Treatment of actinic keratoses: Why, when and how?

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For more than a century, it has been the conviction of dermatologists that actinic keratosis is a precancerous condition. Only recently, the thinking about actinic keratoses is beginning to change, those lesions now being increasingly considered as the earliest visible pattern of squamous cell carcinoma.[1-4]

However, the idea that actinic keratosis is itself a squamous cell carcinoma, is not new. It was in the 1930s, that Richard L. Sutton Jr.[5,6] wrote *"They [actinic keratoses] are called precancerous lesions; they are, in fact, cancerous already, early, superficial and requiring time to manifest those characteristics of cancer with which all clinicians are familiar, but cancerous nevertheless."*[5] In the last decade, A. B. Ackerman and co-workers clarified the nature of actinic keratoses through numerous articles.[7-12] They emphasized that actinic keratosis fulfills histopathologic criteria for an early squamous cell carcinoma because (1) it is made up of epithelial cells that have crowded, large and pleomorphic nuclei, some of which are in mitosis, (2) its cells have an acidophilic cytoplasm in sections of tissue stained by hematoxylin and eosin, (3) epithelial cells show signs of faulty cornification in the form of dyskeratotic cells and parakeratosis, (4) no boundary has been established histopathologically for separating actinic keratosis, with certainty from so-called invasive squamous cell carcinoma.[7-12]

Slowly, the concept of actinic keratosis being a squamous cell carcinoma is beginning to take hold in the brains of dermatologists, dermatopathologists and pathologists. Of course, changing concepts of diseases almost invariably have implications for the treatment of these conditions. The concept that actinic keratosis is a very early squamous cell carcinoma implies that these lesions have to be treated either by removal or by destruction and that their early treatment is preferable to "wait and see". Therefore, it is not surprising that during the last years research has been devoted to new therapeutic strategies for actinic keratoses and that new medications and procedures have been made available to dermatologists in the daily practice. What follows is a brief summary of all these options of treatment.

For most actinic keratoses, *curettage* or *shave excision* is a very effective treatment. Especially for hyperplastic types of actinic keratosis, shave excision is a valuable tool because the tissue removed can be examined by microscopy. The cosmetic result is usually good, but sometimes, shave excisions or curettings might heal with a delled or hypopigmented scar. Another treatment modality is cryotherapy, which is cheap, easy to perform and efficacious, but bearing the risk of persistent hypo- or depigmentation. Ablative laser systems such as Carbon dioxide laser or Erbium:YAG laser have replaced the curette and scalpel in some private practices of dermatology and they may also be used to remove actinic keratoses,

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but ablative laser systems remove tissue by destruction and no viable tissue is sampled for microscopic examination. Ablative laser systems share with curettage and shave excision a small risk of scarring and of hyper- or hypopigmentation. Topical treatment with 5-fluorouracil is a very efficient therapy with good cosmetic results, but patients always suffer from heavy inflammation and in many cases from pain in the treated skin area.[13] Combination of 5-fluorouracil with isotretinoin given orally shortens the duration of treatment considerably.[14] Diclofenac, an inhibitor of cyclo-oxygenase I and II, can be used topically for treatment of very early, i.e., flat, actinic keratoses, but it must be applied for several months.[15] The exact mechanism of action of topical diclofenac in the treatment of actinic keratoses is not known but it has been proposed that the development of actinic keratosis is linked to elevated prostaglandins.[16] It is not very effective, however, in advanced lesions as reported in a study by Fariba *et al*.[17] Imiquimod is an immune response modifier that activates pro-inflammatory cytokines. Administered three times a week overnight, it induces an inflammatory reaction that may cause complete resolution of actinic keratoses.[18] The treatment usually lasts for three to six weeks with severe inflammatory reaction, but cosmetic results are excellent. Photodynamic therapy with methyl-(5-amino-4-oxopentanoat) aminolevulinate cream and red light is another treatment modality that selectively destroys neoplastic keratinocytes.[19] The procedure is quite painful but it allows both, early and advanced, as well as sub-clinical lesions to be treated effectively. The inflammatory response is often heavy but heals within several days or a few weeks with very good cosmetic results.

In sum, noninvasive options for the treatment of actinic keratoses have increased notably. When in times past the question was whether actinic keratoses needed any treatment, the considerations of a dermatologist today are about which treatment to apply for a particular patient and at which time. All of the modalities currently available have advantages and disadvantages. A big plus of operative treatments such as shave or curettage is that tissue can be sampled for microscopic examination, that procedure decreasing the risk of insufficient treatment of invasive squamous cell carcinoma. All topical treatments, no matter whether 5-fluorouracil, imiquimod, diclofenac or photodynamic treatment have in common that they may be inadequate when a lesion is more invasive than suspected on clinical inspection. When lesions are numerous, however, operation may be impossible. Topical medications such as diclofenac, 5-fluorouracil, imiquimod or photodynamic treatment are a major improvement in handling these patients. Cosmetic results of all treatments are more or less comparable.

In our own practice we have developed a pragmatic approach to the treatment of actinic keratoses. Our decision regarding which treatment to use in a particular patient not only takes into account the stage of development of an individual lesion, i.e., early flat lesions or advanced elevated, markedly keratotic ones, but also the number and the site of lesions and the individual situation of the patient biologically, socially and professionally. If lesions are few, we prefer to remove them by shave excision. If lesions are many and flat, we use diclofenac in very early stages and 5-fluorouracil or photodynamic treatment in later stages. If lesions are well advanced and numerous, we perform photodynamic treatment if a patient has limited time. If a patient has no time constraints and is not bothered by several weeks of inflamed skin, we use 5-fluorouracil or imiquimod.

A *caveat* should be added in regard to all these options for treatment considering the increasing demand for evidence-based medicine. Even though many of the rather new topical treatments for actinic keratoses are used frequently in the practices of dermatologists every day, the evidence as to which treatment really is the best for which lesion in which patient is sparse. Comparative and comparable studies on the various topical agents currently available are needed to determine, with surety, the most effective treatment for actinic keratoses in order to develop evidence-based guidelines for dermatologists in clinic and practice.

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