presented in grey boxes were subject to a formalized consenting procedure during the consensus conference.

Disclaimer

Guidelines do not replace the clinicians' knowledge and skills, since guidelines never encompass therapy specifications for all medical decision-making situations. Guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. Deviation from the recommendations may be justified or inevitable in specific situations. The ultimate judgment regarding patient care must be individualized and must be made by the physician and patient in light of all presenting circumstances.

Safety aspects that were considered within these guidelines do not represent a comprehensive assessment of all available safety information for the included interventions. They are limited to those aspects chosen for evaluation and the information available in the included clinical trials. Readers must carefully check the information in these guidelines and determine whether the recommendations (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, up-to-date and appropriate.

International guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Thus, the national medical societies associated with the International League of Dermatological Societies (ILDS) will be responsible for the adoption and implementation of the guidelines on a national level. Particularly, the mode of application of the different treatment options has to be adapted to national approval of the interventions.

Methods

The guidelines development followed a predefined and structured process. The guidelines were elaborated along adapted recommendations by the WHO guidelines review committee[1] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[2, 3]. The quality criteria for guidelines development as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[4] were incorporated into the methodological development of the guidelines. For the underlying systematic literature review on interventions for AK, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions[5] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[6] was adapted.

All recommendations were consented during the consensus conference using a formal consensus methodology[7]. Based on the GRADE approach, strength of recommendation was expressed as shown in Table 1. If expert opinion without external evidence was incorporated into the reasoning for making a certain recommendation, the rationale was provided. For details on the methodology, please refer to the methods report (available online at JEADV DOI: 10.1111/jdv.13179).

Table 1: Strength of recommendations: wording, symbols and implications[45, 46]

Strength	Wording	Symbols	Implications
Strong recommendation for the use of an intervention	"We recommend …"	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation for the use of an intervention	"We suggest …"	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	"We cannot make a recommendation with respect to …"	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no evidence data available, conflicting outcomes, etc.)
Weak recommendation against the use of an intervention	"We suggest not to …"	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation against the use of an intervention	"We recommend not to …"	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

These guidelines will expire on July 31, 2018. The ILDS (International League of Dermatological Societies) will be responsible to initiate an update.

Clinical background of AK

For a more detailed clinical introduction, please refer to the long version of the guidelines (available as online supplement).

Definition and nomenclature of AK

Expressions used synonymously for AK include 'solar keratosis', 'senile keratosis', 'keratosis senilis', 'senile keratoma', 'keratoma senile', 'keratinocytic intraepidermal neoplasia',[8] and 'in situ squamous cell carcinoma Type AK'.[9] Different conceptions of the definition have emerged during scientific debates on the histopathological and clinical significance of AK.[8] AK is either described as intraepithelial keratinocytic dysplasia ('precancerous lesion') that may possibly 'transform' into invasive SCC, or as in situ SCC (intraepidermal proliferation of atypical keratinocytes) that may progress to an invasive stage. More recent characterizations of AK tend to accentuate the latter view of AK as 'superficial SCC'.[8] This view refers to the fact that AK, at the level of cytology, is indistinguishable from SCC and, at the level of molecular biology, has multiple similarities with SCC.[10] Attempts have been made to adapt the nomenclature, owing to the perspective of AK as carcinoma in situ.[9, 11] A classification of AK, as "keratinocytic intraepidermal neoplasia (KIN) 1-3"[11] or "in situ squamous cell carcinoma Type AK I-III"[9] has been suggested.

These guidelines intend advancing the concept of AK towards a widely accepted definition (see Table 2 and Table 4).

Table 2: Recommendations for the terminology and definition of AK

Recommendations for the terminology and definition of AK†	**Evidence**	**Percentage of agreement**
The terms "actinic keratosis (AK)", "keratinocytic intraepidermal neoplasia (KIN)", and "in situ squamous cell carcinoma type actinic keratosis" can be used synonymously*. Other expressions should be avoided. *In some regions / countries, the term "solar keratosis" is frequently used.	expert consensus	≥90%
Actinic keratosis may be considered a form of "in situ squamous cell carcinoma" of the skin. When communicating with patients, this term should be used with caution, because the term "carcinoma" is associated with morbidity that does not correspond to the diagnosis of AK in most cases. At the moment, it is not possible to predict the transformation of single AK lesions to invasive squamous cell carcinoma.	expert consensus	≥90%

† The use of this clinical nomenclature in the document reflects the views of the guidelines committee and the ILDS recognizes that there are alternative classification schemes in everyday use.

Pathophysiology of AK

Chronic exposure to UV radiation plays a central role in the pathogenesis of AK,[12-14] as reflected by the term 'actinic' (referring to 'radiation'), and the synonym 'solar keratosis'. UVB radiation can lead to direct DNA damage, causing the formation of cyclobutane pyrimidine dimers and pyrimidine-pyrimidone 6,4-photoproducts.[15, 16] As a result of DNA mutations, the function of tumour suppressor proteins such as p53 can be suppressed, leading to a clonal expansion of keratinocytes into an AK.[17, 18] A dysregulation of the p53 pathway seems to play the most important role in the development of AK lesions, as well as in the further development of SCC.[19] Absorption of UVA radiation by skin chromophores results in the generation of reactive oxygen species, which oxydize guanine residues on the DNA; these oxidative products are mutagenic.[20, 21]

Some evidence suggests that infections with human papilloma viruses act as cofactors in the development of AK,[22] especially in combination with DNA alterations induced by UV radiation.[23, 24] The role of human papilloma viruses in AK and SCC development is ascribed to expression of the viral oncoproteins E6 and E7 by infected keratinocytes.[25]

Risk factors for the development of AK

Risk factors for the development of AK include advanced age, male gender, cumulative sun exposure and fair skin type.[12, 26, 27] Patients with concomitant immunosuppression have a higher risk for developing AK. This has been especially shown in organ transplant recipients, who are chronically immunosuppressed.[28-31] Genetic syndromes associated with impaired DNA repair mechanisms, or deficiency in melanin biosynthesis, or an increased vulnerability to UV radiation damage, result in a higher risk for the development of AK.

Epidemiology of AK

There are no published population-based incidence rates of people who develop actinic keratosis[32] and prevalence rates of AK display a wide international range, e.g. in Australia, as a country with close proximity to the equator and a large percentage of fair-skinned inhabitants, shows the highest prevalence of AK, with up to 60% of Australians over the age of 40 having AKs.[27, 33, 34]

The natural history/ treatment necessity of AK

Reliable data on the progression rates of single AK lesions are scarce and important methodological limitations apply to the available studies, so that the actual risk of progression of single AK lesions to invasive SCC remains unclear (data reported on the risk of progression into invasive SCC ranged from 0 to 0.53% per AK lesion per year). Although the rate of regression of single AK lesions was generally seen to be 20 to 30% with up to 63% in one study, spontaneous regression of complete fields of AK were only seen in 0 to 7.2% of patients.[35]

The available data indicate that the presence of AK without adequate treatment is a dynamic but chronic condition, with a low chance of a sustained spontaneous complete regression. Due to the inherent risk of progression to invasive SCC and the lack of prognostic tools

concerning the determination of lesions at risk of progression, an adequate treatment of the AK lesions or the affected field is presumed to be necessary.[35]

Assessment of AK

Presentation of AK

Clinically, AKs typically present as scaly or keratotic patches, papules or plaques on an erythematous base. Palpation reveals a sand paper-like texture. The diameter usually does not exceed 1cm,[9] although in some patients lesions can be numerous and confluent. Lesions usually have the same colour as the surrounding skin, but may also present as pink, red or brownish patches, papules or plaques.[19] The surrounding skin may show signs of chronic sun damage, including telangiectasias, dyschromia, elastosis and wrinkles.[36]

Depending on their clinical and histological appearance, various types of AK have been described, including pigmented, atrophic, bowenoid, lichenoid or hyperkeratotic AKs.[9, 26] The anatomic distribution of AK reflects the importance of sun light exposure for their development.

Clinical diagnosis

Fehler! Verweisquelle konnte nicht gefunden werden. shows the recommendations for the assessment of AK lesions consented by the expert panel.

Table 3: Recommendations for the assessment of AK lesions

Recommendations for the assessment of AK lesions	Evidence	Percentage of agreement
Clinical diagnosis of AK is recommended for most of the lesions.	expert consensus	≥90%
The clinical classification following Olsen et al. (1991)[47] is recommended to be used to assess the severity degree of single AK lesions: • Grade 1: mild (slight palpability, with actinic keratoses felt better than seen) • Grade 2: moderate (moderately thick actinic keratoses that are easily seen and felt) • Grade 3: severe (very thick and/or obvious actinic keratoses)	expert consensus	≥90%
A biopsy and histological assessment is recommended in the following cases: • clinical diagnosis unclear with respect to the underlying disease • clinical diagnosis unclear with respect to the biologic behaviour of the lesion. Clinical parameters that may be indicators of progression of AK to invasive SCC are the following (based on Quaedvlieg et al. 2006)[48]: o Major criteria: ulceration, induration, bleeding, diameter > 1cm, rapid enlargement, erythema o Minor criteria: pain, palpability, hyperkeratoses, pruritus, pigmentation • unresponsive AK lesions (no regression or early recurrence despite adequate therapy)	expert consensus	≥90%

Histological definition and assessment of AK

The main histological determinant of the classification of the severity of AK lesions, as suggested by Röwert-Huber, 2007 and Cockerell, 2000, is the extent of the atypical keratinocytes in the epidermis,[11, 19] as shown in Table 4.

Table 4: Recommendations for the histological classification of AK

Recommendations for the histological classification of AK	Evidence	Percentage of agreement
The following histological classification is suggested to assess the severity degree of single AK lesions: • early in situ SCC, Type AK I corresponds to atypical keratinocytes in the basal and suprabasal layers (the lower third) of the epidermis • early in situ SCC, Type AK II is constituted by atypical keratinocytes extending to the lower two thirds of the epidermis • in situ SCC, Type AK III consists of atypical keratinocytes extending to more than two thirds of the full thickness of the epidermis	expert consensus	≥75%

Subgroups of patients presenting with AK

A widely agreed upon definition of degrees of the overall severity of AK could not be identified. Different subgroups of patients presenting with AK, requiring different therapeutic approaches were defined at the beginning of the guidelines development in order to address the demands of clinical practice. The definitions were discussed and consented during the kick-off consensus conference (Table 5).

Table 5: Recommendations for a classification of patients according to the severity of AK

Recommendations for a classification of patient subgroups	**Evidence**	**Percentage of agreement**
The following subgroups of patients should be considered separately: 1) **single AK lesions** At least one and not more than five palpable or visible AK lesions per field or affected body region 2) **multiple AK lesions** At least 6 distinguishable AK lesions in one body region or field 3) **field cancerization** At least 6 AK lesions in one body region or field, and contiguous areas of chronic actinic sun damage and hyperkeratosis 4) **immunosuppressed patients with AK** AK at any of the above-mentioned severity degrees and concomitant immunosuppression (e. g. due to chronic immunosuppressive medication or specific diseases affecting the function of the immune system, such as malignant hematologic disorders)	expert consensus	≥90%

Treatment options

The following treatment options were selected as relevant interventions for actinic keratosis in consensus with ≥ 75% of the expert panel members to be included in the assessment and evaluation. The selection of interventions and their mode of application served as inclusion criteria for the systematic literature assessment. Other interventions and other application modes for the selected interventions were not included into the systematic literature review. This does not imply that other interventions are not possibly suitable for the treatment of AK. Modes of application of the listed interventions might have to be adapted when implementing the guidelines in the national context. When deciding for using certain interventions, users of this guidelines must carefully check the treatment option and its mode of application, e.g. regarding approval status, dose, dosing regimen, adverse effects, contraindications, or drug interactions.

Lesion-directed treatment options for AK aim at the physical destruction or removal of atypical keratinocytes that constitute a singular AK lesion. These treatments are directed towards the clinically manifest (visible or palpable) AK lesions. Field-directed treatment options for AK similarly aim at the destruction, removal or remission of atypical keratinocytes. Here, therapy of latent, subclinical areas of atypical keratinocytes within a field of chronic sun damaged skin and not only a reduction of manifest areas of AK is intended. Table 6 shows a list of lesion-and field-directed treatment options for AK that were selected for evaluation within these clinical guidelines. Please note that the stated mode of application does not imply guidance for the mode of use of the listed interventions, but solely reflects the criteria that had to be fulfilled for inclusion into the systematic review.

Table 6: Lesion- and field-directed treatment options selected for evaluation

Intervention	**Mode of application**
Curettage	Once, repeated up to 2 times
Cryotherapy	Once, repeated up to several times
Carbon dioxide (CO2) laser	Once, repeated up to several times
Er:YAG laser	Once, repeated up to several times
0.5% 5-fluorouracil + 10% salicylic acid	Once daily application for 6 to 12 weeks
5-aminolaevulinic acid photodynamic therapy (ALA-PDT)*	Different concentrations, light sources and application modes of ALA-PDT were included, incubation time had to be at least 1 hour
Methylaminolevulinate photodynamic therapy (MAL-PDT)*	Different light sources and application modes of MAL-PDT were included, incubation time had to be at least 2.5 hours
3% diclofenac in 2.5% hyaluronic acid gel	Twice daily application for 60 to 90 days
0.5% 5-fluorouracil (0.5% 5 FU)	Once daily for 1 to 4 weeks
5% 5-fluorouracil (5% 5 FU)	Once or twice daily for 2 to 4 weeks
2.5% Imiquimod	Once daily application for 2 weeks followed by a rest period of two weeks (One or two treatment cycles)
3.75% Imiquimod	Once daily application for 2 weeks followed by a rest period of two weeks (One or two treatment cycles)

5% Imiquimod	Once daily application at 2 or 3 days per week for a time period of 4-16 weeks; continuously or intermittent.
0.015% Ingenol mebutate for lesions on the face or scalp	Once daily application for 3 days
0.05% Ingenol mebutate for lesions on the trunk or extremities	Once daily application for 2 days

* PDT often included pretreatment of the AK lesions, e.g. with curettage or other topical interventions. These were not classified as 'combination treatments' (see chapter "Combination of interventions"), unless the combination included one of the other selected interventions (except for curettage). For information on the specific mode of application of PDT in the included studies, see the results report (online supplement).

Assessment of treatment options/ rating of outcomes

To be included into the systematic review, studies had to report at least one of the selected outcomes. Outcomes had to be reported as events per patients in case of dichotomous outcomes (the number of events and the number of patients at the time of assessment had to be reported) or as mean difference in case of continuous outcomes (the mean and standard deviation had to be reported). Otherwise studies could not be considered. Efficacy assessment was accomplished for all comparisons. Safety outcomes, patient reported outcomes, and cosmetic outcomes were only assessed for head-to-head comparisons (RCTs with active control).

The following efficacy outcomes were assessed:

- Mean reduction in lesion counts from baseline to assessment (absolute values [preferred] or percentages)

- Participant complete clearance (CC, rate of participants with a complete clearance of all lesions within a predefined field)

- Participant partial clearance (PC, rate of participants with at least a 75% reduction of the AK lesion counts within a predefined field)

- Investigator global improvement index (IGII, rate of participants rated as ‘completely improved’ by the investigator)

- Participants global improvement index (PGII, rate of participants self-assessed as ‘completely improved’).

Efficacy outcomes had to be reported 2 months after the end of treatment or whatever was closest, not more than 6 months after the end of treatment. Studies examining longer treatment periods were not included in the systematic review.

The following secondary outcomes were assessed for all head-to-head comparisons:

Safety outcomes included ‘withdrawals due to adverse events’ and ‘skin irritation’. Due to the numerous different safety outcomes that were assessed for the different comparisons of interventions, experts could chose up to three further safety outcomes for each comparison. Patient reported outcomes included ‘participant’s satisfaction’ (rate of participants ‘satisfied’ or ‘very satisfied), ‘participant’s preference’ (rate of participants preference) and ‘compliance’. ‘Participant’s preference’ could only be assessed in split-patient trials. Up to three cosmetic outcomes could be chosen for all head-to-head comparisons.

Other considerations could be included into the reasoning for making recommendations for specific interventions. These could include expert experience concerning resource use, practicability, adherence or other reasons. These considerations were not assessed systematically.

Recommendations: Treatment of patients with AK

Fehler! Verweisquelle konnte nicht gefunden werden. gives an overview of the strength of recommendations for the treatment of patients who have AK.

Table 7: Overview of the recommendations for the treatment of AK

		single AK lesions ≥ 1 and ≤ 5 palpable or visible AK lesions per field or affected body region	**multiple AK lesions** ≥ 6 distinguishable AK lesions in one body region or field	**field cancerization** ≥ 6 AK lesions in one body region or field, and contiguous areas of chronic actinic sun damage and hyperkeratosis	**Immunocompromised patients with AK** AK at any of the mentioned severity degrees and a concomitant condition of immunosuppression
		Sun protection in all patient subgroups!			
Strength of recommendation	↑↑	Cryotherapy	0.5% 5-FU 3.75% imiquimod Ingenol mebutate 0.015% / 0.05% MAL-PDT, ALA-PDT		-
	↑	Curettage* 0.5% 5-FU, 5% 5-FU 0.5% 5-FU + 10% SA* 3.75% imiquimod 5% imiquimod ingenol mebutate 0.015/0.05% ALA-PDT, MAL-PDT	Cryotherapy** 3% diclofenac in 2.5% HA 5% 5-FU 0.5% 5-FU + 10% SA* 5% imiquimod, 2.5% imiquimod CO2-laser, Er:YAG-laser		cryotherapy** curettage* 5% 5-FU 5% imiquimod*** ALA-PDT, MAL-PDT
	0	3% diclofenac in 2.5% HA 2.5% imiquimod CO2-laser, Er:YAG-laser	Curettage*		3% diclofenac in 2.5 % HA 0.5% 5-FU 0.5% 5-FU + 10% SA 2.5% imiquimod, 3.75% imiquimod Ingenol mebutate 0.015%/0.05%
	↓	-	-		CO2-laser, Er:YAG-laser

* discrete, hyperkeratotic AK lesions
** single or multiple discrete AK lesions, not for treatment of field cancerization
*** For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.

For a detailed description of the results from the systematic literature search, assessment and references of the included studies and additional reasoning, please consider the long version (online supplement) or the results report of the guidelines (available at JEADV DOI: 10.1111/jdv.13179). The information reported in the included studies did not allow to distinguish between the subgroups of patients with multiple AK lesions and patients with field cancerization. Therefore, these two subgroups were generally pooled together in order to make treatment recommendations. In the following chapter, an overview of the recommendations for the different patient subgroups is presented (Table 8, Table 9 and Table 10).

Table 8: Recommendations for patients who have single AK lesions

Intervention	**Evidence / reasoning, see chapter (long version / results report)**	Strength of the recommendation	Percentage of agreement
For patients who have single AK lesions, we recommend using (↑↑) …			
Cryotherapy	8.2 / 4.2	↑↑	≥75%
For patients who have single AK lesions, we suggest using (↑) …			
Curettage (discrete, hyperkeratotic lesions)	8.1 / 4.1	↑	≥90%
0.5% 5-fluorouracil	8.5 / 4.5	↑	≥75%
5% 5-fluorouracil	8.6 / 4.6	↑	≥50%[1]
0.5% 5-fluorouracil + 10% salicylic acid (discrete, hyperkeratotic lesions)[2]	8.13 / 4.13	↑	≥75%
3.75% imiquimod	8.8 / 4.8	↑	≥90%
5% imiquimod	8.9 / 4.9	↑	≥75%
ingenol mebutate 0.015% (lesions on the face or scalp) and ingenol mebutate 0.05% (lesions on the trunk or extremities)	8.10 / 4.10	↑	≥75%
ALA-PDT	8.11 / 4.11	↑	≥75%
MAL-PDT	8.12 / 4.12	↑	≥75%
We cannot make a recommendation (0) for patients who have single lesions with respect to …			
3% diclofenac in 2.5% hyaluronic acid gel	8.4 / 4.4	0	≥75%
2.5% imiquimod	8.7 / 4.7	0	≥90%
CO_2 laser and Er:YAG laser	8.3 / 4.3	0	≥75%

1 *Experts who did not agree voted for making a strong recommendation (↑↑) or no recommendation (0) for the use of 5% 5-fluorouracil in patients with single AK lesions.*

2 *To become effective, most of the treatments need to penetrate properly into the skin. Penetration can be hindered by strong hyperkeratosis and measures to remove the hyperkeratosis may be necessary. Due to the combination with salicylic acid, this treatment is particularly deemed appropriate for the treatment of discrete hyperkeratotic AK.*

Table 9: Recommendations for patients who have multiple AK lesions / field cancerization

Intervention	**Evidence / reasoning, see chapter (long version / results report)**	Strength of the re-commen-dation	Percentage of agreement
For patients who have multiple AK lesions / field cancerization, we recommend using (↑↑) …			
0.5% 5-fluorouracil	8.5 / 4.5	↑↑	≥50%[3]
3.75% imiquimod	8.8 / 4.8	↑↑	≥90%
ingenol mebutate 0.015% (lesions on the face or scalp) and ingenol mebutate 0.05% (lesions on the trunk or extremities)	8.10 / 4.10	↑↑	≥50%[4]
ALA-PDT	8.11 / 4.11	↑↑	≥75%
MAL-PDT	8.12 / 4.12	↑↑	≥75%
For patients who have multiple AK lesions / field cancerization, we suggest using (↑) …			
Cryotherapy (patients with multiple lesions, especially for multiple discrete lesions; not suitable for the treatment of field cancerization)	8.2 / 4.2	↑	≥90%
3% diclofenac in 2.5% hyaluronic acid gel	8.4 / 4.4	↑	≥75%
5% 5-fluorouracil	8.6 / 4.6	↑	≥50%[5]
0.5% 5-fluorouracil + 10% salicylic acid (discrete, hyperkeratotic lesions)[6]	8.13 / 4.13	↑	≥90%
5% imiquimod	8.9 / 4.9	↑	≥75%
2.5% imiquimod	8.7 / 4.7	↑	≥75%
CO_2 laser and Er:YAG laser	8.3 / 4.3	↑	≥50%[7]
We cannot make a recommendation (0) for patients who have multiple AK lesions / field cancerization with respect to …			
Curettage	8.1 / 4.1	0	≥90%

3 *Experts who did not agree voted for making a weak recommendation (↑) for the use of 0.5% 5-fluorouracil in patients with multiple lesions or field cancerization.*

4 *Experts who did not agree voted for making a weak recommendation (↑) for the use of imiquimod in patients with multiple lesions or field cancerization.*

5 *Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% 5-fluorouracil in patients with multiple lesions or field cancerization.*

6 *To become effective, most of the treatments need to penetrate properly into the skin. Penetration can be hindered by strong hyperkeratosis and measures to remove the hyperkeratosis may be necessary. Due to the combination with salicylic acid, this treatment is particularly deemed appropriate for the treatment of discrete hyperkeratotic AK.*

7 *Experts who did not agree to this recommendation voted for making no recommendation (0) for the use of CO2 laser or Er:YAG laser in patients with multiple lesions or field cancerization.*

Table 10: Recommendations for immunocompromized patients who have AK

Recommendations for immunocompromized patients presenting with AK	**Evidence / reasoning: see chapter (long version / results report)**	Strength of the re-commen-dation	Percentage of agreement
For immunosuppressed patients who have AK, we suggest using (↑) …			
Cryotherapy (especially for single lesions or multiple discrete lesions; not suitable for the treatment of field cancerization)	8.2 / 4.2	↑	≥75%
curettage (discrete, hyperkeratotic lesions)	8.1 / 4.1	↑	≥75%
5% fluorouracil	8.6 / 4.6	↑	≥75%
5% imiquimod[8]	8.9 / 4.9	↑	≥50%[9]
ALA-PDT	8.11 / 4.11	↑	≥90%
MAL-PDT	8.12 / 4.12	↑	≥75%
We cannot make a recommendation (0) for immunosuppressed patients who have AK with respect to …			
3% diclofenac in 2.5% hyaluronic acid gel	8.4 / 4.4	0	≥90%
0.5% 5-fluorouracil	8.5 / 4.5	0	≥75%
0.5% 5-fluorouracil + 10% salicylic acid	8.13 / 4.13	0	≥75%
2.5% imiquimod	8.7 / 4.7	0	≥90%
3.75% imiquimod	8.8 / 4.8	0	≥90%
ingenol mebutate	8.10 / 4.10	0	≥90%
For immunosuppressed patients who have AK, we suggest NOT using (↓) …			
CO_2 laser and Er:YAG laser	8.3 / 4.3	↓	≥75%

8 *For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.*

9 *Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% imiquimod in immunosuppressed patients.*

Combination of interventions

Pivotal clinical trials designed to gain government agency approval of a new field therapy employ study protocols whose endpoints maximize efficacy and minimize adverse effects. The adoption by dermatologists of these protocols has been met with some level of resistance due to the inconvenience of prolonged adverse effects, socially unacceptable appearance that can last weeks to months, patient compliance issues and physician reluctance to prescribe field therapies. Following a drug's approval and its widespread availability, dermatologists commonly recommend a modified protocol in an effort to enhance patient compliance, decrease adverse effects and maintain or enhance efficacy. In addition to modifying approved dosing regimens, field therapies have been combined or used sequentially with each other as well as with lesion targeted therapies with the belief that the synergistic effects of the combined mechanisms of action would improve the results.

For more detailed information, please consider the long version (online supplement).

Photoprotection

Protection from sunlight is an integral part of management of patients with AK. There are three components to photoprotection: behavioral modification by seeking shade during the peak UVB hours of 10AM to 2PM, wearing photoprotective outfit (including clothing, wide-brimmed hat and sunglasses) and application of broad spectrum sunscreens with SPF 30 or above. When available, UV index (low: 1-2, to extreme: 11+) can be used as a guide of photoprotection.

The beneficial effect of regular sunscreen application on a daily basis was demonstrated in various clinical trials: several trials provided evidence for a reduced incidence of new AK and a reduction of the total AK lesions count in the groups assigned to regular sunscreen application.[37-40] Furthermore, in one randomized trial, a reduced incidence of SCC in the group assigned to daily sunscreen use was shown during the course of the 4.5 year study[41] and during the 8 year follow-up, as compared to control, discretionary sunscreen use group.[42]

Discussion: Limitations, implications and future directions

For a more detailed discussion of limitations of the systematic literature assessment and the recommendations within these guidelines, please consider the long version (online supplement) or the results report of the guidelines (available at JEADV DOI: 10.1111/jdv.13179).

Due to possible efficacy and safety differences, patients with concomitant immunosuppression were assessed separately. This led to a very limited amount of available data for this patient subgroup. More trials assessing the efficacy and safety of interventions in immunosuppressed patients who have AK are needed. Similarly, data for patients with single AK lesions were very limited and the majority of recommendations for this population is therefore based on expert consensus and indirect evidence from data on patients with multiple AK lesions.

During the categorization of the studies with respect to study populations, studies that did not specify the enrolment of immunosuppressed patients were considered as enrolling immunocompetent participants, even though some of these studies did not contain immunosuppression as an exclusion criterion.

Participant's self-reported outcomes, such as the quality of life, are an increasingly significant concept of efficacy measures in dermatological studies.[43] The number of studies reporting on patient-reported outcomes that were included in this review was very limited. For further research within the field of AK treatment, patient-reported outcomes as part of the primary outcomes should be assessed.

Furthermore, the need for research including long-term efficacy data must be emphasized. Efficacy outcomes included in the systematic literature assessment were limited to six months after treatment to ensure comparability. This time frame was chosen by the expert panel because of the limited number of studies assessing long-term efficacy (e.g. one or two year clearance rates). Studies assessing the long-term efficacy of the different interventions are highly desirable.

The consensus conference was performed as an online conference. Using a questionnaire, participants were asked for their experiences during the conference. One participant reported problems with the online access during a period of the conference, impeding his participation. No further relevant problems were reported.[44]

Supporting material

Supporting material is available:

1.) Long version of the guidelines (online supplement): contains more detailed data on the goals, methodological and clinical background and the results of the guidelines development (available at JEADV DOI: 10.1111/jdv.13180)

2.) Methods and results report (available at JEADV DOI: 10.1111/jdv.13179): detailed description of the guidelines development process and methodology and comprehensive description of the results of the guidelines development including Summary of Findings tables

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