Patient perception of imiquimod treatment for actinic keratosis and superficial basal cell carcinoma in 202 patients

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ABSTRACT

Background/Aims

To document the impact on patient-reported outcomes and health-related quality of life (HRQoL) of treatment with imiquimod cream in patients with actinic keratosis (AK) and superficial basal cell carcinoma (sBCC).

Methods

This open-label, multicenter study included AK and sBCC patients eligible for treatment with imiquimod 5% cream. HRQOL was measured by the Skindex-17 and the Skin Cancer Index (SCI) and treatment satisfaction by the Treatment Satisfaction Questionnaire for Medication.

Results

118 AK patients and 84 with sBCC were included. Low baseline HRQoL impairment was found on both questionnaires, which remained low after treatment, except for a small dip at the end of the application period.

Conclusion

Imiquimod 5% cream treatment has no clinically relevant HRQoL impact in AK and sBCC patients according to the Skindex-17 and SCI. Effect of imiquimod treatment on HRQoL may be limited or these questionnaires do not fully capture relevant issues, such as fear of recurrence.

INTRODUCTION

Actinic keratosis (AK) is regarded as the first clinically relevant sign of sun induced skin damage. This in situ lesion is a precursor lesion for cutaneous squamous cell carcinoma (SCC). It is considered indicative of risk for developing SCC and basal cell carcinoma (BCC), approximately 0.5% per year per lesion progress into SCC.[1, 2] The incidence of cutaneous premalignancies and malignancies is increasing rapidly. Due to the high likelihood of developing multiple lesions during life, it is increasingly being considered as a chronic illness, i.e. "actinic neoplasia syndrome (ANS)".[3-7]

In chronic diseases, patient reported outcomes (PRO) and health-related quality of life (HRQoL) are increasingly important outcomes in daily patient care. Treatment satisfaction is also a part of the PRO, and more applicable to diseases with multiple treatment options. In AK and sBCC, a variety of treatment options is available, including surgery, locally destructive procedures and non-invasive field therapies such as topical 5-fluorouracil, imiquimod, photodynamic therapy and ingenol mebutate.[8-10]

Imiquimod is available in the Netherlands as 5% cream (Aldara®). It acts as an immunomodulator by activating Toll-like receptor (TLR)-7 which stimulates the epidermal and dermal dendritic cells to produce cytokines and attract natural killer cells, and enhances proliferation of B lymphocytes.[11] Clinical trials have shown complete clearance rates around 70% and partial clearance rates around 80% for AK when treated with two four-week treatment courses of applying the cream 3 days a week.[8, 12] For sBCC the reported clearance rates are around 80% in a six-week treatment course, applying the cream 5 days a week.[9, 13]

Adverse events such as fever-like symptoms and application site reactions are common in imiquimod treatment due to the induced inflammatory response. These possible severe local and systemic reactions may have an impact on treatment response, daily life and treatment satisfaction. The objective of this multicenter open label study was to assess HRQOL and treatment satisfaction in patients with AK or sBCC treated with imiquimod.

MATERIAL AND METHODS

Study design

This open label clinical study was conducted in two university medical centers (Erasmus MC University Medical Center Rotterdam and UMC Groningen) and six other non-university hospitals across the Netherlands (Center Oosterwal Alkmaar, Amphia hospital

Breda, Catharina hospital Eindhoven, Reinier de Graaf hospital Delft, Diaconessen hospital Leiden, St. Antonius hospital Nieuwegein) between January 2009 and September 2011. The primary outcome was defined as the impact of treatment on dermatology-specific and disease-specific HRQoL in daily practice conditions. Secondary outcomes were short-term response rates, adverse events and treatment satisfaction. The study protocol was approved by the medical ethical committee (Erasmus MC, no. NL23594.078.08). All patients provided written informed consent.

Patients

Patients over 18 years of age, clinically diagnosed with one or multiple AK, or sBCC, and eligible for treatment (i.e. capable of performing the treatment correctly) with 5% imiquimod cream were invited to participate. Biopsy was only performed if thought necessary by the participating dermatologist. Patients with inadequate understanding of Dutch language to fill in the questionnaires were excluded.

Questionnaires

The questionnaires used in this study are the Dutch version of both the Skindex-17 and the Treatment Satisfaction Questionnaire for Medication (TSQM).[14, 15] To assess the disease-specific HRQoL, the Skin Cancer Index (SCI) was used. Since there was no Dutch version available, we translated the questionnaire based on forward-backward translation, as recommended.[16] To suit the questionnaire for use in AK patients, we replaced ‘skin cancer’ by ‘actinic keratosis’.

Actinic keratosis

Participants with AK were instructed to apply imiquimod 5% cream once daily in a thin layer to the lesion including 5-10 mm of the surrounding skin, 3 days a week for 4 weeks. They were asked to complete the Skindex-17 and SCI at baseline, before treatment (T=0), directly after 4 weeks of treatment (T_{ak}=1) and 8 weeks after baseline (T_{ak}=2). Questions concerning side effects were administered at T_{ak}=1 and T_{ak}=2, and the TSQM at T_{ak}=2. The treating physician reported on patient history and current dermato-oncological status at baseline and answered questions concerning response at T_{ak}=2 and 16 weeks after baseline (T_{ak}=3). Response rates of the imiquimod therapy were assessed 16 weeks after start of therapy and categorized as ‘no response’, ‘partial response’ or ‘complete response’. Complete response was defined as clinically observed complete clearance of the lesion, partial response as clinically observed decrease in size and no response as clinically observed no change in the lesion compared to T=0. Retreatment for another four-week course due to insufficient response was allowed if considered necessary by the local dermatologist.

Superficial basal cell carcinoma

Participants with sBCC were instructed to apply imiquimod 5% cream once daily in a thin layer to the lesion including 5-10 mm of the surrounding skin, 5 days a week for 6 weeks. They were also asked to complete the Skindex-17 and SCI at baseline, before treatment (T=0), directly after 6 weeks of treatment (T_{sBCC}=1) and 18 weeks after baseline (T_{sBCC}=2). Questions concerning side effects were administered at T_{sBCC}=1 and T_{sBCC}=2, and the TSQM at T_{sBCC}=2. The treating physician reported on patient history and current dermato-oncological status at baseline and answered questions concerning response at T_{sBCC}=2. Response rates of the imiquimod therapy were assessed at eighteen weeks and categorized as 'no response', 'partial response' or 'complete response'. These categories were defined similarly as in the AK group.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) and categorical variables are described as frequencies and percentages. If the data was not normally distributed, median and interquartile range (IQR) are displayed.

The Friedman test was performed to compare scores of the Skindex-17 and SCI at T0, T1 and T2. Wilcoxon signed rank tests were performed to assess the change compared to baseline (T0). The α-level for these tests was adjusted by using the Bonferroni correction.

The chi-squared test was used for the comparison of response rates and adverse events. Logistic regression was performed to calculate the p-value for trend, using adverse events as dependent variable and response rates as independent variable.

Pearson's (two continues variables) and point biserial (continues and dichotomous variable) correlation coefficients were used to assess correlations. Statistical significance was set at $p < 0.05$ (two-sided). Statistical analyses were performed using IBM SPSS Statistics, version 20 for Windows.

RESULTS

Study population

A total of 202 patients were included in this multicenter open label trial. The study population consisted of 118 patients with AK and 84 with sBCC. The mean age in the AK group was slightly higher than in the sBCC group (67 *vs.* 62 years). In the AK group 58% was male and 37% in de sBCC group. The medical history and previous treatment also differed. All baseline patient and lesion characteristics are shown in Table 1.

Table 1. Patient characteristics

	Actinic Keratosis N (%)	Superficial BCC N (%)
Total number of patients	118	84
Age (years) Mean (SD)	67 (10)	62 (12)
Missing	3 (3)	5 (6)
Gender: Male	68 (58)	31 (37)
Missing	4 (3)	6 (7)
History of cutaneous malignancy or premalignancy:[a]		
• None	25 (21)	26 (31)
• Actinic keratosis	79 (67)	15 (18)
• Melanoma	6 (5)	1 (1)
• Basal cell carcinoma	42 (36)	55 (66)
• Squamous cell carcinoma	13 (11)	4 (5)
• Other skin malignancy	2 (2)	4 (5)
Previous treatment with:[a]		
• None	24 (20)	27 (32)
• Cryotherapy	75 (64)	20 (24)
• Coagulation	2 (2)	1 (1)
• Imiquimod cream	4 (3)	2 (2)
• Surgery	56 (48)	48 (57)
• 5-Fluorouracil cream	22 (18)	7 (8)
• Photodynamic therapy	18 (15)	18 (21)
Missing	1 (1)	1 (1)
Number of lesions:		
• 1	29 (25)	53 (63)
• 2-4	15 (13)	25 (30)
• 5-9	34 (29)	4 (5)
• ≥ 10	36 (31)	-
Missing	4 (3)	2 (2)
Locations of lesions		
• Face / head / neck	78 (66)	14 (17)
• Scalp	23 (20)	1 (1)
• Torso	16 (14)	47 (56)
• Arms	19 (16)	20 (24)
• Legs	3 (3)	25 (30)
Missing	1 (1)	1 (1)

[a] Patients could choose multiple options, therefore the total may add up to >100%

HRQoL

The low baseline HRQoL impairment, as measured by the Skindex-17 and the SCI, did not improve after imiquimod therapy. (Table 2) The impact of AK and sBCC, as measured by the Skindex-17, demonstrated a modest increase (indicating more impairment) in both the scores of the symptom and the psychosocial domains at the end of the application period (e.g. from 26 to 37 on a standardized scale at week 6 for sBCC patients). The change in the SCI was modest for both AK and sBCC (difference < 3 points on a scale from 0 to 100). Almost all the domains and overall standardized scores were above 80 (with 100 indicating no impairment). Except for a small dip at the end of the application period, the SCI standardized scores remained comparable before and after therapy.

There was no correlation between age, gender or educational level and HRQOL scores (p-value >0.05 for age gender and educational level). AK and sBCC patients with adverse events had more HRQoL impairment compared to patients without adverse events ($p<0.05$), which is a consequence of the symptom-related questions in the HRQoL questionnaires. Patients who experience more adverse events (i.e. symptoms), will score higher at the symptom-related questions, leading to higher overall scores, indicating more HRQoL impairment.

Response rates

Retreatment with another four-week course was necessary in 58% of the patients in the AK group due to insufficient response. Overall, complete response was achieved in 46% of the AK patients and 76% of the sBCC patients. Partial response in 35% of the AK patients and 8% of the sBCC patients. (Table 3)

When these response rates of the AK patients are linked to the percentage reporting adverse events, a significant trend is found ($p=0.001$) between the two, showing a high percentage of adverse events in the complete response group (74%) which decreases among patients with a partial response (39%) and without a response (25%). This was not found in the sBCC group.

Adverse events

About half of the patients using imiquimod cream reported at least some itching, redness and pain/burning sensation of which 26% reported it to be severe. A third of patients noted to have vesicles/bullae or swelling. Approximately 10-15% of all patients self-reported to have fever or influenza-like symptoms. The proportion of patients reporting these adverse events was very comparable between the AK and sBCC group. (Table 4) Overall, 6-7% of patients discontinued therapy due to side-effects and 5% would not use imiquimod again due to adverse events (5,1% of AK and 4,8% of sBCC patients).

Table 2. Health-related quality of life for AK and sBCC patients treated with imiquimod

	Actinic Keratosis					Superficial BCC				
	n	Week 0	Week 4	Week 8	p-value	n	Week 0	Week 6	Week 18	p-value
Skindex-17 standardized scores										
median (IQR) range 0-100										
• psychosocial score	93	0 (0-8.3)	0 (0-16.7)*	0 (0-4.2)*	< 0.001	54	0 (0-9.4)	0 (0-16.7)	0 (0-9.4)	0.305
• symptom score	101	30.0 (10.0-40.0)	30.0 (10.0-50.0)*	20.0 (0-40.0)*	< 0.001	58	20.0 (10.0-40.0)	40.0 (10.0-50.0)*	10.0 (0-30.0)*	< 0.001
Skin Cancer Index standardized scores										
median (IQR) range 0-100										
• Total Emotional Subscale	94	85.7 (75.0-92.9)	82.1 (71.4-89.3)*	85.7 (78.6-92.9)	0.003	58	87.5 (75.0-96.4)	82.1 (70.5-92.9)	85.7 (75.0-96.4)	0.066
• Total Social Subscale	102	100 (95.0-100)	95.0 (85.0-100)*	100 (90.0-100)	< 0.001	63	95.0 (90.0-100)	100 (88.6-100)	97.5 (95.0-100)	0.180
• Total Appearance Subscale	105	91.7 (75.00-100)	91.7 (75.0-100)	100 (83.3-100)*	0.002	63	91.7 (81.3-100)	91.7 (75.0-100)	91.7 (75.0-100)	0.185
• Total Skin Cancer Index	91	89,7 (81.7-96.4)	90.1 (78.5-96.0)*	93.6 (84.5-96.4)	< 0.001	58	91.9 (80.8-97.8)	91.0 (77.8-96.4)	91.7 (80.6-97.8)	0.046

*Bonferroni corrected p-value significant compared to baseline score at Week 0.

Table 3. Response rates at T=2[c] to imiquimod therapy

	Actinic Keratosis			Superficial BCC
	1st cycle N=118 (%)	2nd cycle[a,b] N=69 (%)	Overall N=118 (%)	N=84 (%)
• No response	9 (8)	4 (6)	4 (3)	3 (4)
• Partial response	60 (51)	41 (59)	41 (35)	7 (8)
• Complete response	42 (36)	12 (17)	54 (46)	64 (76)
• Cessation of therapy due to side effects	4 (3)	5 (7)	9 (8)	5 (6)

[a] Excluding those with complete response in 1st cycle, those who ceased therapy and missing.
[b] 69 / 118 needed a 2nd cycle
[c] response rate was assessed at 16 weeks for AK and at 18 weeks for superficial BCC
abbreviations: BCC = basal cell carcinoma

Table 4. Adverse events among AK and sBCC patients treated with imiquimod cream at T=1[a]

Type of reaction N (%)	Actinic Keratosis				Superficial BCC			
	Total	Intensity			Total	Intensity		
	Week 4 N=118	Mild	Moderate	Severe	Week 6 N=84	Mild	Moderate	Severe
Itching	58 (49)	19 (33)	24 (41)	15 (26)	38 (45)	16 (42)	14 (37)	8 (21)
Redness	61 (52)	9 (15)	23 (38)	29 (48)	41 (49)	6 (15)	17 (42)	18 (44)
Pain / Burning sensation	49 (42)	13 (27)	20 (41)	16 (33)	34 (41)	9 (27)	14 (41)	11 (32)
Squamae	42 (36)	15 (36)	23 (55)	4 (10)	17 (20)	8 (47)	7 (41)	2 (12)
Vesicles / Bullae	40 (34)	15 (38)	13 (33)	12 (30)	31 (37)	8 (26)	17 (55)	6 (19)
Swelling	37 (31)	14 (38)	16 (43)	7 (19)	23 (27)	9 (39)	14 (61)	-
Other local complaints	9 (8)	2 (22)	3 (33)	4 (44)	3 (4)	-	1 (33)	2 (67)
Influenza-like symptoms	16 (14)	2 (13)	7 (44)	7 (44)	11 (13)	4 (36)	6 (55)	1 (9)
Fever	11 (9)	4 (36)	2 (18)	5 (45)	9 (14)	3 (33)	4 (44)	2 (22)
Other systemic complaints	7 (6)	-	2 (29)	5 (71)	8 (10)	1 (13)	3 (38)	4 (50)

Patients could report multiple reactions, therefore the total may add up to >100%
[a] T=1 was 4 weeks after treatment for AK and 6 weeks after treatment for sBCC.

Treatment satisfaction

Treatment satisfaction, as measured by the TSQM, showed that patients appreciated the convenience of imiquimod use most (>60 on a scale from 0 to 100), but the overall satisfaction scored less than 60. The side effect domain of the TSQM scores were comparable AK and sBCC patients. (Figure 1) No correlation was found between treatment satisfaction and adverse events or previous treatment. Patients with complete response had higher treatment satisfaction (median TSQM overall score 61 for AK and sBCC) than those with partial (median TSQM overall score 54 for AK and 53 for sBCC) or without a response (median TSQM overall score 22 for AK and 40 for sBCC) in both groups ($p<0.05$).

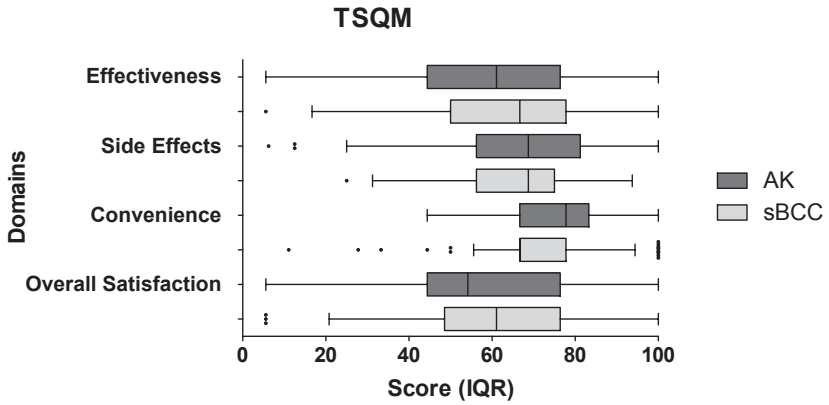

Figure 1. Treatment Satisfaction Questionnaire for Medication (TSQM) scores.
AK = Actinic Keratosis, sBCC = superficial Basal Cell Carcinoma, IQR = Interquartile Range

DISCUSSION

In this study, HRQoL impairment, as measured by the Skindex-17 and SCI, was low prior to treatment and remained low after treatment in both patients with AK and sBCC.

Our results are in line with published data. These results suggests little to moderate impact on HRQoL of AK/BCC treatment or suggest that the available HRQoL instruments are not specific and sensitive enough to record the issues considered important in this large patient population.[17] The Skindex-17 is probably not specific enough to capture specific skin cancer patient concerns. Although the SCI was developed specifically for BCC and SCC patients and demonstrated impairment on the emotional and the appearance subscales in the validation study, in our study standardized scores (0 to 100) were all above 75.[18] This observation implicates that HRQoL impairment in our population (i.e. treated with imiquimod) is less than in patients who will have to be treated surgically, or that the SCI is only suitable for use in patients being treated surgically, since it was developed in a tertiary care Mohs surgery clinic.[19]

Responsiveness, another pivotal feature of HRQoL questionnaires, addressing the effect of treatment, could not be confirmed for the Skindex-17 and the SCI. In the Skindex-17 this can be explained by the more generic aspect of the items in the questionnaire. The SCI however displayed good responsiveness before and after treatment in previous studies. [19, 20] The only treatment assessed however was surgical treatment and the lesions were only located in the head-neck area. Our data suggest only minimal responsiveness in all subscales, but not clinically relevant when considering Norman's "rule of thumb".[21]

We showed that imiquimod scored an overall satisfaction score around 60. It is considered a convenient therapy, but the side effects were scored lower than the overall score by the patients. About half had local side effects and 10-15% systemic reactions. The observed adverse events and response rates were comparable to the large imiquimod RCT.[13]

Application site reactions occurred similarly in both of our groups. The patient reported severity of these reactions are also alike, despite the different treatment regimen in the groups. The intensity was mostly scored as mild or moderate. These findings are in accordance with previous reports.[13, 22-24]

Strengths & Limitations

In our study, we were able to assess HRQoL, treatment satisfaction and short term response rates in daily practice use of imiquimod 5% cream in both AK and sBCC patients. To our knowledge, this is the first study assessing treatment satisfaction using a validated tool. One previous study used a 7-point Likert scale and another an analogue scale [0-10]. [22, 25]

Unfortunately, we have no additional data on all AK and sBCC patients visiting the department. Patient characteristics and reason for non-participation of patients who refused to participate in this study were not available, which hindered the judgment about the presence of a possible selection bias. Selection bias may have occurred if specific patient groups were not included in our study and those patients would have a lower or higher impact on HRQoL or different treatment satisfaction. For example, if older patients refused to participate and the impact of imiquimod on HRQoL among older patients is larger, than the impact of imiquimod in our study on the HRQoL would have been underestimated if only younger patients were included in which the impact was smaller. We deemed selection bias due to age likely because some older patients may not be capable of performing the treatment correctly, and therefore may have refused to participate.

CONCLUSION

In conclusion, this study showed that imiquimod 5% cream treatment has no clinically relevant HRQoL impairment nor improvement after treatment in both AK and sBCC patients according to the Skindex-17 and the SCI. Patients report to tolerate the treatment well, but overall satisfaction is only around 55 to 60% in both groups. The results of this study also suggest that the available HRQoL instruments are not specific and sensitive enough to capture the issues considered important in skin cancer patients.

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