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REVIEW

The Role of Ingenol Mebutate in the Treatment of Actinic Keratoses

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ABSTRACT

Actinic keratoses (AK) are the most common premalignant pathology seen in dermatological practice and represent a burgeoning burden upon health services. Increasingly recognized is the damage to surrounding, perilesional skin, forming the premise for field-directed therapy. Ingenol mebutate gel is a novel agent for field-directed treatment of AK, requiring only 2 or 3 days of application. Following an overview of existing treatment modalities, the authors review recent trials and safety data pertaining to the use of ingenol mebutate gel and discuss its role in the treatment of AK.

Keywords: Actinic keratosis; Field-directed therapy; Ingenol mebutate

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ACTINIC KERATOSES: A BURGEONING BURDEN

Actinic keratoses (AK), also known as solar keratoses, are the most common premalignant dermatological presentation [1, 2]. Increasing exposure to ultraviolet (UV) rays compounded by an aging population, has caused the prevalence of these lesions to be increasing worldwide, reported as being 11–25% across all age groups [3], rising to 34% among men over the age of 70 years [4] and 60% in those over the age of 40 years living in Australia [5]. They are a particular health risk in those with susceptible Fitzpatrick skin types 1 and 2, as they will incur enough sun exposure in normal everyday life to cause AK [2]. Other than genetic susceptibility, risk factors for the development of AK include age, UV radiation, gender (with men being more commonly affected [6]), as well as

immunosuppression, notably in organ transplant recipients [7, 8].

Following an overview of the treatment modalities currently available, this review focuses upon recent phase 3 trials of ingenol mebutate and discusses its future potential for treatment of AK.

PRECANCEROUS NATURE OF THE DISEASE

AK has been considered by some authors to be one end of a carcinogenesis continuum, as early squamous cell carcinoma (SCC) in situ with the potential to progress to invasive SCC [9–11]. Approximately 10% of patients with AK will eventually develop invasive SCC, rising to 40% in immunocompromised patients [12, 13]. Certain genetic conditions, including albinism and xeroderma pigmentosum, also impart a greater risk [14]. Furthermore, it has been shown that the relative risk of SCC increases with the number of AK lesions with an increase from 1% in those with fewer than five lesions to 20% in those with more than 20 [15], thus forming the premise for implementing field therapy in the treatment of multiple AK [6, 16].

METHODS

The authors performed a specific search on MEDLINE, using search terms "PEP005," "ingenol mebutate," and "ingenol-3-angelate." Additional sources of evidence included systematic reviews on AK published since 2000, identified on MEDLINE using the term "actinic keratosis," "actinic keratoses," "solar keratosis," and "solar keratoses." The authors also scrutinized citation lists from retrieved articles.

TREATMENT OPTIONS AND COMPLIANCE

Uncertainty persists as to whether AK should be treated and if so, their optimal management. The 2007 British Association of Dermatologists (BAD) guidelines recommend that, if there is little concern and the patient is not troubled by the lesion, no medical treatment is necessary [8]. This is based on evidence by Harvey et al. showing that 21% of AK resolved spontaneously over a 12-month period. Additionally, there is a low rate of malignant transformation, with less than one in 1,000 per annum reported in some studies [6, 16, 17].

There are several options available for the treatment of AK. There is some evidence that the application of sun block twice daily for 7 months is desirable as a preventative measure for the development of AK [18]. Similar daily application has also demonstrated a reduced incidence of SCC [15]. Emollient use alone is also a reasonable treatment option though it is likely to be managing the clinical symptoms of mild AK rather than reversing any molecular process. The results supporting its use come from the placebo arm of trials assessing other treatments. When hyaluronan was used as a placebo vehicle in a randomized study to compare diclofenac gel, there was resolution of lesions in 44% of participants after 60 days [19]. Comparatively, diclofenac gel resolved 70% of lesions [19].

The most widely used management option for small, isolated lesions is cryotherapy with liquid nitrogen. Evidence supporting its use comes from a randomized study comparing cryotherapy with photodynamic therapy (PDT); after 3 months, complete response was seen in 73% after two cycles of cryotherapy (one session) compared with 69% after a single session of PDT [20]. Cryotherapy can

be associated with pain during application and postprocedural blistering and hypopigmentation.

The use of topical therapies, while effective, is often limited by the protracted course of treatment required and local side effects, which are often not tolerated by patients. One of the most widely recognized of these is 5-fluorouracil (5-FU), a topical chemotherapeutic agent, which works by inhibiting thymidylate synthetase hence disrupting DNA synthesis. When used twice daily for 3 weeks, 5-FU is associated with reduction of lesional area by 70% [21]. This regimen can result in skin irritation, dryness, erythema, and exfoliation, and thus less aggressive schedules are often used, but their efficacy remains to be fully evaluated.

Imiquimod cream 5% is an immune response modifier that acts via stimulation of a toll-like receptor. Randomized controlled trials have demonstrated its efficacy both clinically and histologically over a 16-week treatment course [22, 23]. Complete clinical clearance was achieved in 47% of patients and partial in 64%. It is more expensive, gram for gram, than 5-FU with a similar side effect profile, including severe erythema as well as scabbing and crusting (30%) with some ulceration (10%) [8]. Current dosage recommendations are three times weekly for 4 weeks, evaluating response to treatment after a further 4 weeks, notably a shorter observation period than for other treatments.

FIELD-DIRECTED THERAPY

AK are rarely solitary lesions. The idea of field change was first described in 1953, and more recently, this concept has been demonstrated at molecular level. Patches of genetically altered stem cell clones develop into individual fields that eventually mature into contiguous pastures of precancerous cells [24]. This mandates field therapy rather than targeting individual lesions. Further support for this management concept comes from data showing 82% of SCCs arise within, in close proximity to, or in a region contiguous with AK. Furthermore, it is acknowledged that the risk of surrounding skin to develop SCC is reduced if AK lesions are treated [25].

Cryotherapy can be used in a field-directed manner, in which it is referred to as cryopeeling. Chiarello [26] demonstrated good clinical outcome with a low recurrence rate as well as a lower subsequent incidence of SCC. However, owing to its side effect profile, this treatment modality is rarely used in normal clinical practice.

PDT is particularly useful when lesions are numerous as well as when they are located in areas of poor wound healing [8, 27]. PDT marries the use of a photosensitizing drug with targeted phototherapy to act on rapidly dividing atypical keratinocytes with treatment rates of about 90% reported [20, 28, 29]. In a randomized intraindividual study, Morton et al. compared PDT with double freeze–thaw cryotherapy, repeating treatments at 3 months if required. After 24 weeks both groups had similarly high response rates (PDT 89.1% and cryotherapy 86.1%) but cosmetic outcome and satisfaction was consistently rated significantly higher in the PDT group [30]. This treatment option is, however, limited by the need for a costly dedicated light source, the application of a photosensitizing cream as well as local pain both during and after treatment associated with photosensitivity, which all have an impact on patient compliance.

As newer evidence becomes available, more experts are advocating the early treatment of AK

to reduce the potential risk of it progressing to malignant disease. While there is no chemopreventive approach to eliminate progression to nonmelanoma skin cancer, the various aforementioned treatment options show benefit in terms of skin cancer prophylaxis and extending the time to its development [31]. Problems in the implementation of field-directed therapy include the requirement for adequate volumes of medication (where applicable) and provocation of a wide area of long-lived, inflammatory change and associated discomfort.

INGENOL MEBUTATE

Since 1917, the sap of *Euphorbia peplus*, commonly referred to as petty spurge in the United Kingdom or radium weed in Australia, has been used as a home treatment for dermatological malignancies, including AK and basal cell carcinomas [32–34]. The active ingredient of *E. peplus*, has since been identified as ingenol mebutate (ingenol-3-angelate, previously PEP005), a hydrophobic, macrocyclic diterpene ester [35–37], which was licensed for use in AK by the US Food and Drug Association (FDA) in January 2012.

Ingenol mebutol is believed to have a dual mode of action via both cellular necrosis and neutrophil-mediated, antibody-dependent cellular cytotoxicity [38]. First, exposure of cancerous cells to ingenol mebutate induces mitochondrial depolarization, facilitating intracellular calcium release, disruption of cytoplasmic organelles, and eventual cellular necrosis within 1–2 h of application [35]. Secondly, ingenol mubetate is believed to cause increased production of antibodies directed against the tumor by the humoral immune system. The cytokine and chemokine release that follows ingenol-mebutate-mediated cellular necrosis induces neutrophil recruitment, and subsequent "anti-tumor" antibody-dependent cellular cytotoxicity ensues [38, 39]. Similar histological appearances are seen on normal as on sun-damaged murine skin following ingenol mebutate application, albeit to a much lesser degree [40]. The combined clinical consequence is the expeditious, targeted elimination of dysplastic cells following a short duration of ingenol mebutate application.

Preliminary data from animal models, suggested efficacy of topical ingenol mebutate against human SCC, cervical carcinoma, and melanoma xenografts implanted into murine recipients [35].

Initial phase 1/2 studies trialled *E. peplus* sap in 36 patients (48 lesions) who had refused, failed, or were not suitable for conventional medical or surgical therapy for nonmelanoma skin cancer, thus deemed "relatively unfavorable." Complete clinical response rate at 1 month was 82% for basal cell carcinoma, 94% for carcinoma in situ, and 75% for SCC; for superficial (<16 mm) carcinoma in situ, the corresponding response rate was 100% [41]. The initial human phase 1 study of ingenol mebutate, which utilized a single topical application of 0.01% concentration, showed increased clearance compared with vehicle control and a sound safety profile [42].

Phase 2 dose-escalation studies showed a dose–response effect and concluded that appropriate dosage of ingenol mebutate on the trunk and extremities is 0.05% concentration gel on two consecutive days [36] with higher concentrations (such as 0.075%) predisposing to dose-limiting toxicity, comprising severe crusting and flaking. On the face and scalp, 0.015% concentration gel on three consecutive

days has been used as the maximally efficacious dose with minimal side effects [43].

Two phase 3 randomized studies compared ingenol mebutate gel 0.05% applied on two consecutive days versus vehicle application to a 25 cm^2 contiguous field on AK on the trunk and limbs. Pooled analysis of both trials included 458 patients. In ingenol mebutate versus vehicle groups, individuals showed 34.1% versus 4.7% complete clearance, 49.1% versus 6.9% partial clearance (defined as >75% reduction) and median reduction in the number of AK of 75% versus 0% [43]. Concurrently, two phase 3 trials compared 3 days of 25 cm^2 field-directed application of ingenol mebutate gel 0.025% to the face and scalp versus vehicle control. In the pooled analysis of 547 patients, complete clearance was achieved in 42.2% ingenol mebutate subjects versus 3.7% vehicle control, partial clearance (>75% reduction) in 63.9% versus 7.4% and corresponding median reduction in number of AK of 83% versus 0%.

Long-term follow-up of patients who had achieved clinical clearance in these phase 3 trials showed that 44.0% of patients with AK on trunk and limbs and 46.1% with AK on face and scalp sustained their clearance after 12 months, with a reduction in AK numbers of 86.8 and 87.2%, respectively [43].

Together, these results suggest that 2 days field-directed application of ingenol mebutate 0.05% on the trunk and extremities, or 3 days field-directed application of ingenol mebutate 0.015%, is significantly more efficacious than vehicle control with respect to complete and partial clearance of lesions, ingenol mebutate is well tolerated and its therapeutic effect long-lived.

The most consistently reported side effects of ingenol mebutate are erythema, flakiness, crusting, pruritus, and pain, experienced by up to 97.5% patients, with effects peaking between days 3 and 8 and mostly resolved by day 15 [43]. A favorable safety profile has been consistently reported with no detectable systemic absorption [44]; long-term (12 months) follow-up data showed no treatment-related serious adverse events or deaths [43]. Complete clearance rates are comparable with clinical trials of diclofenac applied for up to 90 days, imiquimod applied for 16 weeks, and 5-FU applied for 4 weeks.

INGENOL MEBUTATE: FUTURE ROLE IN THERAPY

AK represents the most common dermatological premalignant pathology, whose incidence will inevitably increase in the upcoming decades, imposing an increasing burden on our healthcare systems. The use of current treatments, while effective, may be limited by patient tolerance of the protracted courses of treatment required, compliance with therapy and access to secondary care resources (such as phototherapy suites). Ingenol mebutate represents a promising therapy for AK on both facial and extra-facial sites. Requiring only two applications, ingenol mebutate will be of particular value for patients unable to tolerate the side effects endured during a protracted course of treatment with 5-FU or imiquimod and is well suited to patients with AK on sites notorious for poor healing, such as the lower legs. Furthermore, adherence to prescribed therapy is likely to be greater with ingenol mebutate particularly for those patients who, for reasons of dependence, rely upon carers or relatives to assist them with their treatment. With increasing use, more comprehensive medicine information relating to ingenol mebutate will follow, including data relating to application over larger areas and in combination with other agents, and randomized trials more

conclusively comparing ingenol mebutate with its competitors will ensue.

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