The interpretation of clinical studies on the photodynamic treatment of actinic keratosis

Interpretation klinischer Studien zur photodynamischen Therapie der aktinischen Keratose

Abstract

Actinic keratosis is one of the most commonly treated skin conditions. A number of studies have recently been published on the treatment of this ailment using photodynamic therapy. The authors of this letter are concerned about the interpretation of some of these studies and would like to outline possible misinterpretations which may arise due to an incomplete analysis of the study reports available. Clearly, the "ideal" therapy for actinic keratosis should be a carefully chosen compromise between undesired side-effects and therapeutic efficacy and needs to be based on a consideration of all of the relevant clinical studies.

Keywords: dermatology, actinic keratosis, 5-aminolaevulinic acid, methyl-5-aminolaevulinate, photodynamic therapy, light sources

Zusammenfassung

Aktinische Keratosen gehören zu den meistbehandelten Hautschäden. Eine Reihe der in den letzten Jahren veröffentlichten Studien beschäftigte sich mit ihrer Behandlung durch photodynamische Therapie. Die Bewertungen einiger dieser Studien veranlassten die Autoren dieses Briefes, mögliche Missinterpretationen der Daten herauszustellen, die infolge unvollständiger Analyse der einbezogenen Studienberichte und unvollständiger Berücksichtigung ihrer Randbedingungen auftreten können. Unbestritten ist dabei, dass die „ideale" Therapie der aktinischen Keratose ein sorgfältig abgewogener Kompromiss zwischen therapeutischer Wirkung und unerwünschter Nebenwirkung sein muss, der auf der Berücksichtigung aller relevanten klinischen Studien und ihrer Randbedingungen basiert.

Schlüsselwörter: Dermatologie, aktinische Keratose, 5-Aminolävulinsäure, Methyl-5-aminolevulinat, photodynamische Therapie, Lichtquellen

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Letter

In the outpatient setting, actinic keratosis is one of the most commonly treated skin conditions, the prevalence of which increases with cumulative skin exposure and increasing age. Rates of 11–25% have been reported in the northern hemisphere and of 40–60% in Australia [1]. Actinic keratoses are strong predictors of squamous cell carcinomas and are believed to be precursors of squamous cell carcinomas of the skin [1]. This condition therefore presents a growing public health problem.

A number of studies have been published recently concerning modalities of photodynamic therapy (PDT) treatment for actinic keratosis in which the efficacy of several photosensitisers and/or light sources were compared [2], [3], [4], [5]. The most recent of these is the study by Dirschka and colleagues [5] which appeared recently in the British Journal of Dermatology and in which a gel formulation of 5-aminolaevulinic acid (BF-200 ALA) was found to be superior to methyl-5-aminolaevulinate (MAL). In the same study, the narrow-band light sources were found to be more effective than the broad-band light sources, although the narrow-band sources were associated with a higher occurrence and severity of adverse effects, which included pain, burning, erythema and exfoliation, irrespective of the photosensitizer used. While such a multicenter, randomized study is to be commended, the authors – in our opinion – failed to appropriately consider their findings in the light of previous studies, since a number of pertinent and highly relevant articles

were not mentioned. An important study in this context is the study by von Felbert and colleagues [2] with a longer follow-up time of 12 months (compared to 12 weeks in the study of Dirschka et al. [5]) and in which the use of narrow-band and broad-band sources were found to be equally effective. One reason given by von Felbert and colleagues [2] for the comparable efficiency of these sources was the use of a more advanced and efficient broad-band optical filter (in comparison to the broad-band sources used in previous studies). Dirschka et al. [5] however, not only failed to discuss reasons for the differences between the narrow-band and broad-band types of sources used, but also did not comment on the differences found between the various types of broad-band sources employed. Additionally, despite the findings of von Felbert et al. [2] who found the use of a broad-band source with water filter to be associated with less pain than that caused by a narrow-band source, and a study by Apalla et al. [6] who found the use of a broad-band source without a water filter to be associated with pain, Dirschka and colleagues did not consider the fact that broad-band sources would result in absorption over a broader spectral range (and possibly encompassing several maxima) of the photosensitizer as has been discussed previously [7]. Additionally, previous studies in which no differences were found between narrow- and broad-band sources [1], [8], [9] were not considered. Their study also demonstrated that the conditions under which PDT was applied had a pronounced impact on the efficiency of the treatment. For MAL, the von Felbert study [1] also found considerably higher response rates (80% total clearance) as compared to the Dirschka et al. [5] study in which a clearance rate of 64.2% was obtained. Possible reasons for such a pronounced difference between the response rates in these two studies were however not discussed by Dirschka and colleagues [5]. While the extent of pain experienced during photodynamic therapy (which is deemed to be the main side-effect of PDT [6], [7]) was documented by Dirschka et al. [5], possible reasons for the greater incidence of pain during the use of the narrow-band sources were not considered. In the Dirschka et al. study, a comparison of the photosensitizers used showed BF-200 ALA to be superior to MAL, but again, a study with contradictory findings (Gholam et al. [3]) is not discussed. While we do not wish to infer that the study performed by Dirschka and colleagues is in any way erroneous, we would nevertheless like to point out that the discussion of the results and the authors' selection of cited literature appears to be biased towards studies supporting the authors' own findings. The problem of such a bias has recently been outlined [10], together with the need for an up-to-date selection of literature and the recommendation that a concealment of contradictory or critical literature should be avoided. As a result of the rather selective choice of literature provided and the lack of a thorough consideration of the relevant studies already published, the article by Dirschka and colleagues [5] leaves a number of questions unanswered. Furthermore, the corresponding editorial published in the same issue of the British Journal of Dermatology [11] is unfortunately also based on the acceptance of the "superiority" of BF-200 ALA in comparison to MAL as well as the "superiority" of narrow-band in comparison to broad-band sources and fails to address the fact that several other studies have found contradictory results. Certainly, sweeping statements claiming e.g., narrow-band sources to be preferable to broad-band sources or BF-200 to be better than MAL should not be made on the basis of a single study, especially since such statements may lead to rapid and ungrounded propagation of therapeutic protocols.

In conclusion, it would appear that the last word concerning the optimal photosensitizer and radiation source for the treatment of actinic keratosis has not yet been spoken. Obviously, the "ideal" therapy for actinic keratosis should be a carefully chosen compromise between undesired side-effects and therapeutic efficacy and needs to be based on a consideration of all of the relevant clinical studies.

Notes

Competing interests

The authors declare that they have no competing interests.

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