Comparison between narrowband UVB phototherapy and khellin photochemotherapy in the treatment of alopecia areata
Azza M. Abdel Meguida, Dalia A. Attallah and Nawal A.S. Alzzubidi

Background
Alopecia areata (AA) is a highly unpredictable, autoimmune skin disease affecting ~1.7% of the population worldwide. Treatment for AA is generally unsatisfactory. A number of treatments can induce hair growth but none have been shown to alter the course of the disease.

Objective
The aim of this study was to compare the efficacy of narrowband UVB (NB-UVB) phototherapy with that of topically applied khellin followed by UVA irradiation (KUVA) in the treatment of AA.

Patients and methods
This was a comparative study involving 38 patients. The patients were divided into two groups, group I and group II. Patients of group I (n = 19) were treated with KUVA on the scalp and those of group II (n = 19) were treated with NB-UVB irradiation on the scalp. In both groups, irradiation was administered three times weekly for 24 weeks or until complete terminal hair regrowth.

Results
The patient response to KUVA therapy (57.89%) was statistically higher than that to NB-UVB therapy (10.52%, P < 0.05) at the end of the treatment course (24 weeks).

Conclusion
KUVA therapy is better than NB-UVB therapy in the treatment of AA resistant to other treatment modalities.

Keywords:
alopecia areata, khellin photochemotherapy, narrowband UVB

Introduction
Alopecia areata (AA) is a highly unpredictable, autoimmune skin disease resulting in loss of scalp and body hair. It affects ~1.7% of the overall population [1]. Although it is medically benign, it can cause tremendous emotional and psychosocial stress in affected patients and their families [2].

The exact pathogenesis of AA is yet to be established; the most widely accepted hypothesis is that AA is a T-cell-mediated autoimmune condition [2,3]. It may involve the entire scalp (alopecia totalis) or complete body hair [alopecia universalis (AU)] [4,5].

Treatment for AA is generally unsatisfactory. A number of treatments can induce hair growth but none have been shown to alter the course of the disease [6,7].

Phototherapy, which is the exposure to UV radiation for therapeutic use, has been investigated in the treatment of AA [8]. It can be administered in various ways, including photochemotherapy, broadband and narrowband UVB phototherapy (NB-UVB), UVA1, and photodynamic therapy [9,10].

Although NB-UVB phototherapy is a well-established treatment in many dermatoses, it was investigated in AA treatment with encouraging results but with little documented evidence of its efficacy [11,12].

Psoralen photochemotherapy (PUVA) is the combined use of psoralen and UVA radiation [8]. The concerns about phototoxicity and possible carcinogenicity limit the long-term use of oral PUVA and have led to the introduction of other photochemotherapeutic agents such as khellin with low genotoxicity and no long-term side effects and phototoxic skin erythematic responses [11,13]. Khellin photochemotherapy (KUVA) has been studied as a treatment for AA with encouraging results in terms of a high success rate and minimal side effects [14,15].

Therefore, we aimed at comparing the efficacy of NB-UVB phototherapy with KUVA photochemotherapy as two modalities in the treatment of recalcitrant AA.
Patients with a disease duration of more than 6 months or a rapidly progressive course of AA, regardless of the duration of the disease, were included in our study. All patients were resistant to previous topical therapies or systemic steroids, and none of them had a history of phototherapy. No concomitant treatment was administered during the period of the study. Prior treatment was stopped in all patients at least 3 months before inclusion in our study.

Pregnant and lactating women, patients who were currently experiencing significant terminal hair regrowth, and patients who had not received other treatment modalities earlier were excluded from the study.

Detailed history was taken from all patients, including age of the patient, age at onset, duration of AA, previous treatments used and their efficacy, history of associated diseases, and family history of AA.

The clinical form of AA and the baseline ‘Severity of Alopecia Tool score’ (SALT score), according to Olsen et al. [16], were determined for all patients.

To determine the SALT score, the scalp is divided into four areas, namely, the vertex – 40% (0.4) of scalp surface area; right profile of the scalp – 18% (0.18) of scalp surface area; left profile of the scalp – 18% (0.18) of scalp surface area; and posterior aspect of the scalp – 24% (0.24) of scalp surface area. The percentage of hair loss in any of these areas is the percentage hair loss multiplied by the percentage surface area of the scalp in that area.
The SALT score is the sum of the percentage of hair loss in all the above-mentioned areas [16].

All patients gave their formal consent. The protocol was approved by the Ethical Committee of the Faculty of Medicine, Assiut University.

Methods
This study was carried out at the UV Unit at the Department of Dermatology, Assiut University Hospital. Photographs of the four views of the scalp were taken for each patient. In both therapeutic modalities, irradiation was administered three times weekly for 24 weeks or until complete terminal hair regrowth.

Patients were randomly divided by computer-generated random numbers into two groups. Group I (n = 19) patients were treated with topical khellin on the scalp, followed by UVA irradiation (KUVA), and group II (n = 19) patients were treated with NB-UVB irradiation.

Group I (KUVA group)
Nineteen patients were treated with topical 2% khellin paint (Ezalline, Multipharma Co., Cairo, Egypt) applied to the alopecic area on the scalp 30 min before UVA irradiation with an intensity of irradiation between 310 and 380 nm, with a peak emission at 365 nm (Waldmann PUVA 100; Waldmann Medizintechnik, Peter-Henlein, Germany). The starting UVA dose was 1.5 J/cm², with increments of 0.3 J/cm² every two sessions until a maximum dose of 8 J/cm² [17,18] or the effective dose (the dose at which the first regrowth of hair was observed) was reached, and was kept constant until the end of the course.

Excellent results to narrowband UVB therapy in the both responder patients.
Phototherapy in alopecia areata

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Table 1. Demographic and clinical data of the studied groups

<table>
<thead>
<tr>
<th>Items</th>
<th>Group I (KUVA) (n = 19)</th>
<th>Group II (NB-UVB) (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.68 ± 6.04</td>
<td>37.73 ± 12.26</td>
<td>0.392</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 10–47</td>
<td>17–59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male : female</td>
<td>10 (52.6) : 9 (47.41)</td>
<td>11 (57.91) : 8 (42.1)</td>
<td>0.425</td>
</tr>
<tr>
<td>Duration of AA (months)</td>
<td>20.105 ± 17.24</td>
<td>27.31 ± 9.33</td>
<td>0.0825</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 2–120</td>
<td>2–72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of AA (years)</td>
<td>37.39 ± 6.56</td>
<td>34.38 ± 11.74</td>
<td>0.527</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 3.5–46</td>
<td>6–58.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of AA [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male : female</td>
<td>2 (10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophiasis</td>
<td>12 (63.2)</td>
<td>10 (52.6)</td>
<td>0.629</td>
</tr>
<tr>
<td>Patchy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male : female</td>
<td>2 (10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophiasis</td>
<td>2 (10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>2 (10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU</td>
<td>3 (15.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of irradiation sessions for first regrowth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>16.9 ± 7.4</td>
<td></td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Range 7–27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irradiation dose needed for first regrowth (J/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>104.8 ± 75.21</td>
<td>401.96 ± 0.83</td>
<td></td>
</tr>
<tr>
<td>Range 21–204</td>
<td>3.27–5.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline SALT score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48.73 ± 35.79</td>
<td>55.86 ± 36.28</td>
<td>0.546</td>
</tr>
</tbody>
</table>

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; KUVA, khellin photochemotherapy; NB-UVB, narrowband UVB.

*Significant P value.

Table 2. Degree of the clinical response to KUVA (group I) and NB-UVB therapy (group II) among the studied groups

<table>
<thead>
<tr>
<th>Treatment response</th>
<th>KUVA (group I) (n = 19)</th>
<th>NB-UVB (group II) (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>11 (57.89)</td>
<td>2 (10.52)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Excellent</td>
<td>9 (47.37)</td>
<td>2 (10.52)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>2 (10.52)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>8 (42.11)</td>
<td>17 (89.48)</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

KUVA, khellin photochemotherapy; NB-UVB, narrowband UVB.

*P ≤ 0.05, significant.

**P ≤ 0.001, highly significant.

Table 3. Relationship between the clinical response and the extent of AA (based on a SALT score <50%) among the studied groups

<table>
<thead>
<tr>
<th>Baseline SALT score</th>
<th>Treatment response</th>
<th>Group I (KUVA)</th>
<th>Group II (NB-UVB)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>Responders</td>
<td>7 (63.63)</td>
<td>1 (10)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Excellent</td>
<td>5 (45.45)</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>2 (18.18)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>4 (36.37)</td>
<td>9 (90)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>11 (100)</td>
<td>10 (100)</td>
<td></td>
</tr>
</tbody>
</table>

AA, alopecia areata; KUVA, khellin photochemotherapy; NB-UVB, narrowband UVB; SALT score, Severity of Alopecia Tool score.

*P ≤ 0.001, highly significant.

Table 4. Relationship between the clinical response and the extent of AA (based on a SALT score >50%) among the studied groups

<table>
<thead>
<tr>
<th>Baseline SALT score</th>
<th>Treatment response</th>
<th>Group I (KUVA)</th>
<th>Group II (NB-UVB)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50%</td>
<td>Responders</td>
<td>4 (50)</td>
<td>1 (11.11)</td>
<td>0.05*</td>
</tr>
<tr>
<td></td>
<td>Excellent</td>
<td>4 (50)</td>
<td>1 (11.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>4 (50)</td>
<td>8 (88.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>8 (100)</td>
<td>9 (100)</td>
<td></td>
</tr>
</tbody>
</table>

AA, alopecia areata; KUVA, khellin photochemotherapy; NB-UVB, narrowband UVB; SALT score, Severity of Alopecia Tool score.

*P ≤ 0.05, significant.

Group II (NB-UVB group)

Nineteen patients were treated with NB-UVB on the scalp. The NB-UVB source was a Waldmann (TL-01) half cabinet (Waldmann Medizintechnik). The NB-UVB output includes a spectrum of irradiation ranging between 310 and 315 nm, with a peak emission at 311 nm. Irradiation doses started at 0.24 J/cm² [19] and were increased by 10% every session according to the erythema response or until the maximum single dose of 4 J/cm² had been reached [20].

Patients were assessed during every session for any side effects and were also assessed every 4 weeks by direct scalp observation and through photographs.

The treatment endpoints for our patients were either an absence of hair regrowth (either vellus or terminal) after completion of 12 weeks of therapy or the presence of a terminal full regrowth after the treatment course (24 weeks) was completed.
According to the clinical response at the treatment endpoint, the patients were classified as either treatment failures (patients who had no response after 12 weeks of therapy or only vellus hair regrowth at the end of the treatment course) or treatment responders (patients who had terminal hair regrowth).

The percentage of terminal hair regrowth based on the SALT score was calculated using the following equation:

\[
\text{Baseline SALT score} - \text{final SALT score/baseline SALT score} = \% \text{ of scalp hair regrowth.}
\]

The treatment responders were classified according to the percentage of hair regrowth into three categories, namely, excellent (hair regrowth >60%), good (hair regrowth 30–60%), and poor (hair regrowth <30%). Patients demonstrating an improvement underwent a monthly follow-up for at least 3 months to assess the stability of hair regrowth and detect of a relapse.

The classification of patients according to the clinical response:

(1) **Treatment responders**: A total of 11 patients (57.89%) were treatment responders (Fig. 1). Among them, nine patients (47.3%) had an excellent response [six patients (31.6%) had complete hair regrowth, three (15.8%) had terminal hair regrowth >60%]; the remaining two patients (10.52%) had terminal hair regrowth less than 30% at the end of treatment course and were considered as having a poor response.

(2) **Treatment failures**: A total of eight patients (42.11%) were treatment failures. Among them, six patients (31.6%) had no signs of regrowth after 12 weeks of treatment and two patients (10.52%) had only vellus hair regrowth at the end of 24 weeks.

**Clinical response to KUVA therapy**

The classification of patients according to the clinical response:

(1) **Treatment responders**: Two patients (10.52%) were treatment responders (Fig. 2). Both patients (10.52%) had patchy type alopecia and achieved complete hair regrowth (excellent response).

(2) **Treatment failures**: A total of 17 patients (89.48%) were treatment failures. Among them, 10 patients (52.62%) had no signs of regrowth after 12 weeks of treatment and seven patients (36.86%) had only vellus hair regrowth at the end of 24 weeks.

Comparison between the clinical responses to the two therapeutic modalities among the studied groups showed that the patient response to KUVA therapy (57.89%) was statistically higher than that to NB-UVB therapy (10.52%, \(P < 0.05\)). An excellent response was significantly more frequent among the KUVA group (group I, \(P < 0.001\)) (Table 2).

There was no significant correlation between clinical response to both therapeutic modalities with regard to the age at onset of AA \((r = 0.358\) for group I and 0.698 for group II, \(P > 0.05\) for both groups), the duration of AA \((r = 0.492\) for group I and 0.427 for group II, \(P > 0.05\) for both groups), and the extent of AA (based on the SALT score) \((r = 0.283\) for group I and 0.695 for group II, \(P > 0.05\) for both groups).

When the clinical responses in patients of both groups with SALT scores less than 50% were compared, significant differences were seen between the responders of the two groups. A significant difference was also found between the two groups with regard to SALT score greater than 50%. The frequency of the clinical response to KUVA therapy was higher among patients with SALT score less than 50 but did not reach statistical significance (Tables 3 and 4).

In group I, all clinical forms of AA, except AU, responded to KUVA therapy. In contrast, in group II, only patients with patchy AA responded to NB-UVB therapy. Both modalities of treatment were well tolerated by all patients.

**Clinical response to NB-UVB therapy**

The classification of patients according to the clinical response:

**Results**

Demographic and clinical data of the 38 AA patients (21 male and 17 female) included in our study are summarized in Table 1.

**Clinical response to KUVA therapy**

The classification of patients according to the clinical response:

Results

Clinical and demographic data of the 38 AA patients (21 male and 17 female) included in our study are summarized in Table 1.

Clinical response to KUVA therapy

The classification of patients according to the clinical response:


**Discussion**

The first study on KUVA therapy in the treatment of AA was carried out by Trirungtasa et al. [14], which included 10 patients with different types of AA and had encouraging results in terms of high success rates and minimal side effects.

Few studies [21] have been performed on the efficacy of NB-UVB in the treatment of AA. Krook [22] was the first to discover that the use of phototherapy with UVB light was useful in some patients with AA. Thereafter, a pilot study by Bolduc et al. [10] on seven patients with extensive AA demonstrated the effectiveness of NB-UVB in the treatment of AA with minimal side effects.

In our study, KUVA therapy was more effective than NB-UVB therapy in AA patients. Our results showed that 47% of patients treated with KUVA therapy showed an
excellent response to treatment; this is in agreement with
the results of Tritrungtasna et al. [14], who found
excellent results in 50% of AA patients treated with
KUVA therapy. In contrast, we found excellent results in
only 10.52% of patients who were treated with NB-UVB
therapy, which is less than that observed by Bolduc
et al. [10], who reported hair regrowth in 28% of their
seven patients, and by Bayramgürler et al. [12], who
demonstrated that NB-UVB is not an effective treatment,
with excellent results in 20% of 25 patients with AA in
their retrospective study.

Although the mechanism of action of KUVA in AA is
unknown, it was considered to be a modulation of the
immune response, based on the concept that the
mononuclear cells that surround the affected hair follicles
may play a direct pathogenic role and that KUVA therapy
may eradicate this inflammatory cell infiltrate [14].
Furthermore, it has been shown that treatment with a
contact sensitizer changes the composition and localization
of the perifollicular infiltrate in humans [23,24]. The
localization of the inflammatory infiltrate shows a shift
from peribulbar before treatment to the upper dermis
after therapy. However, in human AA, the CD4 : CD8
ratio changed from 4 : 1 before therapy to 1 : 1 after
therapy. Hoffmann et al. [25] demonstrated that after
treatment with a contact sensitizer, the mRNA-expression
of IFN-γ is reduced, whereas the expression of IL-10
is increased. Whether this is due to a Th1–Th2 shift or
whether it is caused by the introduction of regulatory T
cells with a type 2 cytokine profile is unclear.

Furthermore, immunohistochemical studies have shown
that treatment with a contact sensitizer reduces the
aberrant expression of MHC-I and MHC-II molecules on
the lower hair follicle epithelium. From these data it can
be concluded that treatment with a contact sensitizer
restores the immune privilege of the lower hair follicle
epithelium [26].

Although it is known that the immunomodulatory effects
of NB-UVB are very important in the treatment of many skin
diseases, it is also known that UVB is absorbed in the upper
dermis, whereas UVA penetrates to the deeper dermis.
Therefore, NB-UVB cannot penetrate to the lymphocytic
infiltration around the hair follicle [12]. These observations
could explain the better response of our patients to KUVA
therapy compared with NB-UVB therapy.

Lassus et al. [17] reported good prognostic criteria for
PUVA in AA, including late onset of AA, that is after 20
years of age and less than a 5-year duration of alopecia. In
contrast, in the present study, we did not find any
significant correlation between clinical responses to both
therapeutic modalities and the age of onset of AA or the
duration of disease. This is in accordance with the results
of Healy and Rogers [27].

All clinical forms of AA in our study, except AU,
responded to KUVA therapy; this is in agreement with
the results of Tritrungtasna et al. [14]. In addition, the
two patients with AU who were treated with NB-UVB
therapy, in our study, did not respond to therapy.

Lassus et al. [17] mentioned localized AA as being among
the good prognostic criteria for PUVA effectiveness. In
the present study, although the frequency of clinical
response to KUVA therapy was higher among patients
with localized AA with SALT score less than 50% it did
not reach statistical significance. This may be attributed
to the small sample size in our study.

It is important to mention that both treatment modalities
were well tolerated with no phototoxic reactions in any of
our patients. This is in accordance with the results of
Tritrungtasna et al. [14] and Bolduc et al. [10].

Unlike PUVA therapy, which had a very high relapse rate in
the treatment of AA [27], Tritrungtasna et al. [14] reported
that KUVA therapy had no relapse rate; they reported no
recurrence in their patients after a follow-up period of 2
months. This is in contrast to our study in which we found
a relapse rate of 50% in patients treated with KUVA
therapy. This higher relapse rate may be attributed to the
longer duration of follow-up (3 months) and the small
sample size in our study. In addition, no relapse was
detected in the two responders to NB-UVB after 3 months
of termination of therapy, which is in contrast to the results
of Krook [22], who reported a high relapse rate of AA after
UVB therapy. The small number of responders to NB-UVB
in the present study makes commenting on the relapse
rate after termination of therapy difficult.

Conclusion
On the basis of our results, we can conclude that KUVA
therapy is better than NB-UVB therapy in the treatment
of AA resistant to other treatment modalities. All clinical
forms of AA, except AU, are likely to respond to KUVA
therapy, whereas only patients with patchy AA are likely
to respond to NB-UVB therapy. Both treatment
modalities are safe with no phototoxic reactions.

The clinical response to both therapeutic modalities
seems uninfluenced by the age at onset of AA and
duration of the disease.

Recommendations
Further controlled large-scale studies on KUVA and
NB-UVB therapy in the treatment of AA should be
carried out with longer follow-up durations.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

References


