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ORIGINAL ARTICLE

Carcinogenic effects of prolonged daily low-emission phototherapy in psoriasis

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Abstract

Background: Low-dose UV treatment has been shown to be effective in mild psoriasis. However, the prolonged use of this treatment modality may raise concerns about its safety. These concerns are mainly focused on potential carcinogenic risks and overuse of this treatment modality.

Objectives: This study was set out to evaluate possible carcinogenic risks of prolonged low-dose phototherapy.

Methods: Three groups of psoriasis patients were evaluated: patients with local treatment only (n = 15); low-dose UV treatment at home for at least 18 months (n = 39); and patients with conventional NB-UVB (n = 8). Patients underwent visual inspection for signs of photoageing, and p53, CPDs and γH2AX were measured in skin biopsies. Patients undergoing low-dose phototherapy answered a survey about their recent patterns of use in a survey.

Results: In the skin biopsies, low-dose UV treatment caused a lower amount of CPDs (p = .016) and p53 (p = .015) than NB-UVB. γH2AX did not show a significant difference. Self-report in patients undergoing low-dose phototherapy showed only one case of overuse (2.7%). Visual skin inspection showed no difference in signs of photoageing in the three groups.

Conclusion: Prolonged treatment with low-dose UV for 18 months appears at least as safe as a course of conventional NB-UVB.

KEYWORDS
carcinogenic effects, low dose phototherapy, p53, prolonged use, psoriasis, thymidine dimers

1 | INTRODUCTION

Ultraviolet (UV) therapy or phototherapy is a widely used treatment modality for skin manifestations of psoriasis. Although treatment with UV has proven to be very effective in different modalities, concerns were raised about the safety of these UV treatments when psoralen UVA (PUVA) was shown to be carcinogenic.[1,2] Patients treated with PUVA have an elevated risk of developing actinic keratosis[3] and squamous cell carcinoma (SCC).[1–4] However, the *relative risk* of developing SCC has varied greatly between studies performed in Europe and the United States.[1–4]

Although PUVA treatments have now been generally accepted to be potentially carcinogenic, the risk of skin carcinogenesis due to UVB therapy has not been demonstrated.[5–7] UVB therapy, especially narrowband UVB (NB-UVB), is still regarded as a safe treatment modality without an elevated risk of non-melanoma skin cancer (NSMC).

Nonetheless, dermatologists are reluctant to prescribe prolonged courses of UV therapy; they limit the number of courses per year or the cumulative dose. This approach is recommendable as NMSC is known to be caused by recurrent and excessive UV exposure and has a predilection for sun-exposed areas of the body. Another argument against excessive UV therapy is that psoriasis patients are likely to exhibit sun-seeking behaviour upon experiencing positive effects of the treatment on their skin disease.

In a recent position statement, van der Kerkhof and de Gruijl stood up for revisiting the way phototherapy is prescribed.[8] Intervals of conventional phototherapy might not be the best-fitted treatment in a chronic disease such as psoriasis. The authors therefore advocate further research into prolonged low-dose phototherapy.

Low-dose phototherapy has been described in several skin conditions and with several modalities, such as NB-UVB, UVA1 and BB-UVB.[9–15] The majority of studies reported positive results in terms of effectivity. The definition of 'low dose', however, varies widely between these studies. A clinical trial in 2013 with a low-emission phototherapy unit addressed this problem.[14] This unit was designed for treatment at home and emits a fixed dose of UVA and UVB of 1 standard erythemal dose (SED) in 10 min.

Remarkably, the safety of these low-dose treatments has only been sparsely investigated.[16–20] Of the safety studies that have been conducted to date, most have been in cell lines or mice, and very few in patients. In a preliminary safety study in psoriasis patients using the 'fixed' low-dose phototherapy, no significant elevation in the carcinogenic markers p53 and thymidine dimers was detected.[19] Carcinogenic effects are therefore presumed to be low. These results, however, were acquired after just two months of treatment in a study setting. In practice, many patients in the Netherlands continued this treatment for a prolonged period of time, sometimes up to 5 years, or initiated this type of phototherapy without a clear answer as to the safety risks of prolonged use.

Hence, in this study we aimed to investigate (I) the possible long-term carcinogenic effects of low-emission phototherapy and (II) the treatment adherence during the prolonged use of low-emission phototherapy.

2 | MATERIALS AND METHODS

The study design was approved by the Medical Ethics Committee of the Amsterdam UMC (protocol number 2018.490) and was performed in accordance with the Declaration of Helsinki (2008). To investigate the possible carcinogenic effects of prolonged use, an observational cross-sectional cohort study was set up.

2.1 | Population

Three groups of psoriasis patients were included:

1. Patients prescribed daily low-dose phototherapy (Dermasun Helios©) for a period longer than 18 months.
2. Patients without treatment or with local treatment of their skin disease.
3. Patients with hospital-based NB-UVB for at least 1 month.

Patients included were aged 18 years or older and had a clinical diagnosis of psoriasis, ascertained by a dermatologist.

Exclusion criteria were use of systemic immunosuppressants or prolonged, intentional exposure to any UV non-prescribed source (natural or tanning booth) 2 weeks prior to point of measurement.

2.2 | Treatment

Low-dose phototherapy was given using the Dermasun Helios© prescribed for a use of 10 min/day. The equipment emits 1 standard erythemal dose (SED) in 10-minute time of UVA and UVB. Hospital-based NB-UVB was given following the normal standard of care for psoriasis patients. Patients were treated in Waldmann 7002 with Waldmann light bulbs TL-01 (for emission spectrum of the lamps, Figure 1).

The start dose was set at 70% of the estimated mean erythemal dose (MED) according to Fitzpatrick skin type with increments of 10%–20% depending on any erythema reactions. NB-UVB was given 3 times per week in an outpatient setting. An overview of the SED values of both groups is given in Table 1.

2.3 | Procedure

After informed consent, patients underwent a visual inspection of the skin to ascertain any signs of (pre-)malignant changes in the skin. The inspection was performed by a dermatologist. During this inspection, skin type was also recorded, as well as prior history of skin malignancies or actinic keratosis or lentigines.

Subsequently, patients had two 4-mm skin biopsies from the buttock area, as this is, in most patients, not exposed to natural sunlight. The biopsies were taken from non-lesional skin. In patients undergoing NB-UVB or low-dose UV, the biopsies were taken just before the scheduled UV session. In patients with NB-UVB, this was 2–3 days after their last treatment. The interval just before the next scheduled treatment was chosen to exclude acute effects of UV as the dose of both treatments differed. Patients undergoing low-dose UV therapy were asked to refrain from the therapy the day of biopsy, but to continue their normal routine, whether this be evening treatment or morning treatment.

From the obtained biopsies, one was fixed in formalin to be embedded in paraffin for immunohistochemistry, and the other was snap-frozen in liquid nitrogen for DNA extraction for CPD ELISA.

2.4 | Immunohistochemistry—p53 and γH2AX

Paraffin-embedded sections (5 μm) were used for immunohistochemical analysis for histone γH2AX and p53-positive cells. A 1:100

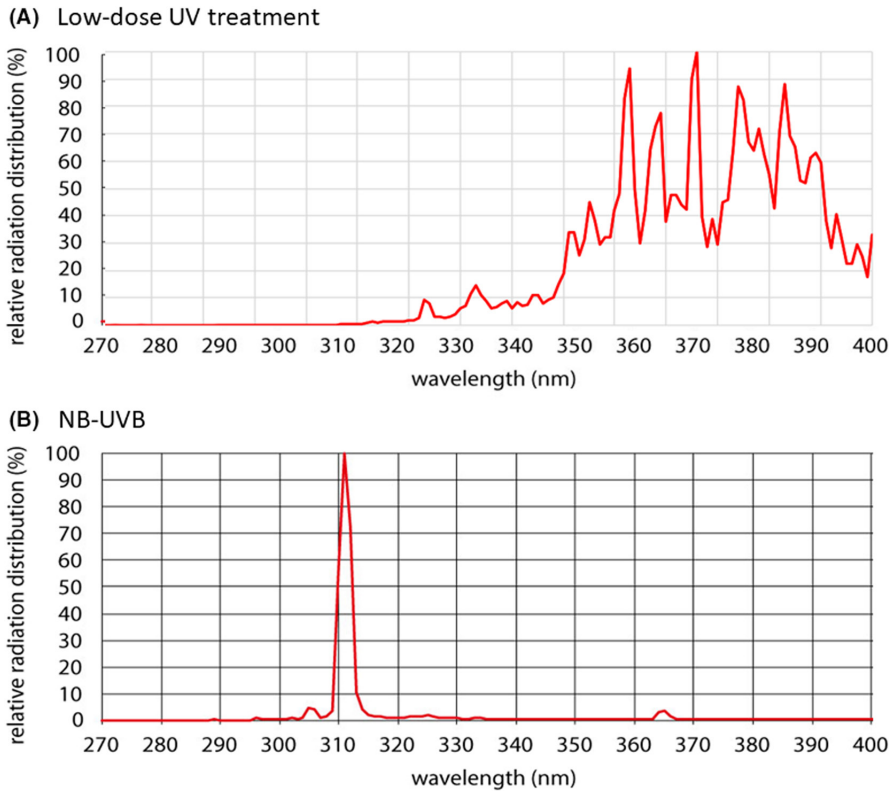

FIGURE 1 Spectral emission as provided by respective manufacturers. (A) low-dose UV treatment (Dermasun Helios®). (B) NB-UVB (Waldmann TL-01)

TABLE 1 Approximated SED in low-dose UV treatment vs conventional NB-UVB. The NB-UVB group would undergo increment of 20%, resulting in culminating values

Skin type	Low-dose UV	NB-UVB start	NB-UVB after 4 weeks
1	1	N/A	N/A
2	1	2.2	5.2
3	1	2.6	7.4
4	N/A	3.3	8.7

Note: Biopsies were taken after 4 weeks of NB-UVB. At this time point, this would result in the dose demonstrated in the last column.

dilution of the H2A.X (Ser139) antibody (clone JBW301, mouse, IgG1; Sigma-Aldrich) was used after antigen retrieval using 0.01 M citrate buffer, pH 6, boiling step. A 1:50 dilution of the p53 antibody (mouse, clone DO-7, IgG2b, Dako, Agilent) was used after antigen retrieval using a 10 mM TRIS/1 mM EDTA buffer, pH 9, boiling step. Both followed by a 15-min. room temperature (RT) incubation with Post-antibody Blocking Gold and a 30-min RT incubation with Poly-HRP-Goat anti-Mouse/Rabbit/Rat IgG Ruby (Brightvision 2-step Colour Detection System; ImmunoLogic) followed by AEC incubation at RT for 10 min. A background staining with haematoxylin was used. Slides were scanned using Vectra Polaris (PerkinElmer) part of the Microscopy and Cytometry Research Core Facility at the Amsterdam UMC location VUmc, and analysed with QuPath: open source software for digital pathology image analysis.[21] Positive cells in epidermis were analysed.

For γH2AX staining, 5 GJ irradiated skin was used as positive control. For p53 staining, a tonsil was used.

2.5 | ELISA—cyclobutane pyrimidine dimers

High-Sensitivity Cyclobutane Pyrimidine Dimer (CPD) ELISA (ver2.0 Cosmo Bio LTD) was performed on 0.4 μg/ml DNA extracted with QIAamp DNA Mini Kit (Qiagen) from the snap-frozen 4-mm skin biopsy according to the manufacturer's instructions. Shortly, 50 μl 0.4 μg/ml of denatured DNA was coated overnight by a 37°C incubation on a pre-coated protamine sulphate 96-well plate. After 5 washes with wash buffer, the plate was incubated for 30 min at 37°C with a primary anti-CPD antibody followed by 5 washes and a biotinylated secondary antibody incubation for 30 min. at 37°C. After an additional 5 washes, the plate was incubated for another 30 min at 37°C with streptavidin-peroxidase solution, and after another 5 washes with wash buffer, the plate was incubated for 30 min at 37°C with OPD solution. After adding stop solution, absorbance was determined using a Berthold Mithras 940 ELISA reader.

As positive and negative controls, DNA supplied by manufacturer was used and DNA of ex vivo skin and UV-treated ex vivo skin was used.

2.6 | Use of low-dose phototherapy

Patients using daily low-dose phototherapy were asked to fill in a survey about their actual use of the phototherapy installation. This was a retrospective survey.

The survey comprised of questions about the time the low-dose therapy was used per session, the number of sessions per day or week, changes in use and the number of months patients already had access to this treatment modality.

2.7 | Statistics

2.7.1 | Sample size calculation

The sample size calculation was done assuming that the smallest difference is consistent with prior results (no UV treatment vs low-dose UV treatment patients; difference of 5 points with $\sigma = 5$), and the groups are distributed in a 2:1:1 fashion (daily low-dose UV treatment: local treatment: conventional NB-UVB). The power (1-β) was set to 90%, and the significance level α to 0.05/3 to correct for multiple testing.

With these parameters, 88 participants were necessary. Correcting for technical failures, analytical failure and dropout of 20% of 110 patients would be needed. The anticipated number of patients would be (daily low-dose UV treatment: local treatment: conventional NB-UVB) 55:28:28.

2.8 | Statistical analysis

Categorical variables are described by frequency and percentage, and continuous variables by mean and standard deviation (SD) in case of normal distribution and by median and range in case of non-normal distribution. The categorical variables were compared between the three treatment arms (controls with local treatment only, patients undergoing low-dose UV treatment and patients undergoing conventional UV treatment) using a chi-squared test, and continuous variables were compared with each other with an ANOVA test after ln-transformation, as the values of the markers were not normally distributed. In case of significant difference between the three treatments arms, a post hoc analysis was carried out with the Bonferroni correction for multiple testing.

Correlation between markers and the use of low-dose UV treatment and correlation between the markers were analysed using a Spearman correlation test.

3 | RESULTS

Patients were included from May 2019 up to March 2020. Due to the outbreak of the COVID-19 pandemic, downscaling of outpatient care and restrictions, further inclusions were not feasible.

Due to these circumstances, the sample size was not met.

Thirty-nine patients with daily low-dose UV treatment, 15 patients using only local treatment and 8 patients undergoing conventional NB-UVB were included in the study. Patient characteristics are shown in Table 2. There was no significant difference in gender, age or Fitzpatrick skin type between the groups.

3.1 | Use of daily low-dose UV treatment

Patients using the daily low-dose UV treatment had access to the cabin for a median time of 30 months. The machine was used for a median of 40 min/week, although a large range was seen varying from 5 up to 140 minutes. Table 3 gives a clear overview of the self-reported use of the low-dose UV treatment. Of note is that all patients but 1 reported to comply with the instructions not to exceed a daily treatment frequency. Sixty-one per cent reported not to use the treatment on a daily basis. None exceeded the maximum of 10 min/session.

3.2 | Skin inspection

All patients underwent a complete visual skin assessment during their study visit. In 12 patients, a sign of photoageing was found in the current inspection or had a prior diagnosis of skin malignancies (Table 4): nine patients in the low-emission phototherapy group, 2

TABLE 2 Patient characteristics

	Low-dose UV ($n = 39$)		Local treatment ($n = 15$)		NB-UVB ($n = 8$)		*p*-value
Age							
Mean (SD)	48.3	14.3	48.7	16.5	51.3	18.0	.89
Gender							
Male	29	74.4%	7	46.7%	6	75.0%	.13
Female	10	25.6%	8	53.3%	2	25.0%	
Skin type fitzpatrick							
1	5	12.8%	1	6.7%	0	0.0%	.30
2	26	66.7%	10	66.7%	5	62.5%	
3	8	20.5%	2	13.3%	2	25.0%	
4	0	0.0%	1	6.7%	1	12.5%	
5	0	0.0%	1	6.7%	0	0.0%	

in the local therapy group and 1 in the NB-UVB. The difference between the findings was not significant ($p = .63$).

3.3 | Skin biopsies

In skin biopsies, the percentage of p53 cells showed a clear difference between the groups ($p < .001$; Table 5). The low-dose UV treatment group had a significantly lower percentage of p53-positive cells ($p = .015$) than the NB-UVB group. As p53 is upregulated in psoriatic skin, patients were only included if the diagnosis of psoriasis had been confirmed. The group using only local therapy, the baseline group, were also found to have a significantly lower percentage of p53-positive cells compared with NB-UVB ($p < .001$). The difference between the low-dose treatment group and the local therapy group was not significant ($p = .065$). The staining of the skin biopsies is shown in Figure 2.

CPDs were measured in optical units. Again, a difference was found between the groups ($p < .001$): low-dose UV showed a lower amount of CPDs than NB-UVB ($p = .016$) and local therapy ($p < .001$). CPDs in local therapy, which can be considered background activity, were significantly lower than NB-UVB ($p < .001$).

To ascertain whether the self-reported frequency of low-dose UV therapy could be a factor in the lack of significant difference between the low-dose UV treatment group and the control group undergoing local therapy only, a subselection of low-dose treatment patient using the treatment more intensively was chosen (Figures 3 and 4). When patients using the low-dose UV treatment 3× per week or more were selected, post hoc analysis showed a marked difference in the amount of CPDs and percentage of p53-positive cells in the epidermis between low-dose UV treatment and NB-UVB (percentage of p53, $p = .039$; CPD, $p = .034$), low-dose UV treatment and controls with local therapy only (percentage of p53, $p = .011$; CPD, $p < .001$) and lastly, as reported before, between the controls without UV treatment and the group with conventional NB-UVB (percentage of p53, $p < .001$; CPD, $p < .001$). Table 6 shows the specifics of the analysis. Patients reporting a strict adherence to the low-dose UV treatment (ie daily use) showed similar significant results of CPDs (NB-UVB vs controls, $p = .022$; low-dose UV vs NB-UVB, $p < .001$; and low-dose UV treatment vs controls, $p < .001$). For the percentage of p53-positive cells, a significant difference was found between NB-UVB and controls ($p < .001$), but not between low-dose UV treatment and NB-UVB ($p = .053$) or low-dose UV treatment and controls ($p = .17$).

To evaluate whether the chosen markers for carcinogenicity showed a correlation to each other within the patients, Spearman's test was used. This showed a clear correlation between the markers with the exception of CPDs and γH2AX. The results are shown in Table 7.

In patients using low-dose UV therapy, a clear link was found in the amount CPDs when correlated to the self-reported time of use per session ($p = .009$). This is demonstrated in Table 8.

No such correlation was found with p53 markers or γH2AX. A correlation was found, however, in the time patients had access to the low-dose UV therapy unit and the absolute amount of γH2AX.

TABLE 3 Overview of self-reported use of low-dose UV treatment

Use		
<1×/week	1	2.8%
1×/week	1	2.8%
2×/week	3	8.3%
3×/week	4	11.1%
4×/week	7	19.4%
5×/week	5	13.9%
6×/week	1	2.8%
1×/day	13	36.1%
2×/day	1	2.8%
Median (range)	40 min/week	(5–140)
Months of access		
Median (range)	30	(18–96)

Note: Of note, 3 patients did not return the questionnaire, these data are therefore lacking.

4 | DISCUSSION

This study sets out to investigate safety aspects of prolonged use of low-dose phototherapy in psoriasis patients, focusing on possible carcinogenic effects. Low-dose phototherapy is used at home. Treatment adherence was therefore an important parameter, more specifically that patients did not overexpose themselves. Although the calculated sample size was not met, the power reached with current included patients in the study was 94% for p53 results and 99% for CPD results.

4.1 | Carcinogenic effects

To measure the carcinogenic effects of phototherapy on the skin p53 activation, cyclobutane pyrimidine dimers (CPDs) and γH2AX were selected as markers.

p53 is a well-known tumour suppressor gene. It regulates cell-cycle control after DNA damage, activates DNA-repair mechanisms or initiates apoptosis. It is activated after cell damage of different kinds, and mutations in p53 have been found in many different tumours, including NMSC.[22]

Activation of p53 provides information on DNA damage and the need for repair (or apoptosis) in tissue.

UV light causes direct genotoxic effects as DNA is a strong chromophore of UVB. UVB energy is readily absorbed by DNA and can cause mutations as covalent bonds are formed between adjacent pyrimidines. Mutations occur especially in dipyrimidine sites, causing the two most characteristic UVR lesions: pyrimidine (6-4) pyrimidone photoproducts and CPD. They are known as UVR-signature

TABLE 4 Signs of photoageing or malignancy in physical examination and history of (pre-)malignant skin disease in participants

Study number	Study arm	Age	Gender	Physical examination	Number of Δ	History of malignancy
41102	Local therapy	76	Female	Lentigo solaris	2	
70608	Local therapy	55	Female	Freckles	100	
40902	Low-dose UV	67	Male	AK	1	
41101	Low-dose UV	67	Female	Lentigo solaris	1	
50901	Low-dose UV	41	Male	Freckles	60	
50904	Low-dose UV	55	Female			Basal cell carcinoma > 30 years ago
151001	Low-dose UV	76	Male	Freckles	500	
				Lentigo solaris	1	
190602	Low-dose UV	64	Female	Lentigo solaris	3	
221104	Low-dose UV	61	Male	Freckles	300	
261101	Low-dose UV	26	Female	Freckles	10	
261103	Low-dose UV	66	Female			Basal cell carcinoma, 2011
270606	NB- UVB	59	Female	Lentigo solaris	7	

TABLE 5 Median value (range) of p53, CPDs and γH2Ax in biopsies of all patients

	Local therapy ($n = 15$)		Low-dose UV ($n = 39$)		NB-UVB ($n = 8$)		*p*-value
p53%	1.4	0.12–11.4	2.597	0.12–14.0	7.3	2.8–58.6	<.001
p53 absolute	89.1	7.4–809.9	177.44	8.5–1565.0	365.0	1.1–716.5	.113
CPDs	0.1	0.010–0.11	0.16	0.020–0.78	0.4	0.14–0.94	<.001
γH2Ax %	0.6	0–19.4	0.9206	0–6.7	0.7	0.57–5.5	.833
γH2Ax absolute	41.6	0–19794.5	78.93	0–575.6	40.9	0–381.2	.772

Note: A significant difference is found in patients undergoing conventional NB-UVB compared with local therapy and NB-UVB compared with low-dose UV. The difference between the control group with local therapy does not show a significant difference when compared to all patients undergoing low-dose UV therapy in the p53 parameter.

mutations when a C->T or CC ->TT mutation occurs.[23] CPDs are not evenly distributed in genomic DNA. There seem to be preferential hot spots, in particular in the p53 gene. In NMSC, mutations at these sites appear to be frequent and have been associated with a UV signature.[24]

The phosphorylated variant of histone H2Ax, γH2AX, is known to be produced in response to DNA damage that involves the formation of DNA double-stranded breaks (DSB) after ionizing radiation. It has also been observed in UVB-irradiated cells, but reports on the occurrence of γH2AX after UVA irradiation have been conflicting. Several studies have implicated oxidative stress due to UVR as a cause of the phosphorylation of γH2AX, instead of the direct genotoxic effect seen in ionizing radiation.[25–27]

In this study, psoriasis patients treated with low-dose phototherapy showed a significantly lower amount of p53 activation and CPDs as compared to patients undergoing conventional NB-UVB. No significant difference was found in p53 activation and CPDs in patients treated with low-dose phototherapy as compared to a control group using local therapy only, when all patients were taken into account. When patients using the low-dose phototherapy thrice weekly or more were selected, the difference between the control group and the patients undergoing low-dose phototherapy became significant. This demonstrates a clear dose-effect ratio: when used more frequently, low-dose phototherapy causes p53 activation and CPDs. This corroborates findings of previous studies that the extent of UV exposure correlates with induced 'damage' in keratinocytes. This damage is, however, clearly lower in prolonged use of low-dose phototherapy than in conventional NB-UVB.

These findings suggest that the prolonged use of low-dose phototherapy for at least 18 months is not more harmful for psoriasis patients than conventional NB-UVB. Further research into the effects of even longer treatment of low-dose UV therapy is warranted, as are studies to evaluate the longevity of the current markers after cessation of (conventional and low-dose) phototherapy.

4.2 | Visual signs of photodamage

Patients undergoing NB-UVB, low-dose phototherapy and controls using local treatment only underwent visual skin examination to ascertain any signs of photodamage. Although the groups were small, no difference was found in the presence of these signs. A

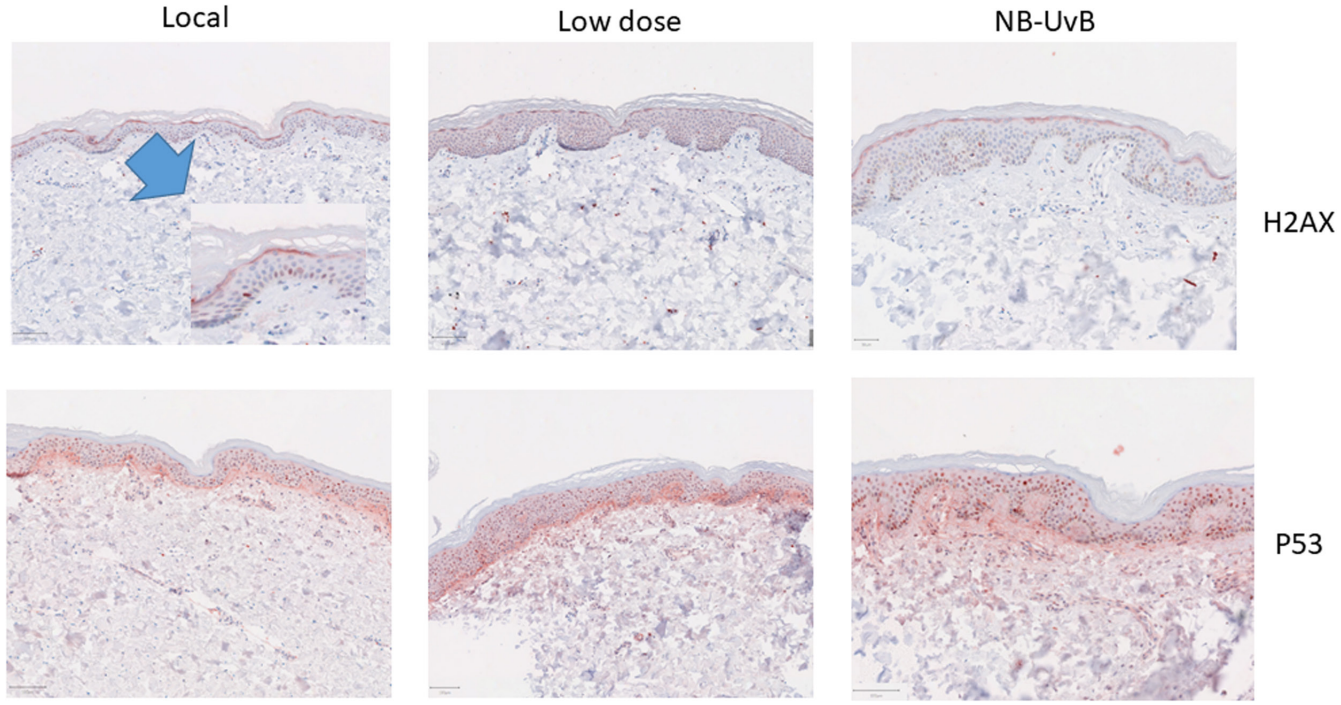

FIGURE 2 Immunohistochemical staining of the skin biopsies. At the arrow, a zoomed-in version

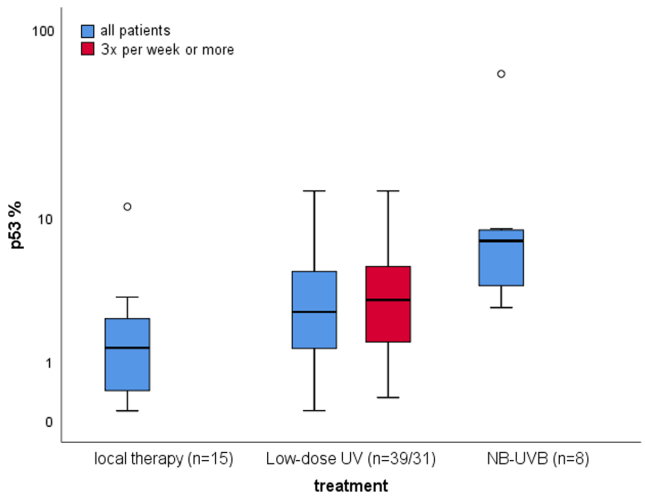

FIGURE 3 Median and range values of percentage of p53-positive cells in the three treatment groups. For the low-dose UV group, results are shown for all included patients (blue box) and for the selection of patients reporting treatment frequency with a minimum of 3× a week or more (red box)

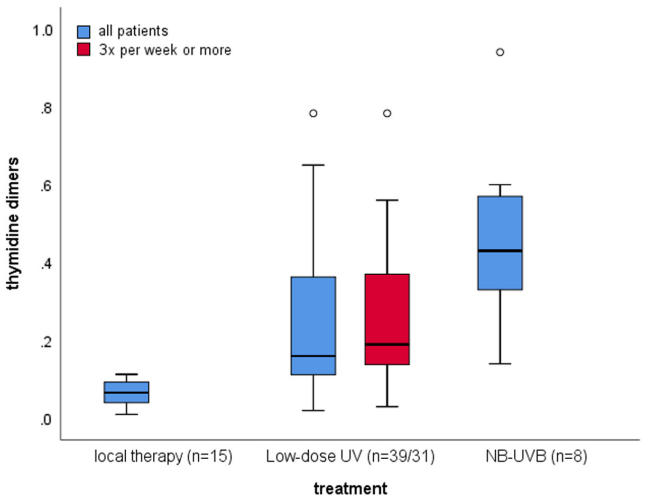

FIGURE 4 Median and range values of CPDs in the three treatment groups. For the low-dose UV group, results are shown for all included patients (blue box) and for the selection of patients reporting treatment frequency with a minimum of 3x a week or more (red box)

prospective study registering these signs after any form of (medical) phototherapy could shed more light on the clinical meaning of elevated markers such as p53 and CPDs. Is there a possible cut-off value (ie cumulative UV dose, specific p53 values) when these signs appear? Such a study would be extremely valuable, albeit very hard to undertake as it would be difficult to take into account the sun-seeking behaviour of psoriasis patients. Advocating due caution, regular (eg biannual) visual skin examination should be considered when prescribing any kind of phototherapy.

4.3 | Correlation between the markers

The p53 and CPDs significantly differed between the treatment groups. Surprisingly, the last marker, γH2AX, did not show a significant activation, even when patients using the therapy >3× per week were selected. To further investigate the relevance of this immunohistochemical staining, the correlation between all carcinogenic markers was assessed. A significant correlation was found between

TABLE 6 Median value (range) of p53, CPDs and γH2Ax when patients were selected undergoing low-dose UV treatment 3 times a week or more compared with the control groups

	Local therapy ($n = 15$)		Low-dose UV ($n = 31$)		NB-UVB ($n = 8$)		*p*-value
p53%	1.4	0.12–11.4	3.1	0.31–14.0	7.3	2.8–58.6	<.001
p53 absolute	89.1	7.4–809.9	223.0	21.5–1565	365.0	1.1–716.5	.059
CPDs	0.1	0.010–0.11	0.2	0.030–0.78	0.4	0.14–0.94	<.001
γH2AX %	0.6	0–19.4	1.0	0–6.7	0.7	0.57–5.5	.878
γH2AX absolute	41.6	0–19794.5	82.5	0–575.6	40.9	0–381.2	.765

Note: A significant difference is now found in p53% and CPDs between all groups.

TABLE 7 Correlation between the markers in the complete cohort of patients analysed with Spearman's test

	p53%	p53 absolute		CPDs		γH2AX %		γH2AX absolute	
	p-value	correlation	*p*-value	correlation	*p*-value	correlation	*p*-value	correlation	*p*-value
p53%				0.48	<.001	0.50	<.001	0.44	<.001
p53 absolute				0.45	<.001	0.54	<.001	0.52	<.001
CPDs	<0.001	0.45	<.001			0.25	.056	0.22	.087
γH2AX %	<0.001	0.54	<.001	0.25	.056				
γH2AX absolute	<0.001	0.52	<.001	0.22	.087				

Note: Although no correlation is found between CPD and γH2AX, the other markers do show a clear correlation.

TABLE 8 Markers of carcinogenesis p53, CPDs and γH2AX correlated to the self-reported time of use of low-dose UV therapy and the 'time of access': time the machine has been in the home of patients

	Self-reported time of use		Self-reported time of access	
	correlation	*p*-value	correlation	*p*-value
p53%	0.07	.705	0.10	.564
p53 absolute	0.06	.707	0.13	.456
CPDs	0.44	.009	0.00	.985
γH2AX %	0.08	.637	0.28	.103
γH2AX absolute	0.09	.605	0.34	.040

all groups, with the exception of CPDs and γH2AX. There was, however, a clear trend for correlation ($p = .06$ and $p = .09$) between those. This implies mutual coherence between the markers, and the test was valid. A possible explanation for the lack of correlation or statistically significant activation in the examined biopsies could lie in the relatively small sample size, the timing of the samples or a different activation pathway.

4.4 | Use of low-dose phototherapy

Due to the carcinogenic risks associated with UV exposure, dermatologists are reluctant to prescribe prolonged and repeated courses of phototherapy. In-hospital treatment provides a sense of control over the treatment use and facilitates adjustments of the treatment. Home-based treatment lacks these benefits. In this study, all patients used low-dose phototherapy for at least 18 months but one reported not to overuse their home-based treatment. Although a retrospective survey was used to ascertain this phenomenon, the immunohistochemical and ELISA findings support this phenomenon.

There was a clear correlation between the amount of CPDs and the reported amount of time the machine was used per week. The CPDs rose when low-dose phototherapy was used more frequently. The CPDs, however, remain significantly lower compared with conventional NB-UVB. Overall, the low-dose phototherapy is safe when compared to one course of conventional NB-UVB and it is not notably 'overused'. On the contrary, 61% of patients who filled out the survey indicated using the low-dose phototherapy less than originally prescribed. Only one (2.7%) reported overuse. It seems desirable, however, for such a home-based unit to have a control mechanism monitoring its use.

5 | CONCLUSION

Patient safety is the primary obstacle in home-based phototherapy: patients have unsupervised access to the UV-emitting device. Excessive or prolonged use causes photodamage and, in the long run, skin malignancies. The current results show that patients using low-dose phototherapy at home for at least 18 months had significantly lower activation of p53 and CPDs than patients undergoing conventional NB-UVB. Patients also did not show more signs of photoageing (lentigines, actinic keratosis) or skin malignancies.

The groups in our study, however, were small. Only 68 patients participated. Although this was enough to demonstrate the significant difference, further studies are warranted to evaluate the risks of even longer use. Ideally, these studies would be performed prospectively, including an electronic system monitoring the actual use of the home-based phototherapy device.

Conventional NB-UVB is generally accepted as a safe treatment in psoriasis. Overall, the current findings show that low-dose UV during a period of 18 months causes less p53 and CPDs (of damage) than this 'safe' NB-UVB. It can therefore be considered as a safe treatment in psoriasis patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Lindelöf B, Sigurgeirsson B, Tegner E, et al. PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol*. 1999;141(1):108-112.
2. Stern RS, Laird N, Melski J, Parrish JA, Fitzpatrick TB, Bleich HL. Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med*. 1984;310(18):1156-1161.
3. Chuang TY, Heinrich LA, Schultz MD, Reizner GT, Kumm RC, Cripps DJ. PUVA and skin cancer. A historical cohort study on 492 patients. *J Am Acad Dermatol*. 1992;26(2 Pt 1):173-177.
4. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26(Suppl 3):22-31.
5. Hearn RM, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol*. 2008;159(4):931-935.
6. Weischer M, Blum A, Eberhard F, Röcken M, Berneburg M. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Derm Venereol*. 2004;84(5):370-374.
7. Jo SJ, Kwon HH, Choi MR, Youn JI. No evidence for increased skin cancer risk in Koreans with skin phototypes III-V treated with narrowband UVB phototherapy. *Acta Derm Venereol*. 2011;91(1):40-43.
8. van de Kerkhof PCM, de Gruijl FR. Phototherapy in the perspective of the chronicity of psoriasis. *J Eur Acad Dermatol Venereol*. 2020;34(5):926-931.
9. Chiu SH, Liu IL, Chen YW, Lan CE. Low-dose UVB therapy is comparable with conventional UVB phototherapy for treatment of vitiligo: A pilot study. *J Dermatol Sci*. 2018;92(2):218-220.
10. de Rie MA, Out TA, Bos JD. Low-dose narrow-band UVB phototherapy combined with topical therapy is effective in psoriasis and does not inhibit systemic T-cell activation. *Dermatology*. 1998;196(4):412-417.
11. Kleinpenning MM, Smits T, Boezeman J, van de Kerkhof PC, Evers AW, Gerritsen MJ. Narrowband ultraviolet B therapy in psoriasis: randomized double-blind comparison of high-dose and low-dose irradiation regimens. *Br J Dermatol*. 2009;161(6):1351-1356.
12. Rose RF, Turner D, Goodfield MJ, Goulden V. Low-dose UVA1 phototherapy for proximal and acral scleroderma in systemic sclerosis. *Photodermatol Photoimmunol Photomed*. 2009;25(3):153-155.
13. Vieyra-Garcia P, Fink-Puches R, Porkert S, et al. Evaluation of low-dose, low-frequency oral psoralen-UV-A treatment with or without maintenance on early-stage mycosis fungoides: a randomized clinical trial. *JAMA Dermatol*. 2019;155(5):538-547.
14. Franken SM, Witte B, Pavel S, Rustemeyer T. Psoriasis and daily low-emission phototherapy: effects on disease and vitamin D level. *Photodermatol Photoimmunol Photomed*. 2015;31(2):83-89.
15. Paul BS, Stern RS, Parrish JA, Arndt KA. Low-intensity selective UV phototherapy. A clinical trial in outpatient therapy for psoriasis. *Arch Dermatol*. 1983;119(2):122-124.
16. Drigeard Desgarnier MC, Fournier F, Droit A, Rochette PJ. Influence of a pre-stimulation with chronic low-dose UVB on stress response mechanisms in human skin fibroblasts. *PLoS One*. 2017;12(3):e0173740.
17. Liao Y, Feng J, Zhang Y, Tang L, Wu S. The mechanism of CIRP in inhibition of keratinocytes growth arrest and apoptosis following low dose UVB radiation. *Mol Carcinog*. 2017;56(6):1554-1569.
18. Shorrocks J, Paul ND, McMillan TJ. The dose rate of UVA treatment influences the cellular response of HaCaT keratinocytes. *J Invest Dermatol*. 2008;128(3):685-693.
19. Franken SM, Witte BI, Rustemeyer T. P53 and thymidine dimer induction in daily low emission broad band UV treatment. *MOJ Immunology*. 2016;4(2):e00123. http://medcraveonline.com/MOJI/MOJI-04-00123.pdf
20. Tian Y, Liu W, Niu T, et al. The injury and cumulative effects on human skin by UV exposure from artificial fluorescence emission. *Photochem Photobiol*. 2014;90(6):1433-1438.
21. Bankhead P, Loughrey MB, Fernández JA, et al. QuPath: open source software for digital pathology image analysis. *Sci Rep*. 2017;7(1):16878.
22. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA*. 1991;88(22):10124-10128.
23. Howard BD, Tessman I. Identification of the altered bases in mutated single-stranded DNA. 3. Mutagenesis by ultraviolet light. *J Mol Biol*. 1964;9:372-375.
24. Kim SA, Ryu YW, Kwon JI, Choe MS, Jung JW, Cho JW. Differential expression of cyclin D1, Ki-67, pRb, and p53 in psoriatic skin lesions and normal skin. *Mol Med Rep*. 2018;17(1):735-742.
25. Sedelnikova OA, Redon CE, Dickey JS, Nakamura AJ, Georgakilas AG, Bonner WM. Role of oxidatively induced DNA lesions in human pathogenesis. *Mutat Res*. 2010;704(1–3):152-159.
26. Svobodová AR, Galandáková A, Sianská J, et al. DNA damage after acute exposure of mice skin to physiological doses of UVB and UVA light. *Arch Dermatol Res*. 2012;304(5):407-412.
27. Marti TM, Hefner E, Feeney L, Natale V, Cleaver JE. H2AX phosphorylation within the G1 phase after UV irradiation depends on nucleotide excision repair and not DNA double-strand breaks. *Proc Natl Acad Sci USA*. 2006;103(26):9891-9896.

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