Phototherapy for Vitiligo
A Systematic Review and Meta-analysis

Jung Min Bae, MD, PhD; Han Mi Jung, MD; Bo Young Hong, MD, PhD; Joo Hee Lee, MD; Won Joon Choi, MD; Ji Hae Lee, MD, PhD; Gyong Moon Kim, MD, PhD

IMPORTANCE References to the expected treatment response to phototherapy would be helpful in the management of vitiligo because phototherapy requires long treatment durations over several months.

OBJECTIVE To estimate the treatment response of vitiligo to phototherapy.

DATA SOURCES A comprehensive database search of MEDLINE, EMBASE, and the Cochrane library from inception to January 26, 2016, was performed for all prospective studies. The main keywords used were vitiligo, phototherapy, psoralen, PUVA, ultraviolet, NBUVB, and narrowband.

STUDY SELECTION All prospective studies reporting phototherapy outcome for at least 10 participants with generalized vitiligo were included. Of 319 studies initially identified, the full texts of 141 studies were assessed for eligibility, and 35 were finally included in the analysis. Of these, 29 studies included 1201 patients undergoing narrowband UV-B (NBUVB) phototherapy, and 9 included 227 patients undergoing psoralen–UV-A (PUVA) phototherapy.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted the following data: study design, number and characteristics of the participants, phototherapy protocol, and rate of repigmentation based on the quartile scale. Single-arm meta-analyses were performed for the NBUVB and PUVA groups. Sample size–weighted means were calculated using a random-effects model for the repigmentation rates of the included studies.

MAIN OUTCOMES AND MEASURES The primary outcomes were at least mild (≥25%), at least moderate (≥50%), and marked (≥75%) responses on a quartile scale. Response rates were calculated as the number of participants who showed the corresponding repigmentation divided by the number of all participants enrolled in the individual studies.

RESULTS The meta-analysis included 35 unique studies (1428 unique patients). For NBUVB phototherapy, an at least mild response occurred in 62.1% (95% CI, 46.9%-77.3%) of 130 patients in 3 studies at 3 months, 74.2% (95% CI, 68.5%-79.8%) of 232 patients in 11 studies at 6 months, and 75.0% (95% CI, 60.9%-89.2%) of 512 patients in 8 studies at 12 months. A marked response was achieved in 13.0% (95% CI, 2.1%-23.9%) of 106 patients in 2 studies at 3 months, 19.2% (95% CI, 11.4%-27.0%) of 266 patients in 13 studies at 6 months, and 35.7% (95% CI, 21.5%-49.9%) of 540 patients in 9 studies at 12 months. For PUVA phototherapy, an at least mild response occurred in 51.4% (95% CI, 28.1%-74.7%) of 103 patients in 4 studies at 6 months and 61.6% (95% CI, 20.2%-100%) of 72 patients in 3 studies at 12 months. In the subgroup analyses, marked responses were achieved on the face and neck in 44.2% (95% CI, 24.2%-64.2%), on the trunk in 26.1% (95% CI, 8.7%-43.5%), on the extremities in 17.3% (95% CI, 8.2%-26.5%), and on the hands and feet in none after at least 6 months of NBUVB phototherapy.

CONCLUSIONS AND RELEVANCE Long-duration phototherapy should be encouraged to enhance the treatment response in vitiligo. The greatest response is anticipated on the face and neck.

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Vitiligo is a common, chronic, acquired cutaneous depigmentation disorder causing loss of melanocytes in the skin and mucosa. The reported prevalence rate is 1% to 2% of the population for both sexes and all races. Vitiligo is one of the best-known autoimmune diseases, and depigmentation can evolve throughout life in affected persons, especially in the case of generalized vitiligo. Vitiligo has major effects on self-esteem and social life, and quality of life is highly impaired in patients with this disease.2

Although several interventions are available to treat patients with vitiligo, no definite cure has yet been developed.3 Phototherapy, including psoralen–UV-A (PUVA) and narrowband UV-B (NBUVB) therapy, constitutes the principal treatment modality for generalized vitiligo, whereas excimer laser therapy and various topical agents are used to treat localized disease. However, phototherapy demands frequent clinic visits and requires long treatment durations for several months to years, sometimes resulting in disappointing outcomes. Thus, management of vitiligo is quite challenging, and patient adherence and clinician confidence are crucial for successful phototherapy treatment. References to expected treatment responses of vitiligo to phototherapy would be helpful in the management of this disease.

Since Njoo et al4 first reviewed the effectiveness of nonsurgical therapeutic methods for vitiligo in 1998, to our knowledge, no comprehensive systematic reviews have been performed to estimate treatment responses to phototherapy for vitiligo. In the present study, we update the results of the previous study with subsequent accumulated experiences. We performed a systematic review and meta-analysis of all relevant prospective studies to determine the repigmentation rates of NBUVB and PUVA phototherapy across different treatment durations. Additional meta-analyses were performed to delineate the treatment responses to NBUVB phototherapy by body site.

Methods

We performed a systematic review and meta-analysis to estimate the treatment response of vitiligo to phototherapy. The study was conducted according to the PRISMA guidelines2 and was registered with PROSPERO, an international prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO/).

Search Strategy

A comprehensive database search using predefined search terms (eTable 1 in the Supplement) was performed in MEDLINE, EMBASE, and the Cochrane library from inception to January 26, 2016. The main keywords used were vitiligo, phototherapy, psoralen, PUVA, ultraviolet, NBUVB, and narrowband. All prospective studies were included with no language restriction, and the reference lists in relevant review articles were scanned manually. All identified articles were screened independently by 2 reviewers (J.M.B. and H.M.J.).

Study Selection

Selection was performed based on the following inclusion criteria: (1) prospective study, including randomized and nonrandomized clinical trials and open trials; (2) participants of all age groups with a diagnosis of generalized or symmetrical vitiligo; (3) at least 1 phototherapy group, including NBUVB or PUVA; (4) at least 10 participants in each treatment arm, regardless of the dropout rate; (5) treatment duration of at least 12 weeks or at least 24 treatment sessions; (6) outcomes measured based on all vitiligo lesions on the participant’s whole body or at least half of the body; and (7) outcomes measured according to the degree of repigmentation based on the quartile scale (≥25%, ≥50%, and ≥75%). Exclusion criteria consisted of (1) duplicate publication; (2) retrospective or observational study; (3) segmental or focal vitiligo; (4) vitiligo refractory to previous conventional treatment; (5) phototherapy other than NBUVB and PUVA; (6) receiving therapies in addition to phototherapy; and (7) outcomes based on separate patches. The types of phototherapy evaluated in this review were restricted to NBUVB and PUVA because other phototherapies have not been widely used for treatment of vitiligo. We also excluded targeted phototherapy, such as excimer laser and light, which are usually used to treat localized vitiligo. Combination therapies with any other intervention, such as topical agents, systemic corticosteroids, and antioxidants, were also not included.

Two reviewers (J.M.B. and H.M.J.) independently identified relevant articles by searching the titles and abstracts. If the abstract did not provide enough information to include or exclude the study, full-text evaluation was performed to determine eligibility. The reviewers compared the results, and discrepancies were resolved through discussion or, if necessary, by arbitration by a third reviewer (B.Y.H.). All included studies were evaluated with levels of evidence as suggested by Shekelle et al.6

Outcomes of Interest

The outcome of interest was the repigmentation rate. Repigmentation was graded based on a quartile scale with at least mild (≥25% repigmentation), at least moderate (≥50% repigmentation), and marked (≥75% repigmentation) responses. The rates (percentages) were calculated as the number of participants who achieved the corresponding degree of repigmentation divided by the total number of enrolled participants in each study. The degree of repigmentation was evaluated based on all lesions in...
responsetoNBUVBphototherapybybodysite,categorizedas

Weperformedsubgroupanalysestoinvestigatethetreatment
effectivenessofNBUVBandPUVAphototherapy,8,10,19,23and

armstudies,9,11,13-16,21,22,24,27,379werewithin-
patientsstudiestargetinggeneralizedvitiligo,9,11,12,14,15,21,22,24,27,37

DataSynthesis

Meta-analyseswereperformedseparatelyaccordingtothetype
ofphototherapy(NBUVBandPUVA)anddurationoftreat-
ment (≤3, ≤6, and ≤12 months). We included oral and topical
PUVA in the PUVA group in this review.

SubgroupAnalyses

Weperformedsubgroupanalyses toinvestigatethe treatment
response to NBUVB phototherapy by body site, categorized as

(1)faceandneck, (2) trunk, (3) extremities, and (4) hands and
feet. The outcomes by body site for subgroups containing at
least10participants, wereincluded, andwedecidedata per-
taining to other body parts. Only the treatment responses to
NBUVB were evaluated owing to the rarity of reports on PUVA
phototherapy. We restricted treatment duration to at least 6
months because a period of less than 6 months was not suffi-
cient to evaluate treatment response.

StatisticalAnalyses

Thestatisticalmethods followedtheprocedure used by Njoo
et al,4 which was adapted from the method of Einarson,7 in
which data across studies were combined to produce a point es-
timate and a 95% CI. Sample size–weighted means were cal-
culated using a random-effects model for each phototherapy
type by dividing the total numbers of participants who achieved
the corresponding repigmentation by the total number of partici-
pants in the included studies.4 The means and 95% CIs were cal-
culated using Microsoft Excel 2010 (version 14.0; Microsoft Corp)
and R (version 3.3.1; R Foundation for Statistical Computing).

Results

SearchResults

A total of 572 records were identified through computerized
database searches, and 141 articles remained after the inde-
pendent reviewers screened the titles and abstracts (Figure 1).
A total of 141 full-text articles were assessed for eligibility, 106
of which were excluded for the following reasons: (1) duplica-
terreport (n = 7); (2) published only in abstract form (n = 15); (3)
not a prospective study (n = 1); (4) not predetermined pho-
totherapy, such as UV-A phototherapy without psoralen, broad-
bandUV-Bphototherapy, targetedphototherapy, and home-
basedphototherapy (n = 24); (5) participants did not receive
monotherapy (n = 6); (6) difference in outcome measures
(n = 31); (7) not a whole-body study (n = 10); (8) fewer than 10
participants included (n = 2); (9) refractory vitiligo (n = 6); or
(10) not available after contacting authors (n = 4). Finally, 35
unique studies involving 1428 unique patients fulfilled the in-
clusion criteria for this review. Of these, 29 studies with 1201
patients were included in the NBUVB group5-36 and 9 studies
with 227 patients were included in the PUVA group19,23,31-37,42
techniques in the Supplement).

Description of the Included Studies

All included studies were prospective studies in which
patients with generalized vitiligo were treated using
NBUVB or PUVA (Table 1). Of the 35 articles, 11 were single-
armstudies,9,11,13,16,21,22,24,27,379werewithin-
patient trials,12,18,20,21,25,26,28,29,31,33,38,42 and 15 were parallel
trials.8,10,17,19,20,21,25,26,28,29,31,33,38,42 Five studies compared
the efficacy of NBUVB and PUVA phototherapy,8,10,19,23,31 and
12 compared the efficacy of phototherapy and combination
therapy with topical agents.10,17,18,26,29,30,34,36,39,40 or sys-
temic antioxidants.20,23 Three studies targeted children,9,13,14
8 targeted adults,12,20,23,25,28-30,38 and the remaining 24 tar-
ged participants of all ages.8,10,11,15-19,21,22,24,26,27,31,37,39-42

NBUVBindicatesnarrowbandUV-B; PUVA, psoralen–UV-A.
### Table 1. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Subtype, Body Surface Area</th>
<th>Treatment Duration</th>
<th>Fitzpatrick Skin Type</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Age, Mean (Range), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>al-Aboosi and Ajam, 1995</td>
<td>Iraq</td>
<td>Nonblind single-arm</td>
<td>IV</td>
<td>Generalized vitiligo, ND</td>
<td>6-18 mo</td>
<td>III, IV</td>
<td>PUVA</td>
<td>29</td>
<td>23.0 (14-32)</td>
</tr>
<tr>
<td>Westerhof and Neuwieder-Krohova, 1997</td>
<td>The Netherlands</td>
<td>Nonblind parallel trial</td>
<td>II A</td>
<td>Active, extensive, and generalized vitiligo, ND</td>
<td>3-12 mo</td>
<td>II, III, IV, V</td>
<td>1: NBUVB 2: Topical PUVA</td>
<td>1: 51</td>
<td>1: 36.0 (7-70) 2: 36.7 (8-63)</td>
</tr>
<tr>
<td>Njoo et al, 2000</td>
<td>The Netherlands</td>
<td>Single-arm open trial</td>
<td>IV</td>
<td>Generalized vitiligo, ≥5%</td>
<td>12 mo</td>
<td>II, III, IV, V</td>
<td>NBUVB</td>
<td>51</td>
<td>9.9 (4-16)</td>
</tr>
<tr>
<td>Cestari et al, 2001</td>
<td>Brazil</td>
<td>Double-blind parallel RCT</td>
<td>IB</td>
<td>Vitiligo, &lt;2%</td>
<td>3 mo</td>
<td>II, III, IV, V</td>
<td>1: Topical PUVA (4-dimethoxyamoidina, 2%) 2: Topical PUVA (8-MOP)</td>
<td>1: 14</td>
<td>1: 23.9 (ND) 2: 15.2 (ND)</td>
</tr>
<tr>
<td>Ermis et al, 2001</td>
<td>Turkey</td>
<td>Double-blind within-patient RCT</td>
<td>IB</td>
<td>Generalized vitiligo, ≥5%</td>
<td>3 mo</td>
<td>II, III, IV</td>
<td>PUVA 1: NBUVB + topical calcipotriol, 0.005%</td>
<td>1: 35</td>
<td>28.9 (16-64)</td>
</tr>
<tr>
<td>Al Rubaie, 2002</td>
<td>United Arab Emirates</td>
<td>Nonblind parallel trial</td>
<td>IB</td>
<td>Generalized vitiligo, ND</td>
<td>6-12 mo</td>
<td>IV, V</td>
<td>NBUVB 1: NBUVB + topical calcipotriol 2: PUVA + topical calcipotriol</td>
<td>1: 13</td>
<td>28.6 (9-65)</td>
</tr>
<tr>
<td>Chetif et al, 2003</td>
<td>Tunisia</td>
<td>Nonblind within-patient trial</td>
<td>III</td>
<td>Bilateral and symmetrical NSV, ND</td>
<td>15 wk</td>
<td>IV, V</td>
<td>PUVA 1: NBUVB + topical calcipotriol, 0.005% 2: PUVA + topical calcipotriol</td>
<td>1: 23</td>
<td>36 (19-73)</td>
</tr>
<tr>
<td>Park et al, 2003</td>
<td>Korea</td>
<td>Nonblind single-arm</td>
<td>IV</td>
<td>Vitiligo, ND</td>
<td>&gt;6 mo</td>
<td>III, IV, V</td>
<td>NBUVB</td>
<td>13</td>
<td>36.6 (11-66)</td>
</tr>
<tr>
<td>Hamzavi et al, 2004</td>
<td>Canada</td>
<td>Nonblind within-patient RCT</td>
<td>IB</td>
<td>Vitiligo on the trunk and extremities, &gt;5%</td>
<td>6 mo</td>
<td>II, III, IV, V</td>
<td>NBUVB 1: No treatment 2: No treatment</td>
<td>22</td>
<td>47 (23-77)</td>
</tr>
<tr>
<td>Brazzelli et al, 2005</td>
<td>Italy</td>
<td>Nonblind single-arm open trial</td>
<td>IV</td>
<td>Vitiligo in children, ND</td>
<td>6 mo</td>
<td>II, III, IV</td>
<td>NBUVB</td>
<td>10</td>
<td>9.7 (6-14)</td>
</tr>
<tr>
<td>Kanwar and Dogra, 2005</td>
<td>India</td>
<td>Uncontrolled single-arm open trial</td>
<td>IV</td>
<td>Generalized vitiligo, ≥5%</td>
<td>≤12 mo</td>
<td>IV, V</td>
<td>NBUVB</td>
<td>26</td>
<td>10.6 (5-14)</td>
</tr>
<tr>
<td>Kanwar et al, 2005</td>
<td>India</td>
<td>Nonblind single-arm</td>
<td>IV</td>
<td>Vitiligo vulgaris, ≥5%</td>
<td>12 mo</td>
<td>IV, V</td>
<td>NBUVB</td>
<td>15</td>
<td>12 (12-56)</td>
</tr>
<tr>
<td>Anbar et al, 2006</td>
<td>The Netherlands</td>
<td>Uncontrolled single-arm open trial</td>
<td>IV</td>
<td>NSV, ND</td>
<td>&gt;6 mo</td>
<td>II, III, IV</td>
<td>NBUVB</td>
<td>135</td>
<td>24.5 (4-65)</td>
</tr>
<tr>
<td>Arca et al, 2006</td>
<td>Turkey</td>
<td>Nonblind parallel RCT</td>
<td>IB</td>
<td>Stable NSV, ≥10%</td>
<td>10 wk</td>
<td>ND</td>
<td>NBUVB 1: NBUVB + topical calcipotriol, 0.005% 2: PUVA + topical calcipotriol</td>
<td>1: 24</td>
<td>1: 22.0 (ND) 2: 21.5 (ND)</td>
</tr>
<tr>
<td>Goktas et al, 2006</td>
<td>Turkey</td>
<td>Nonblind within-patient trial</td>
<td>II A</td>
<td>Generalized symmetrical NSV, ≥20%</td>
<td>6 mo</td>
<td>II, III</td>
<td>NBUVB 1: NBUVB + topical calcipotriol, 0.005% 2: PUVA + topical calcipotriol</td>
<td>1: 28</td>
<td>34.2 (16-53)</td>
</tr>
<tr>
<td>Bhatnagar et al, 2007</td>
<td>India</td>
<td>Single-blind parallel RCT</td>
<td>IB</td>
<td>NSV, ≥5%</td>
<td>12 mo</td>
<td>IV, V</td>
<td>NBUVB 1: No treatment 2: PUVA</td>
<td>1: 25</td>
<td>29.0 (ND) 2: 26.6 (ND)</td>
</tr>
<tr>
<td>Nicolaidou et al, 2007</td>
<td>Greece</td>
<td>Single-arm open trial</td>
<td>IV</td>
<td>NSV, ≥5%</td>
<td>12 mo</td>
<td>I, II, III, IV, V</td>
<td>NBUVB</td>
<td>84</td>
<td>39.5 (8-68)</td>
</tr>
<tr>
<td>Sitek et al, 2007</td>
<td>Norway</td>
<td>Single-arm open trial</td>
<td>IV</td>
<td>Generalized vitiligo, ND</td>
<td>≤12 mo</td>
<td>II, III, IV, V</td>
<td>NBUVB</td>
<td>34</td>
<td>ND (ND)</td>
</tr>
</tbody>
</table>

(continued)
Table 1. Characteristics of the Included Studies (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Study Design</th>
<th>Level of Evidencea</th>
<th>Subtype, Body Surface Area</th>
<th>Treatment Duration</th>
<th>Fitzpatrick Skin Type</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Age, Mean (Range), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percivalle et al, 2008</td>
<td>Italy</td>
<td>Single-arm open trial</td>
<td>IV</td>
<td>Localized or generalized vitiligo, ND</td>
<td>≤12 mo</td>
<td>II, III, IV, V, VI</td>
<td>NBUVB</td>
<td>53</td>
<td>36.5 (3-74)</td>
</tr>
<tr>
<td>Esfandiarpour et al, 2009</td>
<td>Iran</td>
<td>Double-blind parallel RCT</td>
<td>IB</td>
<td>NSV, ND</td>
<td>3 mo</td>
<td>ND</td>
<td>1: NBUVB 2: NBUVB + topical pimecrolimus, 1%</td>
<td>1: 25</td>
<td>1: 34.6 (15-72) 2: 25.9 (16-56)</td>
</tr>
<tr>
<td>Kishan Kumar et al, 2009</td>
<td>India</td>
<td>Single-arm open trial</td>
<td>IV</td>
<td>Localized and generalized vitiligo, ND</td>
<td>≤12 mo</td>
<td>IV, V</td>
<td>NBUVB</td>
<td>150</td>
<td>ND (3-70)</td>
</tr>
<tr>
<td>Stinco et al, 2009</td>
<td>Italy</td>
<td>Nonblind parallel RCT</td>
<td>IB</td>
<td>Stable vitiligo, ND</td>
<td>6 mo</td>
<td>II, III, IV</td>
<td>1: NBUVB 2: Topical pimecrolimus, 1% 3: Topical tacrolimus, 0.1%</td>
<td>1: 13</td>
<td>2: 1:15 3: 3:16</td>
</tr>
<tr>
<td>Yuksel et al, 2009</td>
<td>Turkey</td>
<td>Nonblind parallel trial</td>
<td>IIA</td>
<td>Generalized NSV, ≥20%</td>
<td>6 mo</td>
<td>ND</td>
<td>1: NBUVB 2: NBUVB + topical tacrolimus, 0.1%</td>
<td>1: 15</td>
<td>2: 1:15</td>
</tr>
<tr>
<td>Nordal et al, 2011</td>
<td>Norway</td>
<td>Double-blind within-patient RCT</td>
<td>IB</td>
<td>Stable NSV, ND</td>
<td>3 mo</td>
<td>II, III, IV, V, VI</td>
<td>1: NBUVB 2: NBUVB + topical tacrolimus, 0.1%</td>
<td>46</td>
<td>ND (23-69)</td>
</tr>
<tr>
<td>Bansal et al, 2013</td>
<td>India</td>
<td>Nonblind parallel RCT</td>
<td>IB</td>
<td>NSV, ≥5%</td>
<td>5 mo</td>
<td>ND</td>
<td>1: NBUVB 2: Psoralen-NBUVB</td>
<td>1: 20</td>
<td>2: 20</td>
</tr>
<tr>
<td>Satyanarayan et al, 2013</td>
<td>India</td>
<td>Nonblind within-patient RCT</td>
<td>IB</td>
<td>Generalized NSV, 5%-50%</td>
<td>36 wk</td>
<td>III, IV</td>
<td>1: NBUVB 2: NBUVB + topical tacrolimus, 0.1%</td>
<td>25</td>
<td>ND (14-36)</td>
</tr>
<tr>
<td>Singh et al, 2013</td>
<td>India</td>
<td>Nonblind parallel RCT</td>
<td>IB</td>
<td>NSV, ≥2%</td>
<td>36 wk</td>
<td>III, IV</td>
<td>1: PUVA (8-MOP) 2: PUVA sol</td>
<td>1: 18</td>
<td>2: 1:17</td>
</tr>
<tr>
<td>Baldo et al, 2014</td>
<td>Italy</td>
<td>Nonblind within-patient RCT</td>
<td>IB</td>
<td>Stable vitiligo, ND</td>
<td>36 wk</td>
<td>ND</td>
<td>1: NBUVB 2: Topical tacrolimus, 0.1%</td>
<td>48</td>
<td>27.0 (6-67)</td>
</tr>
<tr>
<td>Khullar et al, 2014</td>
<td>India</td>
<td>Nonblind within-patient RCT</td>
<td>IB</td>
<td>Slowly progressive NSV, 5%-50%</td>
<td>24 wk</td>
<td>III, IV</td>
<td>1: NBUVB 2: NBUVB + topical calcipotriol, 0.005%</td>
<td>27</td>
<td>24.4 (12-37)</td>
</tr>
</tbody>
</table>

Abbreviations: MOP, methoxypsoralen; NBUVB, narrowband UV-B; ND, not determined; NSV, nonsegmental vitiligo; PUVA, psoralen–UV-A; RCT, randomized clinical trial.

* IB indicates randomized controlled studies; IIA, nonrandomized controlled studies; III, comparative studies, correlation studies, and case-control studies; and IV, expert committee reports or opinions and case reports. 6
Treatment Response to NBUVB Phototherapy

An at least mild response (≥25% repigmentation) to NBUVB phototherapy occurred in 62.1% (95% CI 46.9%-77.3%) of 130 patients in 3 studies at 3 months,8,17,30 in 74.2% (95% CI, 68.5%-79.8%) of 232 patients in 11 studies at 6 months,8,11-13,18,23,25,29,31,34,36 and 75.0% (95% CI, 60.9%-89.2%) of 512 patients in 8 studies at 12 months.8-10,16,19,22,24,27 (Figure 2A and Table 2).

Treatment Response to PUVA Phototherapy

An at least mild response to PUVA phototherapy was achieved in 51.4% (95% CI, 28.1%-74.7%) of 103 patients in 4 studies at 6 months23,31,38,40 and 61.6% (95% CI, 20.2%-100%) of 72 patients in 3 studies at 12 months.19,37,42 A marked response to PUVA phototherapy was achieved in 8.5% (95% CI, 0%-18.3%) of 88 patients in 3 studies at 6 months23,31,39 and 13.6% (95% CI, 4.2%-22.9%) of 72 patients in 3 studies at 12 months19,37,42 (Figure 2A and Table 2).

Treatment Response to NBUVB Phototherapy Depending on Body Site

After at least 6 months of NBUVB phototherapy, an at least mild response occurred on the face and neck in 82.0% (95% CI, 68.2%-95.8%), trunk in 75.0% (95% CI, 70.8%-92.6%), and extremities in 79.0% (95% CI, 75.8%-82.2%) of patients.8-10,16,19,22,24,27

Abbreviations: NA, not applicable; NBUVB, narrowband UV-B; PUVA, psoralen–UV-A.

Table 2. Summary of Findings for Phototherapy for Vitiligo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Response Rate, % (95% CI)</th>
<th>Quality of Evidencea</th>
<th>Grade of Recommendationb</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBUVB phototherapy, duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>13.0 (2.1-23.9)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>6 mo</td>
<td>19.2 (11.4-27.0)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>12 mo</td>
<td>35.7 (21.5-49.9)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>PUVA phototherapy, duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>8.5 (0-18.3)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>12 mo</td>
<td>13.6 (4.2-22.9)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>NBUVB phototherapy, 6-12 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face and neck</td>
<td>44.2 (24.2-64.2)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>Trunk</td>
<td>26.1 (8.7-43.5)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>Extremities</td>
<td>17.3 (8.2-26.5)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>Hands and feet</td>
<td>0 (NA)</td>
<td>A</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NBUVB, narrowband UV-B; PUVA, psoralen–UV-A.

a Indicates quality of evidence as described by Robinson et al,46 where A indicates systematic review and meta-analysis, randomized clinical trial with consistent findings, or all-or-none observational study.

b Indicates grade of recommendation as described by Robinson et al,46 where 1 indicates strong recommendation with high-quality, patient-oriented evidence.
68.2%-95.8%) of 153 patients in 5 studies, \(^{16,19,21,32,35}\) on the trunk in 81.7% (95% CI, 70.8%-92.6%) of 134 patients in 5 studies, \(^{16,18,19,32,35}\) on the extremities (excluding hands and feet) in 79.0% (95% CI, 65.9%-92.2%) of 162 patients in 5 studies, \(^{16,18,19,32,35}\) and on the hands and feet in 11.0% (95% CI, 5.1%-16.9%) of 172 patients in 6 studies, \(^{16,18,19,28,32,35}\) Marked responses were achieved on the face and neck in 44.2% (95% CI, 24.2%-64.2%) of 153 patients in 5 studies, \(^{16,19,21,32,35}\) on the trunk in 26.1% (95% CI, 8.7%-43.5%) of 134 patients in 5 studies, \(^{16,18,19,32,35}\) on the extremities in 17.3% (95% CI, 8.2%-26.5%) of 162 patients in 5 studies, \(^{16,18,19,32,35}\) and on the hands and feet in none of 172 patients in 6 studies\(^ {16,18,19,28,32,35}\) (Figure 2B and Table 2).

**Discussion**

Phototherapy has been the mainstay of treatment for vitiligo for decades. Since PUVA phototherapy was first introduced for the treatment of vitiligo in 1948,\(^ {4}\) it has been widely adopted as a promising therapeutic modality. Although PUVA phototherapy is effective, it has several limitations, including phototoxic effects, nausea, and the potential risk for skin cancer.\(^ {44}\) Moreover, PUVA phototherapy cannot be applied to children or pregnant women because of the systemic use of psoralen. Since NBUVB phototherapy was first reported to be effective for treatment of vitiligo in 1997,\(^ {8}\) it has gradually taken the place of PUVA phototherapy. The lack of a photosensitizer, the lower cumulative dose, and fewer adverse effects are considered to be major advantages of NBUVB over PUVA, and NBUVB even showed superior efficacy over PUVA.\(^ {44}\) Narrowband UV-B phototherapy is also associated with adverse events such as erythema, itching, and mild burning or pain, which are well tolerated and spontaneously disappear a few hours after treatment in most cases. Therefore, NBUVB phototherapy is now considered to be the criterion standard therapy for generalized vitiligo, whereas PUVA phototherapy is still considered under special conditions, such as cases of spreading vitiligo with deeper penetration of UV-A.\(^ {45}\)

In the present study, we reveal the treatment response of vitiligo to phototherapy by treatment duration. We verify that phototherapy requires at least 1 year to achieve a maximal treatment response, although we could not determine the appropriate treatment duration based on our results. For example, 56.8% achieved an at least moderate response (≥50% repigmentation) to 12 months of NBUVB phototherapy, although 62.1% of patients achieved an at least mild response (≥25% repigmentation) within 3 months. Furthermore, 37.4% of patients achieved an at least moderate response (≥50% repigmentation) within 6 months of NBUVB phototherapy, with 35.7% achieving a marked response (≥75% repigmentation) within 12 months. A longer treatment duration was assumed to enhance the treatment response. In a disappointing finding, 25.8% and 25.0% of patients did not achieve a mild response (≥25% repigmentation) within 6 or 12 months of NBUVB phototherapy, respectively. We postulated that some patients would not respond to NBUVB phototherapy despite 12 months of treatment. However, 3 months is not sufficient to discriminate nonresponders from late responders because 37.9% of patients did not achieve a mild response within 3 months. Our results suggest that at least 6 months of treatment is required to determine the responsiveness to NBUVB phototherapy.

With PUVA phototherapy, we also showed that the treatment response after 12 months of treatment was better than that after 6 months. However, the overall treatment response to PUVA phototherapy was inferior to that to NBUVB, although statistical comparisons were not conducted in our study. Five studies\(^ {8,10,19,23,31}\) compared the efficacy of NBUVB with that of PUVA phototherapy. Westerhof and Nieuweboer-Kroboleva\(^ {8}\) first reported that NBUVB phototherapy was more effective than topical PUVA but without statistical significance. Yones et al\(^ {25}\) demonstrated the superiority of NBUVB phototherapy to oral PUVA therapy in their randomized clinical trial. In their study, the rate of more than 50% repigmentation was significantly higher in the NBUVB group (64%) than in the PUVA group (36%) after 6 months of treatment. Moreover, the repigmented skin showed excellent color match in all patients in the NBUVB group but only 44% of those in the PUVA group.\(^ {23}\)

We also examined the treatment response to NBUVB phototherapy by different body sites in all relevant studies that presented the outcomes of more than 10 patients per body site treated for at least 6 months. The most responsive body site was the face and neck, for which the marked repigmentation rate was 44.2%, followed by the trunk (26.1%), extremities (17.3%), and hands and feet (0%). The treatment responses on hands and feet were extremely low, and a mild response was observed in only 11.0% of patients. Meanwhile, the rates of an at least mild response were 82.0% on the face and neck, 81.7% on the trunk, and 79.0% on the extremities, and the proportion of enrolled patients who failed to show a response was similar (approximately 20%), regardless of body site, except for the hands and feet. Certain shared host factors might hinder repigmentation, such as disease activity, autoimmune state, large involved body surface area, and presence of poliosis.

The present study demonstrated the treatment response of vitiligo to phototherapy according to phototherapy type, treatment duration, and body site. In the clinical setting, treatment outcome might be better than our results because this review exclusively included studies of phototherapy alone. Various adjuvant treatments, including topical calcipotriol,\(^ {18}\) topical calcineurin inhibitors,\(^ {26,30}\) and systemic antioxidants,\(^ {20,25}\) could be used in addition to phototherapy to enhance the treatment response in practice. Nevertheless, our findings would be a useful guide for clinicians and patients for establishment of the treatment strategy. Because phototherapy usually requires a long duration, reassuring and encouraging patients to achieve the maximal treatment response are critical.

**Limitations**

Our systematic review had some limitations. First, the study design, characteristics of the enrolled patients, and phototherapy protocol had considerable heterogeneity. The included studies may have been conducted with different objectives and different comparisons, even within a single arm. Therefore, we excluded retrospective studies to minimize unidentified biases and assumed that the degree of repigmentation after a given
protocol would represent the efficacy of phototherapy in prospective studies. Second, the quantitative quartile scale may be somewhat arbitrary. Moreover, the degree of repigmentation itself cannot indicate treatment success in vitiligo management. However, the quartile scale is the most commonly used measure to date, and the overall treatment response should be estimated as objectively as possible based on the degree of repigmentation. Finally, a meta-analysis of a single arm could have methodologic weaknesses. However, we attempted to integrate the outcomes of all relevant prospective studies and used the statistical methods validated in the previous studies.4,7 Furthermore, our results were supported by the high quality of evidence and strong grade of recommendation (Table 2).46

Conclusions

The present systematic review and meta-analysis revealed the treatment response to phototherapy for vitiligo based on all relevant prospective studies in the literature. A longer treatment duration should be encouraged to enhance the treatment response, and a period of at least 6 months is required to assess the responsiveness to phototherapy. The overall treatment response to NBUVB phototherapy was better than that to PUVA therapy. The most effective response is anticipated on the face and neck, whereas the hands and feet show minimal response.

REFERENCES


Henry Radcliffe Crocker—From the Elephant Man to the Textbook

Kishore L. Jayakumar, BS; Jules B. Lipoff, MD

Henry Radcliffe Crocker (1845-1909) was a British dermatologist and a pioneering educator in his field. At the age of 16 years, he left school to apprentice with a general practitioner. From 1870 to 1875, he attended medical school at University College Hospital, London, while also working as a dispenser to supplement his income. In 1876, he became assistant medical officer to the Skin Department at University College Hospital and studied dermatology under his mentor William Tilbury Fox, who he succeeded as department chair in 1879.

In March 1885, Crocker’s career took an unexpected turn. While attending a meeting of the Pathological Society of London, he heard British surgeon Sir Frederick Treves present the case of Joseph Merrick, famously exhibited at a show as the Elephant Man. On hearing this presentation, Crocker was the first to propose a diagnosis. He suggested that Merrick’s skin condition resulted from the coexistence of 2 disorders referred to as dermatolysis (cutis laxa) and pachydermatocoele (plexiform neurofibroma), and that his bone abnormalities had somehow resulted from changes in his nervous system. Though Merrick’s diagnosis remains unconfirmed, the 2 most supported hypotheses are neurofibromatosis type 1 and Proteus syndrome. In any case, Crocker’s diagnosis seems to have been reasonable, especially given dermatology’s nascent at the time.

In 1888, when Crocker published his landmark textbook, Diseases of the Skin: Their Description, Pathology, Diagnosis and Treatment, he paid tribute to Merrick by discussing his case in detail in the section on fibromas. The text itself was widely regarded as the definitive dermatologic reference of the era and cemented his reputation as a leading educator in dermatology. Nearly a half-century later, in 1933, British dermatologist Arthur Whitfield called the book “the best work on dermatology that has been produced in any language.”

Crocker’s accomplishments in his later years were no less remarkable. An avid watercolor painter, he often sketched his patients’ conditions and reproduced them in his books. In 1894, he published a book titled Atlas of Diseases of the Skin (1896), which was the first to describe erythema elevatum diutinum (1894) and the first to name granuloma annulare (1902). In 1907, he became the first president of the Dermatological Section of the Royal Society of Medicine. When he died suddenly of heart failure in 1909, his obituary in the BMJ commented: “the opinion of Radcliffe Crocker in difficult and unusual cases was eagerly invited, for it was felt that if any light could be thrown on the matter, he was the one man able to shed it.”

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