

SPECIAL REPORT

New Topical Treatment Options for Actinic Keratosis: A Systematic Review

Eggert STOCKFLETH¹, Gillian C. SIBBRING² and Ivette ALARCON³

¹Direktor der Universitätsklinik St. Josef-Hospital, Bochum, Germany, ²Complete Clarity, Macclesfield, UK, ³Melanoma Unit, Department of Dermatology, Hospital Clinic of Barcelona, Barcelona, Spain

This systematic review compared the relative efficacy of 5-fluorouracil 0.5% in salicylic acid 10% (5-FU/SA), ingenol mebutate (IMB) and imiquimod 2.5%/3.75% (IMI) for actinic keratosis on the face, forehead or scalp. Only 11 publications, relating to 7 randomised controlled trials, met inclusion criteria and 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, 42.2, and 25.0–30.6/34.0–35.6%, 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%). 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. Key words: 5-fluorouracil; salicylic acid; imiquimod; ingenol mebutate; sustained clearance; skin cancer.

Accepted Jun 8, 2015; Epub ahead of print Jun 12, 2015

Acta Derm Venereol 2016; 96: 17–22.

Ivette Alarcon, Melanoma Unit, Department of Dermatology, Hospital Clinic of Barcelona, Villarroel 170, ES-08036 Barcelona, Spain. E-mail: ivette.alarcon13@gmail.com

Actinic keratosis (AK) can be a biological marker of an increased rate of non-melanoma skin cancer (1) and reflects some morphological and histological features of invasive squamous cell carcinoma (SCC) (2, 3). AK could be considered a very early stage of cancer or carcinoma *in situ*, since the majority of invasive SCCs arise from AK (4). AK is confined to the epidermis, whereas an invasive SCC extends more deeply into the dermis. Thus, to limit the morbidity and mortality associated with invasive SCC, treatment of AK is generally recommended in clinical guidelines (4–8). Symptoms of AK can include bleeding and pain (7). A number of treatment options are available for the treatment of AK including surgical procedures, cryotherapy, laser therapy, and topical treatments such as diclofenac/hyaluronic acid, 5-fluorouracil (5-FU), and imiquimod 5% (IMI,

Aldara®), and the newer topical treatments such as 5-FU 0.5% in salicylic acid 10% (5-FU/SA, Actikerall®), IMI 2.5%/3.75% (Zyclara®) and ingenol mebutate (IMB, Picato®). Each of the topical treatment options vary in their dosing, efficacy and safety (7).

To date there have been no direct head-to-head comparisons of the newer topical treatments indicated for AK: 5-FU/SA, IMB and IMI. Therefore, an indirect comparison of the relative safety and efficacy of these treatments could be extremely helpful in informing prescribing decisions. The overall objective of this project was therefore to 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.

METHODOLOGY

Eligibility criteria

Inclusion/exclusion criteria. The inclusion criteria for the systematic review conformed to the following PICOS description (9); namely, studies meeting the following criteria were considered for inclusion:

- Patients: 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
- Comparator: standard of care, placebo/vehicle, all concentrations of IMB, 2.5%/3.75% IMI cream
- Outcome(s): all outcomes of efficacy and safety were considered
- Study type(s): RCTs, systematic reviews and meta-analyses of clinical studies in patients with AK.

Studies investigating patients who received treatment on areas other than the face, forehead and scalp, sequential treatment or combination therapy, more than one previous treatment for hyperkeratosis, or any other previous treatment were excluded.

Systematic literature search

RCTs, systematic reviews and meta-analyses in patients with AK, published between January 2011 and January 2014, were retrieved by conducting a systematic search of The Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and BIOSIS (limited to the previous 3 years) on 29th January 2014, using EBSCO (11) to search the Cochrane databases and ProQuest (12) to search all other databases. Additional trials were identified by

reviewing the reference lists of published systematic reviews and meta-analyses identified in the search. In addition, searches of the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites, and conference websites for the British Association of Dermatologists, American Academy of Dermatology, European Society for Dermatological Research and British Society for Medical Dermatology, were conducted on 7th February 2014 to identify abstracts published in the last two years.

A comprehensive search string was developed, including both indexed and free terms for actinic keratosis and all proprietary and generic names of the drug therapies of interest, as well as specific filters for retrieving RCTs, meta-analyses and systematic reviews.

English language restrictions were not applied to the search; where an English language abstract was available, the abstract was screened. Reference Manager Software (version 11.0) was used to store and organise the retrieved studies.

Study selection, data extraction and critical appraisal

Publications that did not exhibit one or more of the inclusion criteria were excluded from the review. Studies for which there was insufficient information for exclusion remained in the review until it was confirmed that they did not meet the inclusion criteria (positive exclusion).

A first-pass checklist was applied to the titles and abstracts (if available) of all publications identified by the search. A second-pass checklist was then applied to the full-text publications meeting the inclusion criteria.

The studies eligible for data extraction underwent critical appraisal to assess whether they represented robust sources of information for subsequent statistical or qualitative analyses. Since the review followed Cochrane methodology, quality assessment was conducted using the Cochrane Collaboration 'Risk of bias' assessment tool (13). Furthermore, the results of the quality assessments conducted in the current study were compared and validated against those for trials included in the Cochrane review of interventions for AK (7).

The screening, data extraction and critical appraisal were conducted by two reviewers working independently. Any disagreements or inconsistencies were resolved through discussion until consensus was reached.

RESULTS

Literature searches

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (14) diagram (Fig. S1¹) shows the total number of papers identified during the literature search, and details the exclusion of papers at each stage of the screening process. A total of 481 articles were identified, 437 of which were unique.

Relevant data were only available in 11 publications, which related to 7 RCTs reporting data on the head region (10), details of which are grouped by active treatment in Table S1¹ (15–25). Where the same data were presented in more than one publication for a given study, data were extracted from the full publication; only additional data not presented in the full publica-

tion were extracted from associated abstracts, posters and presentations.

One publication was excluded as it was a duplicate of a study already identified (7). Another was excluded as the majority of data it presented were duplicated in another study and any unique data that were presented could not be compared with the data presented in other included studies owing to differences in outcome definitions (26). A further 6 reports were excluded as they were superseded by publications that contained more detailed reporting of the data (27–32).

Quality assessment

Studies from which data were extracted were assessed for robustness as sources of information using the Cochrane Collaboration 'risk of bias' assessment tool (13). All RCTs were double-blind. Overall, risk of bias in the included studies was mostly low or unclear. Quality assessment of studies for which data were extracted indicated 3 studies that represented high-quality or robust sources of information (17, 18, 21, 22), as they were deemed to be of high quality by the majority of quality assessment criteria. However, at least one 'unclear' rating was awarded for each of these studies, which could indicate that the level of reporting was not sufficient to determine an accurate assessment of robustness. Three studies, one IMB and two IMI, were assessed as displaying a 'high risk of bias' according to the risk of bias assessment tool (19, 20, 23). A single study was deemed to have mostly 'unclear' ratings, which prevented useful interpretation of the data (15). However, since so few studies meeting the inclusion criteria were identified, none was excluded from the review on the grounds of poor study quality.

Characteristics of the included studies

Study populations. Details of reported patient baseline characteristics from the 11 included studies are grouped by active treatment and presented in Table SII¹ (15–25). The age range of the patients was similar for studies investigating IMB and IMI (63–70 years), but slightly higher for the 5-FU/SA study (> 70 years). In all studies that reported ethnicity, most patients were White or Caucasian and there was a similar ratio of male:female patients with a higher proportion of males (> 70%). Fitzpatrick skin type was similar for patients receiving all treatments, with approximately 50–63% of patients being type I or II and 37–50% of patients being type III or IV. However, the inclusion criteria for the 5-FU/SA studies specified skin type I–IV (Table S1¹) (17, 22) and all patients had skin types I–IV in the IMB studies (15, 16, 18, 21, 23–25), whereas 2–4% of patients included in the IMI studies had Fitzpatrick skin type V (19, 20). Furthermore, the 5-FU/SA study was the only one to specify that AK should be histo-

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2167>

logically confirmed and clinically classified as grade I (mild intensity) or II (moderate intensity) according to Olsen et al. (10) (Table SI¹) (15–25).

Whilst the eligibility criteria for this systematic review specified AK on the face, forehead and scalp, the included studies separated patients into different categories. Studies of 5-FU/SA separated patients with AK on the face or forehead, on the scalp, or on the scalp and face, whereas the IMB and IMI studies separated patients with AK on the face or on the scalp.

Patients with hypertrophic or hyperkeratotic lesions were excluded from the IMB studies reported by Lebwohl et al. (18, 25) and Berman et al. (24), and patients with markedly hyperkeratotic lesions were excluded from the IMB study reported by Siller et al. (21). In the IMI studies, patients with visible or palpable AKs were included and patients with atypical lesions (e.g., > 1 cm²) were excluded (19, 20). The 5-FU/SA study was the only one identified that specifically included patients with hyperkeratotic AK lesions (17, 22).

Treatments. Of the 11 reports, 2 studied 5-FU/SA, 7 studied IMB and 2 studied IMI. However, a variety of drug concentrations and treatment regimens were used. 5-FU/SA is a combination of 0.5% 5-FU with 10% SA, and this was used in the RCT and follow-up study. IMB and IMI were used at a range of concentrations (IMB: 0.0025, 0.005, 0.01, 0.015 or 0.05%; IMI: 2.5 or 3.75%). Whilst all treatments were applied once daily, 5-FU/SA was applied for a maximum of 12 weeks, IMB for 2 or 3 days and IMI for two 2-week cycles separated by a 2-week no-treatment interval or for two 3-week cycles separated by a 3-week no-treatment interval. The licensed dose for IMB is 0.015% once daily for 3 days and for IMI is 2.5% or 3.75% once daily for two 2-week cycles separated by a 2-week no-treatment interval (33, 34).

There were also differences in the excipients of the vehicles between treatments (35–38). The 5-FU/SA vehicle included dimethyl sulfoxide (DMSO), ethanol, ethyl acetate, pyroxyline, polybutylmethacrylate or methylmethacrylate, all of which were absent in the vehicles for IMB and IMI. IMB and IMI vehicles both contained benzyl alcohol and purified water, but all other excipients differed between the two treatments (35–37).

Of the 11 reports, 9 studying 5-FU/SA or IMB restricted the treatment area to 25 cm² or less (15, 17, 18, 24), whereas in the two reports investigating IMI the treatment area was greater than 25 cm² (19, 20, 26), as specified in the summary of product characteristics (35–37).

Outcome parameters

The majority of studies reported ‘complete clearance’ of AK lesions as a primary outcome or, more specifically, complete clinical clearance (18–20, 23–26), complete histological clearance (22) or sustained clinical

clearance (for follow-up studies) (16, 17). The 5-FU/SA study was the only one to report complete histological clearance as a primary outcome (22).

There were some differences between definitions of the outcomes reported between the studies. However, the following outcomes were identified that could be compared with those reported for other studies.

Complete clinical clearance

Five papers reported data relating to the number of patients with complete clinical clearance of AK lesions at the end of the study period (18–20, 22, 23). These 5 studies included data for 5-FU/SA, IMB and IMI. However, Spencer (23) (investigating IMB) only presented *p*-values for the comparison between different treatment arms rather than patient numbers. There was some variation in trial duration and treatment regimen. Data were reported for 5-FU/SA at 8 weeks post-treatment, whereas for IMB data were reported at 8–12 weeks post-treatment and for IMI at 8 weeks post-treatment. Differences in the duration of the follow-up period were due to variation in the typical time taken for resolution of skin reactions between the 3 products.

Sustained clinical clearance

The two follow-up studies investigating 5-FU/SA and IMB reported sustained clinical clearance of AK that was cleared in the original study and remained clear after a further 12 months (16, 17). However, Lebwohl et al. (16) reported the number of patients who achieved sustained clearance of the entire treatment area, whereas Stockfleth et al. (17) reported the total number of sustained cleared lesions in all patients.

Comparison of complete clinical clearance

Complete clinical clearance was statistically significantly superior for 5-FU/SA, IMB and IMI compared to their respective vehicle controls (18–20, 22).

It was not possible to perform statistical indirect comparisons of the data for complete clinical clearance between treatments due to differences in study design, population, treatment duration and vehicle composition. However, a qualitative comparison was conducted, which showed that, despite a higher vehicle response rate for 5-FU/SA (15.1% for 5-FU/SA vs. 3.8% for IMB and 5.5–6.3% for IMI), the complete clinical clearance was greater for 5-FU/SA (55.4% vs. 15.1% for vehicle) than for IMI (25.0–35.6% vs. 5.5–6.3% for vehicle) or IMB (42.2% vs. 3.7% for vehicle), although the difference was smaller (Table SIII¹) (18–20, 22).

Comparison of sustained clinical clearance

Data for sustained clinical clearance were only collected in the 5-FU/SA and IMB studies. However, the

data were reported differently in each of the long-term follow-up studies (Table SIV¹) (16, 17). However, inspection of a further report for the IMB study included in this systematic review (18) referred to a conference abstract in October 2011 (39) which reported the number of patients for whom one or more lesions developed or recurred in the treatment area 12 months after the end of study (Table SV¹) (39). Unpublished data from a clinical trial of 5-FU/SA were scrutinised and comparable data were found (Almirall. Data on file. 2014).

The recurrence rate reported for patients 12 months after end of study for 5-FU/SA was 32.7%, whilst the recurrence rate for IMB was 53.9% (Table SV¹).

DISCUSSION AND CONCLUSIONS

This systematic review identified 11 articles reporting 7 RCTs investigating the use of 5-FU/SA, IMB and IMI in the treatment of AK on the face, forehead and scalp (Table SI¹) (10, 15–25). Three key studies (18, 20, 22) (one of which was a pooled analysis) were identified that utilised the licensed dose for each treatment.

Despite the small number of included studies and other limitations, qualitative comparisons were made between all 3 treatments for complete clinical clearance and for recurrence of lesions after completion of treatment. Overall, 5-FU/SA and IMB appear to result in a more favourable complete clinical clearance rate than IMI, although the effect on complete clinical clearance was slightly greater for 5-FU/SA compared to IMB. The 5-FU/SA study included patients with hyperkeratotic lesions who were not included in either the IMB or IMI studies. Hyperkeratotic AK are more severe, with a potentially higher rate of malignant transformation (40, 41). The higher rate of complete clinical clearance seen in patients treated with 5-FU/SA than in those treated with IMB is therefore pertinent given the inclusion of higher-risk patients in the study population. A comparison of the data for 5-FU/SA and IMB suggests that 5-FU/SA is associated with a lower AK recurrence rate at 12 months than IMB (32.7% vs. 53.9%) and may therefore have a greater long-term clinical benefit.

The quality assessment identified the IMI studies as displaying ‘a high risk of bias’ according to the Cochrane Collaboration risk of bias assessment tool; however, due to the lack of available studies meeting the inclusion criteria, data were nevertheless extracted from these reports and included in the analysis. A major limitation of this review was the lack of studies meeting the inclusion criteria; however, this is a reflection of the paucity of data available on topical AK treatments. There were differences in baseline characteristics between the studies, and trial duration and follow-up varied. Moreover, there was also a wide range of outcomes measured in the different trials.

For example, the 5-FU/SA study was the only one to report the number of patients with complete histological clearance as a primary outcome (22). In this study, 5-FU/SA was superior to vehicle and diclofenac treatments ($p < 0.0001$ and $p < 0.01$, respectively). A study of IMB also reported data for complete histological clearance as a secondary outcome (21) but there was no statistically significant difference in complete histological clearance rate between the treatment groups. This was not a primary or secondary outcome in the pivotal studies of IMB or IMI (18–20, 24, 25). In the 5-FU/SA study, one lesion was biopsied pre-treatment and a second clinically identical, predefined lesion was biopsied post-treatment. In contrast, in the IMB study, the same AK lesion was biopsied pre- and post-treatment, which may have affected the observed histological clearance rate (21). Data for IMB were obtained from studies that used an unlicensed dose. For the reasons detailed above, clinically meaningful comparisons cannot be made between these data.

A number of definitions were utilised for outcomes relating to partial AK lesion clearance including median percentage change or reduction in AK lesion count, reduction in mean number of lesions per patient, mean reduction in lesion area, and number of patients achieving $\geq 75\%$ or $\geq 80\%$ clearance. This presented difficulties when attempting to compare outcomes between studies. Accordingly, since it was unclear whether differences were calculated based on the total lesion count for the population of patients, or on a per patient lesion count, this outcome was not analysed.

Treatment regimens and study duration also varied, with adverse events (AEs) reported at different time points in each study. Furthermore, there were no data for the vehicle arm for this outcome in the 5-FU/SA study (22). Two studies investigating 5-FU/SA and IMB reported the number of patients experiencing treatment-emergent AEs (18, 22). However, differences in treatment regimens, study durations, vehicle excipients and incidence thresholds complicate comparisons between treatments. It is unclear whether the 5-FU/SA study reported the number of patients experiencing a treatment-emergent AE, or the number of events. Five reports investigating IMB reported data on application-site reactions (ASRs) but these were not classified as treatment-related (18, 21, 23–25). In the IMB studies, local skin responses (LSRs) were measured using a separate, active assessment and were not recorded as application-site AEs. Thus, whilst treatment-emergent application-site AEs were reported, these did not include LSRs, which diluted the overall incidence rate of application-site AEs (42). ASR and LSR data were not comparable due to the varied ways in which they were reported. Differences in vehicle composition precluded comparisons of AE data, including ASRs,

for the different interventions. The differences between the excipients in each of the vehicles for the different studies could negate clinically meaningful comparisons; for example excipients such as DMSO and ethanol in the vehicle for 5-FU/SA may cause skin reactions that prevent meaningful comparisons from being drawn (43). These uncertainties and complications made analysis of AE-related outcomes impossible with the available published data.

Importantly, the data in the IMB study were non-comparative since only patients who achieved complete clinical clearance when treated with IMB in the initial randomised studies were enrolled in the follow-up study. It was therefore not possible to assess the long-term effect of vehicle on recurrence rates. Patients who did not achieve complete clearance and were excluded from the follow-up study may be considered at a higher risk of progression to cancer. Since AK is a chronic disease and there is a risk of progression to invasive SCC (2, 3), it is important that therapies are as effective as possible in order to reduce this risk and this should be addressed in long-term studies of potential treatment options.

There are limited published data comparing topical treatments for AK, and no comparisons involving all of the treatments included in this systematic review. Our search identified 6 systematic reviews that presented data for 5-FU/SA, IMB or IMI (7, 44–48), of which just two included data for all of the treatments but neither drew any comparisons between them (46, 47). The systematic review reported by Ghuznavi et al. (47) did not seek to make any indirect comparisons but merely summarised the available data for the current and emerging treatments for AK. In addition, the systematic review by Nashan et al. (46) concluded that there is no best practice to treat AK but did show that combined therapies and newer options resulted in incremental progress in AK treatment. They reported that, despite limited evidence, it is to be expected that 5-FU/SA offers comparable therapeutic efficacy to 5-FU but with the benefit of fewer AEs. They also reported that the limited evidence suggested that IMI 2.5% resulted in a lower complete clearance rate than IMI 5% but there was too little evidence to draw this conclusion for the 5% and 3.75% formulations. No comparisons were made between IMB and other treatments. Moreover, Nashan et al. highlighted several limitations of studies conducted in AK and underlined the problems associated with comparing clinical outcomes, including the incomparable nature of histological and clinical results, observer variations between dermatologists, short-term results leading to an overestimation of treatment benefit, and clinical variability of AKs and different locations of AKs leading to different response rates (46).

Further to these systematic reviews, Gupta and colleagues have published a comprehensive Cochrane systematic review (7) and subsequent meta-analysis (44) of

interventions for AK. It is of note that these publications did not include 5-FU/SA or IMI 2.5%/3.75%; however, the authors did rank the two other 5-FU formulations (5-FU 5.0% and 5-FU 0.5%) first in terms of complete clearance, ahead of IMI 5%, IMB, 5-aminolaevulinic acid, cryotherapy, 3% diclofenac in 2.5% hyaluronic acid, methyl aminolaevulinate and photodynamic therapy. The authors warned that their ranking should be interpreted with caution due to the possibility that the result was influenced by factors such as baseline severity and bias, which were difficult to assess due to the variability in definitions and parameters used to describe AK severity.

Gupta et al. (7) did note, however, that poorer efficacy was not systematically associated with increased severity at baseline, while increased efficacy was not associated with milder disease at baseline. This is a pertinent outcome given our finding that 5-FU/SA was associated with the highest rate of complete clearance despite having patients with greater disease severity at baseline, which suggests that treatment efficacy in AK may be independent of disease severity.

It is important to mention here that the Cochrane review and meta-analysis faced similar limitations to our systematic review, namely a lack of similar outcomes, variability in the reporting of outcomes, differences in outcome definitions and variable follow-up assessment timings. With regard to bias, the authors of the meta-analysis noted that the higher ranking therapies in terms of complete clearance typically carried increased risk of bias, with the exception of cryotherapy, and suggested this as a reason to approach their ranking with caution; however, they did affirm that this ranking was generally consistent with the conclusions of the pairwise analyses of the Cochrane review (7).

Further studies utilising comparable outcomes validated by clinical experts are required in patients with AK to understand which of these treatments may be most likely to be associated with complete and sustained clearance of lesions. Such studies will help corroborate findings from the trials identified in this systematic review. There is also a need for a more standardised approach to conducting clinical trials in AK to facilitate indirect comparisons, for example, definitions of standard outcome measures, patient baseline characteristics and treatment duration could be facilitated by FDA or EMA guidance on conducting clinical trials for novel AK treatments; however, to date such guidance does not exist. To gain a deeper understanding of the differences between treatment options and to inform therapeutic guidelines, there is a need for clinical trials that directly compare topical treatments for AK. Furthermore, more clinical data in general for topical treatments of AK, including longer-term trials, greater than one year, are required to address the lack of data identified in this systematic review.

ACKNOWLEDGEMENTS

We acknowledge Tom Morrish and Jane A. Moorhouse (Complete Clarity) for conducting the systematic literature review and preparing the manuscript and K. Ian Johnson (Complete Clarity) for preparation and critical appraisal of the manuscript.

Conflicts of interest: ES received honorarium from Almirall S.A. for his clinical expert opinion during the conduct of the systematic review. He is a co-author of studies identified as part of this systematic review.

TM, JAM, GCS and KIJ were employees of Complete Clarity at the time the study was undertaken, a company sponsored by Almirall S.A. to conduct this study and prepare the manuscript.

IA received honoraria from Almirall S.A. as a scientific advisor at the time the study was undertaken.

Funding. The study was funded by Almirall S.A., who commissioned Complete Clarity to undertake the systematic review and prepare the manuscript.

Ethics, Consent and CONSORT. This review is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

REFERENCES

- Ramsay HM, Fryer AA, Hawley CM, Smith AG, Nicol DL, Harden PN. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. *J Am Acad Dermatol* 2003; 49: 397–406.
- Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma (“actinic keratosis”). *J Am Acad Dermatol* 2000; 42: 11–17.
- Feldman SR, Fleischer AB, Jr. Progression of actinic keratosis to squamous cell carcinoma revisited: clinical and treatment implications. *Cutis* 2011; 87: 201–207.
- Guideline Subcommittee “Actinic Keratoses” of the European Dermatology Forum. Guideline on Actinic Keratosis. Available from: <http://www.euroderm.org/index.php/edf-guidelines>.
- de Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratoses. *Br J Dermatol* 2007; 156: 222–230.
- Del Rosso JQ. Current regimens and guideline implications for the treatment of actinic keratosis: proceedings of a clinical roundtable at the 2011 Winter Clinical Dermatology Conference. *Cutis* 2011; 88: Suppl 1–8.
- Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database Syst Rev* 2012; 12.
- Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H. Development of a treatment algorithm for actinic keratoses: a European Consensus. *Eur J Dermatol* 2008; 18: 651–659.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.
- Olsen EA, Abernethy ML, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. *J Am Acad Dermatol* 1991; 24: 738–743.
- EBSCO. Available from: <http://www.ebscohost.com/>.
- ProQuest Dialog. Available from: <http://search.proquest.com/>.
- Higgins JPT, Green S. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
- Weiss J, Zibert JR. Measurement of patient satisfaction and the characterization of application-site pain with ingenol mebutate 150mcg/g gel in patients treated on the face or scalp. *J Dtsch Dermatol Ges* 2013; 11: 946–947.
- Lebwohl M, Shumack S, Stein Gold L, Melgaard A, Larson T, Tying SK. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. *JAMA Dermatol* 2013; 149: 666–670.
- Stockfleth E, Zwingers T, Willers C. Recurrence rates and patient assessed outcomes of 0.5% 5-fluorouracil in combination with salicylic acid treating actinic keratoses. *Eur J Dermatol* 2012; 22: 370–374.
- Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. *N Engl J Med* 2012; 366: 1010–1019.
- Hanke CW, Beer KR, Stockfleth E, Wu J, Rosen T, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. *J Am Acad Dermatol* 2010; 62: 573–581.
- Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol* 2010; 62: 582–590.
- Siller G, Gebauer K, Welburn P, Katsamas J, Ogbourne SM. PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. *Australas J Dermatol* 2009; 50: 16–22.
- Stockfleth E, Kerl H, Zwingers T, Willers C. Low-dose 5-fluorouracil in combination with salicylic acid as a new lesion-directed option to treat topically actinic keratoses: histological and clinical study results. *Br J Dermatol* 2011; 165: 1101–1108.
- Spencer J. Multicenter, randomized, double-blind, vehicle-controlled, dose-ranging study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel 0.005%, 0.01%, and 0.015% when used to treat actinic keratoses on the head (Poster P2913). 68th Annual Meeting of the American Academy of Dermatology, Miami, FL, USA, 2010 Mar 5–9.
- Berman B, Marmur E, Larsson T, Melgaard A. Three-day topical treatment with ingenol mebutate gel 0.015% for actinic keratoses on the face and scalp: analysis of data pooled from two trials (Poster P5623). 70th Annual Meeting of the American Academy of Dermatology, San Diego, CA, USA, 2012 Mar 16–20.
- Lebwohl M, Swanson N, Kobayashi K, Melgaard A. Local skin responses associated with ingenol mebutate gel for the treatment of actinic keratosis: two analyses of pooled data (Poster P4997). 70th Annual Meeting of the American Academy of Dermatology, San Diego, CA USA, 2012 Mar 16–20.
- Swanson N, Smith CC, Kaur M, Goldenberg G. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: two phase 3 multicenter, randomized, double-blind, placebo-controlled studies. *J Drugs Dermatol* 2013; 12: 1278–1282.
- Gupta A, Paquet M. Mixed treatment comparisons meta-analysis of interventions for actinic keratosis. *J Am Acad Dermatol* 2013; 68: AB162.
- Berman B, Melgaard A, Marmur E, Larsson T. Three-day

- topical treatment with ingenol mebutate gel, 0.015% for actinic keratoses on the face and scalp: Analysis of data pooled from two trials. *J Am Acad Dermatol* 2012; 66: AB3.
29. Leibold M, Melgaard A, Kobayashi K, Swanson N. Local skin responses associated with ingenol mebutate gel for the treatment of actinic keratosis: Two analyses of pooled data. *J Am Acad Dermatol* 2012; 66: AB153.
 30. Stockfleth E, Ulrich M, Kerl H, Willers C. Long-term sustained efficacy of low dose 5-fluorouracil combined with 10% salicylic acid as a lesion directed treatment for actinic keratoses. *Melanoma Res* 2011; 21: e53.
 31. Gupta AK, Villanueva E, Brintnell W, Paquet M. Interventions for actinic keratosis: a Cochrane review (Poster). 70th Annual Meeting of the American Academy of Dermatology, San Diego, CA, USA, 2012 Mar 16–20.
 32. Gupta AK, Paquet M. Mixed treatment comparisons meta-analysis of interventions for actinic keratosis (Poster). 71st Annual Meeting of the American Academy of Dermatology, Miami, FL, USA, 2013 Mar 1–5.
 33. European Medicines Agency. Assessment Report Picato. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002275/WC500135329.pdf.
 34. European Medicines Agency. Assessment Report Zyclara. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002387/WC500132263.pdf.
 35. European Medicines Agency. Zyclara Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002387/WC500132261.pdf.
 36. European Medicines Agency. Picato Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002275/WC500135327.pdf.
 37. European Medicines Consortium. Actikerall Summary of Product Characteristics. Available from: <http://www.medicines.org.uk/emc/medicine/24614/SPC/Actikerall%205mg%20g%20+%20100mg%20g%20Cutaneous%20Solution/>.
 38. Scottish Medicines Consortium. Actikerall advice document. Available from: http://www.scottishmedicines.org.uk/files/advice/fluorouracil_and_salicylic_acid_Actikerall_FINAL_September_2011_for_website.pdf.
 39. Swanson N, Stein Gold L, Larsson T, Melgaard A. Long-term follow-up studies of ingenol mebutate gel for the treatment of actinic keratosis. Fall Clinical Dermatology Las Vegas, NV, USA, 2011 Oct 27–30.
 40. Quaedvlieg PJ, Tirsi E, Thissen MR, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? *Eur J Dermatol* 2006; 16: 335–339.
 41. Suchniak JM, Baer S, Goldberg LH. High rate of malignant transformation in hyperkeratotic actinic keratoses. *J Am Acad Dermatol* 1997; 37: 392–394.
 42. US Food and Drug Administration. Center For Drug Evaluation and Research. Medical Review. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202833Orig1s000MedR.pdf.
 43. Swanson BN. Medical use of dimethyl sulfoxide (DMSO). *Rev Clin Basic Pharm* 1985; 5: 1–33.
 44. Gupta AK, Paquet M. Network meta-analysis of the outcome ‘participant complete clearance’ in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *Br J Dermatol* 2013; 169: 250–259.
 45. Gupta AK, Paquet M. Ingenol mebutate: a promising treatment for actinic keratoses and nonmelanoma skin cancers. *J Cutan Med Surg* 2013; 17: 173–179.
 46. Nashed D, Meiss F, Müller M. Therapeutic strategies for actinic keratosis – a systematic review. *Eur J Dermatol* 2013; 23: 14–32.
 47. Ghuznavi N, Nocera NF, Guajardo AR, Weinberg JM. Emerging medical treatments for actinic keratoses, squamous cell carcinoma and basal cell carcinoma. *Clin Invest* 2012; 2: 909–921.
 48. García C. Imiquimod in cutaneous oncology. *Dermatologia Revista Mexicana* 2009; 53: 167–172.