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ORIGINAL RESEARCH

Cost–Utility of First-Line Actinic Keratosis Treatments in Finland

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ABSTRACT

Introduction: Cost–utility assessment of first-line actinic keratosis (AK) treatments for max 25 cm^2 AK field.

Methods: A probabilistic, 2-year decision tree model was used to assess costs, quality-adjusted life-years (QALY), incremental cost-effectiveness ratio (ICER), cost-effectiveness efficiency frontier, cost-effectiveness acceptability frontier (CEAF), and expected value of perfect information (EVPI) of AK treatments from the Finnish health care payer perspective with 3% discounting per annum. In the model, the first-line AK treatment resulted in complete clearance (CC) or non-CC with or without local skin responses (LSR), or AK recurrence. Non-CC AK was treated with methyl aminolevulinate + photodynamic therapy (MAL + PDT), and AK recurrence was retreated with the previous effective treatment. Costs included primary and secondary health care, outpatient drugs, and LSR management. QALYs were assessed with the EuroQol (EQ-5D-3L). Result robustness was assessed with sensitivity analyses.

Results: The mean simulated per patient QALYs (costs) were 1.526 (€982) for MAL + PDT, 1.524 (€794) for ingenol mebutate gel (IngMeb) 0.015% (3 days), 1.522 (€869) for IngMeb 0.05% (2 days), 1.520 (€1062) for diclofenac 3% (12 weeks), 1.518 (€885) for imiquimod 3.75% (6 weeks), 1.517 (€781) for imiquimod 5% (4/8 weeks), and 1.514 (€1114) for cryosurgery when treating AK affecting any body part. IngMeb 0.015% was less costly and more effective (dominating) than other AK treatments indicated for face and scalp area with the exception of imiquimod 5% for which

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the ICER was estimated at €1933/QALY gained and MAL + PDT, which had an ICER of €82,607/QALY gained against IngMeb 0.015%. With willingness-to-pay €2526–18,809/QALY gained, IngMeb 0.015% had >50% probability for cost-effectiveness on the CEAF. IngMeb 0.05% dominated AK treatments indicated for trunk and extremities. EVPIs for face and scalp (trunk and extremities) analyses were €26 (€0), €86 (€58), and €250 (€169) per patient with the willingness-to-pay of €0, €15,000, and €30,000 per QALY gained, respectively.

Conclusion: IngMebs were cost-effective AK treatments in Finland.

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Keywords: Actinic keratosis; Cost-effectiveness; Cryosurgery; Diclofenac; Economic evaluation; Imiquimod; Ingenol mebutate; Modeling; Photodynamic therapy; Solar keratosis

INTRODUCTION

Actinic keratosis (AK) is a common pre-malignant skin disease that impairs patients' quality of life (QoL) [1–4] and causes a significant burden to the health care system [5–9]. A key cause for AK is cumulative exposure to ultraviolet light. Clinically, AK is described as "keratotic macules, papules or plaques with superficial scales on a red base" [2].

The prevalence of AK is 11–25% worldwide [10–12]. The largest AK prevalence has been reported in the southern hemisphere [13, 14], in populations near the equator and in countries with a high proportion of white inhabitants [2]. AK's prevalence increases with age, for example, 34% and 18% of males and females over the age of 70 had AK in the United Kingdom (UK), respectively [11]. Histologically, AKs are considered to be precursors of squamous cell carcinoma (SCC), because AK can regress, persist unchanged or progress to invasive SCC [2, 15]. Over a decade, 1–16% of AKs progress to invasive SCC [2].

The incidence of SCC has increased [16, 17]. In Finland, this increase has been 2.5% per annum [15] and there were 1366 registered new cases of SCC in Finland in 2009 [18]. Non-melanoma skin cancer (NMSC, including SCC and also basal cell carcinoma of the skin) is among the top five most costly cancers [19] and a major cost driver for health care [9, 20]. Based on Finnish hospital discharge register (FHDR) [21] data with nationwide public health care coverage from 2009, around 19% of incident NMSCs were histologically confirmed SCCs in Finland. 18% of these histologically confirmed SCC patients had an AK diagnosis during the past 10 years.

Actinic keratosis lesions are commonly located on the head (75% based on the incident FHDR data from 2009). Typically, multiple lesions are present in a field of UV-damaged skin with subclinical lesions surrounding visible lesions (so-called field cancerization) [2, 9, 15]. SCC risk is higher in patients with more than five AK lesions [22]. However, SCC development is impossible to predict. It is recommended that multiple AK lesions are treated with field treatment that can target both visible and subclinical lesions [2, 12, 15, 23–31].

The goal of AK treatment is to achieve complete clearance (CC) of lesions, thereby potentially preventing the AK lesions from developing into SCC [15, 32]. Finnish AK articles have been published [9, 15, 33–37] and, generally speaking, Finnish treatment practice seems to be in line with European approaches [2, 38] with one exception: 5-fluorouracils (5-FU) are not commonly used

in Finnish clinical practice. Currently, only intravenous 5-FUs are available in the Finnish market, whereas 5-FU topical is not reimbursed by the Finnish Social Insurance Institution and they do not have listed prices. In Finland, commonly used AK treatments include cryosurgery for head (face or scalp) or body (trunk or extremities), topical 5% imiquimod (Aldara®, head area indication) for 4 or 8 weeks depending on the 4-week treatment response, and methyl aminolevulinate (Metvix®, head area indication) + photodynamic therapy (MAL + PDT) [37]. Diclofenac (Solaraze®) 3% for 12 weeks is used less frequently [37] and is generally considered for older or institutionalized AK patients in Finland.

Newer topical AK treatments include a 6-week treatment with 3.75% imiquimod (Zyclara®, head area indication), and 3- or 2-day treatments with ingenol mebutate gel (IngMeb, Picato®) 0.015% for head area or 0.05% for body area, respectively [9, 15]. IngMeb is a pleiotropic effector with a dual action mechanism and short treatment duration. IngMeb-associated skin reactions typically resolve within 2–4 weeks depending on the treated area [39–50].

Our study seeks to assess the cost–utility of common first-line treatments for AK field (max. 25 cm^2) affecting any body part. The cost-effectiveness of AK treatments has not been previously assessed in the Finnish context. Furthermore, to our knowledge, our analysis is the first to include imiquimod 3.75% and IngMebs.

METHODS

Cost–utility analysis (CUA) is a health economic evaluation method simultaneously comparing both costs and quality-adjusted survival (quality-adjusted life-years, QALY) gained with different treatment options. The key outcome of a CUA is incremental cost-effectiveness ratio (ICER), the ratio of cost and QALY differences between the treatment options given as €/QALY gained. Cost-effectiveness is assessed in relation to the willingness-to-pay (WTP) for additional QALY. In the Finnish setting, the interpretation of cost-effectiveness is complicated by the fact that the WTP threshold used for decision making has not been publicly announced. Based on our experience, the maximum threshold for AK may be around €30,000/QALY gained, and values below €15,000/QALY gained are likely to indicate a very good cost-effectiveness.

For this assessment, the mean cost and effectiveness results for each treatment alternative were graphed on the cost-effectiveness plane with payer costs (resources) plotted on the horizontal axis and QALYs (outcomes) on the vertical axis. The cost-effectiveness efficiency frontier (CEEF) was then drawn to depict the non-dominated treatment alternatives. In the CEEF, a purely dominant treatment is both more effective and less costly in comparison to an alternative treatment. If a combination of treatments is more effective and less costly than an alternative treatment, the alternative treatment is then extendedly dominated by the combination of treatments. Lastly, if a treatment is more effective and more costly in comparison to an alternative treatment, the acceptance of a more effective and costly treatment is based on the decision maker's WTP (e.g., €/QALY gained).

The significance of QALY and cost differences between treatments was assessed conservatively by estimating 0.25–0.75 percentiles for the QALY and cost differences between treatments in the performed 2000 model simulations. The difference was

considered significant, if zero was not within the 0.25–0.75 percentiles.

Setting

Cost–utility analysis was done on the basis of the direct impact that the compared treatments had on the max 25 cm^2 AK field, adverse events (based on local skin responses [LSR]) and the probability of AK's recurrence after successful treatment. Due to the uncertainty regarding the impact of different AK treatments on SCC incidence and consequent mortality, a 24-month analytical time horizon (not including SCC development and mortality) was considered adequate. Since the recurrence of AK lesions after treatment response was expected to occur within 12 months of the primary response (e.g., [46]), the 24-month timeframe was anticipated to fully capture the costs, health benefits and LSRs associated with AK treatments.

The base case analysis was conducted from the public health care payer perspective, considering the direct health care costs related to AK and its management in line with the Finnish [51] and most international guidelines (e.g., [52–61]) on performing health economic assessments. Following the Finnish guidance, results were discounted by 3% per annum. The analysis in this article was based on previously conducted studies, and did not involve any new studies of human or animal subjects performed by any of the authors.

Cost-Effectiveness Model

A sequential, probabilistic, 2-year decision tree model (Fig. 1) in Microsoft Office Professional 2007 Excel version 12 was used to carry out the CUA. CUAs are unavoidable simplifications of complex reality, and some assumptions were a necessity due to data scarcity and for simplicity. Based on the Finnish clinical expertise, incident FHDR data, reimbursement data of the Social Insurance Institution of Finland, and recent local, national (e.g., [9, 15]) and international expert opinions (e.g., [62]), the following structural assumptions were made in the assessment. In the model, the treatments resulted in CC or non-CC after 6 months, and both outcomes could be achieved with or without short-term LSRs. In the case of CC, a patient was at risk of recurrence at 12 months. Non-CC AK was assumed to be treated with MAL + PDT whereas first-line AK recurrence after CC was retreated with the previous effective treatment.

Efficacy and Safety Inputs

Health effects included in the CUA were CC, time to CC, safety in terms of LSR risks and durations, recurrences, and QoL. CC inputs (AK affecting any body part) were based on random effects results of a Bayesian network meta-analysis [63] (Supplementary Appendix 1). LSR and recurrence probabilities were pooled trial results (Table 1) based on the meta-analysis material. For LSR assessment, studies with a very low number of patients (<8 patients/treatment arm) or reporting only serious adverse events were excluded.

Quality of Life Inputs

Quality of life scores were applied to patients for the duration of the model. AK and LSRs have a detrimental effect on QoL, whereas successful treatment leads to improvements, the magnitude of which will depend on whether the patient achieves CC [1, 4]. At the time of analysis, the QoL scores by Wilson et al. [3] were most representative values found for the different AK states included in the model.

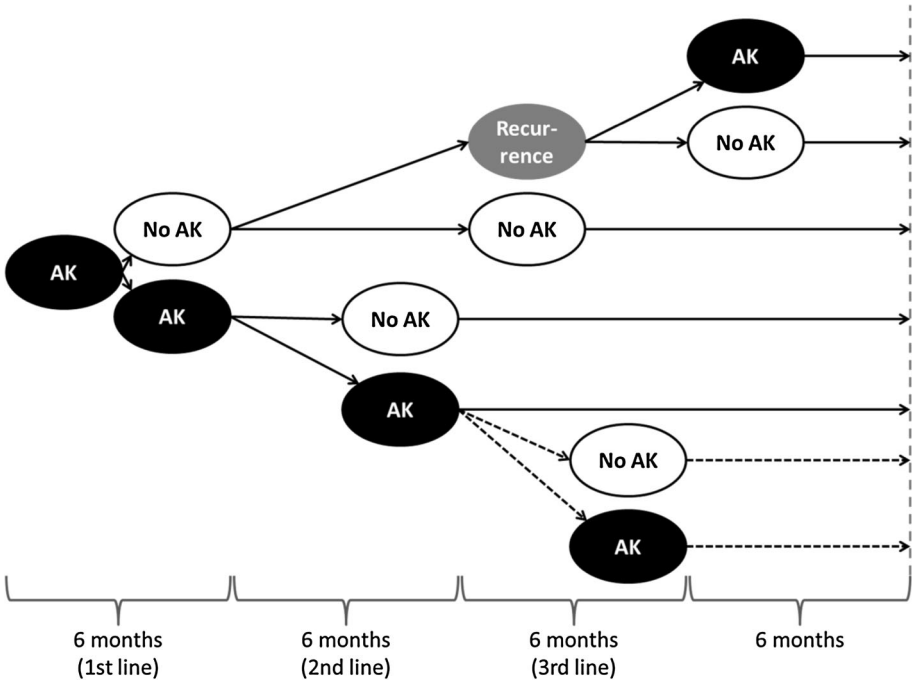

Fig. 1 Simplified presentation of the 2-year decision tree model (in addition to the 6-month complete clearance and 12-month recurrence status, the model included short-term treatment-related adverse events). *Dashed arrows* show the path of third treatment line (not considered in the base case analysis). *AK* actinic keratosis

Table 1 Clinical inputs by treatment

Outcome	CC		LSR			Recurrence
Treatment	LOR	Weeks to CC	Probability	Duration (weeks)	Weeks of work (sensitivity only)	Probability
Cryosurgery	1.693	2.5	42.0[a]	0.0	0.0	90.0[h]
Diclofenac 3%	1.660	16.0	43.0[b]	4.0	4.0	39.0[j]
Imiquimod 3.75%	2.208	10.0	40.0[c]	8.0	7.5	39.0[j]
Imiquimod 5% 4 weeks	3.238	8.0	64.0[d]	6.0	5.5	39.0[i]
Imiquimod 5% 8 weeks	2.347	12.0	64.0[d]	10.0	9.5	39.0[i]
IngMeb 0.015%	3.098	3.0	30.0[e]	2.5	2.0	53.9[e]
IngMeb 0.05%	2.182	4.0	23.0[e]	3.5	3.0	50.0[e]
MAL + PDT	5.517	2.5	66.0[f]	1.0	1.0	24.0[k]
Second-line treatment[g]	5.517	2.5	66.0	1.0	1.0	24.0

CC complete clearance, *LSR* local skin response, *LOR* log odds ratio, *IngMeb* ingenol mebutate gel, *MAL + PDT* methyl aminolevulinate photodynamic therapy

Pooled trial results based on: [a] [64–71], [b] [72–76], [c] [77, 78], [d] [76, 79–86], [e] [45], total LSRs, [f] [64–66, 68, 87–91], [g] MAL + PDT after topicals, [h] [92, 93], [i] [80, 94], [j] Imiquimod 5% (assumption), [k] [89, 91]

The QoL scores of Wilson et al. [3] were anchored to Finland using the average EuroQol (EQ-5D-3L) QoL score of 0.776 for Finnish people aged 65–74 years [95]. This resulted in 0.776 QoL for CC and 0.765 QoL for AK (non-CC). These values were considered to be valid regardless of AK site, because the lesion site has not statistically been shown to significantly impact the QoL [96]. The applied QoL impact of LSR was −0.085 [3] and the duration of LSRs is given in Table 1. After LSR resolution, the QoL was assumed to recover back to the level experienced in the AK health state, until the time of potential CC was reached.

Cost Inputs

The cost estimation was based on Finnish treatment practices and guidelines [51]. Drug costs, primary care (PC) clinician visits, specialist visits, procedures, hospitalizations, and LSR management were considered in the base case analysis. Drug costs were from 1/2015 (excluding value-added tax 10%, Table 2) and other costs were indexed with official Finnish communal health care price index for public services [97] to 2013 real values. Incident AK patients (year 2009, $n = 3409$, 46 organ transplant patients excluded; 61.0% women with the mean age of 74.6 years and 39.0% men with the mean age of 73.4 years) were identified from the FHDR to assess AK related 2-year secondary health care costs (including visits, hospitalizations, and procedures) in 2013 value for first-line patients initiating different treatment regimens. Supplementary Appendix 2 shows the secondary health care resource use and applied expected costs.

In Finland, topical AK treatments are mostly prescribed in specialized health care (patient enters the system through PC visit) [38]. In the model, 2% of all topical treatments were prescribed in the PC setting (with full secondary care costs in order not to underestimate the base case costs of topicals) and the remaining 98% were prescribed in

Table 2 Drug costs based on Finnish medicines tariff (1/2015)

Treatment	Drug pack		Drug unit		Drug[a]
	Units	Price	Cost (€)	/Course	Cost (€)
Diclofenac (3%): 2 × daily (12 wks)	100 g	122.44	122.44	1	122.44[b]
Imiquimod (3.75%): 1 × daily (6 wks)	28 sachets	125.86	4.50	28	125.86[b]
Imiquimod (5%): 3 × wk (4/8 wks)[c]	12 sachets	72.97	6.08	12/24	72.97/145.94
IngMeb (0.015%): 1 × daily (3 days)	3 tubes	106.54	35.51	3	106.54
IngMeb (0.05%): 1 × daily (2 days)	2 tubes	106.54	53.27	2	106.54

Methyl aminolevulinate photodynamic therapy and cryosurgery drug costs were assumed to be included in the Finnish hospital discharge register data (Supplementary Appendix 2)

IngMeb ingenol mebutate gel, *wk* week

[a] First-line treatment and again for the potential treatment of recurrence for the drug costs part after complete clearance

[b] Wholesale price for hospital product and/or non-reimbursed product; excludes significant cost margin of the Finnish pharmaceutical pricing scheme [98]

[c] Imiqimoid 5% for 4 and 8 week treatments were combined and a revisit took place for the 8-week treatment. Based on the Finnish social insurance institution data covering all reimbursed AK treatments during year 2011, 17.5% of imiquimod 5% users with age >55 years undergo the 8-week treatment

specialized health care, and MAL + PDT and cryosurgery were administered only in the specialized health care setting. Short-term LSRs led to a phone contact with health care professional in 25% of the cases. It was assumed that no particular treatment would be given for the LSRs, because LSRs may precede CC and they are not commonly treated. The indexed unit costs for the PC visit and phone call were €116.18 and €27.46, respectively [97, 99]. After non-CC with the first-line treatment, all patients were assumed to receive MAL + PDT (additional cost for PDT €418.31 based on the FHDR). Instead, recurrent AK was always retreated using the same initially efficacious treatment.

Sensitivity Analyses

Cost-effectiveness acceptability frontier (CEAF) and expected value of perfect information (EVPI) were selected to demonstrate the parameter uncertainty in the base case modeling. The CEAF shows the optimal treatments with the highest expected net benefit as the function of WTP. The EVPI demonstrates the monetary value of parameter uncertainty that can be resolved by acquiring additional evidence for the model parameters (the value of optimal parameter evidence) or alternatively the expected consequences of the wrong decision (the opportunity costs) in monetary terms. The EVPI for each simulation (here 2000) can be calculated row-by-row as the net monetary benefit lost (between the optimal treatment for the simulation and the treatment to be selected in decision making based on the highest average net monetary benefit); conditional to WTP. Then the EVPI per patient is estimated by taking the average of 2000 simulation-based EVPIs ranging from zero upwards; conditional to WTP. In this probabilistic analysis, distributions (normal: log odds ratio for CC and QoL values; gamma: time to CC, time with LSR and costs; beta: risks related to LSR and AK recurrence, and LSR resource use) with known standard errors or an assumed standard error equal to 10% of the mean value (when true standard error was not known) were applied.

Sensitivity analysis scenarios demonstrate the sensitivity of the probabilistic results to modeling assumptions. The performed scenarios cover all model inputs with importance. The scenarios include methodological, treatment strategy, effectiveness and cost changes: 1 year (within-trial for IngMebs) time horizon, no discounting of results, rough inclusion of gender-weighted mortality, QoL not anchored to Finland, beta distribution for QoL values, fixed-effect meta-analysis results for CC, similar incidence (30% assumed) and duration (4 weeks assumed) of LSRs for the treatments, inclusion of topical treatment discontinuation (20% for imiquimod, 10% for other topicals), similar recurrence of AK after successful treatment (50% assumed), MAL + PDT assumed for the recurrence treatment, active recurrence treatment after AK CC with the second-line treatment, third-line treatment for topicals (second-line retreatment assumed), second-line treatments and recurrences ignored, 30% IngMeb used in PC, all topicals used in PC, and societal perspective. The societal perspective sensitivity analysis also included traveling costs to health care and productivity losses due to AK treatment. The cost of round trip travel was €37.53 to secondary and €7.35 to PC in year 2014 value ([100, 101] excluding value-added tax). The proportion of working persons with AK was estimated based on the FHDR AK patient's gender-specific age distribution (men/women: 35–44 years 1/0%,

45–54 years 4/4%, 55–64 years 14/13%, 65–74 years 31/27%, 75–84 years 37/37%, 85 years or older 12/18%, respectively) and gender-specific age distribution of working people in Finland in 2011 based on the official statistics [102], which resulted in an average employment rate of 15% among the AK patients. The value of a working week lost was €773.40 based on the human capital approach [99, 103].

RESULTS

During the 2-year time period, the mean simulated probabilistic per patient QALYs in decreasing QALY order and 3% annual discounting were 1.526 (95% confidence interval 1.524–1.528) for MAL + PDT, 1.524 (1.522–1.525) for IngMeb 0.015%, 1.522 (1.521–1.524) for IngMeb 0.05%, 1.520 (1.518–1.521) for diclofenac, 1.518 (1.516–1.519) for imiquimod 3.75%, 1.517 (1.515–1.519) for imiquimod 5%, and 1.514 (1.512–1.515) for cryosurgery when treating AK affecting any body part. According to the used measure of significance (zero not included within the 0.25–0.75 percentiles of outcome differences), significant QALY differences in the head area analysis were observed only for MAL + PDT vs. imiquimod 5%, IngMeb 0.015% vs. imiquimod 5%, and diclofenac vs. cryosurgery. No significant QALY differences were found in the body area analysis.

The respective payer costs were €982 for MAL + PDT, €794 for IngMeb 0.015%, €869 for IngMeb 0.05%, €1060 for diclofenac, €885 for imiquimod 3.75%, €781 for imiquimod 5%, and €1114 for cryosurgery. Apart from IngMeb 0.015% vs. imiquimod 5% and diclofenac vs. cryosurgery, all between-treatment cost differences for the head area were significant. Also, all between-treatment

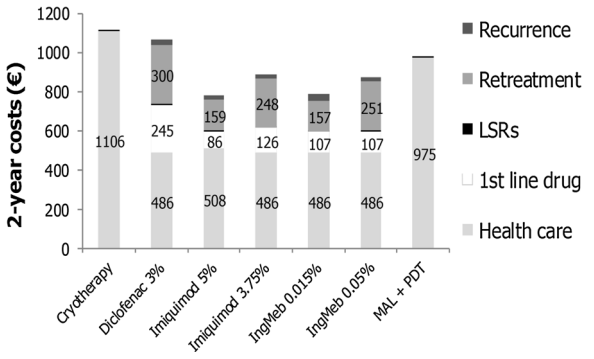

Fig. 2 Deterministic dispersion of 2-year actinic keratosis treatment costs. *LSR* local skin responses, *MAL + PDT* methyl aminolevulinate photodynamic therapy

cost differences for the body area were significant with the exception of insignificant difference between diclofenac and cryosurgery. Figure 2 depicts the deterministic dispersion of costs by treatment and cost type. LSR and recurrence management constituted a minor proportion of total costs. Health care, retreatment and first-line drug were the key cost drivers.

Table 3 shows the ICERs based on the treatment indications. The CEEF for AK in face and scalp included only two treatments: imiquimod 5% and IngMeb 0.015% (upper part of Fig. 3). IngMeb 0.015% dominated the other AK treatments indicated for the face and scalp area with the exception of imiquimod 5% for which the ICER was estimated at €1933/QALY gained and MAL + PDT, which has the ICER of €82,607/QALY gained against IngMeb 0.015% (Table 3; Fig. 3). IngMeb 0.05% dominated other treatments indicated for trunk and extremities as shown by the cost-effectiveness plane in the lower part of Fig. 3.

Based on the CEAF for AK treatments with face and scalp area indication (upper part of Fig. 4), IngMeb 0.015% was the optimal treatment (i.e., treatment with highest expected net benefit) when WTP was between €1933 and 82,607/QALY gained. IngMeb 0.015% was also potentially cost-effective (i.e.,

Table 3 Base case incremental cost-effectiveness ratios (ICER, €/quality-adjusted life-year gained) based on the indication area

Area	Head ICERs					
Body ICERs	*Treatment*	*IngMeb 0.015%/ 0.05%*	Diclofenac	*Imiquimod 3.75%*	*Imiquimod 5%*	*Cryosurgery*
	MAL + PDT	82,607	MAL + PDT dominant	11,898	21,900	MAL + PDT dominant
	IngMeb 0.05%/ 0.015%	–	IngMeb 0.015% dominant	IngMeb 0.015% dominant	1933	IngMeb 0.015% dominant
	Diclofenac	IngMeb 0.05% dominant	–	97,709	98,590	Diclofenac dominant
	Imiquimod 3.75%	na	na	–	100,128	Imiquimod 3.75% dominant
	Imiquimod 5%	na	na	na	–	Imiquimod 5% dominant
	Cryosurgery	IngMeb 0.05% dominant	Diclofenac dominant	na	na	–

Head ICERs are in the upper right side and body ICERs in the lower left side of the Table 3
Dominant the mentioned treatment dominates the comparator, *ICER* incremental cost-effectiveness ratio, *IngMeb* ingenol mebutate gel, *MAL + PDT* methyl aminolevulinate photodynamic therapy, *na* not applicable (one or both of the treatments do not have the indication)

optimal treatment with the probability of cost-effectiveness >50%) with the WTPs between €2526 and 18,809/QALY gained. None of the treatments were potentially cost-effective when WTP was between 18,810 and 701,081/QALY gained. The EVPIs per patient were €26, €86, €250, and €504 with the WTP of €0, €15,000, €30,000, and €50,000 per QALY gained, respectively. The respective cost-effectiveness probabilities for IngMeb 0.015% were 43%, 54%, 41%, and 31%.

Based on the CEAF for AK treatments indicated for trunk and extremities (lower part of Fig. 4), IngMeb 0.05% was the optimal and a potentially cost-effective treatment with all plausible (e.g., €0–50,000/QALY gained) WTP levels. The EVPIs per patient were €0, €58, €169, €330 with the WTP of €0, €15,000, €30,000, and €50,000 per QALY gained, respectively. The respective cost-effectiveness probabilities for IngMeb 0.05% were 100%, 80%, 71%, and 66%.

Sensitivity Scenarios

Probabilistic mean QALYs and costs of sensitivity analysis scenarios are given in Table 4. Based on the sensitivity analyses, IngMeb 0.015% and 0.05% were generally cost-effective. MAL + PDT could be cost-effective from the full societal perspective, if the WTP per QALY gained for the societal perspective exceeds €28,802—yet, IngMeb 0.015% dominated imiquimod 5% in the same analysis. IngMeb 0.015% dominated imiquimod 5% also when a 1-year time horizon, fixed-effects meta-analysis, 30% of IngMeb in the PC setting or all topicals in the PC setting inputs were used.

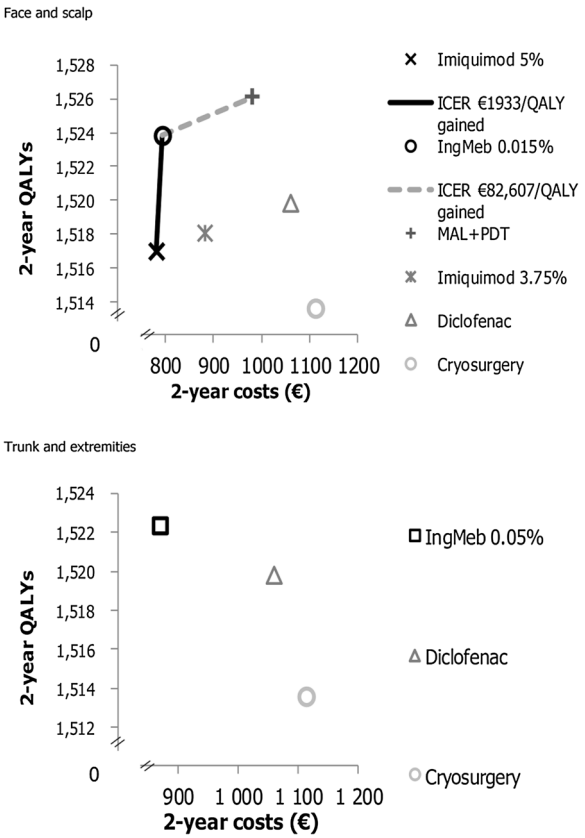

Fig. 3 Cost-effectiveness efficiency frontier (*black* and *dashed gray lines*, *upper part of figure*) in cost-effectiveness plane for actinic keratosis in head area. The *lower part of the figure* shows the outcomes for body area (trunk, extremities) treatments in the cost-effectiveness plane. *ICER* incremental cost-effectiveness ratio, *IngMeb* ingenol mebutate gel, *MAL + PDT* methyl aminolevulinate photodynamic therapy, *QALY* quality-adjusted life-year

The ICERs of MAL + PDT vs. IngMeb 0.015% were most sensitive to changes in LSR impact (similar assumption for both increased the ICER with €99,906/QALY gained in comparison to the base case) and the proportion of topicals prescribed in the PC (the 100% topical prescriptions in PC basis increased the ICER with €79,087/QALY gained).

DISCUSSION

This study compared the cost–utility of all relevant AK treatment options for the treatment of a 25-cm^2 AK field in the Finnish setting, and was the first to include IngMebs and imiquimod 3.75%. Based on this study, IngMebs can result in effectiveness (QALY) gains at acceptable costs in their indication, significant cost and effectiveness differences can exist between the treatments, and treating AK in the PC setting (where feasible) can result in cost savings.

For face and scalp AK, MAL + PDT was projected to be the most effective treatment, but its effectiveness came with high payer costs. There was no significant difference in 2-year effectiveness between MAL + PDT and IngMeb 0.015%, and a high ICER of €82,706/QALY gained was estimated for MAL + PDT against IngMeb 0.015%. The respective ICER was €28,807/QALY gained in the full societal perspective analysis—the setting which is not recommended to be used alone without the payer perspective [51]. Even though there are no published ICER thresholds in Finland, it seems that ICERs exceeding €50,000/QALY gained are rarely considered cost-effective for other than very severe diseases and that ICERs should be <€20,000/QALY gained for more common and/or less severe conditions, which is in line with, for example, the UK thresholds [61].

Based on this analysis, MAL + PDT's 2-year payer costs should be at least 15% lower to meet the €20,000/QALY gained. The result and affordable tendered cost with potential drug sharing were assumed for MAL (for topicals, official list costs were used). Yet, in comparison with commonly used imiquimod 5%, IngMeb 0.015% was significantly more effective and resulted in a low ICER of €1993/QALY gained for the face and scalp AK. The cost-effectiveness of imiquimod 5% was, however, uncertain because IngMeb 0.015% dominated imiquimod 5% when a 1-year time horizon,

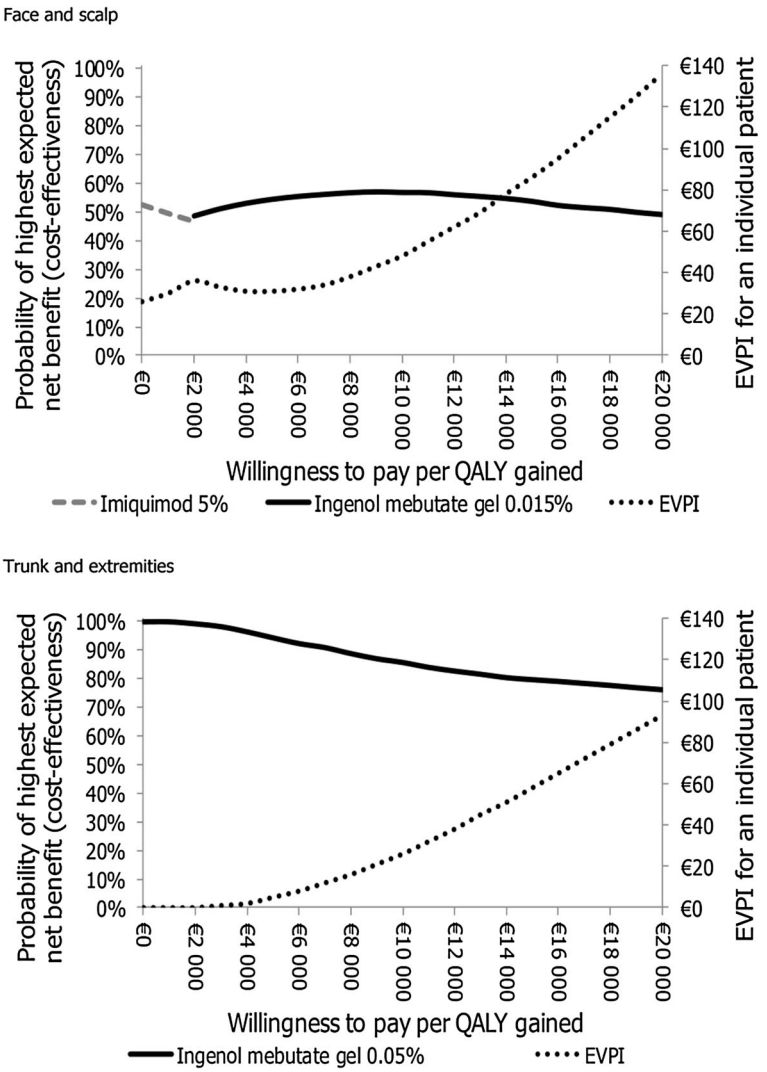

Fig. 4 CEAF and EVPI for the treatments indicated for actinic keratosis on face and scalp (cryosurgery, diclofenac, imiquimod 3.75%, imiquimod 5%, ingenol mebutate gel 0.015%, methyl aminolevulinate photodynamic therapy) are presented in the *upper part of the figure*. The CEAF and EVPI for actinic keratosis treatments indicated for trunk and extremities (cryosurgery, diclofenac, ingenol mebutate gel 0.05%) are presented in the *lower part of the figure*. *CEAF* cost-effectiveness acceptability frontier, *EVPI* expected value of perfect information *QALY* quality-adjusted life-year

fixed-effects meta-analysis, MAL + PDT for the treatment of recurrence, 30% of IngMeb in the PC setting, all topicals in the PC setting or the societal perspective inputs were used. Furthermore, IngMeb 0.05% was the most effective and cost-saving treatment for AK in trunk and extremities in all analyses. Consequently, both formulations of IngMeb were cost-effective in the Finnish setting.

The modeled results were used to assess the value of perfect information. The EVPI per patient can be interpreted as the maximum average sum per patient that is worthwhile to invest in the gathering of additional evidence for the varying model parameters. When the per patient EVPI of €136 for head (€93 for body) area with €20,000/QALY gained is compared against the potential cost of additional research

Table 4 Sensitivity analyses: quality-adjusted life-years above, costs (€) below

Scenario[a]	MAL + PDT	IngMeb 0.015%	IngMeb 0.05%	Diclofenac	Imiq 3.75%	Imiq 5%	Cryosurgery	ICER[b] (€/QALY) gained		Delta ICER[c]
Methodological basis										
Base case	1.526	1.524	1.522	1.520	1.518	1.517	1.514	1	1933	0
	982	794	869	1062	885	781	1114	2	82,607	0
Deterministic base case	1.526	1.523	1.521	1.519	1.517	1.516	1.511	1	1438	−495
	981	789	869	1064	886	779	1111	2	59,142	−23,465
1-year time horizon	0.773	0.771	0.770	0.767	0.766	0.765	0.767	1	Dom.	−2347
	856	715	799	990	819	718	978	2	80,471	−2136
No discounting	1.547	1.545	1.543	1.540	1.539	1.538	1.534	1	1854	−79
	985	797	869	1063	886	784	1115	2	81,972	−635
Mortality roughly included	1.508	1.506	1.504	1.501	1.500	1.499	1.494	1	1576	−357
	981	792	868	1059	880	781	1111	2	78,522	−4085
Effectiveness										
QoL not anchored	1.965	1.963	1.961	1.957	1.956	1.956	1.948	1	1661	−272
	980	794	867	1060	883	782	1111	2	64,751	−17,856
Beta distribution for QoL	1.526	1.523	1.521	1.518	1.517	1.516	1.512	1	1805	−128
	983	797	871	1061	884	785	1114	2	53,930	−28,678
Fixed-effects meta-analysis	1.524	1.522	1.521	1.518	1.517	1.515	1.511	1	Dom.	−2820
	980	803	865	1060	883	809	1108	2	81,928	−679
Similar LSRs	1.521	1.520	1.518	1.515	1.517	1.516	1.508	1	3076	1143
	981	794	865	1060	884	784	1110	2	182,513	99,906
Topical's discontinuation	1.526	1.522	1.521	1.518	1.516	1.515	1.514	1	3824	1891
	980	772	841	1027	828	744	1111	2	53,398	−29,209

Table 4 continued

Scenario[a]	MAL + PDT	IngMeb 0.015%	IngMeb 0.05%	Diclofenac	Imiq 3.75%	Imiq 5%	Cryosurgery	ICER[b] (€/QALY) gained		Delta ICER[c]
Similar AK recurrence	1.524	1.522	1.521	1.518	1.516	1.515	1.513	1	1314	−619
	982	793	865	1060	883	784	1111	2	92,155	9547
Treatment strategies										
MAL + PDT for recurrence	1.525	1.523	1.522	1.519	1.518	1.518	1.513	1	Dom.	−2321
	980	761	848	1033	862	763	1113	2	135,515	52,908
Treated second-line recurrence	1.524	1.521	1.520	1.517	1.516	1.515	1.512	1	1613	−319
	980	793	867	1062	884	782	1111	2	82,069	−538
Third-line treatment included	1.523	1.522	1.521	1.518	1.516	1.515	1.512	1	1824	−109
	983	812	891	1088	905	800	1115	2	95,276	12,668
Recurrence/second treatment ignored	1.525	1.518	1.514	1.510	1.510	1.513	1.514	1	1161	−771
	763	479	479	619	500	473	879	2	40,615	−41,993
Costs										
30% of IngMeb in PC	1.525	1.522	1.521	1.518	1.516	1.516	1.511	1	Dom.	−10,293
	981	727	800	1060	885	784	1111	2	100,170	17,563
100% of topicals in PC	1.525	1.522	1.521	1.518	1.516	1.515	1.512	1	Dom.	−3173
	984	556	626	820	643	565	1112	2	161,694	79,087
Societal perspective	1.526	1.523	1.522	1.519	1.518	1.516	1.512	1	Dom.	−63,067
	1157	1087	1200	1525	1500	1524	1395	2	28,802	−53,805

AK actinic keratosis, *ICER* incremental cost-effectiveness ratio, *Imiq* imiquimod, *IngMeb* ingenol mebutate gel, *LSR* local skin response, *MAL + PDT* methyl aminolevulinate photodynamic therapy, *PC* primary care, *QoL* quality of life, *QALY* quality-adjusted life-year

[a] All probabilistic with payer perspective and 3% discounting/year, if not otherwise stated

[b] $ICER^1$ = IngMeb 0.015% vs. imiquimod 5%. $ICER^2$ = MAL + PDT vs. IngMeb 0.015%. Dom = IngMeb 0.015% dominates imiquimod 5%

[c] Difference in ICER compared to the base case

per studied patient, the decision on whether to invest in additional research may not be supported. On the other hand, if the EVPI is interpreted as the opportunity cost for choosing a particular optimal treatment for all patients, and given that the optimal treatment decision would be an incorrect one for some patients (opportunity cost), the EVPI per patient with €20,000/QALY gained was rather low in comparison to, for example, costs associated with different treatments. This also means that it may not be worthwhile from the perspective of cost-effectiveness to find patients to whom the average optimal treatment is not really optimal.

The assessment of AK field treatment was important for several reasons. First, where multiple AK lesions are present there is likely to be an underlying and surrounding area of actinic damage (field change); the extent of this area may not be evident visually or by physical examination. Second, field change can have a role in the development of SCC or other NMSCs. Third, cryotherapy is a commonly used lesion-directed therapy that does not target actinic changes in the sun-damaged skin surrounding the individual lesion [2, 30]. Fourth, before IngMeb, there was medical (adherence) need for field directed therapies with shorter and simpler treatment regimens and less long-term irritation and inflammation [31].

Direct comparative data between the relevant treatment options were not available and thus, CCs were included on the basis of Bayesian network meta-analysis [63]. In comparison with one alternative meta-analysis available [104] that includes IngMeb without any further specification, we chose the meta-analysis assessed by the authorities for the following reasons: IngMeb 0.015% and 0.05% were included and separated (they are essentially different treatments for different indications), and imiquimod 5% for 8 weeks and 3.75% for 6 weeks were included. However, on aggregate level, the results of these meta-analyses concur, and in both analyses, frequently used cryotherapy is inferior.

One reason for cryosurgery's relatively poor result can be related to the fact that primarily destructive therapies of individual AKs do not prevent the progression of AK into SCCs in adjacent dysplastic tissues. According to the European Dermatology Forum guidelines management strategies that counteract the effects of systemic immunosuppression via the induction of a locally restricted, tumor-specific immune response, the induction of apoptosis in dysplastic keratinocytes or the use of phototoxic agents can provide viable options for treatment of the AK field [2].

Some studies assessing the economic value or cost-effectiveness of treating AK with different treatment response assessment times have been done [3, 6, 105–113]. Generally, the treatment of AK has been found to be cost-effective. However, MAL + PDT and sometimes cryosurgery treatment have been found to be relatively costly, which is in line with the results of this analysis. Some of the published studies were based on cost estimates and other assumptions that are not applicable or reproducible in Finnish (e.g., [110, 111]) or other settings [113]. We included a wide spectrum of outcomes. The average time to assess the response was 6 months in the trials and 6 months was also an adequate time to assess CC based on the Finnish clinical practice. We also accounted for the treatment specific time to CC and time with LSR in addition to a 12 months recurrence risk. Furthermore, when considering the European perspective of resources used and associated costs, the Finnish setting represents the average quite well for skin cancers [38].

This modeled assessment had some key limitations. First, a decision tree approach was chosen as a more appropriate and simpler approach consistent with the nature of AK and its treatments. In particular, the differential timing of treatment responses and LSRs (and also productivity losses in a sensitivity analysis scenario) with different treatments had to be considered, and was included as a distribution. In the Markov model setting, the inclusion of these characteristics would have necessitated a very short cycle length (e.g., 1 week) and the derivation of transition probabilities would have become very difficult or impossible. It should be noted that in conventional Markov models, instant response to treatment is usually assumed and the timing of events is then "adjusted" with, for example, a life table method of half-cycle correction which would not have been an unbiased approach in this AK setting. Another valid approach in addition to the flexible decision tree would have been a discrete event simulation which was not considered due to lack of patient-level data or equations based on the patient-level data.

Second, the decision tree had a 2-year time horizon, which was selected due to multiple reasons. Development of SCC over time is uncertain and it is uncertain whether the AK treatments have similar or different impacts on the risk of developing SCC. Furthermore, the development of AK fields other than the initial field would have to be accounted for. In addition, costs of drugs can change over time, and the effectiveness of multiple treatment times (in the case of multiple recurrences) to the same field is likely to decrease by the treatment line (but there is no data to confirm this assumption which is needed for a longer than 2-year model). In addition, the AK patient group is rather old and for a longer time horizon model, mortality would have to be accounted for and currently there is no data on whether the AK treatments impact mortality. Consequently, we see that extension of the time horizon would complicate the model and require many major assumptions without any scientific evidence to support them. The impact of longer time horizon to the assessment question (the cost-effectiveness of treating a particular 25 cm^2 AK field) would be marginal from the perspective of current data, and would potentially have a negative risk–benefit ratio (i.e., the risks due to inherent major modeling assumptions could potentially bias the results).

Third, the modeling assumed that treatment responses are assessed at 6 months after treatment. However, in real-life clinical practice, the assessment may take place earlier; this assumption was considered plausible since the model accounts for the varying time to treatment response and time with LSR when calculating QALYs. The 6-month interval was based on the mid-point assessment range of clinical trials that were identified for the Bayesian network meta-analysis [63]. Furthermore, a static time point was required for a decision tree structure, to allow all comparisons to be treated equally.

Fourth, patients entered the model when initiating the first-line therapy. IngMeb has the potential to be used more in the PC setting. For that, a scenario with 30% PC use was assessed. As an extreme sensitivity analysis scenario and to improve result comparability to other settings, all topicals were assumed to be used in the PC setting.

Fifth, all patients were assumed to complete the first course of treatment in the base case analysis because the used efficacy data are based on an intention-to-treat setting, which therefore already incorporated the impact of treatment discontinuations [114, 115]. Also, the treatment response/success was measured in terms of CC (no AK lesions remaining), which is the strictest definition of treatment success,

but well in line with the AK treatment objectives. This is easy to understand and may be a less biased outcome in comparison with, e.g., proportion of AK lesions cleared.

Sixth, the study lacked the data for subgroup analysis based on patient characteristics. Hypothetically speaking, differences in QALYs could be marginally larger for men or for younger than average patients based on their population values [95]. In a longer time horizon modeling including mortality, the potential difference between men and women is likely to be meaningless.

Last, these estimated treatment costs and benefits due to AK management are not negligible. If AK could be increasingly treated in PC, treatment costs could be significantly reduced compared with the current situation. Future studies should focus on the relationship between the AK treatment outcome and NMSC, which may further highlight the need for AK field treatment. In other settings, the CEAs may also include 5-FU. Furthermore, the results for subgroups (e.g., younger and older patients, men and women) may be regarded relevant, if value for money is assessed based on patient characteristics or at individual level.

CONCLUSION

IngMeb 0.015% and 0.05% resulted robustly in quality of life gains at acceptable costs when compared with all relevant AK treatment options in Finland. Relatively low EVPI at €250 per patient with the maximum expected WTP of €30,000 per QALY gained was estimated.

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Conflict of interest. EJS is an employee, shareholder, and board member of ESiOR Oy, Kuopio, Finland. EJS is also the CEO of ESiOR Oy. ESiOR Oy carries out studies, statistical analysis, consultancy, education, reporting and health economic evaluations for several pharmaceutical (including companies producing and marketing AK treatments), food industry, diagnostics and device companies, hospitals and academic institutions. TH is an employee, shareholder, and board member of ESiOR Oy, Kuopio, Finland. Neither EJS nor TH holds drug company shares. ALS is employed by LEO Pharma Oy, Vantaa, Finland. KS has received speaker honorariums and consultancy fees from Leo Pharma Oy. All authorship decisions were made on the basis of scientific consideration.

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