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A trial-based cost-effectiveness analysis of topical 5-fluorouracil vs. imiquimod vs. ingenol mebutate vs. methyl aminolaevulinate conventional photodynamic therapy for the treatment of actinic keratosis in the head and neck area performed in the Netherlands*

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Conflicts of interest

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Summary

Background Actinic keratosis (AK) is a common premalignant skin condition that might have the ability to progress into squamous cell carcinoma. Due to the high incidence of AK, treatment of this disease significantly impacts healthcare spending.
Objectives To determine which commonly prescribed field-directed treatment is the most cost-effective, when comparing 5-fluorouracil (5-FU) 5%, imiquimod (IMQ) 5%, ingenol mebutate (IM) 0·015% and methyl aminolaevulinate photodynamic therapy (MAL-PDT) for AK in the head and neck region.
Methods We performed an economic evaluation from a healthcare perspective. Data were collected alongside a single-blinded, prospective, multicentre randomized controlled trial with 624 participants in the Netherlands. The outcome measure was expressed as the incremental cost-effectiveness ratio, which is the incremental costs per additional patient with ≥ 75% lesion reduction compared with baseline. This trial was registered at ClinicalTrials.gov, number NCT02281682.
Results The trial showed that 5-FU was the most effective field treatment for AK in the head and neck region. Twelve months post-treatment, the total mean costs for 5-FU were significantly lower (€433) than the €728, €775 and €1621 for IMQ, IM and MAL-PDT, respectively. The results showed that 5-FU was a dominant cost-effective treatment (more effective and less expensive) compared with the other treatments, 12 months post-treatment.
Conclusions Based on these results, we consider 5-FU 5% cream as the first-choice treatment option for multiple AKs in the head and neck area.

What is already known about this topic?

- Due to the increasing incidence of actinic keratosis (AK), the recommended treatment results in a considerable socioeconomic burden for (dermatological) healthcare.
- Although cost-effectiveness modelling studies have been performed in which different treatments for AK were compared, a prospective clinical trial comparing four

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frequently prescribed treatments on effectiveness and resource consumption within a time horizon of 12 months has never been conducted.

What does this study add?

- This is the first study examining the cost-effectiveness of 5-fluorouracil 5% cream, imiquimod 5% cream, ingenol mebutate 0·015% gel and methyl aminolaevulinate photodynamic therapy, with data collected in a randomized controlled trial over a time horizon of 12 months.
- We found that 5-fluorouracil was a dominant cost-effective treatment (more effective and less costly), based on data from the Netherlands.

Actinic keratosis (AK) is a premalignant cornification disorder of the skin, caused by DNA damage in the basal keratinocytes as a result of chronic exposure to the sun.[1] It occurs mostly on sun-exposed skin, such as the scalp and hands.[1] AK is a frequently seen skin problem, and in white residents in the Netherlands aged > 45 years the prevalence is 49% for men and 28% for women.[2] The incidence is still increasing, due to the ageing population and higher ultraviolet radiation exposure.[3] When left untreated, AK might develop into cutaneous squamous cell carcinoma, although the risk of an individual lesion to progress varies in different studies from 0·025% to 16% per year.[4–6] Generally, AK is still considered a premalignant lesion and is therefore often treated.

Usually multiple, either visible or subclinical lesions develop in the same area, so called field cancerization.[7,8] For this field cancerization, patients are treated with one of the available topical field-directed treatments, which have a widespread variation of mode of action, effectiveness, treatment schedule and cost. Due to the increasing incidence, the recommended treatment of AK results in a considerable socioeconomic burden for (dermatological) healthcare.[9] The costs of managing AK in the U.S.A. are an estimated $1·2 billion in healthcare each year.[10,11] Considering the impact on healthcare costs, it is important to know which treatment is the most cost-effective. Although cost-effectiveness modelling studies have been performed in which different treatments for AK were compared, a prospective clinical trial comparing four frequently prescribed treatments on effectiveness and real resource consumption with a time horizon of 12 months has never been conducted.[12–17]

Recently, we showed, that 5-fluorouracil (5-FU) 5% is the most effective field-directed treatment for the management of AK in the head and neck area, compared with imiquimod (IMQ) 5%, ingenol mebutate (IM) 0·015% and methyl aminolaevulinate photodynamic therapy (MAL-PDT).[18] In this study we evaluated the differences in costs between these four topical treatment modalities for AK in the head and neck area to define the most cost-effective treatment.

Patients and methods

Study design and population

Data for the economic evaluation were collected in a single-blinded, prospective, multicentre randomized controlled trial (RCT) performed in the Netherlands. In total 624 patients were randomized to four treatments: 5-FU, IMQ, IM or MAL-PDT. To meet the inclusion criteria patients had to be 18 years or older with a Fitzpatrick skin type I–IV, with at least five AKs (Olsen grade I–III) in an area of 25–100 cm^2 in the head and neck region. The exclusion criteria were treatment of AK in the target area within 3 months prior to inclusion, malignancies in the study area, use of immunosuppressive drugs or retinoids (or use 3 months prior to the trial), porphyria, soy or peanut allergy, pregnancy or breastfeeding, and genetic skin cancer disorders. The trial was executed in accordance with the Declaration of Helsinki and was approved by the local medical ethical committee. All patients provided written informed consent. Full details of the clinical trial have been reported previously.[18]

Therapeutic procedures

In all patients, superficial curettage of the lesions was performed prior to the treatment.

5-Fluorouracil

5-Fluorouracil 5% cream (Efudix®; Meda Pharma B.V., Amstelveen, the Netherlands) was applied by the patient twice a day during 4 weeks. Each patient received one tube of 40 g. This amount was sufficient to cover one treatment cycle, irrespectively of the size of the treatment area.

Imiquimod

Imiquimod 5% cream (Aldara®; Meda Pharma B.V., Solna, Sweden) was applied by the patient once a day, 3 days a week (e.g. Monday, Wednesday and Friday), during four consecutive weeks. Per treatment area of 25 cm^2 one sachet of 250 mg per application per day was prescribed.

Ingenol mebutate

Ingenol mebutate 0·015% gel (Picato®; LEO Pharma B.V., Ballerup, Denmark) was applied by the patient once a day for three consecutive days. Per treatment area of 25 cm^2 one tube of 0·47 g per application per day was used.

Methyl aminolaevulinate photodynamic therapy

PDT was performed by trained nurses during an outpatient visit. Per treatment area of 25 cm^2, 2 g of MAL (Metvix®; Galderma, Lausanne, Switzerland) was applied in a thin layer of 1 mm and subsequently covered by an ultraviolet-blocking foil and bandages (Tegaderm®; 3M, Leiden, the Netherlands; or Cutisoft®; BSN Medical, Hamburg, Germany). After 3 h, the cream was wiped off and the area was exposed to a light-emitting diode, either Aktilite® (Galderma SA) or Omnilux® (Waldmann, London, U.K.), with an optimal wavelength of 635 ± 18 nm (fluency of 37 J cm^{-2}) during 7 min. Directly after the treatment the target area was covered with bandages to prevent ultraviolet exposure for 24 h.

Patients visited our outpatient clinic at baseline, and 3 months and 12 months post-treatment. This follow-up scheme was in accordance with the Dutch guidelines for AK.[19] In patients randomized to 5-FU, IM and MAL-PDT, initial treatment response was evaluated 3 months post-treatment. In patients randomized to IMQ treatment, initial response was evaluated at 1 month post-treatment, in accordance with the summary of product characteristics (SPC) guidelines.[20] In case of initial insufficient response, defined as < 75% lesion reduction compared with baseline, the same treatment was repeated once. Twelve months post-treatment, patients were classified as having treatment success if they had ≥ 75% lesion reduction compared with baseline. Treatment failure was defined as patients who had < 75% lesion reduction 3 months after the last treatment (initial failure) or 12 months after initial successful treatment.

If necessary, for example in case of side-effects, other treatments were given, such as topical antibacterial treatments. As an additional treatment, cryotherapy was used for single lesions in case of insufficient response to the study treatment. Full details of the treatment strategy have been reported previously.[18]

Outcome measures

The primary outcome was expressed as the incremental cost-effectiveness ratio (ICER), which was defined as the incremental costs per additional patient with ≥ 75% lesion reduction. The ICER was calculated as the difference in the total mean costs per treatment divided by the difference in the percentage of patients with ≥ 75% lesion reduction at 12-month follow-up.

Economic evaluation

The economic evaluation was performed from a healthcare perspective, because it was expected that out-of-pocket costs and use of services outside the healthcare would be low. In addition, productivity loss as a result of the condition and treatment was assumed to be minimal. The Dutch guidelines for economic evaluation were used to execute the cost-effectiveness analysis.[21]

A distinction was made between pretreatment costs, treatment costs and post-treatment costs. Pretreatment costs consisted of an outpatient baseline visit and curettage prior to the treatment. Treatment costs included the study medication and, in case of MAL-PDT, personnel costs, use of materials and a light source. The costs of the light source per session were calculated with the help of the purchase price, depreciation period, interest and the number of annual sessions. In contrast to the treatment with topical creams or gel, MAL-PDT was an in-hospital treatment. Therefore, a general hospital overhead of 38% was calculated over the total treatment costs as an overall percentage.[21] Post-treatment costs included outpatient control visits after (re)treatment, additional cryotherapy, biopsy in case of suspicion of an invasive tumour and topical treatments, telephone consultation and extra outpatient visits or visits to the general practitioner in case of side-effects.

An overview of the costs per unit is shown in Table 1. Unit costs were calculated by multiplying volumes of use by the costs per unit. Real resource consumption was measured during the trial. As all data with regard to the costs and effectiveness were collected within 1 year, no discounting was applied. All costs are presented in euros and were indexed for annual inflation to the year 2018.[22]

Analysis

The cost-effectiveness analysis was performed according to the modified intention-to-treat (mITT) principle. The mITT population included patients who were randomized and received treatment and for whom the primary outcome was available. All data were collected in SPSS 23·0 (IBM, Armonk, NY, U.S.A.). As cost data generally have a skewed distribution, a nonparametric bootstrap analysis (1000 samples) was performed to generate confidence intervals (CIs) around the difference in mean costs and to quantify the uncertainty surrounding the ICER. A bootstrap method estimates the sampling distribution of a statistic through a large number of simulations, based on sampling with replacement from the original data.[23] The results are presented in a cost-effectiveness plane, which is a graphical presentation in which the additional costs and health outcome effects of two therapies are compared. The bootstrap analysis was performed using Microsoft Excel 2010. To test the robustness of the cost-effectiveness results, sensitivity analyses were conducted. Firstly, the effectiveness parameter was varied to investigate the impact on the ICER. Treatment effect 12 months post-treatment was varied by taking the upper bound of the 95% CI for the treatments IMQ, IM and MAL-PDT and the lower bound of the 95% CI for 5-FU. Secondly, an analysis was performed according to the per protocol principle.

Results

Clinical outcomes

In total 624 patients were eligible for inclusion: 155 were randomized to 5-FU (151 received treatment, six lost to

Table 1 Unit costs of the resources used within the trial

Resource use	Unit	Cost (€)	Reference
University hospital	Outpatient visit	169·61	Dutch manual for costing[21]
General hospital	Outpatient visit	83·24	Dutch manual for costing[21]
Telephone consultation	Phone call	21·24	MUMC+
Biopsy	Test	107·35	MUMC+
Curettage	Curette	3·55	MUMC+
Cryotherapy	Session	16·24	MUMC+
Treatment costs 5-fluorouracil			
Cream	Grams (40)	31·31	Pharmacotherapeutic Compass[28]
Treatment costs imiquimod			
Cream	Grams (0·25)	4·72	Pharmacotherapeutic Compass[28]
Treatment costs ingenol mebutate			
Cream	Grams (0·47)	25·77	Pharmacotherapeutic Compass[28]
Treatment costs MAL-PDT			
Personnel (nurse)	Minute	0·47	MUMC+
Cream	Grams (2)	202·42	Pharmacotherapeutic Compass[28]
Aktilite®	Session	7·98	MUMC+
Material	Multiple	1·93	MUMC+
Topical treatments in case of side-effects			
Chlorhexidine	Grams (30)	8·07	Pharmacotherapeutic Compass[28]
Fusidic acid	Grams (30)	6·92	Pharmacotherapeutic Compass[28]
Triamcinolone	Grams (30)	3·42	Pharmacotherapeutic Compass[28]
Chloramphenicol	Grams (5)	3·03	Pharmacotherapeutic Compass[28]
Mometasone	Grams (30)	3·88	Pharmacotherapeutic Compass[28]
Cetomacrogol	Grams (30)	2·50	Pharmacotherapeutic Compass[28]
Betamethasone	Grams (30)	3·52	Pharmacotherapeutic Compass[28]
Silver sulfadiazine	Grams (50)	2·99	Pharmacotherapeutic Compass[28]
Additional			
General practitioner	Consultation	34·34	Dutch manual for costing[21]

MAL-PDT, methyl aminolaevulinate photodynamic therapy; MUMC+, Maastricht University Medical Centre+.

follow-up), 156 to IMQ (153 received treatment, nine lost to follow-up), 157 to IM (151 received treatment, four lost to follow-up) and 156 to MAL-PDT (155 received treatment, three lost to follow-up).[18] Eight crossovers occurred before the assigned treatment was started. These eight patients preferred a different therapy. Of five patients who initially were randomized to MAL-PDT, three patients received 5-FU and two IM. One patient received MAL-PDT instead of 5-FU and two patients received 5-FU instead of the initial IMQ and IM treatment.[18]

The proportions of patients with treatment success 12 months post-treatment were 74·7% for patients treated with 5-FU (95% CI 66·8–81·0), 53·9% for IMQ (95% CI 45·4–61·6), 28·9% for IM (95% CI 21·8–36·3) and 37·7% for MAL-PDT (95% Cl 30·0–45·3).[18]

Cost analysis

Table 2 shows the cost analysis results for the four treatment groups at the 12-month follow-up. The total mean pretreatment costs were comparable between the four treatments. The mean treatment and post-treatment costs were lower for 5-FU than for IMQ, IM and MAL-PDT. The total mean costs were €433 for 5-FU, €728 for IMQ, €775 for IM and €1621 for MAL-PDT. The total mean costs for 5-FU were significantly lower than for the three other treatments.

Annual depreciation costs for the Aktilite® device (€11 800 including VAT) were calculated over 10 years with an interest of 4·2%. Division of these costs by the total annual procedures led to €7·98 per session.

Cost-effectiveness analysis

As shown in Table 3, 5-FU was a dominant cost-effective treatment (more effective and less expensive) compared with IMQ, IM and MAL-PDT, based on the ICER. The cost-effectiveness plane illustrates that 100% of all ratios of all three comparisons were located in the lower right quadrant (Fig. 1). The lower right quadrant shows less costly and more effective treatments. Thus, in all cases, 5-FU was a more effective and cost-saving treatment than IMQ, IM or MAL-PDT.

Sensitivity analysis

Table 4 shows the results of the sensitivity analyses. Varying the effectiveness rate for 5-FU according to the lower bound of the 95% CI, and the upper bound for IMQ, IM and MAL-PDT, showed similar results for the ICER. Treatment with 5-

Table 2 Cost analysis of 5-fulorouracil (FU), imiquimod (IMQ), ingenol mebutate (IM) and methyl aminolaevulinate photodynamic therapy (MAL-PDT)

	Mean cost (€)				Difference (95% CI)		
	5-FU	IMQ	IM	MAL-PDT	IMQ − 5-FU	IM − 5-FU	MAL-PDT − 5-FU
Number of patients	149	149	150	154			
Pretreatment costs							
Baseline outpatient visit	117	117	116	118			
Curettage	3·50	3·50	3·50	3·50			
Total pretreatment costs	121	121	120	122			
Treatment costs							
First treatment cycle	40	180	242	954[a]			
Second treatment cycle	4	51	102	256[a]			
Total treatment costs	44	231	344	1210[a]	187 (164–210)	300 (267–333)	1166 (1070–1266)
Post-treatment costs							
Outpatient follow-up visits	243	342	275	262			
Extra biopsy	1·50	2	2	3·50			
Cryotherapy	7	12	13	12			
Side-effects							
Outpatient visits	6	11	10	3			
Telephone consultation	2·50	2	2·50	0·50			
Topical treatment	8	7	8	7·50			
General practitioner visit	0·20	0	0	0			
Total post-treatment costs	268	376	311	289	108 (81–138)	43 (13–71)	21 (−1–44)
Total mean treatment costs	433	728	775	1621	295 (253–337)	342 (290–394)	1188 (1090–1278)

CI, confidence interval. [a]An additional hospital overhead of 38% is applied to the treatment cost of MAL-PDT.

Table 3 Incremental cost-effectiveness ratios (ICERs)

Treatment	Costs (€)	Effectiveness	ICER
5-Fluorouracil	433	0·747	Dominant[a]
Imiquimod	728	0·539	
Difference	−295	0·208	
5-Fluorouracil	433	0·747	Dominant
Ingenol mebutate	775	0·289	
Difference	−342	0·458	
5-Fluorouracil	433	0·747	Dominant
MAL-PDT	1621	0·377	
Difference	−1188	0·370	

MAL-PDT, methyl aminolaevulinate photodynamic therapy.
[a]Dominant means more effective and less expensive.

FU was still dominant. When performing a per protocol analysis, similar results were found.

Discussion

The results of our economic evaluation showed that treatment with 5-FU cream was a dominant cost-effective field-directed treatment for AK compared with IMQ, IM and MAL-PDT after 12 months of follow-up.

To the best of our knowledge, this is the first study examining the cost-effectiveness of 5-FU, IMQ, IM and MAL-PDT with data collected in an RCT and a time horizon of 12 months. Although a number of previous modelling studies examined the cost-effectiveness of treatments for AK, comparing our results with these studies is difficult because of the use of different outcome measures, different treatment comparators and sometimes the use of a shorter time horizon.[12–16]

A modelling study by Wilson compared the costs and effectiveness of treatment with IMQ or MAL-PDT using a decision tree.[24] They found total annual costs of £360 ± 453 for IMQ and £534 ± 672 for MAL-PDT. These costs were lower than those that we calculated, probably because they were based on hypothetical patients with smaller treatment areas.

In a real-life cohort study by van Rijsingen *et al.*, treatments with 5-FU, IMQ and MAL-PDT were compared.[17] They found that treatment with 5-FU 5% had the lowest annual costs (€738), compared with IMQ (€877) and MAL-PDT (€1950), and resulted in the largest reduction of lesions.[17] Our total annual costs for treatment with 5-FU (€433), IMQ (€728) and MAL-PDT (€1621) were lower, which might be explained by the fact that their patients were more severely affected than ours. However, the conclusions of both studies are comparable.

In our study, the higher total mean costs in the groups assigned to IMQ, IM and MAL-PDT were mainly attributable to the higher treatment costs. As one tube of 40 g of 5-FU covers a treatment area of 100 cm^2, a single tube was sufficient irrespectively of the size of the treatment area. This was in contrast with the other treatments, in which the amount of cream was dependent on the size of the affected area. One sachet or tube of IMQ, IM or MAL-PDT covered a treatment area of only 25 cm^2, as advised in the SPC. Thus, not only were the costs per unit higher, but the amount of prescribed units was also higher for treatment with IMQ, IM and MAL-PDT.

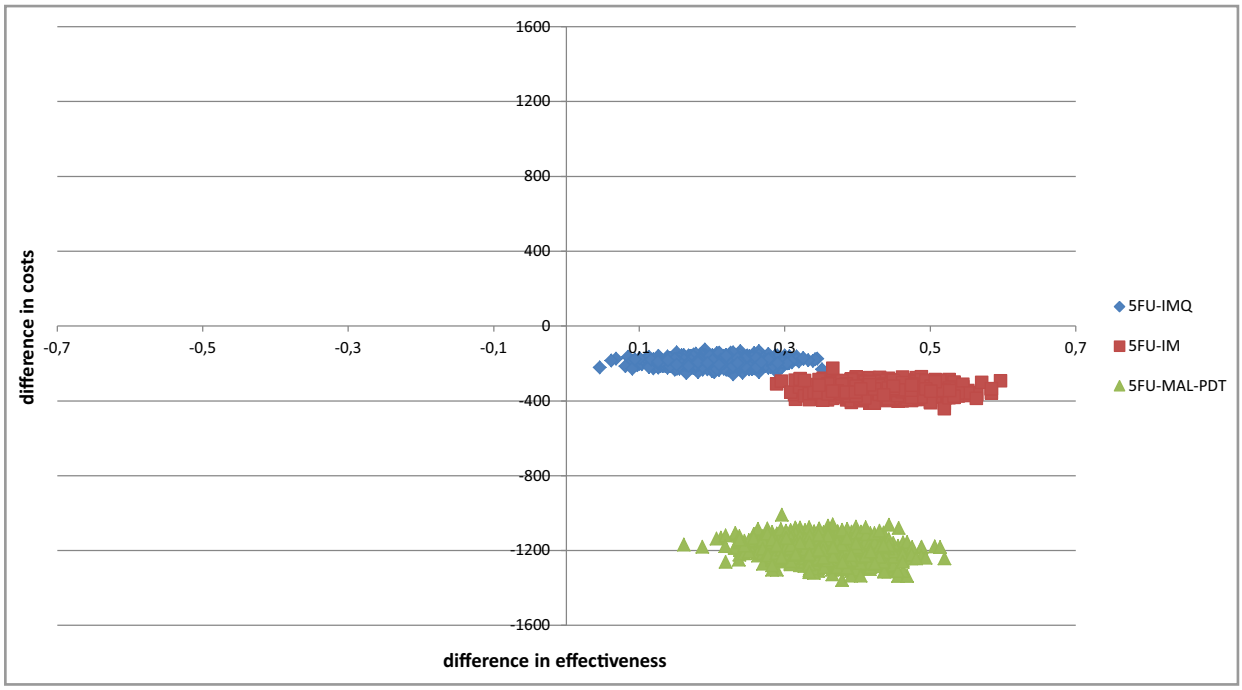

Figure 1 Cost-effectiveness plane for 5-fluorouracil (5-FU) vs. imiquimod (IMQ), 5-FU vs. ingenol mebutate (IM) and 5-FU vs. methyl aminolaevulinate photodynamic therapy (MAL-PDT). The bootstrapped incremental cost-effectiveness ratios of 5-FU compared with the other treatments cover 100% of the quadrant in which 5-FU is a dominant treatment. Therefore it is a more effective and cost-saving treatment.

Table 4 Sensitivity analysis for incremental cost-effectiveness ratios (ICERs)

					Difference		
	5-FU	IMQ	IM	MAL-PDT	5-FU − IMQ	5-FU − IM	5-FU − MAL-PDT
Variation upper and lower bound 95% CI							
Total mean costs (€)	433	728	775	1621	−295	−342	−1188
Effectiveness	0·668	0·616	0·363	0·453	0·052	0·305	0·215
ICER					Dominant[a]	Dominant	Dominant
Per protocol							
Total mean costs (€)	432	710	756	1614	−278	−324	−1182
Effectiveness	0·767	0·587	0·332	0·431	0·180	0·435	0·336
ICER					Dominant	Dominant	Dominant

CI, confidence interval; 5-FU, 5-fluorouracil; IM, ingenol mebutate; IMQ, imiquimod; MAL-PDT, methyl aminolaevulinate photodynamic therapy. [a]Dominant means more effective and less expensive.

The interpretation of a disease-specific cost-effectiveness ratio can be difficult, because the maximum acceptable cost for treatment of AK has not yet been determined. This maximum amount is what decision makers or insurance companies are willing to pay to achieve an additional patient with ≥ 75% reduction of AK. A more common outcome measure for effectiveness is the quality-adjusted life-year (QALY). The QALY represents the impact on both the quantity and the quality of life.[25] In this study we did not use the QALY as an outcome measure, because it was expected that AK would not have an effect on life expectancy and on general health-related quality of life. In addition, AK had a low impact on the skin-related quality-of-life scores.

Our data were collected alongside an RCT and therefore real resource consumption was measured. This maximized the information available for analysis.[26] However, it can be questioned whether collecting data from an RCT could lead to more outpatient follow-up visits, which implicates protocol-driven extra costs. In our study, all the outpatient follow-up visits were in accordance to the Dutch guidelines for AK and the SPC guidelines.[19,20] By following these guidelines, we tried to make our trial data as representative as possible for daily practice. No extra study visits were scheduled. Sensitivity analyses were performed to test the robustness of our outcome. These analyses showed similar findings to the mITT results, indicating the robustness of our results.

In our study 22 patients (3·5%) were lost to follow-up at 12 months post-treatment, which is deemed acceptable.[27] We used a multiple imputation technique to minimize potential bias due to loss to follow-up.[27]

Our study was performed in the Netherlands. The costs are based on the Dutch healthcare system, and Dutch cost-prices were used. The costs can vary between different countries. Furthermore, the availability of 5-FU 5% differs between countries. In our opinion unavailability of 5-FU is a loss, as it is the most effective field-directed treatment for AK and the cheapest treatment.

In conclusion, the results of our economic evaluation show that 5-FU cream was a dominant cost-effective treatment for multiple AKs in the head and neck area, compared with IMQ, IM and MAL-PDT, 12 months post-treatment, based on data from the Netherlands. Based on these results, we consider 5-FU cream the first-choice treatment option for multiple AKs.

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