Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Ingenolmebutat

Stand: September 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Ingenolmebutat [topische Behandlung von aktinischen Keratosen] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	– 5 Fluorouracil (topisch) – Diclofenac-Hyaluronsäure-Gel Teilweise Übereinstimmung im Anwendungsgebiet: – 5 Fluorouracil plus Salicylsäure – Imiquimod – Aminolevulinsäure (im Rahmen einer PDT) – Methylaminolevulinat (im Rahmen einer PDT)
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	– chirurgische Exzision – Kryotherapie (Vereisung mit flüssigem Stickstoff) – Kürettage – Chemisches Peeling Keine Leistungspflicht der GKV: – Photodynamische Therapie (PDT) – Lasertherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 04.07.2013 zu Ingenolmebutat
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ibenolmebutat Picato® (D06 BX02)	Picato® ist indiziert für die topische Behandlung von nicht-hyperkeratotischen, nichthypertrophen Aktinischen Keratosen bei Erwachsenen. Aktinische Keratosen im Gesicht und auf Kopfhaut: Picato® 150 Mikrogramm/Gramm Gel Aktinische Keratosen am Rumpf und an den Extremitäten: Picato® 500 Mikrogramm/Gramm Gel
Diclofenac-Hyaluronsäure Solaraze 3%® Gel (D 11 A X 18)	Zur Behandlung von aktinischen Keratosen Die Anwendungsdauer beträgt normalerweise 60 bis 90 Tage. Die größte Wirkung wurde bei Behandlungszeiten am oberen Ende dieses Zeitraums beobachtet. Eine vollständige Heilung der Läsion(en) bzw. eine optimale therapeutische Wirkung kann unter Umständen erst in einem Zeitraum von 30 Tagen nach abgeschlossener Therapie eintreten. [Stand FI 01/2018]
5 Fluorouracil Efudix® Creme (L 01 B C 02)	Prämaligne Hautveränderungen wie aktinische Keratosen […] *Dauer der Anwendung* Efudix zweimal täglich in so ausreichendem Maße auftragen, dass die betroffenen Läsionen abgedeckt sind. Die Behandlung soll so lange fortgesetzt werden, bis die entzündliche Reaktion das Erosionsstadium erreicht hat. Dann soll die Anwendung von Efudix abgesetzt werden. Gewöhnlich dauert die Therapie bei aktinischen Keratosen 2 bis 4 Wochen. Eine vollständige Abheilung der Läsionen kann unter Umständen erst nach 1 bis 2 Monaten sichtbar werden. [Stand FI 02/2016]
5 Fluorouracil plus Salicylsäure Actikerall® Lösung (L 01 B C 52)	Actikerall wird zur topischen Behandlung leicht tastbarer und/oder mäßig dicker hyperkeratotischer aktinischer Keratosen (Grad I/II) bei immunkompetenten erwachsenen Patienten angewendet. Die Intensitätsstufe Grad I/II basiert auf der vierstufigen Skala von Olsen et al. (1991) *Dauer der Anwendung* Bereits nach sechs Wochen kann ein Ansprechen auf das Arzneimittel festgestellt werden. Dieses verstärkt sich im Laufe der Zeit. Daten liegen über die Behandlung für bis zu 12 Wochen vor. Eine vollständige Heilung der Läsion(en) oder die optimale therapeutische Wirkung kann möglicherweise erst bis zu acht Wochen nach Behandlungsende sichtbar sein […] [Stand FI 01/2017]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Imiquimod Aldara 5 % Crème (D 06 B B 10)	Imiquimod-Creme ist bestimmt für die topische Behandlung von: […] Klinisch typischen, nicht hyperkeratotischen, nicht hypertrophen aktinischen Keratosen (AKs) im Gesicht oder auf der Kopfhaut bei immunkompetenten Erwachsenen, wenn die Größe oder die Anzahl der Läsionen die Wirksamkeit und/oder die Akzeptanz einer Kryotherapie begrenzen und andere topische Behandlungsmöglichkeiten kontraindiziert oder weniger geeignet sind. *Dauer der Anwendung* Imiquimod-Creme soll 4Wochen lang jeweils dreimal wöchentlich (Beispiel: Montag, Mittwoch und Freitag) vor dem Zubettgehen aufgetragen und ca. 8 Stunden lang auf der Haut belassen werden. Es soll ausreichend Creme aufgetragen werden, um den Behandlungsbereich ganz zu bedecken. Nach einem vierwöchigen behandlungsfreien Zeitraum soll dann die Abheilung der AKs beurteilt werden. Wenn noch Läsionen vorhanden sind, soll die Behandlung weitere 4Wochen fortgesetzt werden. Die empfohlene Maximaldosis ist der Inhalt eines Beutels. Wenn im Behandlungsbereich keine vollständige Abheilung aller Läsionen bei der Kontroll-Untersuchung rund 8 Wochen nach dem letzten 4-wöchigen Behandlungszeitraum festgestellt wird, kann eine weitere 4-wöchige Behandlung mit Aldara Creme in Erwägung gezogen werden. Eine andere Behandlung wird empfohlen, wenn die behandelte(n) Läsion(en) unzureichendes Ansprechen auf Aldara zeigt bzw. zeigen. Aktinische Keratose Läsionen, welche nach einem oder zwei 4-wöchigen Behandlungszeitraumen abgeheilt waren, später aber wieder auftreten, können erneut, nach einer mindestens 12-wöchigen Behandlungspause, mit einem oder zwei weiteren 4-wöchigen Behandlungszeiträumen von Aldara Creme behandelt werden (siehe Abschnitt 5.1). [Stand FI 06/2018]
Imiquimod Zyclara 3,75 % Crème (D 06 B B 10)	Zyclara ist angezeigt für die topische Behandlung von klinisch typischer, nicht hyperkeratotischer, nicht hypertropher, sichtbarer oder tastbarer aktinischer Keratose (AK) im Gesicht oder auf der unbehaarten Kopfhaut bei immunkompetenten Erwachsenen, wenn andere topische Behandlungsmöglichkeiten kontraindiziert oder weniger geeignet sind. [Stand FI 02/2018]
Aminolevulinsäure Alacare® Pflaster (L 01 X D 04)	Einmalige Behandlung von leichten aktinischen Keratosen (AK) im Gesicht und auf der Kopfhaut (unbehaarte Bereiche) mit einem Durchmesser von maximal 1,8 cm. *Art und Dauer der Anwendung* Zur Behandlung von AK mit einer Sitzung photodynamischer Therapie (PDT) können dem Patienten bis zu sechs Alacare-Pflaster auf sechs verschiedene Läsionen in einer Therapie-Sitzung appliziert werden. [Stand FI 11/2015]
Aminolävulinsäure Ameluz® Gel (L 01 X D 04)	Behandlung aktinischer Keratosen leichter bis mittelschwerer Intensität im Gesicht und auf der Kopfhaut (Grad 1 bis 2 nach Olsen) *Art und Dauer der Anwendung*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Für die Behandlung von aktinischen Keratosen (AK) soll eine Sitzung der photodynamischen Therapie (mit Tageslicht oder Rotlichtlampe) für einzelne oder mehrere Läsionen oder ganze kanzerisierte Felder (Hautpartien, bei denen mehrere AK-Läsionen von einem begrenzten Areal mit aktinischen und sonnenbedingten Schäden umgeben sind) angewendet werden. Aktinische Keratoseläsionen oder Felder sollen drei Monate nach der Behandlung nachuntersucht werden. Behandelte Läsionen oder Felder, die nach 3 Monaten nicht vollständig abgeheilt sind, sollen erneut behandelt werden. […] [Stand FI 03/2018]
Methylaminolevulinat Metvix® (L 01 X D 03) (Synonym: Methyl (5-amino-4-oxopentanoat)	Behandlung von dünnen oder nicht-hyperkeratotischen und nicht-pigmentierten aktinischen Keratosen auf Gesicht oder Kopfhaut, wenn andere Therapien als weniger geeignet angesehen werden. Art und Dauer der Anwendung *AK […] unter Verwendung von Rotlicht* Zur Behandlung der Aktinischen Keratose (AK) sollte eine photodynamische Therapie- Sitzung durchgeführt werden. Die behandelten Läsionen sollten nach 3Monaten beurteilt werden. Bei unvollständigem Ansprechen kann eine zweite Therapie-Sitzung durchgeführt werden. *AK unter Verwendung von Tageslicht* Die Tageslichtbehandlung kann bei leichten bis mittelschweren AK-Läsionen angewendet werden. Es sollte eine Therapie-Sitzung durchgeführt werden. Die behandelten Läsionen sollten nach 3 Monaten beurteilt werden. Bei unvollständigem Ansprechen kann eine zweite Therapie-Sitzung durchgeführt werden. [Stand FI 03/2017]

Quellen: Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Ingenolmebutat

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	5. Juni 2018

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis 3
1 Indikation 4
2 Systematische Recherche 4
3 Ergebnisse 5
3.1 IQWiG Berichte/G-BA Beschlüsse 5
3.2 Cochrane Reviews 5
3.3 Systematische Reviews 5
3.4 Leitlinien 13
4 Detaillierte Darstellung der Recherchestrategie 20
Referenzen 22

Gemeinsamer Bundesausschuss

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
5-FU/SA	5-Fluorouracil/Salicylsäure
AK	Actinic Keratoses
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
c-PDT	Konventionelle PDT
DAHTA	DAHTA Datenbank
DHA	Diclofenac-Hyaluronsäure-Gel
DL-PDT	Tageslicht-PDT
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IMB	ingenol mebutate
IMI	Imiquimod
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	Keine Angabe
KI	Konfidenzintervall
LoE	Level of Evidence
MAL	Methylaminolevulinat
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PDT	Photodynamic Therapy
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

zur topischen Behandlung von aktinischen Keratosen bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation aktinische Keratosen durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 30.05.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 117 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 8 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2013 [3].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ingenolmebutat

Siehe auch IQWiG, 2013 [4].

Anwendungsgebiet

Picato® ist indiziert für die topische Behandlung von nicht-hyperkeratotischen, nichthypertrophen Aktinischen Keratosen bei Erwachsenen.

Zweckmäßige Vergleichstherapie

Diclofenac-Hyaluronsäure Gel (3 %) oder 5-Fluorouracil (5-FU) in der topischen Anwendung oder (chirurgische) Kryotherapie bei der Behandlung von Einzelläsionen.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Patel G et al., 2014 [5].

Efficacy of Photodynamic Therapy vs Other Interventions in Randomized Clinical Trials for the Treatment of Actinic Keratoses: A Systematic Review and Meta-analysis

Fragestellung

to determine the effectiveness of PDT for the treatment of AKs relative to other methods.

Methodik

Population:

- patients with a clinical and/or a histologic diagnosis of AK.

Intervention/Komparator:

- topical PDT compared with an alternative, non-PDT treatment.

Endpunkt:

- lesion resolution as part of their outcome measures and/or cosmetic outcomes after PDT relative to an alternative treatment.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Web of Knowledge, and Cochrane Central Register. No restrictions on years were placed, and all searches extended to the year of each database inception. Our search was conducted on March 20, 2013.

Qualitätsbewertung der Studien:

- Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 studies for inclusion in our final synthesis, of which 4 were eligible for final meta-analysis. The only comparator for which meta-analysis was performed was cryotherapy. The meta-analysis consisted of 641 participants, with a total of 2174 AKs treated with cryotherapy and 2170 AKs treated with PDT.

Qualität der Studien:

- The 13 identified studies received a Jadad score ranging from 1 to 3 (scores of 0-3 indicating poor methodologic quality; 4-5, good methodologic quality).

Studienergebnisse:

- Compared with cryotherapy, the pooled relative risk for the meta-analysis for complete response (lesion clearance) was 1.14 (95%CI, 1.11-1.18) at 3 months after treatment.
- Visual inspection of a funnel plot revealed no publication bias, which was confirmed by the Begg test (P = .80).

Anmerkung/Fazit der Autoren

For thin AKs on the face or scalp, PDT has a 14%better chance of lesion clearance compared with cryosurgery. Although not studied via meta-analysis, cosmetic outcomes after PDT were uniformly positive. Data regarding other comparators such as imiquimod, fluorouracil, and fractionated CO2 laser were more limited and prevented inclusion in our meta-analysis. Given that all of the studies included in our meta-analysis and in the cosmetic evaluations were unblinded, bias cannot be excluded.

Kommentare zum Review

- The primary deficits in quality were the lack of double-blind design and description of randomization methods.

Stockfleth E et al., 2016 [6].

New Topical Treatment Options for Actinic Keratosis: A Systematic Review.

Fragestellung

compare the relative safety and efficacy of 3 topical treatments for AK in a systematic review of randomised controlled trials (RCTs) of 5-FU/SA, IMI and IMB.

Methodik

Population:

- immunocompetent adults (≥ 18 years) diagnosed with grade I (slightly palpable, more easily felt than seen) or II (moderately thick hyperkeratotic, easily felt) AK (10) on the face, forehead and scalp

Intervention:

- 5-FU/SA

Komparator:

- standard of care, placebo/vehicle, all concentrations of IMB, 2.5%/3.75% IMI cream

Endpunkt:

- all outcomes of efficacy and safety were considered

Recherche/Suchzeitraum:

- between January 2011 and January 2014

Qualitätsbewertung der Studien:

- Cochrane methodology

Ergebnisse

Anzahl eingeschlossener Studien:

- Only 11 publications, relating to 7 randomised controlled

trialsQualität der Studien:

- All RCTs were double-blind. Overall, risk of bias in the included studies was mostly low or unclear.

Studienergebnisse:

- Note: It was only possible to compare the effect of all 3 treatments on complete clinical clearance, and the effect of 5-FU/SA and IMB on actinic keratosis recurrence rate.
- Despite a higher vehicle response rate for 5-FU/SA, complete clinical clearance was higher than IMB and IMI (55.4, 42.7, and 25.0/30.6%, respectively).
- 5-FU/SA was also associated with lower actinic keratosis recurrence rate than IMB at 12 months post-treatment (32.7 vs. 53.9%).

Anmerkung/Fazit der Autoren

Although qualitative assessment suggested a numerical advantage of 5-FU/SA over IMB and IMI in terms of complete clinical clearance and sustained clearance, clinical data from longer term trials, with comparable outcome measures, are required to corroborate these findings.

Tomás-Velázquez A et al., 2016 [7].

Switching From Conventional Photodynamic Therapy to Daylight Photodynamic Therapy For Actinic Keratoses: Systematic Review and Meta-analysis

Fragestellung

systematic literature review and performed a meta-analysis of the available evidence on the efficacy and safety of daylight PDT as compared to conventional PDT in the treatment of actinic keratosis and/or field cancerization.

Methodik

Population:

- in humans with AK

Intervention/Komparator:

- daylight PDT versus conventional PDT

Endpunkt:

- Primär: lesion response rate and pain caused by the procedure
- Sekundär: AK grade, other adverse effects, patient satisfaction, cosmetic results

Recherche/Suchzeitraum:

- The first search was done in June 2015. The same search strategy was repeated in December 2015.

Qualitätsbewertung der Studien:

- Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 randomized trials comparing daylight PDT to conventional PDT were included in this systematic review

Charakteristika der Population:

- These 3 all treated 2 symmetrical areas in the same patients (intra individual comparison) and used MAL as the photosensitizing agent. After application of MAL, daylight exposure of 1 of the areas started before 30 minutes had elapsed; exposure continued for 2 to 2.5 hours. On the comparator area, the photosensitizer was left incubating for3 hours, after which the skin was exposed to red light.

Qualität der Studien:

Table 2 Characteristics Found in the 3 Trials Selected.[a]

	Wiegell et al.[12]	Rubel et al.[19]	Lacour et al.[20]
Title and abstract			
Title. Structure and content of abstract			
Introduction			
Background and objectives			
Methods			
Inclusion criteria (trial participants)			
Description of interventions			
Variables specified a priori			
Assessment procedure explained			
Sample size			
Randomization process explained (sequence, blinding, implementation)			
Assignment masking			
Statistical analysis explained			
Results			
Flow chart (participants)			
Recruitment			
Baseline data			
Per-protocol and intention-to-treat analyses			
95% CIs reported			
Frequency and description of adverse effects			
Discussion			
Limitations			
Generalizability			
Interpretation			
Other			
Trial registration number			
Funding			

[a] Green filler indicates the information was given and was sufficient; blue, information given but was insufficient; red, information not given.

Studienergebnisse:

- Wiegell et al.12found that the 2 modalities had statistically similar levels of efficacy (P = .13) and saw that response to day light PDT did not vary with light intensity. Rubel et al., who established 20% as the margin of difference to demonstrate non inferiority, found that the rate of complete response to daylight PDT (89.2%) was not statistically inferior to the response to conventional PDT (92.8%)at 12 weeks (difference,---3.6%; 95% CI, −6.8% to −0.3%).Moreover, clearance was maintained by 96% of the mild lesions at 24 weeks. The findings of Lacour et al. were consistent with the other 2 trials. Using a non inferiority margin of 15%, they observed complete response rates of 70% for daylight PDT and 74% for conventional PDT (difference: 4%;95% CI, −9.5% to 2.4%). They also concluded that daylight PDT was effective in different weather conditions. Thus, daylight PDT is effective and not inferior to conventional PDT.
- Patient-Reported Pain: Pain was significantly greater in the area treated with conventional PDT (P < .0001) in the trial of Wiegell et al. although that result was unrelated to the level of PpIX fluorescence (P = .065), it was related to the effective light dose received (P = .041). Patients in the Australian19andEuropean20trials found daylight PDT to be nearly pain-less and certainly less painful than conventional PDT (P < .001).
- Adverse Effects: Wiegell et al. reported that erythema and crusts formed after both the daylight and conventional PDT treatments to a statistically similar degree and that the

effects did not differ between treatment areas in 38% of the patients. Adverse effects in the phase III trials were all dermatologic and mild. The most common effect was a skin rash, and in one of the trials 79% of patients treated with daylight PDT were not inconvenienced by any adverse effect. Thus, daylight PDT does not have adverse effects that cause discomfort to patients.

- Patient Satisfaction: Sixty-two percent of the patients treated by Wiegell et al. preferred daylight PDT. Satisfaction with this modality was also greater (P < .001) in the Australian trial. In the European trial, 64.8% of the patients were highly satisfied with daylight PDT (vs 18.9% with conventional PDT).
- Cosmetic Results: Cosmetic results after both treatment modalities were rated good or excellent by 90% to 99.7% of the patients in the 2phase III trials.

Meta-analysis

- We meta-analyzed the results of only the 2 phase III trials (N= 186 patients in the PP analysis and 208 in the ITT analysis
  - The difference between response rates (PP analysis) was 3.6% in the Australian trial19and 4% in the European20one.The global estimate of the mean response rate difference was −3.69% in favor of conventional PDT. Because the estimate of effect size in the Australian trial was closer to the estimated effect derived from meta-analysis, greater weight was assigned to this trial (77.02% vs 22.98% to the European trial). The I2test result was 0.0%, as heterogeneity was very low between the 2 trials, whose design and results were similar (Fig. 2). Therefore, we did not perform further measures of heterogeneity. The results of the ITT analysis were similar, yielding a global effect estimate of 3.4% in favor of conventional PDT.Thus, although conventional PDT is associated with higher response rates than daylight PDT, the difference is not clinically important, as it is less than the difference mar-gins (20% and 15%) established a priori. The 95% CIs of the global effect estimates ranged from −6.54% to −0.84% and−6.10% to −0.70% in the PP and ITT analyses, respectively. Therefore, daylight PDT can be considered non inferior to conventional PDT.

Anmerkung/Fazit der Autoren

Daylight PDT is not inferior to conventional PDT in the treatment of mild to moderate AK and field cancerization. The efficacy of this modality does not depend on weather conditions and has been applied at different latitudes. The procedure is practically painless, is better tolerated than conventional PDT, and does not have important adverse effects. Cosmetic outcomes are very good and patient satisfaction is high. Daylight PDT's profile of efficacy, tolerability and safety will probably make this modality a treatment of choice for AK and field cancerization.

Calzavara-Pinton P et al., 2016 [1].

Bucher's indirect comparison of daylight photodynamic therapy with methyl aminolevulinate cream versus diclofenac plus hyaluronic acid gel for the treatment of multiple actinic keratosis

Fragestellung

to conduct an adjusted indirect comparison between MAL DL-PDT and DHA, using MAL c-PDT as a common comparator. The outcome of interest was complete lesion response rate at 12 weeks.

Methodik

The Bucher et al. approach was used for the calculation of the indirect adjusted comparison. Odds-ratios (ORs) were used as a measure of treatment effect. → This method is usually considered as the approach with minimal bias, especially if the sample size is balanced across treatment arms. This method is recommended by IQWiG.

Population:

- Patients with AK

Intervention/Komparator:

- randomised controlled trials assessing at least two interventions of interest (i.e. MAL DL-PDT or MAL c-PDT and DHA) which the lesion

Endpunkt:

- complete lesion response rate at Week 12 for mild, moderate, and mild and moderate lesions; complete response was defined as the percentage of pre-existing and treated lesions at baseline that were considered to be cleared at Week 12

Recherche/Suchzeitraum:

- A systematic literature review was conducted to identify randomised controlled trials assessing at least two interventions of interest (Electronic searches were conducted in MEDLINE, MEDLINE-IN-PROCESS, EMBASE and the Cochrane CENTRAL registry of controlled trials

Qualitätsbewertung der Studien:

- The quality of each trial was assessed according to the tool recommended by IQWiG

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of three studies were included in the indirect comparison.

Qualität der Studien:

- COMET and COMET2 were multicentre, randomised, intra-individual phase III studies conducted in Australia and Europe, respectively. Patients were treated with MAL DLPDT on one side of the face or the scalp and MAL c-PDT on the contralateral side. The trial reported by Zane et al. were randomised with adequate randomisation (i.e.a computer-generated list), and were investigator-blinded. COMET and COMET2 involved a base case analysis conducted on the per protocol population (due to the non-inferiority analysis), leading to the exclusion of 8 and 12 patients, respectively, compared to the intention-to-treat analysis. In the Zane et al. publication, missing data were not adjusted, resulting in the exclusion of patients lost to follow-up (2/100 patients from the c-PDT arm and 0/100 patients from the DHA arm).

Studienergebnisse:

- Results of the indirect comparison between MAL DL-PDT and DHA for each type of lesion are summarised in figure 2.

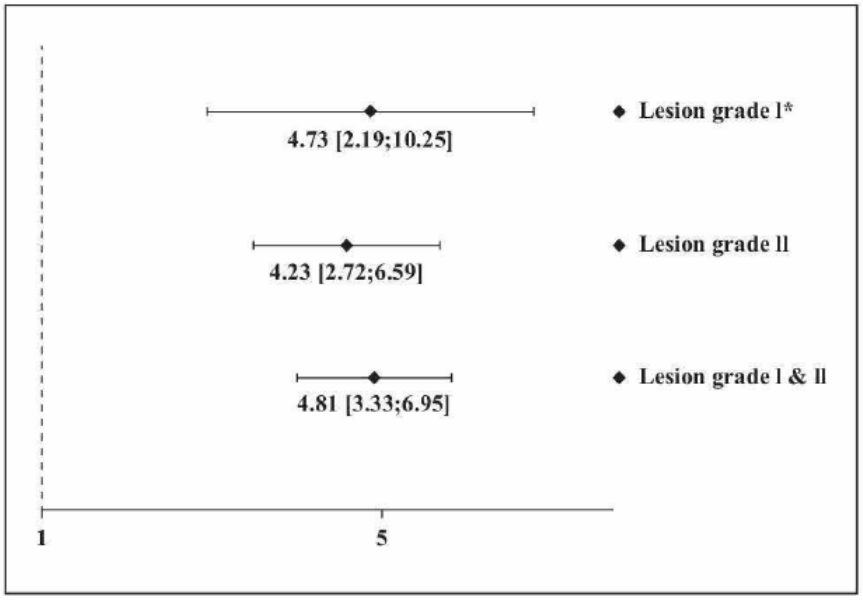

Figure 2. Forest plot for the indirect comparison of MAL DL-PDT vs DHA.
*OR based on Peto's method

- Peto's estimate was used in the Zane et al. study given that the MAL c-PDT arm was associated with zero mild lesions with non-complete response. All three types of lesions (mild, moderate, and mild and moderate lesions) treated with MAL DL-PDT were more than four times more likely to have a complete response than lesions treated with DHA at 12 weeks, with ORs ranging from 4.23 to 4.81. Results were all statistically significant.

Anmerkung/Fazit der Autoren

Finally, this study showed that MAL DL-PDT was significantly more effective than DHA at Week 12 in the treatment of AK on mild and moderate lesions, with ORs ranging from 4.23 to 4.81. Further research is needed to assess the long-term efficacy of these interventions (i.e. six months and beyond), as well as safety and patient-reported outcomes.

Kommentare zum Review

- Localisation of lesions was not reported in the publication by Zane et al. It was therefore not possible to adjust for this patient characteristic, which is a limitation of our analysis
- small number of publications with only one publication reporting a comparison between MAL c-PDT and DHA
- the indirect comparison was only conducted on efficacy endpoints (complete lesion response rate). Overall satisfaction outcome was not available in COMET and COMET2, and patient response outcome and overall cosmetic outcome were not comparable in the three studies

3.4 Leitlinien

De Berker D et al., 2017 [2].

British Association of Dermatologists'

British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017

Leitlinienorganisation/Fragestellung

to provide up-to-date, evidence-based recommendations for the management of actinic keratosis (AK).

Methodik

Grundlage der Leitlinie

Stakeholder involvement and peer review The Guideline Development Group (GDG) consisted of consultant dermatologists. The draft document was circulated to the BAD membership, the British Dermatological Nursing Group, the Primary Care Dermatological Society, the British Society for Skin Care in Immunosuppressed Individuals, and Age U.K. for comments. These comments were actively considered by the GDG, and peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to publication.

This set of guidelines has been developed using the BAD recommended methodology, with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument.

Recommendations were developed for implementation in the National Health Service (NHS) using a process of considered judgement based on the evidence. The PubMed, MEDLINE and EMBASE databases were searched for meta-analyses, randomized and nonrandomized controlled clinical trials, case series, case reports and open studies involving AK published in the English language from January 2004 to February 2016.

The full papers of relevant material were obtained. The structure of the 2007 guidelines was then discussed and re-evaluated, with headings and subheadings decided; different coauthors were allocated separate subsections. Each coauthor then performed a detailed appraisal of the selected literature with discussions within the GDG to resolve any issues. All subsections were subsequently collated and edited to produce the final guideline.

LoE

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a]
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal[a]
3	Nonanalytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

GoR

Class	Evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results, or Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.

Sonstige methodische Hinweise

- *This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines, and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English language references was a pragmatic decision, but the authors recognize this may exclude some important information published in other languages.*

Active treatments

All topical therapies for AK may result in side-effects of irritation. Some AKs proceed to ooze, crusting and soreness with local swelling. Details are cited in this guideline for the individual treatments and are included in the relevant PILs. It is important that the patient understands the extent of the area to be treated and anticipates the side-effects. The size of area will depend on a range of factors including the therapy, focal or scattered pathology and the conceptual model (field- or lesion-based treatment). Where morbidity is an ascendant concern, treatment should be initiated over a small area such as 4–10 cm2 with flexible frequency to establish tolerance and confidence. Some treatments define a ceiling of surface area based on the aliquot of prescribed item, for example one tube of ingenol mebutate is a single dose for 25 cm2. Imiquimod 5% is issued in 250-mg sachets where directions include ‘one sachet only’ and to ‘cover the area’ typically with a centimeter margin around any pathology. Others recommend a maximum based on toxicity, such as 500 cm2 for 5-FU 5%. Patients should be provided with advice on how to manage side-effects, with strategies including a break in treatment, altering the frequency of application, use of emollient and in some instances application of topical steroid.

Key recommendations: topical therapies

- Emollient and sunscreen with advice on sun protection might be a satisfactory treatment for people with fluctuating grade 1 AKs.
- Education at the outset of using active topical therapies is important to ensure a full understanding of how to apply treatment and the nature of the side-effects, which can be marked.

- Active topical therapy is suited to use in primary and secondary care. Where possible, a management plan should be formulated that enables the patient to be managed in primary care.
- Topical therapy is suited to use as lesion- and field based treatment. Where used for field treatment, the size of the field needs to be defined with the patient to ensure anticipation and tolerance of side-effects.
- Failure of an individual lesion to respond to topical therapy indicates a need for further evaluation. This may include referral from primary care to secondary care or surgery to obtain histology and extend treatment.

Empfohlene aktive Therapien ohne explizite Priorisierung:

- 5-Fluorouracil (strength of recommendation A, level of evidence 1++)
- Imiquimod 5% cream (strength of recommendation A, level of evidence 1++)
- Diclofenac gel (strength of recommendation A, level of evidence 1+)
- Ingenol mebutate cream (150 ug g-1 face and scalp, 500 ug g-1 limbs and trunk) (strength of recommendation A, level of evidence 1+)
- Topical retinoids (strength of recommendation B, level of evidence 1+)

Key recommendations: physical and systemic therapies

- Education at the outset of using physical therapies is important to ensure a full understanding of the side effects, which can be marked and include scarring and altered pigmentation.
- Cryosurgery is a flexible and effective form of lesion based physical therapy that removes the patient involvement in their own care and requires administration in a service with cryosurgery.
- Curettage can be warranted for thicker (grade 3) AKs, where they are resistant to topical therapy and where there is suspicion that they may represent early SCC. Histology must always be obtained. Diagnostic biopsy may be warranted on the same basis, but is subject to sampling error.
- PDT is an effective treatment for confluent AKs, such as on the scalp, which are difficult to manage or resistant to treatment in the absence of invasive disease.
- PDT has low scarring potential and less risk of poor healing in comparison with other physical therapies at vulnerable sites such as the lower leg.
- Pretreatment with topical therapy can increase the efficacy of physical therapies.
- Failure of an individual lesion to respond to physical therapy indicates a need for further evaluation. This could include formal excision.
- Systemic therapy is usually given in the context of multiple grade 3 AKs, a history of serial SCCs and immunosuppression. Therapy might be preventive with a retinoid and should be undertaken as part of a multidisciplinary decision, which might include alternatives such as the reduction of immunosuppression.
  - Cryosurgery (strength of recommendation A, level of evidence 1++)
  - Surgery: There are no trials of surgery for AKs
  - Systemic therapy (strength of recommendation C, level of evidence 2+)
  - Photodynamic therapy (strength of recommendation A, level of evidence 1+)
  - Laser therapy (strength of recommendation B, level of evidence 1+)

- Combination treatment (k.A.)

Werner R et al., 2015 [8].

International League of Dermatological Societies in cooperation with the European Dermatology Forum

Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum – Short version

Leitlinienorganisation/Fragestellung

The goal of these evidence- and consensus-based guidelines was the development of treatment recommendations appropriate for different subgroups of patients presenting with AK. A secondary aim of these guidelines was the implementation of knowledge relating to the clinical background of AK, including consensus-based recommendations for the histopathological definition, diagnosis and the assessment of patients.

Methodik

Grundlage der Leitlinie

The guidelines development followed a pre-defined and structured process. For the underlying systematic literature review of interventions for AK, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was adapted. All recommendations were consented during a consensus conference using a formal consensus methodology. Strength of recommendations was expressed based on the GRADE approach. If expert opinion without external evidence was incorporated into the reasoning for making a certain recommendation, the rationale was provided. The Guidelines underwent open public review and approval by the commissioning societies.

LoE/GoR

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.

Sonstige methodische Hinweise

- **Hinweis**! → These guidelines will expire on 31 July 2018. The ILDS will be responsible to initiate an update.

Treatment of patients with 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 CO_2-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 CO_2-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%
	↓	–	–		CO_2-laser, Er:YAG-laser

5-FU, 5-fluorouracil; AK, actinic keratosis; ALA-PDT, 5-aminolaevulinic acid photodynamic therapy; HA, hyaluronic acid; MAL-PDT, methylaminolevulinate photodynamic therapy.

*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 (haematological 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.

Table 8 Recommendations for patients who have single AK lesions

Intervention	Evidence/reasoning, see chapter (long version/results report)[1]	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*
0.5% 5-fluorouracil + 10% salicylic acid (discrete, hyperkeratotic lesions)†	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

AK, actinic keratosis; ALA-PDT, 5-aminolaevulinic acid photodynamic therapy; MAL-PDT, methylaminolevulinate photodynamic therapy.
*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.
†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)[1]	Strength of the recommendation	Percentage of agreement
For patients who have multiple AK lesions/field cancerization, we recommend using (↑↑) . . .			
0.5% 5-fluorouracil	8.5/4.5	↑↑	≥50*
3.75% 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†
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‡
0.5% 5-fluorouracil + 10% salicylic acid (discrete, hyperkeratotic lesions)§	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¶
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

AK, actinic keratosis; ALA-PDT, 5-aminolaevulinic acid photodynamic therapy; MAL-PDT, methylaminolevulinate photodynamic therapy.
*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.
†Experts who did not agree voted for making a weak recommendation (↑) for the use of imiquimod in patients with multiple lesions or field cancerization.
‡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.
§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.
¶Experts who did not agree to this recommendation voted for making no recommendation (0) for the use of CO_2 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)[1]	Strength of the recommendation	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*	8.9/4.9	↑	≥50†
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

AK, actinic keratosis; ALA-PDT, 5-aminolaevulinic acid photodynamic therapy; MAL-PDT, methylaminolevulinate photodynamic therapy.
*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 (haematological 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.
†Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% imiquimod in immunosuppressed patients.
[1]The long version of the guidelines is available as online supplement, the results report has been published at JEADV DOI: 10.1111/jdv.13179

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.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 29.05.2018

#	Suchfrage
1	MeSH descriptor: [Keratosis, Actinic] explode all trees
2	(actinic or solar* or senil* or (non next hyperkeratotic) or nonhyperkeratotic or (non next hypertrophic) or nonhypertrophic):ti,ab,kw (Word variations have been searched)
3	(keratos* or keratoma* or hyperkeratos* or cheilitis):ti,ab,kw (Word variations have been searched)
4	#2 and #3
5	#1 or #4
6	#5 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 29.05.2018

#	Suchfrage
1	actinic keratosis[MeSH Terms]
2	"Actinic cheilitis" [Supplementary Concept]
3	(((((actinic[Title/Abstract]) OR solar*[Title/Abstract]) OR senil*[Title/Abstract])) OR (non-hyperkeratotic[Title/Abstract] OR nonhyperkeratotic[Title/Abstract])) OR (non-hypertrophic[Title/Abstract] OR nonhypertrophic[Title/Abstract])
4	(((keratos*[Title/Abstract]) OR keratoma*[Title/Abstract]) OR hyperkeratos*[Title/Abstract]) OR cheilitis[Title/Abstract]
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#7) AND ("2013/05/01"[PDAT] : "3000"[PDAT])

Gemeinsamer Bundesausschuss

Leitlinien in Medline (PubMed) am 29.05.2018

#	Suchfrage
1	actinic keratosis[MeSH Terms]
2	"Actinic cheilitis" [Supplementary Concept]
3	(((((actinic[Title/Abstract]) OR solar*[Title/Abstract]) OR senil*[Title/Abstract])) OR (non-hyperkeratotic[Title/Abstract] OR nonhyperkeratotic[Title/Abstract])) OR (non-hypertrophic[Title/Abstract] OR nonhypertrophic[Title/Abstract])
4	(((keratos*[Title/Abstract]) OR keratoma*[Title/Abstract]) OR hyperkeratos*[Title/Abstract]) OR cheilitis[Title/Abstract]
5	(#3) AND #4
6	((#1) OR #2) OR #5
7	"Precancerous Conditions"[Mesh:NoExp]
8	((((((((((((((((((((((precancer*[Title/Abstract]) OR praecancer*[Title/Abstract]) OR pre-cancer*[Title/Abstract]) OR prae-cancer*[Title/Abstract]) OR premalignan*[Title/Abstract]) OR praemalignan*[Title/Abstract]) OR pre-malignan*[Title/Abstract]) OR prae-malignan*[Title/Abstract]) OR preneoplas*[Title/Abstract]) OR praeneoplas*[Title/Abstract]) OR pre-neoplas*[Title/Abstract]) OR prae-neoplas*[Title/Abstract]) OR pretumour*[Title/Abstract]) OR praetumour*[Title/Abstract]) OR pre-tumour*[Title/Abstract]) OR prae-tumour*[Title/Abstract]) OR pretumor*[Title/Abstract]) OR praetumor*[Title/Abstract]) OR pre-tumor*[Title/Abstract]) OR prae-tumor*[Title/Abstract]) OR precursor[Title/Abstract]) OR praecursor[Title/Abstract]) OR pre-cursor[Title/Abstract]) OR prae-cursor[Title/Abstract]
9	(#7) OR #8
10	(cutaneous[Title/Abstract]) OR skin[Title/Abstract]
11	(#9) AND #10
12	(#6) OR #11
13	(#12) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
14	(#13) AND ("2013/05/01"[PDAT] : "3000"[PDAT])

Referenzen

1. **Calzavara-Pinton P, Zane C, Pacou M, Szeimies RM.** Bucher's indirect comparison of daylight photodynamic therapy with methyl aminolevulinate cream versus diclofenac plus hyaluronic acid gel for the treatment of multiple actinic keratosis. Eur J Dermatol 2016;26(5):487-492.
2. **De Berker D, McGregor JM, Mohd Mustapa MF, Exton LS, Hughes BR.** British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. Br J Dermatol 2017;176(1):20-43.
3. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ingenolmebutat vom 4. Juli 2013 [online]. Berlin (GER): G-BA; 2013. [Zugriff: 30.05.2018]. URL: https://www.g-ba.de/downloads/39-261-1764/2013-07-04_AM-RL-XII_Ingenolmebutat_BAnz.pdf.
4. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Ingenolmebutat - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-04 [online]. Köln (GER): IQWiG; 2013. [Zugriff: 30.05.2018]. (IQWiG-Berichte; Band 158). URL: https://www.iqwig.de/download/A13-04_Ingenolmebutat_Nutzenbewertung_%2035a_SGB_V.pdf.
5. **Patel G, Armstrong AW, Eisen DB.** Efficacy of photodynamic therapy vs other interventions in randomized clinical trials for the treatment of actinic keratoses: a systematic review and meta-analysis. JAMA Dermatol 2014;150(12):1281-1288.
6. **Stockfleth E, Sibbring GC, Alarcon I.** New Topical Treatment Options for Actinic Keratosis: A Systematic Review. Acta Derm Venereol 2016;96(1):17-22.
7. **Tomás-Velázquez A, Redondo P.** Switching From Conventional Photodynamic Therapy to Daylight Photodynamic Therapy For Actinic Keratoses: Systematic Review and Meta-analysis. Actas Dermosifiliogr 2017;108(4):282-292.
8. **Werner RN, Stockfleth E, Connolly SM, Correia O, Erdmann R, Foley P, et al.** Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. J Eur Acad Dermatol Venereol 2015;29(11):2069-2079.