Photodynamic therapy leads to significant improvement of actinic keratosis area and severity index (AKASI)

L Schmitz[1#*], C von Dobbeler[#2], G Gupta[3], T Gambichler[1], RM Szeimies[4], CA Morton[5], T Dirschka[2,6]

1Department of Dermatology, Venereology and Allergology, Ruhr-University, Bochum, Germany
2CentroDerm Clinic, Heinz-Fangman-Straße 57, Wuppertal, Germany
3Department of Dermatology, Monklands Hospital, Lanarkshire, and University of Glasgow, UK
4Department of Dermatology and Allergology, Vest Hospital, Academic Teaching Hospital University of Bochum, Recklinghausen, Germany
5Department of Dermatology, Stirling Community Hospital, Stirling, UK
6Faculty of Health, University Witten-Herdecke, Alfred-Herrhausen-Straße 50, Witten, Germany

Running head: PDT improves AKASI

Word count: abstract: 237; article: 2432

General data: 19 references, 1 table, 3 figures

IRB Approval: obtained

Funding source: None

Keywords: actinic keratosis, AKASI, photodynamic therapy, ALA, NMSC

# contributed equally

***Corresponding author:** Dr. Lutz Schmitz

Address: Department of Dermatology, Ruhr-University, Gudrunstr. 56, D-44791 Bochum, Germany

Phone: +49 (0)234 5090

Fax: +49 (0)234 509 3445

Email: l.schmitz@klinikum-bochum.de

Conflict of interest disclosures:

L. Schmitz: Lecture fees for Almirall, Biofrontera, Galderma, Meda, Riemser

C. von Dobbeler: none

G. Gupta: Lecture fees for Abbvie, Galderma, Leo and Meda. Member of advisory boards for Almirall, Leo, Meda and Novartis.

T. Gambichler: Lecture fees for Novartis, Roche, NeraCare, BMS.

R.-M. Szeimies: Lecture fees for Almirall, Biofrontera, Galderma, Leo, photonamic; member of advisory boards for Almirall, Biofrontera, Galderma, Leo; grants from European Commission

C.A. Morton: Travel support from Biofrontera, Galderma, Leo; member of advisory boards for Almirall, Biofrontera, Leo

T. Dirschka: Lecture fees for Almirall, Biofrontera, Galderma, Leo, Meda, Riemser, Janssen; member of advisory boards for Almirall, Biofrontera, Leo, Meda, Novartis, Riemser, Janssen; unrestricted grants from Meda and Galderma

HIGHLIGHTS

- First study providing data on AKASI after conventional PDT
- Establishment of AKASI 50, 75, 100 as tool to easily compare treatment modalities
- Significant differences between pre-treated and treatment naïve patients

ABSTRACT

Background Actinic keratosis area and severity index (AKASI) is a new quantitative tool for assessing AK severity on the head and can be used to monitor outcomes of different therapies. The aim of this study was to determine treatment outcomes of AK applying AKASI three months after conventional photodynamic therapy (PDT).

Methods We performed a retrospective analysis of patients who have undergone PDT on the head and had a documented AKASI evaluation prior to PDT and at follow-up visits.

Results Of the 33 patients included, 32 (97.0 %) patients showed an AKASI reduction and 1 (3.0%) patient an increase of AKASI at follow-up visits compared to baseline. The median (range) follow-up period was 96 days (70-161). The median difference of AKASI values between both visits was 73.7% (-34.8-100.0%). The Wilcoxon test showed highly significant differences ($P < 0.0001$) between visits. 14 (42.4%) patients showed an AKASI 100 (complete clearance), 16 (48.5%) an AKASI 75 and 24 (72.7%) an AKASI 50, respectively.

The Mann-Whitney U test showed in a subgroup analysis of patients with a positive history of at least more than one intervention and treatment naïve patients significant differences in these two groups (P = 0.0302).

Conclusions AKASI represents a feasible and comparable tool for objectively assessing field-directed treatment modalities such as PDT in daily routine. The establishment of AKASI 50, 75, 100 serves as an objective measure to compare treatment outcomes to baseline severity of AK.

INTRODUCTION

Actinic keratoses (AK) are commonly located on UV-damaged skin sites and present as erythematous macules, keratotic patches or plaques.[1] They are regarded as early in-situ squamous cell carcinoma (SCC) and the risk of a single AK lesion to progress into an invasive SCC ranges between 0.025 to 16% per year.[2, 3] Due to changed leisure activities and an ongoing demographic change in industrial countries an increasing prevalence of AKs can be observed. Predominantly elderly male patients and people with fair skin types are affected by field cancerisation.[4] In these sun-damaged skin regions, subclinical and non-visible AK lesions are present adjacent to clinical apparent AKs.[5] A recent study reveals that already early AK lesions can progress into invasive SCC.[6] Another study showed that thin AKs show the same severity of dysplasia and consequently clinical thickness cannot predict aggressiveness of AKs.[7] Hence, it is not possible to predict if and which lesion will become invasive. Therefore, it is mandatory to monitor and treat the whole field of actinic damage.

However, established clinical classification schemes are based on lesion counts assessing the overall thickness of single AKs.[8] To redress these lesion-directed classifications recently a new field-directed assessment tool to evaluate AK severity on the head has been suggested.[9] As AKs are considered as chronic disease, the “actinic keratosis area and severity index” (AKASI) has been developed on the basis of other chronic disease monitoring tools such as the psoriasis area and severity index (PASI). To calculate AKASI, the head is divided into 4 regions (scalp, face, right/left cheek, chin, nose and ear) and each region is estimated for the affected area by AKs. AK lesions are evaluated due to characteristic clinical signs such as erythema, thickness and distribution. Besides evaluation of disease severity, AKASI objectively

monitors treatment outcomes of different therapeutic modalities, thus allows comparison of the pre and after treatment situation. So far, there is a lack of data expressing therapeutic efficacy as AKASI values and analyses outcome thresholds such as AKASI improvements of 50%, 75% and 100%. In other chronic skin disease such as psoriasis and its assessment tool PASI, these thresholds resemble established and comparable evaluation instruments to determine treatment outcome.

Thus, the aim of the underlying study was to analyse the treatment outcome of patients who have undergone photodynamic therapy (PDT) by means of AKASI on the head. PDT is a well-established and very effective therapy in patients presenting field cancerisation.[10, 11] The mode of action of PDT is based on a photosensitizer, a light source for activating the sensitizer and oxygen. A topical prodrug such as aminolevulinic acid (ALA) or methyl aminoevulinate (MAL) are applied to the actinically damaged field and incubated. Meanwhile neoplastic cells selectively accumulate the active photosensitizer protoporphyrin IX (PPXI) owing to their altered metabolism. Subsequently, the field is illuminated either by artificial light with a convenient wavelength and energy or by natural daylight. Thereby, neoplastic cells of both clinical apparent as well as subclinical lesions are selectively destroyed.[12] (Field cancerization: from molecular basis to selective field-directed management of actinic keratosis. Philipp-Dormston)

This is the first study to investigate treatment outcome by means of AKASI thresholds such as AKASI 100, 75 and 50 as feasible assessment tool.

MATERIALS AND METHODS

Study population

This retrospective study was performed at the Skin Cancer Centre of the Ruhr-University Bochum (Bochum, Germany). The study was conducted according to the Declaration of Helsinki and approved by the ethics review board of the Ruhr-University Bochum (No.: 17-5984-BR). The database of our Skin Cancer Centre was searched for patients who have undergone PDT for AKs located on the head. Patients with documented AKASI before PDT and at a follow-up visits were included. The follow-up period after PDT is typically around three months. We included only patients who have been rated by the same physician at both visits (V0 and V1) to avoid inter-rater differences. Patients under immunosuppressive therapy or who had a documentation of an incomplete PDT (i.e. due to adverse events during intervention such as pain) were excluded from this study. All patients included into this study only have undergone one PDT between baseline AKASI and follow-up AKASI. Patients who received ~~more than one PDT or~~ other interventions (e.g. topical treatment or ablative laser treatment) due to AK lesions on the head were not included.

Data assessment

AKASI is routinely evaluated in all patients with AKs on the head to monitor disease severity. These assessments of the study population were performed by two investigators (TG, LS). To determine AKASI, the head is divided into four regions (scalp, forehead, left and right side of the face [cheek, ear, nose, and chin]. According to the extent of each area, the scalp is weighted with 40% and the other three areas with 20%. In each region, the percentage of the area affected by AKs is estimated (0-100% of the separate area), and the severities of three clinical signs (distribution,

thickness and erythema) of AK were assessed using a quantitative scale from 0 (none) to 4 (severe). Due to an algorithm, all sub scores for each region were calculated and added to give a total AKASI of the head. This total AKASI can range from 0 to 18. The "modified" AKASI was calculated by summing up only sub scores of regions which had been treated at both visits, accordingly. The total modified AKASI can have a maximum index for 3 regions of 14.4 (scalp included) or 10.8 (scalp excluded).

Photodynamic therapy

Field-directed PDT was performed with BF-200 ALA (Ameluz®, Biofrontera, Leverkusen, Germany) as photosensitizer and BF-RhodoLED lamp (narrow emission spectrum of 635nm ± 9nm) as light source. Prior to exposure, the skin was degreased and crusts or hyperkeratoses of AK lesions were thoroughly removed by gentle curettage. Afterwards, ALA gel was applied to the treatment field and covered with an occlusive, light protecting dressing (plastic foil (e.g. 3M Tegaderm™) and aluminium foil). After an incubation time of approximately 3 hours, the occlusion was removed and topical residuals were wiped off. Subsequently, the treatment field was illuminated for 10 minutes at a distance of 5-8cm from the skin surface, resulting in a total light dose of 37J/cm². If required, the patients were allowed to cool the skin with cool packs after intervention.

Statistical analysis

Data analysis was performed using the statistical package MedCalc software version 17.4.4 (Ostend, Belgium). The distribution of data was assessed by the D`Agostino-Pearson test. If there was normal distribution, data were expressed as mean and standard deviation (SD); if not, data were expressed as median and range. Data were

statistically analysed using the Wilcoxon test for paired samples and the Mann-Whitney U test for unpaired samples. Data with P-values less than 0.05 were considered to be statistically significant.

.

RESULTS

In total, 33 patients with a mean (standard deviation) age of 72.8 (8.1) years were included in this study. The majority of patients presented Fitzpatrick skin type II (93.9%) and were male (84.8 %). 60.6% of the study population had a positive history of at least more than one topical treatment of their AKs. The median AKASI at baseline visit was 3.8 (1-7.8) and the median follow-up period was 96 days (70-161). Further demographic and clinical characteristics are shown in **table 1**.

Overall, 32 (97.0 %) patients showed a reduction and 1 (3.0%) patient an increase of AKASI at the follow-up visit compared to the baseline visit. The median (range) absolute difference was 2.6 (-1.6-5.4) and relative 73.7% (-34.8-100.0%). The Wilcoxon test showed highly significant differences ($P < 0.0001$) between both visits. (**Fig 1a**). 14 (42.4%) patients showed an AKASI 100 (complete clearance), 16 (48.5%) an AKASI 75 and 24 (72.7%) an AKASI 50, respectively. Subgroup analysis of the 32 patients with AKASI reduction offered a median (range) value of 75.3% (13.6-100.0%). Subgroup analysis of patients with a positive history of at least more than one intervention and treatment naïve patients showed a median AKASI difference of 61.1% (-34.8-100.0%) and 100.0% (13.6-100.0%), respectively (**Fig 2**). The Mann-Whitney U test showed significant differences between the AKASI changes in these two groups ($P = 0.0302$). (**Fig 3**)

Analysis of modified AKASI (only areas which were treated was summed up) show a median (range) reduction of 80.8% (-8.7-100.0%). The Wilcoxon test presented highly significant differences ($P < 0.0001$) between both visits (**Fig 1b**). 16 (48.5%) patients showed an AKASI 100 (complete clearance), 19 (57.6%) an AKASI 75 and 25 (75.8%) an AKASI 50, respectively.

DISCUSSION

Current clinical classification systems for AKs are based on the evaluation of single lesions and mainly restricted to the clinical criteria thickness of individual lesions.[13] As it has been demonstrated that neither thickness of AK lesions predict its aggressiveness nor the clinical appearance correlate with the underlying histologic grading, a field-directed monitoring tool is highly demanded.[7, 14] The new quantitative assessment tool AKASI provides the possibility to compare evaluated discrete AKs and areas of field cancerisation on the head. This is the first study to investigate the treatment outcome in patients who have undergone PDT on the head using AKASI and new defined thresholds such as AKASI 100, 75 and 50.

This study demonstrated an overall median AKASI improvement of 73.3%. Until there are further studies using AKASI data of treatment outcome, these values are hard to compare with common endpoints of clinical trials of AK therapies. Many trials exclusively rely on a clinical count of single AK lesions. But even experienced dermatologists show marked heterogeneity when conducting lesion counts.[15] Efficacy endpoints for AK therapy studies are usually defined as “patient complete clearance rate” (PCCR) or as “lesion complete clearance rate” (LCCR) but no graduated response reflecting area of disease has been reported to date. PCCR can be compared with an AKASI improvement of 100% (AKASI 100). The study showed an AKASI 100 in 42.4% of patients, which reveals a slightly less effective outcome compared to three randomized controlled trials (RCT) conducted with equivalent requirements concerning photosensitizer, narrow band light source and PDT protocol. These trials showed PCCR of 78%[16], 53%[17] and 62%[18] after one PDT after 12 weeks of follow-up. This difference can be based on the fact that the PCCR just evaluates AK lesions within the treated field and not the entire head. In contrast, the

standard AKASI takes all lesions of the whole head into account. Moreover, an AKASI 100 can only be achieved in patients who presented AKASI sub scores solely in regions of the head which were undergoing an intervention. To overcome this problem, only sub scores of regions which had been treated were summed up to calculate a “modified” AKASI. The modified AKASI 100 of the treatment area was 48.5%. It still shows lower complete clearance rates in this analysis, which might be due to different factors: non RCT, done in daily routine, AKASI differs in general from PCCR, more clinical characteristic signs of AK for assessing AKASI might be more sensitive for evaluating minor AK residuals. It is questionable if it will be necessary to compare these measures in the future once AKASI is used more widely.

In contrast to the rest of the study population, one patient presented an increased standard AKASI of 34.8% and modified AKASI of 8.7%, respectively. There might be several reasons for this effect: The patient had a long follow-up period of 120 days. Moreover, the patient developed AKs in a non-treated area, which was covered by the modified AKASI. Nevertheless, the AKASI of the scalp presented slightly higher at follow-up than at the baseline visit. Obviously, this patient appears refractory to PDT and/or shows high recurrence rates requiring continuous monitoring as well as more frequent AK treatments.

AKASI is a more differentiated assessment tool with comparable and graduated values. Assessment of treatment modalities which do not provide high PCCRs, as seen after PDT, benefit from a better graduated evaluation tool. Thus, AKASI can be used to precisely monitor therapy regimes.

The rationale of evaluating a complete lesion clearance in a chronic skin disease such as AKs must be questioned. To determine “time-to-relapse” is a better characteristic of therapeutic efficacy in a highly chronic disease such as AK.[19] Additionally, field-

directed measurements are needed to assess the efficacy of treatment approaches addressing field cancerisation. This study demonstrated AKASI and especially its thresholds such as AKASI 100, 75 and 50 to be a very feasible and easy-to use tool in daily clinical routine. These parameters could be also assigned as targets in clinical trials.

Interestingly, the difference of treatment outcome in treatment naïve patients and patients who has received at least one or more interventions prior to the recorded PDT was striking, although in a small study sample. Treatment naïve patients had significantly better outcomes than patients with a treatment history while there were no significant differences of AKASI at baseline in both groups. One hypothesis could be that patients presenting recurrent disease may be more refractory to treatment modalities as a whole. If this effect should be reproducible further studies with larger populations and other treatment approaches are mandatory.

Limitations of our study are the retrospective design and the small number of patients included. Moreover, the median AKASI at baseline visit of 3.8 ranges between mild-to-moderate diseases when compared to the pivotal results.[9] Further studies should provide a broader range of disease severity in patients with AKs.

In conclusion, AKASI is a feasible tool to monitor treatment outcomes in patients with field cancerisation on the head. In analogy to other chronic skin disease such as psoriasis, AKASI 100, 75 and 50 worked out as easy-to apply and comparable assessment approach.

ACKNOWLEDGEMENTS

None.

REFERENCES

[1] Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000;42:4-7.

[2] Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol. 2000;42:23-4.

[3] Rowert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol. 2007;156 Suppl 3:8-12.

[4] Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H, et al. Development of a treatment algorithm for actinic keratoses: a European Consensus. Eur J Dermatol. 2008;18:651-9.

[5] Ulrich M, Maltusch A, Rowert-Huber J, Gonzalez S, Sterry W, Stockfleth E, et al. Actinic keratoses: non-invasive diagnosis for field cancerisation. Br J Dermatol. 2007;156 Suppl 3:13-7.

[6] Fernandez-Figueras MT, Carrato C, Saenz X, Puig L, Musulen E, Ferrandiz C, et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. J Eur Acad Dermatol Venereol. 2015;29:991-7.

[7] Heerfordt IM, Nissen CV, Poulsen T, Philipsen PA, Wulf HC. Thickness of Actinic Keratosis Does Not Predict Dysplasia Severity or P53 Expression. Sci Rep. 2016;6:33952.

[8] Olsen EA, Abernethy ML, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. J Am Acad Dermatol. 1991;24:738-43.

[9] Dirschka T, Pellacani G, Micali G, Malvehy J, Stratigos AJ, Casari A, et al. A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index. J Eur Acad Dermatol Venereol. 2017.
[10] Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol. 2013;27:536-44.
[11] Philipp-Dormston WG, Sanclemente G, Torezan L, Tretti Clementoni M, Le Pillouer-Prost A, Cartier H, et al. Daylight photodynamic therapy with MAL cream for large-scale photodamaged skin based on the concept of 'actinic field damage': recommendations of an international expert group. J Eur Acad Dermatol Venereol. 2016;30:8-15.
[12] Philipp-Dormston WG. Field cancerization: from molecular basis to selective field-directed management of actinic keratosis. Curr Probl Dermatol. 2015;46:115-21.
[13] Wolf JE, Jr., Rigel DS. Understanding efficacy end-points in studies of field-directed therapy for actinic keratosis. Int J Dermatol. 2013;52:1063-70.
[14] Schmitz L, Kahl P, Majores M, Bierhoff E, Stockfleth E, Dirschka T. Actinic keratosis: correlation between clinical and histological classification systems. J Eur Acad Dermatol Venereol. 2016;30:1303-7.
[15] Chen SC, Hill ND, Veledar E, Swetter SM, Weinstock MA. Reliability of quantification measures of actinic keratosis. Br J Dermatol. 2013;169:1219-22.
[16] Szeimies RM, Radny P, Sebastian M, Borrosch F, Dirschka T, Krahn-Senftleben G, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic

keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. Br J Dermatol. 2010;163:386-94.
[17] Dirschka T, Radny P, Dominicus R, Mensing H, Bruning H, Jenne L, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. Br J Dermatol. 2012;166:137-46.
[18] Reinhold U, Dirschka T, Ostendorf R, Aschoff R, Berking C, Philipp-Dormston WG, et al. A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz((R))) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED((R)) lamp. Br J Dermatol. 2016;175:696-705.
[19] Hofbauer G, Anliker M, Boehncke WH, Brand C, Braun R, Gaide O, et al. Swiss clinical practice guidelines on field cancerization of the skin. Swiss Med Wkly. 2014;144:w14026.

TABLE LEGEND

Table1. Demographic and clinical characteristics (N=33)

Characteristic	n (%)
Sex	
Male	28 (84.8)
Female	5 (15.2)
Age, years	72.8 (8.1)[a]
Skin Type (Fitzpatrick)	
I	2 (6.1)
II	31 (93.9)
III - V	0 (0)
UV Exposure (increased)	24 (72.7)
leisure activities	23 (95.8)*
occupational	1 (4.2)*
History	
median time since AKs first diagnosed, years	3 (0-15)[b]
treatment naïve patients	13 (39.4)
history of at least > 1 treatment of AKs	20 (60.6)
ablative intervention (e.g. curettage, laser)	16 (80.0)*
photodynamic therapy	14 (70.0)*
DFS	4 (20.0)*
5-FU/SA	1 (5.0)*
skin cancer history (invasive)	19 (57.6)
Follow-up, days	96 (70-161) [b]

AK: actinic keratosis;

DFS: 3% diclofenac sodium in 2.5% hyaluronic acid gel;

5-FU/SA: 0.5% %-Fluorouracil in 10% salicylic acid (topical solution)

[a] *Data are mean (standard deviation)**;***

[b] *Data are median (range);*

** % referring to absolute value of next upper category in this row;*

FIGURE LEGEND

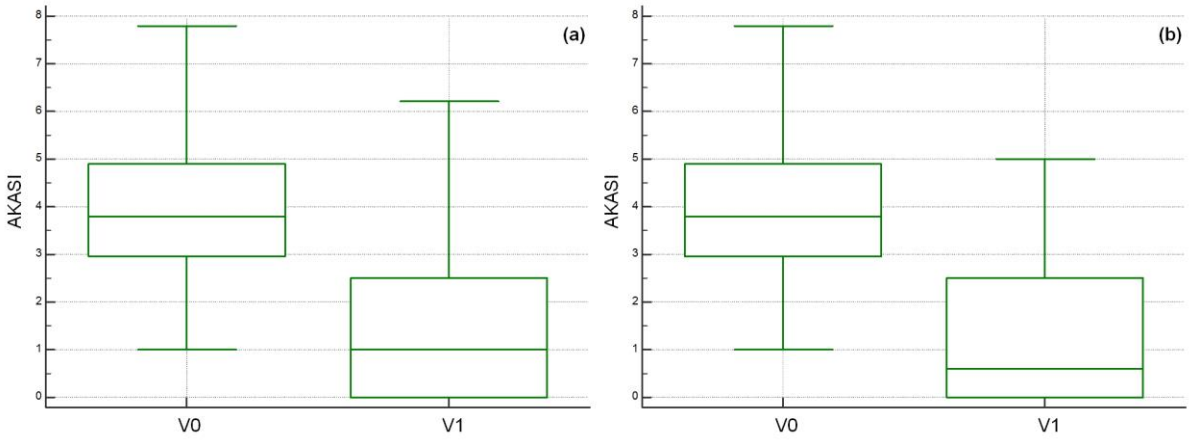

Fig 1.

Box-and-Whisker Plot concerning the differences in AKASI prior and after treatment. Wilcoxon test shows highly significant differences ($P < 0.0001$) between AKASI at baseline visit (V0) and at the follow-up visit (V1) for both the standard AKASI **(a)** and the modified AKASI **(b)** (only treated areas were summed up).

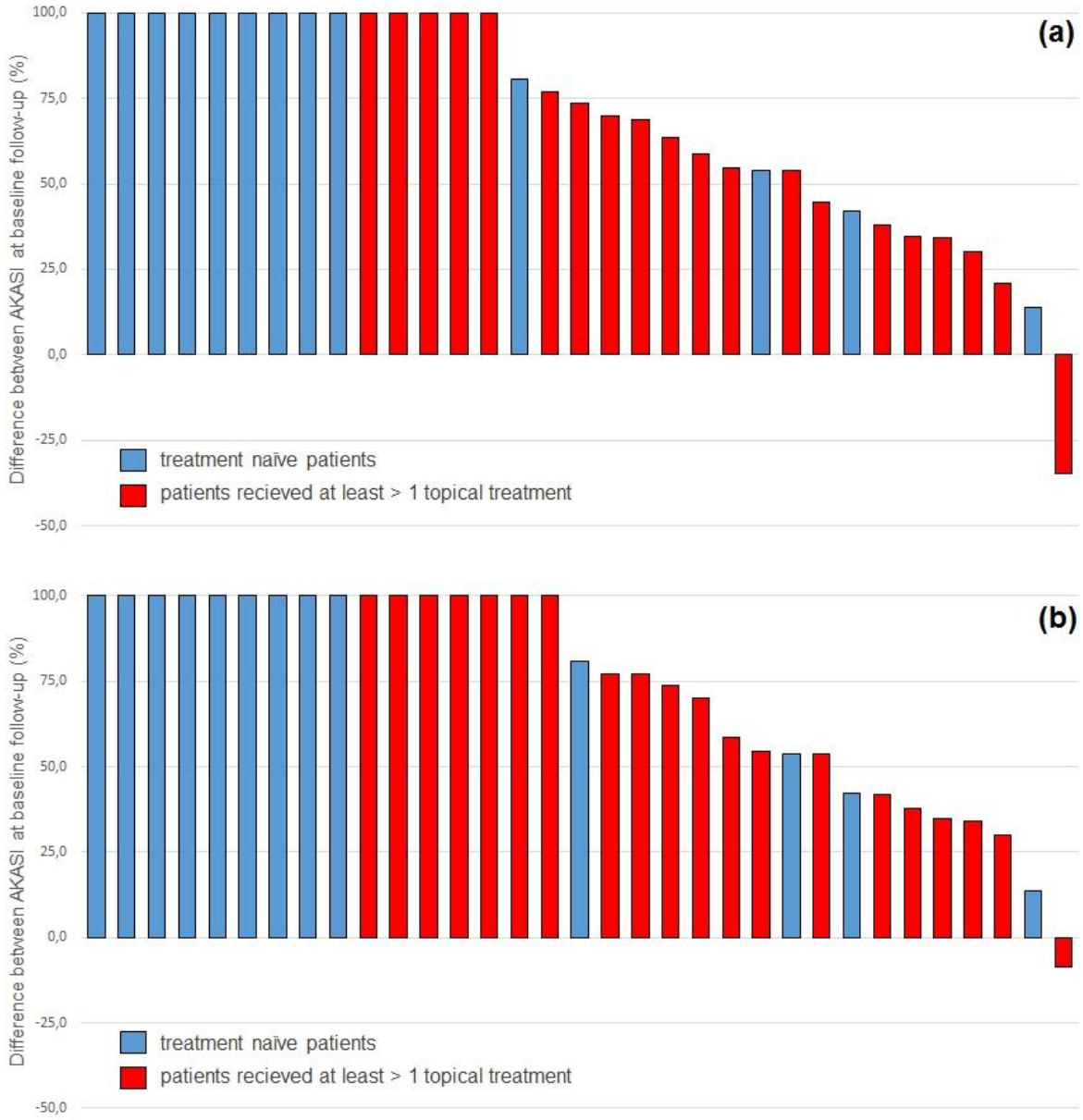

Fig 2.

Differences of AKASI when compared baseline to follow-up visits.

Treatment naïve patients (n=13; 39.4%) illustrated as blue columns and patients who had received any intervention (n=20; 60.1%) are illustrated as red columns. Differences between standard AKASI **(a)** and modified AKASI (only treated areas were summed up) **(b)**. 14 (42.4%) patients when using the standard AKASI **(a)** and 16 (48.5%) patients using the modified AKASI **(b)** showed a complete clearance at follow-up visit.

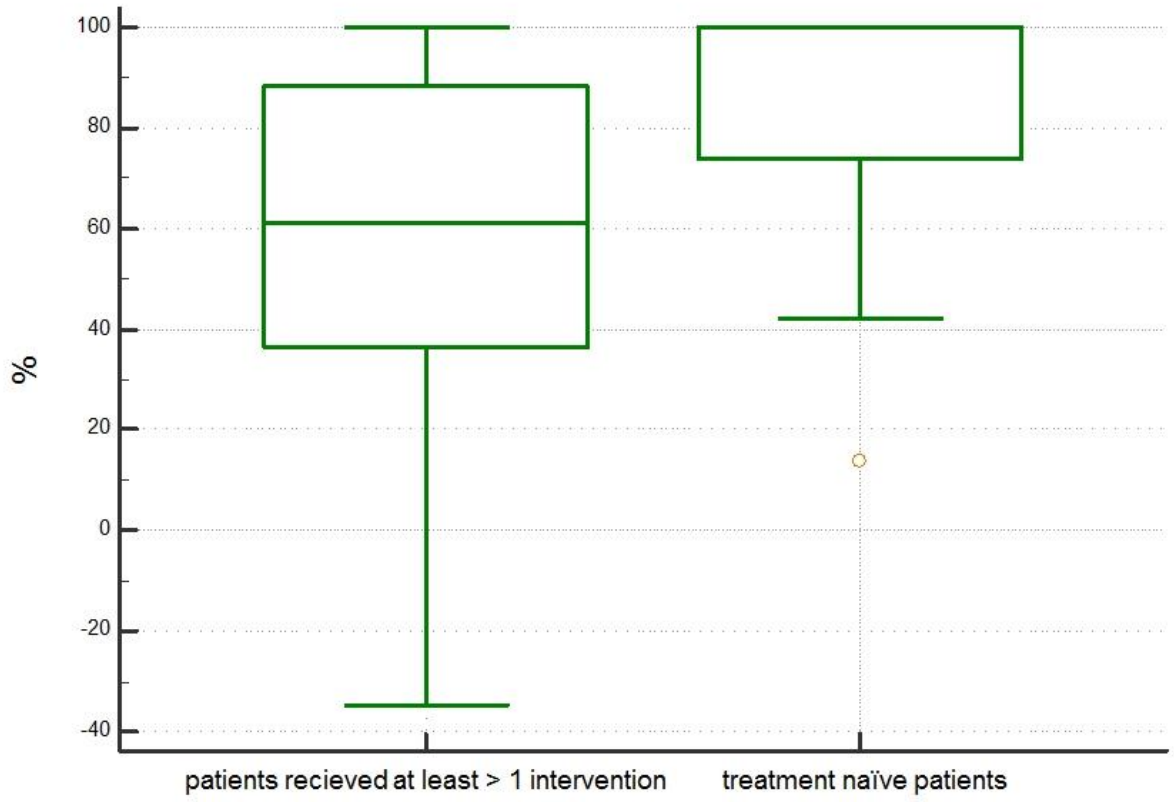

Fig. 3.

Box-and-Whisker Plot concerning the AKASI changes between baseline and follow-up visit comparing treatment naïve patients and patients who had received any intervention. Mann-Whitney U test shows significant differences (P = 0.0302) between both groups.

Orange °: Outlier > less than 3/2 times of lower quartile