

The Effect of Four Approaches to Treat Actinic Keratosis on the Health-Related QOL, as Assessed by the Skindex-29 and Actinic Keratosis QOL



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TO THE EDITOR

To evaluate the impact of actinic keratosis (AK) and the effect of four AK treatments on the health-related QOL (HRQOL), the Skindex-29 and AK QOL (AKQOL) questionnaires were completed by 624 patients with AK participating in a randomized controlled trial comparing 5% fluorouracil cream (Efudix, Meda Pharma B.V., Amstelveen, the Netherlands), 5% imiquimod cream (Aldara, Meda Pharma B.V., Solna, Sweden), methyl aminolevulinate (Metvix, Galderma SA, Penn Pharmaceutical Services, Gwent, UK) photodynamic therapy (MAL-PDT), and 0.015% ingenol mebutate gel (Picato, LEO Pharma A/S, Bellerup, Denmark) (Jansen et al., 2019). In this trial, the probability of treatment success at 12 months was 74.7% for fluorouracil, 53.9% for imiquimod, 37.7% for MAL-PDT, and 28.9% for ingenol mebutate. Patients completed the questionnaires at baseline and at 12 months after treatment.

The Skindex-29 consists of 29 items covering three domains: symptoms, emotions, and functioning (Chren et al., 1997). The overall and domain scores range from 0 to 100, with higher scores indicating more impairment of HRQOL. For interpretation of the Skindex-29 scores in clinical practice, the cutoff scores defined by Prinsen et al. (2011) were used to classify patients as having mild (25–32), moderate (32–44), and severe (≥ 44) impairment of HRQOL.

The AKQOL is the only validated AK-specific questionnaire, consisting of nine questions covering three domains:

emotion (three items), function (three items), and control of life (two items) and one single global item (“my quality of life is decreased because of my sun damaged skin”) (Esmann et al., 2013). The sum of all questions leads to the total score (0–27), with higher scores indicating more impairment of HRQOL.

For analysis, the mean change in Skindex-29 and AKQOL scores from baseline was compared between treatment groups, and independent samples *t*-test was used to test for significance.

Of all the 624 patients, 89% were male, and the mean age was 72.64 (SD = 7.49) years. Skindex-29 and AKQOL scores at 12 months after treatment were available for 575 and 576 patients, respectively.

The mean baseline Skindex-29 score was 12.65 (SD = 9.45). A total of 557 patients (89.3%) reported less than mild impairment, 36 patients (5.8%) reported mild impairment, 24 patients (3.8%) reported moderate impairment, and 7 patients (1.1%) reported severe impairment of their HRQOL. Patients scored highest on the symptoms domain (mean = 27.28, SD = 17.05) and lower on the emotions (mean = 13.10, SD = 12.23) and functioning (mean = 3.70, SD = 7.16) domains.

The mean AKQOL baseline score (scale 0–27) was 4.22 (SD = 3.54), and the mean domain scores were 0.94 (SD = 1.07) for control of life domain (scale 0–6), 1.56 (SD = 1.69) for emotion domain (scale 0–9), 1.54 (SD = 1.34) for functioning domain (scale 0–9), and 0.17 (SD = 0.44) for the global item (scale 0–3).

Table 1 and Figure 1 show small improvements in HRQOL after treatment. The largest impact on HRQOL as measured by the Skindex-29 was observed in the symptoms domain. The improvement in the symptoms domain after treatment with fluorouracil—the treatment that was most effective in terms of lesion reduction—was significantly larger than after treatment with MAL-PDT ($P = 0.001$), but the differences with the other less effective topical treatments were not significant. Treatment of AK also led to some improvement in the emotions domain, whereas improvement in the functioning domain was very small.

As seen in Table 1, patients who reported mild or moderate and/or severe impairment at baseline had more benefit from the treatment than patients with less than mild impairment, but the differences in the magnitude of HRQOL improvement between the four treatments remained small.

The results of this study showed generally low impairment of HRQOL in patients with AK before the start of their therapy. The score changes from baseline reflect small improvements in HRQOL in all the four treatment groups, although HRQOL score changes were more substantial in patients who reported mild to severe impairment at baseline. There is no obvious trend toward more improvement with increasing treatment effectiveness in terms of lesion reduction. All the three home-applied creams and gel (even with the least effective ingenol mebutate) were associated with similar improvements in HRQOL scores. An explanation for this finding may be that the HRQOL score also reflects the degree of discomfort associated with a treatment. Ingenol mebutate had to be applied for only 3 days, whereas fluorouracil had to be used for 4 weeks.

Abbreviations: AK, actinic keratosis; AKQOL, actinic keratosis QOL; HRQOL, health-related QOL; MAL-PDT, methyl aminolevulinate photodynamic therapy

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Table 1. The Mean Changes (\pm SD) in the Skindex-29 and AKQOL Scores after Treatment in Patients with Less Than Mild, Mild, and Moderate to Severe Impairment at Baseline

Questionnaire	Treatments	All Patients (N = 575)	Less Than Mild Impairment at Baseline (n = 515)	Mild Impairment at Baseline (n = 34)	Moderate to Severe Impairment at Baseline (n = 26)
Skindex-29	Fluorouracil	-4.89 (6.88)	-4.15 (6.10)	-12.45 (8.73)	-20.26 (14.02)
	Imiquimod	-4.80 (9.54)	-3.14 (7.59)	-17.61 (7.50)	-21.43 (16.43)
	MAL-PDT	-2.93 (7.55)	-1.56 (5.70)	-13.28 (11.74)	-13.79 (11.33)
	Ingenol mebutate	-4.30 (8.29)	-2.72 (6.35)	-13.47 (8.69)	-16.90 (13.71)
	Overall	-4.22 (8.12)	-2.90 (6.51)	-14.00 (9.27)	-17.54 (13.42)
AKQOL	Fluorouracil	-0.90 (3.08)	-0.81 (3.04)	-1.67 (3.67)	-4.00 (1.41)
	Imiquimod	-0.99 (2.66)	-0.60 (2.42)	-4.29 (2.69)	-4.57 (1.99)
	MAL-PDT	-0.18 (2.86)	-0.02 (2.73)	-1.40 (3.10)	-2.14 (4.14)
	Ingenol mebutate	-1.14 (3.47)	-0.70 (2.69)	-1.88 (4.52)	-6.10 (6.61)
	Overall	-0.80 (3.05)	-0.52 (2.75)	-2.18 (3.57)	-4.46 (4.84)

Abbreviations: AKQOL, actinic keratosis QOL; HRQOL, health-related QOL; MAL-PDT, methyl aminolevulinate photodynamic therapy. Negative values reflect improved scores. Larger changes indicate more improvement in HRQOL. Interpretation of the Skindex-29 scores is based on [Prinsen et al. \(2011\)](#).

MAL-PDT treatment is more effective than ingenol mebutate but can be painful and requires a visit to the hospital.

The largest improvement was seen in the symptoms domain of the Skindex-29 questionnaire. Patients scored very low on the functioning

domain, and changes in scores after treatment were very small. Because the majority of items of the Skindex-29 questionnaire (12 of the total 29

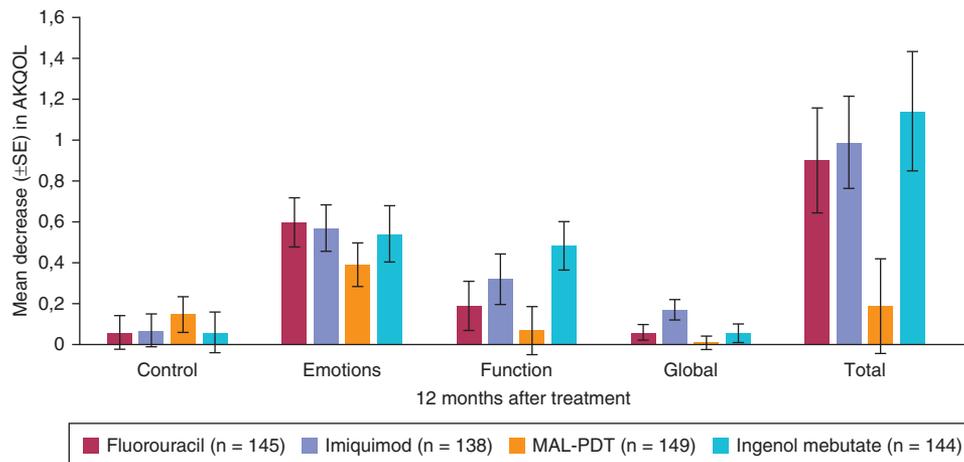
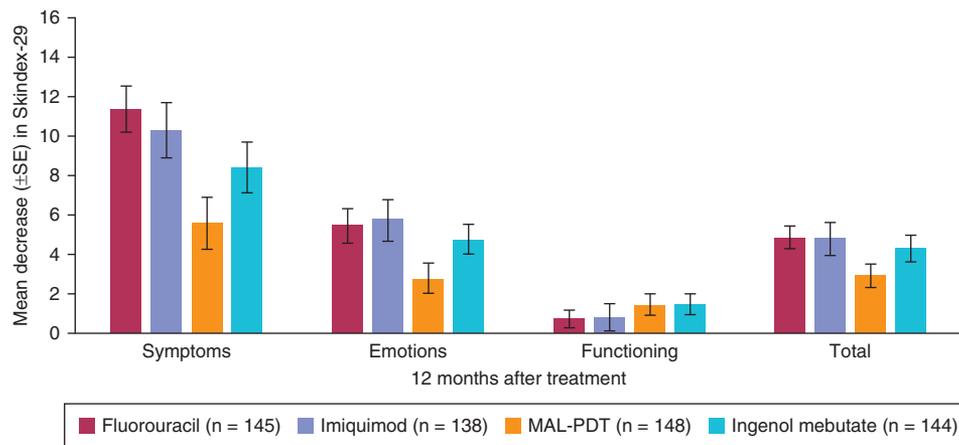


Figure 1. Mean decrease (\pm SE) in Skindex-29 (total and domain scores scale 0–100) and AKQOL score (total scale 0–27, control of life scale 0–6, emotions scale 0–9, functioning scale 0–9, global item scale 0–3) from baseline at 12 months. A larger decrease indicates more improvement in HRQOL. AKQOL, actinic keratosis QOL; HRQOL, health-related QOL; MAL-PDT, methyl aminolevulinate photodynamic therapy; SE, standard error.

items) relate to functioning, they have a large influence on the overall score. This might explain the limited impact of AK treatment on the total HRQOL score changes.

It has been hypothesized that the disease-specific AKQOL questionnaire is more suitable to capture changes in HRQOL after treatment than the Skindex-29 questionnaire, which was designed for all kinds of skin diseases (Tennvall et al., 2015; Vis et al., 2018). The nine-item AKQOL questionnaire also covers emotions and functioning, each with three items. However, the mean changes in the total AKQOL score of about 1 point on a scale from 0 to 27 were not larger than the mean changes in the total Skindex-29 score of about 4 points on a scale of 0–100. Therefore, the findings in this study do not indicate that the AKQOL questionnaire is more responsive than the Skindex-29 questionnaire.

The results of other studies that reported the impact of AK treatment on HRQOL scores varied from no impact with imiquimod treatment to a temporary impact with PDT and fluorouracil (Gholam et al., 2013; Pomerantz et al., 2017; Waalboer-Spuij et al., 2015). These studies had a short follow-up period (4–8 weeks) and did not compare multiple treatment modalities. The strength of our study is that data were collected in a large multicenter randomized controlled trial with 1-year follow-up and allow for HRQOL comparison between different treatment groups. To the best of our knowledge, treatment impact on HRQOL with the AKQOL has not been previously reported.

In conclusion, in the majority of patients, AK and its treatments have a limited impact on HRQOL scores, although substantial improvement can be achieved in patients who report moderate to severe impairment at baseline. Most patients with AK experience few skin-related emotional and functional problems. Because items in these two domains are the main components of the HRQOL questionnaires, clinical effectiveness in terms of lesion reduction is not well-reflected by total HRQOL scores.

ETHICS STATEMENT

This study was reviewed and approved by Maastricht University Medical Center and Ethics Committee (#142052).

Data availability statement

Datasets related to this article can be found at <https://doi.org/10.34894/SGKIMW>, hosted at DataVerseNL (<https://dataverse.nl/dataverse/MUMC>).

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: SA, KM, MHEJ, PJN, BABE; Formal Analysis: SA; Investigation: SA, MHEJ, JPHMK; Methodology: SA, PJN, BABE; Project Administration: SA; Supervision: KM, PJN, NWJKS; Writing - Original Draft Preparation: SA, KM, PJN, MHEJ, NWJKS, BABE, JPHMK

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