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Treatment of Actinic Keratosis: Does Effectiveness Depend on the Location?

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This is a comment on a network meta-analysis that evaluated the ranking of treatments for actinic keratosis outside the head and neck. The results of a limited number of heterogeneous studies contrast with the results of studies in the head and neck area. The extent to which these results can be generalized to larger treatment fields or areas with extensive field cancerization is uncertain.

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In the recently published review by Steeb et al. (2020), the currently available evidence on interventions for actinic keratosis (AK) in nonscalp and nonface localizations was systematically analyzed using network meta-analysis (NMA). Steeb et al. (2020) synthesized the limited and heterogeneous evidence and concluded that the most effective treatments in nonscalp and nonface localizations are cryosurgery, ingenol mebutate, or photodynamic therapy (PDT). The assumption was made that the anatomical site is an important

factor to consider for clinical decision making. Most available studies investigating the treatments of AK have focused on lesions in the head and neck area. Studies comparing different treatments in nonscalp and nonface locations are limited in number, and the meta-analysis included 13 such studies. Cryosurgery was independently ranked highest for the endpoints participant complete clearance rate and lesion-specific clearance rate, suggesting its high efficacy for AK in nonscalp and nonface localizations.

“Whether the results of a network meta-analysis that evaluated a few studies about the treatments of actinic keratosis (AK) outside the head and neck will guide decisions on optimal care more effectively than contradicting the results of studies evaluating AK treatment in the head and neck area will require further study.”

Cryosurgery was also superior to PDT regarding the participant complete clearance rate, whereas no significant difference with ingenol mebutate was observed. Treatment with 5-fluorouracil (5-FU) cream seemed to be less effective than with PDT and ingenol mebutate.

These results contrast sharply with those from a recently published trial with a head-to-head comparison of the four most frequently used field-directed treatments for AK in the head and neck area (Jansen et al., 2019). After 1 year of follow-up, treatment with 5% 5-FU cream was significantly more effective than ingenol mebutate, 5% imiquimod cream, and PDT. This difference in study results is remarkable and raises some questions.

The first question is whether or not the assumption underlying the NMA that lesions in the nonscalp and nonface areas are usually more difficult to treat than AK on the scalp and face is valid. This assumption is based on the clinical perspective of the authors and two references to studies in which AKs of the hands were treated in a small number of patients (Hashim et al., 2016; Kohl et al., 2017). Hashim et al. (2016) included hypertrophic AK, of which treatment can be challenging also on other body sites. In the trial by Jansen et al. (2019), it was found that grade III lesions were associated with lower rates of treatment success. However, most importantly, the studies referred to by Steeb et al. (2020) gave no information as to whether the effectiveness of the studied treatments differed for AK lesions on other body areas. The hypothesis that the effectiveness of a treatment depends on the location of AK on the body is interesting, but it needs to be corroborated by convincing evidence. In this respect, it is unfortunate that studies comparing treatments of AK in the head and neck area were excluded from this meta-analysis. It would have been interesting to know whether the ranking of treatments in the subgroup of studies on AK in the head and neck area is indeed different from the ranking that was established for the subgroup of

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studies on AK outside the head and neck area.

The second question is why the results of the NMA are so different from the results of the recent randomized controlled trial of [Janssen et al. \(2019\)](#) for the treatment of AK in the face and scalp. The authors explain the differences between the results of the NMA and this trial by arguing that the baseline number of lesions in the primary studies of the NMA was lower and that the presence of field cancerization was poorly reported. They acknowledge that there was also much variation in types of lesions, locations, and endpoints, which may have biased the results. They also indicate that their results may not be fully generalizable to larger treatment fields or areas with extensive field cancerization. However, what is the value of an NMA, on the basis of a limited number of heterogeneous studies, on the effectiveness of treatment of AK outside the head and neck area? The NMA included 13 studies, 11 of which investigated PDT. The high number of PDT trials may reflect the influence of industry on the current literature. The evidence of nonindustry-sponsored studies is very sparse. Regarding the PDT studies, almost none used the same protocol. In three trials included in the NMA, two PDT sessions were given, which is allowed in clinical trials, but it is not standard care. It should be noted that other treatments are usually not repeated in trials. For example, in the trial by [Perret et al.](#), also included in the NMA, PDT was compared with 5-FU in seven immune-suppressed patients with nonscalp and nonface AKs, and although two sessions were allowed for PDT, 5-FU was given for only 3 weeks. In the trial by [Jansen et al. \(2019\)](#), not 3 but 4 weeks of treatment was the standard for 5-FU cream, and all treatments could be repeated, which allows for a fairer comparison.

The results of the NMA indicate superior effectiveness of cryotherapy. This lesion-directed treatment may be very effective to achieve complete

clearance in solitary or a few AK lesions, but for patients with multiple lesions in extended areas, it is challenging to achieve complete clearance of all the lesions. In addition, lesions can be clinically invisible in an area of field cancerization and may require treatment later. In these cases, it seems more realistic to use field-directed treatments with the aim to reduce the number and severity of lesions but also to treat those clinically invisible lesions, postponing the need for retreatment. In the NMA, three studies were included in which cryotherapy was compared with PDT ([Kaufmann et al., 2008](#); [Robert, 2012](#); [Szeimies et al., 2002](#)). These studies, of which one has not been published, had very small sample sizes, and follow-up duration was short ([Kaufmann et al., 2008](#); [Szeimies et al., 2002](#)).

Considering the limitations of the NMA, we are now confronted with the question of how we should interpret the results of the NMA favoring cryosurgery, ingenol mebutate, or PDT for AK in nonscalp and nonface localizations. In our opinion, the NMA represents an interesting exploration and summary of the results of studies on AK outside the face and neck areas. However, we do not share the view that there is already firm evidence that these AKs respond differently to specific treatments from the AK lesions in the face and neck areas. We think that the inferences that can be made from this NMA on which treatment is optimal for AK lesions outside the face and neck areas are limited. However, we agree that high-quality research is needed to provide convincing evidence about the comparative effectiveness of field-directed treatment of AK lesions at sites other than the face or scalp. Definite evidence should come from a randomized trial comparing frequently used treatments of AK lesions in various regions. It should enable fair comparison by the use of optimal dosing schedules for all treatments and AK locations. A preplanned subgroup analysis can then be performed

to evaluate whether the ranking of treatments depends on the location of AK lesions. The detection of significant differences between subgroups with sufficient power requires a large sample size, and this can be challenging.

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CONFLICT OF INTEREST

The authors state no conflicts of interest.

REFERENCES

- Hashim PW, Nia JK, Singer S, Goldenberg G. An investigator-initiated study to assess the safety and efficacy of ingenol mebutate 0.05% gel when used after cryosurgery in the treatment of hypertrophic actinic keratosis on dorsal hands. *J Clin Aesthet Dermatol* 2016;9:16–22.
- Jansen MHE, Kessels JPHM, Nelemans PJ, Kouloubis N, Arits AHMM, van Pelt HPA, et al. Randomized trial of four treatment approaches for actinic keratosis. *N Engl J Med* 2019;380:935–46.
- Kaufmann R, Spelman L, Weightman W, Reifenberger J, Szeimies RM, Verhaeghe E, et al. Multicentre intraindividual randomized trial of topical methyl aminolaevulinatophotodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. *Br J Dermatol* 2008;158:994–9.
- Kohl E, Popp C, Zeman F, Unger P, Koller M, Landthaler M, et al. Photodynamic therapy using intense pulsed light for treating actinic keratoses and photoaged skin of the dorsal hands: a randomized placebo-controlled study. *Br J Dermatol* 2017;176:352–62.
- Robert C. Análise comparativa entre terapia fotodinâmica com ácido 5-aminolevulínico versus crioterapia no tratamento da queratose actínica: estudo prospectivo randomizado. 2012. 86 f. Dissertação (mestrado) - Universidade Estadual Paulista, Faculdade de Medicina de Botucatu. <http://hdl.handle.net/11449/88076>; 2012 (accessed September 28, 2017).
- Steeb T, Wessely A, Schmitz L, Heptt F, Kirchberger MC, Berking C, et al. Interventions for actinic keratosis in nonscalp and nonface localizations: results from a systematic review with network meta-analysis. *J Invest Dermatol* 2021;141:345–54.
- Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinatate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002;47:258–62.