

Pharmacoeconomic evaluations in the treatment of actinic keratoses

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Abstract

Actinic keratoses (AKs) develop as a consequence of chronic ultraviolet (UV) exposure and exist on a continuum with squamous cell carcinoma (SCC). As one of the most common conditions treated by dermatologists, AK places a significant burden on patients and the healthcare system. A range of treatments are used, including topical treatments that target the visible and subclinical lesions. The goal of such therapies is to achieve complete clearance of AKs and eliminate the risk of progression to SCC. Robust meta-analyses of trial data can provide valuable information for the optimal management of AK and cost-effectiveness evaluations of topical treatments, such as ingenol mebutate gel and diclofenac. These outcomes can facilitate prescribing physicians' decisions and shape therapeutic guidelines. Peer-reviewed meta-analysis publications and treatment guidelines favoured ingenol mebutate efficacy over diclofenac and the relative cost-effectiveness of ingenol mebutate. We discuss and critique recent evidence, from a cost-effectiveness analysis of 3% diclofenac sodium and ingenol mebutate in the treatment of AK in Italy, which has challenged this view.

Keywords

actinic keratosis (AK), cost-effectiveness, diclofenac, ingenol mebutate, pharmacoeconomic

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Introduction

Actinic keratosis (AK) is one of the most common conditions treated by dermatologists¹ and manifests predominantly in areas of sun-exposed skin such as the scalp, face and hands. Skin keratinocytes within these areas are predisposed to malignant transformation by cumulative exposure to ultraviolet (UV) light, otherwise known as field cancerisation.^{2–5} Evidence supports the view that AKs exist on a continuum with squamous cell carcinoma (SCC)^{6–9} and areas of field cancerisation may contain both clinical and subclinical AKs.¹⁰ Although the progression of an individual AK lesion to SCC cannot be predicted,¹¹ there is a risk of SCC progression of 0.6% over one year and 2.57% over four years.¹² Progression to SCC can further impact patient health-related quality of

life¹³ and carries a mortality risk.¹⁴ The burden on healthcare systems cannot be underestimated either, for example in Sweden the estimated cost of treating AK and non-melanoma skin cancer in 2011 was more than €18 million and €42 million, respectively.¹⁵ Therefore, treatments that target both clinically visible and subclinical AKs can

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lower the risk of malignant progression and potentially reduce the burden on patients and healthcare systems.

A range of topical field treatments for AK exist; these include ingenol mebutate gel (Picato®) and diclofenac 3% cream (Solaraze™). Ingenol mebutate is a novel topical field therapy for AK, applied once daily for two or three days depending on body location.^{16,17} Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), applied twice daily for up to 90 days.¹⁸ In order to make informed healthcare decisions about new treatments in AK such as ingenol mebutate, healthcare authorities require robust evidence of efficacy and cost-effectiveness. Randomised, controlled, direct head-to-head trials of two interventions are preferred. However, most AK trials are vehicle-controlled and few include an active comparator. Network meta-analyses (NMAs) can provide a valid statistical alternative providing estimates of the comparative efficacy of different treatment approaches based on direct and indirect evidence.^{19–22} These evaluations can then inform pharmacoeconomic assessments of the costs and healthcare benefits of new treatments, such as ingenol mebutate, and assist clinical practice and policymaking.

Discussion

A pharmacoeconomic analysis of 3% diclofenac sodium versus 0.015% ingenol mebutate in the treatment of AK, from an Italian Healthcare System perspective, reported that diclofenac was more cost-effective than ingenol mebutate.²³ Estimated total costs over 12 months for treating 500 patients with diclofenac were €82,594 versus €95,416 for ingenol mebutate. As there was little difference in quality-adjusted life-years per patient between the two treatments, the analysis interpreted this as an additional cost of €19.65 to treat a patient with ingenol mebutate, with no additional benefit over diclofenac by assuming equal efficacy.²³ These findings diverge from previous publications on the relative efficacy and cost-effectiveness of ingenol mebutate. However, we offer a critique of this new pharmacoeconomic analysis.

In our view, the reported comparison is inadequate and subject to bias, because several randomised controlled trials (RCTs) with diclofenac (and ingenol mebutate) are excluded, the trials selected for

efficacy estimation do not have comparable designs, and there is a lack of transparency around the methodology used to identify trials for analysis.

The efficacy of ingenol mebutate has previously been established in large, randomised, placebo-controlled trials. In the recent analysis,²³ four placebo-controlled trials involving 1,142 patients were used to estimate the efficacy.²⁴ In contrast, estimates of diclofenac efficacy were based on one, phase IV, open-label trial involving 76 patients, of which 52 patients completed a 12-month follow-up.^{25,26} Notably, the phase IV diclofenac trial^{25,26} used in this recent analysis was deselected in a previous NMA because it lacked a RCT design.²⁷

Another challenge regarding the new analyses,²³ is that the differences between trials in placebo effect are not accounted for. For example, trials of diclofenac that are not included in the new analyses²³ have observed the placebo effect to be as high as 23.6%,²⁸ while the placebo effect in the ingenol mebutate trials was 3.7%.²⁴ Failing to compensate for the placebo effect in any analysis will have a substantial impact on the outcome. In the aforementioned NMA of AK treatments, an overall placebo effect of 6% was assumed based on evidence observed in the network.²⁷ Therefore, the NMA estimated that the diclofenac complete clearance rate was 24.7%, compared with 54.5% for ingenol mebutate.²⁷

By implementing an appropriate meta-analysis methodology, e.g. an NMA based on a systematic review, a robust health economic analysis can be achieved. In contrast, the recent pharmacoeconomic data²³ are based on naïve indirect comparisons and in our view, given the availability of published meta-analysis evidence, do not provide a robust evidence base for an economic evaluation of AK therapies.

In addition to the challenge with trial design and placebo effect, this recent estimation of recurrence of AKs²³ are misleading because there is inconsistency in the definition of recurrence between the selected trials. ‘Recurrence’ in AK refers to the reappearance of AKs within an area of skin which was at first successfully cleared of AK. ‘Recurrence’ figures for diclofenac in the recent analyses²³ were taken from the Target Lesion Number Score (TLNS) which was measured in the patients who completed the trial, rather than patients who at first achieved complete clearance. This measure does not capture the appearance of new AKs within the

previously treated area of skin. A different approach was used to estimate recurrence rates for ingenol mebutate. The reported 12.8% ‘recurrence’ at month 12 for ingenol mebutate²³ is inaccurate and was based on a statistic describing the number of AK lesions as a proportion of baseline lesions one year post-study start, in patients who achieved complete clearance at time of optimal treatment efficacy (day 57). This statistic was designed to measure the overall reduction in AKs at one year (this is 87.2%). It is not a binary measure reflecting whether AKs recurred or not²⁹ and is reflected in the summary of product characteristics (SmPC) for ingenol mebutate.³⁰ Long-term efficacy for diclofenac has not been established and cannot be calculated due to lack of data.^{18,27}

Further, the comparison of ‘severe adverse events (AEs)’ for diclofenac (5%) not related to treatment,²⁵ and ‘any adverse event’ (37.2%) for ingenol mebutate²⁴ in this recent analysis,²³ in our view is not an appropriate comparison and results in misleading assumptions about safety. The rate of ‘severe AEs’ reported in the pivotal trials for ingenol mebutate on face and scalp is 2.2%.²⁴ More reliable estimates of AEs for diclofenac are captured in the product’s SmPC;¹⁸ conjunctivitis, contact dermatitis and application site reactions are the most commonly reported AEs.

Conclusions

In conclusion, the recent analysis²³ of the relative cost-effectiveness of ingenol mebutate and diclofenac is incomplete and should be considered in the context of the limitations outlined within this article and the existing literature. In our view it would be ill-advised to make strong conclusions about the efficacy, effectiveness and safety of ingenol mebutate and diclofenac based on this recent analyses.²³ Although there are currently no head-to-head data published, peer-reviewed meta-analysis publications favour ingenol mebutate efficacy over diclofenac.^{27,31} The recent International League of Dermatological Societies/European Dermatology Forum S3 guidelines for the treatment of AK also rank ingenol mebutate higher than diclofenac in the treatment of patients with multiple AK lesions or field cancerisation.³² We believe that also in Italy, as it was found in the context of other countries, valuable peer-reviewed economic evaluations should support the relative cost-effectiveness of ingenol mebutate over diclofenac.^{31,33,34}

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Declaration of conflicting interests

Thomas Larsson and Lasse Rytting are both full-time employees of LEO Pharma. Pier Giacomo Calzavara-Pinton has received some funding from Leo, Galderma and Roche over the past two years for projects and/or speaker honorarium for congresses, but all were unrelated to actinic keratosis. Giuseppe Argenziano has received speaker honorarium from Leo, Galderma and Roche for lectures on actinic keratosis. Keith Tolley declared no potential conflicts of interest.

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