Treatment of vitiligo

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Nonsurgical repigmentation therapies in vitiligo
Meta-analysis of the literature

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ABSTRACT

Objective: To assess the effectiveness and safety of nonsurgical repigmentation therapies in localized and in generalized vitiligo by means of a meta-analysis.

Data Sources: Computerized searches of bibliographic databases, a complementary manual literature search and contacts with researchers and pharmaceutical firms.

Study Selection: Predefined selection criteria were applied to both randomized and nonrandomized controlled trials.

Data Extraction: Two investigators independently assessed the articles for inclusion. When there was a disagreement, a third investigator was consulted.

Results: Sixty-three studies were found on therapies for localized vitiligo. Of these, 10 of 11 randomized controlled trials and 29 of 110 patient series were included. One hundred seventeen studies on therapies for generalized vitiligo were found. Of these, 10 of 22 randomized controlled trials and 46 of 231 patient series were included.

Among randomized controlled trials on localized vitiligo, the pooled odds ratio versus placebo was significant for topical class 3 corticosteroids (14.32; 95% confidence interval [CI], 2.45 to 83.72). In the patient series, topical class 3 corticosteroids and class 4 corticosteroids carried the highest mean success rates (56%; 95% CI, 50% to 62% and 55%; 95% CI, 49% to 61% respectively). Side effects were reported mostly with topical psoralens and intralesional- and class 4 corticosteroids.

In the randomized controlled trials on generalized vitiligo, the odds ratio versus placebo was significant for oral methoxsalen plus sunlight (23.37; 95% CI, 1.33 to 409.93), oral psoralen plus sunlight (19.87; 95% CI, 2.37 to 166.32) and oral trioxsalen plus sunlight (3.75; 95% CI, 1.24 to 11.29). In the series, the highest mean success rates were achieved with narrowband UV-B (63%; 95% CI, 50% to 76%), broadband UV-B (57%; 95% CI, 29% to 82%) and oral methoxsalen plus UV-A therapy (51%; 95% CI, 46% to 56%). Oral methoxsalen plus UV-A was associated with the highest rates of side effects. No side effects were reported with UV-B therapy.

Conclusion: Class 3 corticosteroids and UV-B therapy are the most effective and safest therapies for localized and for generalized vitiligo, respectively.
INTRODUCTION

Vitiligo is an acquired skin disorder characterized by sharply demarcated depigmented lesions with variable size and shape that have the tendency to expand over time. It is estimated that about 0.5% of the world population is affected by the disease, regardless of age, sex and skin colour.

There are several possible approaches in the management of vitiligo. Some patients can be reassured simply by explaining the nature of the skin condition and by giving advice on the use of camouflage products and sunprotective measures. In others, especially in the dark skinned population, vitiligo may cause disfigurement that can lead to serious impairment of the quality of life. In certain cultures, patients with vitiligo are still regarded as social outcasts. For these groups of patients, active treatment can be considered.

Nonsurgical repigmentation therapies represent the first-line active treatment modality in vitiligo. Currently best studied and therefore most applied are oral and topical psoralen plus ultraviolet-A (PUVA), phenylalanine plus UV-A, oral and topical k hellin plus UV-A, UV-B broadband and narrowband therapy and corticosteroids (oral, topical and intralesional).

There are many studies reporting on the clinical effectiveness and safety of the various treatments in vitiligo. Guidelines and review articles have been published on how and in which patients these treatments should be applied. However, these recommendations were based on data obtained from only a limited number of references and on personal and institutional preferences. No methodological information was given on how these guidelines had been developed. Because none of these articles included a systematic literature search, it is likely that relevant studies were missed. It has been shown that review articles in journals or in textbooks, even if they were recently published, contain unsound, imprecise and biased information.

According to the principals of “evidence based medicine”, the best medical care is provided by integrating the “best external evidence, as obtained from clinically relevant research studies into the daily practice”. Combining all relevant studies in a “meta-analysis” can increase the power and precision of estimates on effectiveness and side-effects profiles. The development of guidelines for the choice of the most effective and safest therapy in vitiligo should be based also on the available evidence in the literature. We therefore performed a meta-analysis of the available literature on the most widely used forms of nonsurgical repigmentation therapy, with regard to both effectiveness and safety.
Meta-analysis of nonsurgical repigmentation therapies

METHODS

DATA SOURCES

The computerized bibliographic databases MEDLINE (National Library of Medicine, Bethesda, Maryland, USA) and EMBASE (Elsevier Science BV, Amsterdam, The Netherlands) were screened for clinical trials from January 1966 to December 1997 (last update 15 December 1997). No language restrictions were applied. As main key words (including analogues and derivatives) we used “vitiligo”, “phototherapy”, “PUVA therapy”, “ultraviolet therapy”, “phenylalanine”, “khellin”, “glucocorticosteroids synthetic” and “anti-inflammatory agents”. Other sources were abstract books of symposia and congresses, theses, textbooks, monographs, reviews, editorials, letters to the editor, free or rapid communications and the reference lists from all the articles retrieved. Also 21 leading authorities in the field of vitiligo and 9 pharmaceutical companies were contacted to provide us with any additional published and unpublished references.

The studies were divided into those describing therapies for localized vitiligo and those reporting on therapies for generalized vitiligo. “Localized” vitiligo was defined in literature as vitiligo affecting less than 20% of the total body surface.

STUDY SELECTION: INCLUSION AND EXCLUSION CRITERIA

Two investigators (M.D.N. and W.W.) independently assessed the articles for inclusion. When there was a disagreement, a third investigator (P.M.M.B.) was consulted.

Included were both randomized controlled trials (RCTs) and nonrandomized controlled trials on oral and topical psoralens plus sunlight or artificial UV-A (both sources were termed UV-A) including methoxsalen (8-methoxypsoralen), trioxsalen (4′,5′,8-trimethylpsoralen), bergapten (5-methoxypsoralen) and unsubstituted psoralen (further termed as “PS”), UV-B broadband and narrowband, phenylalanine plus sunlight or UV-A, oral and topical khellin plus sunlight or UV-A and corticosteroids (oral, topical and intralesional). Topical corticosteroids were divided into class 3 (“potent corticosteroids”), which included the drugs betamethasone valerate and halomethasone, and into class 4 (“very potent corticosteroids”) which included clobetasol propionate. With regard to intralesional administration of corticosteroids, studies using triamcinolone acetonide were included. In studies on photochemotherapy, both natural sunlight and artificial UV-A were used in the same patient series. These UV-sources were regarded as equally effective, provided that sun exposure was performed between 11 AM and 2 PM. Excluded were double publications, combination therapies, studies that used obsolete drug(s) or dosage
schemes, studies that reported on fewer than five patients, and studies with insufficient data on effectiveness.

Nonrandomized controlled trials were also analyzed as patient series. Because comparative or placebo controlled trials can contain a description of at least two patient series, the total number of patient series could exceed the total number of studies included. In case of double publications, the most elaborate publication was selected.

DATA EXTRACTION

Analysis of RCTs

Treatment was regarded as successful when more than 75% repigmentation was achieved. The odds ratio (OR) was used as the effect measure in this meta-analysis because it is regarded as the most satisfactory metric with which to combine across trials with discrete outcomes\(^{20}\). The OR describes the odds of a successful event (i.e. > 75% repigmentation) in a patient receiving the active therapy relative to a patient receiving the placebo. As a result, an OR greater than one indicates greater effectiveness of the active therapy compared with the placebo.

To obtain a more precise estimate of the treatment effect, ORs were combined across similar trials. A random effects model according to DerSimonian and Laird\(^ {21}\) was used to pool these ORs and to calculate their 95% confidence intervals (CI). The random-effects model was preferred over the fixed-effects model because study populations and treatment outcomes in these trials were expected to be statistically heterogeneous although all RCTs met the specific selection criteria. Calculations were done with Meta-Analyst software for MS-DOS (Joseph Lau, Boston, Massachusetts, USA, 1990-1997).

Analysis based on patient series

Sample size-weighted averages were calculated for each modality by dividing the total number of patients who achieved more than 75% repigmentation by the total number of patients in the included series. The 95% CIs of these averages were calculated with the computer program Confidence Interval Analysis for MS-DOS by means of the exact method (version 1.0 1989 compiled by M.J. Gardner and D.G. Altman, British Medical Journal, London).

The treatment duration (range and mean values) was also determined for each treatment modality. Treatment-specific side effects were estimated by dividing the number of patients with side effects by the total number of patients studied. For each study, sample size-weighted averages of these frequencies and their 95% CIs were calculated with the same
software as was used for calculation of the success rates.

RESULTS

Fifteen of the 21 leading authorities and 7 of the 9 pharmaceutical firms contacted, replied and provided us with further relevant references. No study required a third reviewer to resolve disagreements about selection.

THERAPIES FOR LOCALIZED VITILIGO
Randomized Controlled Trials

Literature Search.
With regard to therapies for localized vitiligo, 63 studies were found. Eleven RCTs were identified of which 10 met our eligibility criteria (Table 1). One study on therapy with class 3 corticosteroids was excluded because it was a double publication (same trial published in two languages). The method of randomization was not reported in any of the studies found.

Table 1. Therapy for localized vitiligo: Results of the literature search *

<table>
<thead>
<tr>
<th>Methoxsalen</th>
<th>Trioxsalen</th>
<th>PS + UV-A</th>
<th>Kellin (2-3%)</th>
<th>Kellin (5%)</th>
<th>Corticosteroids</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV-A</td>
<td>UV-A</td>
<td>UV-A</td>
<td>UV-A</td>
<td>UV-A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of studies found</td>
<td>21</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>No. found through databases</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hit rate for databases, %</td>
<td>33</td>
<td>100</td>
<td>40</td>
<td>80</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>No. of randomized controlled trials</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* PS indicates unsubstituted psoralen

Effectiveness.
Pooled ORs showed nonsignificant differences between class 4 corticosteroids (OR, 1.00; 95% CI, 0.16 to 6.21), intralesional corticosteroids (OR, 1.42; 95% CI, 0.31 to 7.78), topical khellin (2%-3%) plus UV-A (OR, 1.18; 95% CI, 0.38 to 3.62) or topical khellin (5%) plus UV-A (OR, 1.00; 95% CI, 0.39 to 2.54) and their respective placebos. Class 3 corticosteroids had a pooled OR of 14.32 (95% CI, 2.45 to 83.72) versus placebo (Table 2)
# Table 2. Therapies for localized vitiligo and pooled ORs and 95% CIs (random effects model)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study, year</th>
<th>No. of patients</th>
<th>Active group, No. of Responders/Total</th>
<th>Placebo group, No. of Responders/Total</th>
<th>OR (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 3 corticosteroids</td>
<td>Koopmans-van Dorp, 1973</td>
<td>21 (L-R)</td>
<td>9/21</td>
<td>0/21</td>
<td>32.68 (1.75 - 610.81)</td>
</tr>
<tr>
<td></td>
<td>Kandil, 1974</td>
<td>17 (L-R)</td>
<td>6/17</td>
<td>0/17</td>
<td>19.78 (1.01 - 386.03)</td>
</tr>
<tr>
<td></td>
<td>Bleehen, 1976</td>
<td>10 (L-R)</td>
<td>1/10</td>
<td>0/10</td>
<td>3.32 (0.12 - 91.60)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects</td>
<td>96</td>
<td>16/48</td>
<td>0/48</td>
<td>14.32 (2.45 - 83.72)</td>
</tr>
<tr>
<td>Class 4 corticosteroids</td>
<td>Bleehen, 1976</td>
<td>10 (L-R)</td>
<td>0/10</td>
<td>0/10</td>
<td>1.00 (0.02 - 55.27)</td>
</tr>
<tr>
<td></td>
<td>Clayton, 1977</td>
<td>23 (L-R)</td>
<td>2/23</td>
<td>2/23</td>
<td>1.00 (0.13 - 7.70)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects</td>
<td>66</td>
<td>2/33</td>
<td>2/33</td>
<td>1.00 (0.16 - 6.21)</td>
</tr>
<tr>
<td>Intralosional corticosteroids</td>
<td>Vasistha and Singh, 1979</td>
<td>25 + 10</td>
<td>17/25</td>
<td>6/10</td>
<td>1.42 (0.31 - 6.47)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Topical khellin (2-3%)</td>
<td>Orcchio and Perfetti, 1992</td>
<td>41 (L-R)</td>
<td>0/41</td>
<td>0/41</td>
<td>1.00 (0.02 - 51.60)</td>
</tr>
<tr>
<td></td>
<td>Procaccini et al., 1995</td>
<td>30 (L-R)</td>
<td>8/30</td>
<td>7/30</td>
<td>1.19 (0.37 - 3.85)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects</td>
<td>142</td>
<td>8/71</td>
<td>7/71</td>
<td>1.18 (0.38 - 3.62)</td>
</tr>
<tr>
<td>Topical khellin (5%)</td>
<td>Procaccini et al., 1993</td>
<td>12 (L-R)</td>
<td>4/12</td>
<td>4/12</td>
<td>1.00 (0.18 - 5.46)</td>
</tr>
<tr>
<td></td>
<td>Procaccini et al., 1995</td>
<td>29 (L-R)</td>
<td>9/29</td>
<td>9/29</td>
<td>1.00 (0.33 - 3.04)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects</td>
<td>82</td>
<td>13/41</td>
<td>13/41</td>
<td>1.00 (0.39 - 2.54)</td>
</tr>
</tbody>
</table>

OR indicate odds ratio; CI, confidence interval, L-R: left-right double blind placebo controlled comparative study; and NA, not applicable.

* As a standard option, the computer program Meta-Analyst (Joseph Lau, Boston, MA, USA) corrects a 0 value by 0.5.

**Patient Series**

### Literature Search.

A total of 110 patient series could be identified, of which only 29 series could be included, reporting on 993 patients (Table 3). Thirteen series with topical methoxsalen plus UV-A were excluded because obsolete drug compositions were used (such as methoxsalen plus 8-isoamyleneoxypsoralen) or because 1% concentration instead of the currently advised 0.1% concentration of methoxsalen solution was used. Reasons for exclusion of patient series are listed in Table 3. In cases in which several criteria of exclusion were applicable, only the most important one was listed.

### Effectiveness.

Figure 1 shows that class 3 corticosteroids had the highest percentage of patients achieving more than 75% repigmentation (56%; 95% CI, 50% to 62%), followed by class 4 corticosteroids (55%; 95% CI, 49% to 61%).

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TREATMENT OF VITILIGO

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Meta-analysis of nonsurgical repigmentation therapies

Table 3. Therapy for localized vitiligo: Reasons for exclusion of patient series *

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of patient series identified</th>
<th>No. (%) of series</th>
<th>Included</th>
<th>Excluded</th>
<th>Reasons for exclusion of patient series, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxsalen + UV-A</td>
<td>29</td>
<td>(14)</td>
<td>4</td>
<td>25</td>
<td>-Double publication</td>
</tr>
<tr>
<td>Trioxsalen + UV-A</td>
<td>3</td>
<td>(67)</td>
<td>2</td>
<td>1</td>
<td>-Combined with another (experimental) drug</td>
</tr>
<tr>
<td>PS (2.3%) + UV-A</td>
<td>13</td>
<td>(25)</td>
<td>3</td>
<td>10</td>
<td>-Obsolete drug or dosage scheme</td>
</tr>
<tr>
<td>Khellin (2.3%) + UV-A</td>
<td>12</td>
<td>(25)</td>
<td>3</td>
<td>9</td>
<td>-Compared or placebo-treated patient series</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>25</td>
<td>(25)</td>
<td>6</td>
<td>19</td>
<td>-Series of fewer than 5 patients</td>
</tr>
<tr>
<td>Class 3</td>
<td>10</td>
<td>(40)</td>
<td>2</td>
<td>8</td>
<td>-Inadequate or insufficient data on effectiveness</td>
</tr>
<tr>
<td>Class 4</td>
<td>10</td>
<td>(40)</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Intralesional</td>
<td>10</td>
<td>(40)</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PS indicates unsubstituted psoralen

Figure 1 Effectiveness of therapies for localized vitiligo. Analysis was based on patient series (sample size-weighted averages and 95% confidence intervals). PS indicates unsubstituted psoralen

Side Effects.

Of the 29 included series, 28 (97%) reported side effects. Of the topical PUVA group, methoxsalen had the highest proportion of patients developing phototoxic reactions (58%; 95% CI, 51% to 65%), followed by trioxsalen (39%; 95% CI, 23% to 56%) and PS (25%; 95% CI, 12% to 38%). Atrophy was the most common side effect with local corticosteroids, occurring mostly in patients receiving intralesional corticosteroids (33%; 95% CI, 22% to 43%) followed by patients using class 4 corticosteroids (14%; 95% CI, 10% to 18%) and class 3 corticosteroids (2%; 95% CI, 1% to 5%). Other less commonly reported side effects of corticosteroids were telangiectasia, corticosteroid-induced acne and hypertrichosis. Studies on topical khellin (2%, 3% and 5%) plus UV-A did not report any side effects (Table 4).

The mean treatment duration did not vary much, from 5 to 8 months (Table 4). One
Table 4: Therapy for localized vitiligo: Side effects *

<table>
<thead>
<tr>
<th>Methoxsalen + UV-A</th>
<th>Trioxsalen + UV-A</th>
<th>PS + UV-A (2.3%)</th>
<th>Khellin + UV-A (5%)</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of included patient series</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Treatment duration, range (mean), months</td>
<td>4-6 (5)</td>
<td>1-6 (5)</td>
<td>6-7 (7)</td>
<td>3-9 (5)</td>
</tr>
<tr>
<td>No. of series with side effects reported</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>176</td>
<td>33</td>
<td>40</td>
<td>81</td>
</tr>
<tr>
<td>Patients with local side effects †</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrophy</td>
<td>5 (2)</td>
<td>39 (14)</td>
<td>26 (33)</td>
<td></td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Corticosteroid induced acne</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>16 (7)</td>
<td>25 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phototoxic reactions (erythema and blistering)</td>
<td>102 (58)</td>
<td>13 (39)</td>
<td>10 (25)</td>
<td>0</td>
</tr>
<tr>
<td>(erythema and blistering)</td>
<td>[51-65]</td>
<td>[23-56]</td>
<td>[12-38]</td>
<td>0</td>
</tr>
</tbody>
</table>

* PS indicates unsubstituted psoralen
† Data are reported as number of patients with sample size weighted average percentages in parentheses and 95% confidence intervals between brackets.

... study reported the prolonged, but intermittent use of class 3 corticosteroids for a period of 21 months 30. In general, the duration of treatment strongly depended on the response; when there was no response after 2 to 3 months, therapy was discontinued.

THERAPIES FOR GENERALIZED VITILIGO

Randomized Controlled Trials

_Literature Search._

A total of 117 studies on therapies for generalized vitiligo were found. Twenty two RCTs were identified of which 10 were included (Table 5)31-38. Eight studies (from 4 publications) were excluded because they described combination therapies31,33,39,40. Of these eight studies, 4 RCTs were found on oral corticosteroids combined with oral PUVA. Four other studies (from 2 publications) were excluded because of insufficient data on outcome measures (“mean achieved percentage repigmentation” was used as outcome measure)39,40. No RCTs were found on oral bergapten plus UV-A, broadband UV-B and narrowband UV-B. The method of randomization was not reported in any of the studies found.
Meta-analysis of nonsurgical repigmentation therapies

Table 5. Therapy for generalized vitiligo: Results of the literature search *

<table>
<thead>
<tr>
<th></th>
<th>Methoxsalen</th>
<th>Trioxsalen</th>
<th>Bergapten UV-A</th>
<th>PS + UV-A</th>
<th>Phenylalanine + UV-A</th>
<th>Khellin + UV-A</th>
<th>UV-B Broadband</th>
<th>UV-B Narrowband</th>
<th>Oral Corticosteroids</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies found</td>
<td>35</td>
<td>23</td>
<td>5</td>
<td>6</td>
<td>20</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>14</td>
<td>117</td>
</tr>
<tr>
<td>No. found through databases</td>
<td>17</td>
<td>17</td>
<td>2</td>
<td>5</td>
<td>13</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>Hit rate for databases, %</td>
<td>49</td>
<td>74</td>
<td>40</td>
<td>83</td>
<td>65</td>
<td>56</td>
<td>100</td>
<td>33</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>No. of randomized controlled trials</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>22</td>
</tr>
</tbody>
</table>

* PS indicates unsubstituted psoralen

Table 6. Therapies for generalized vitiligo and pooled ORs and 95% CIs (random effects model)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study, year</th>
<th>No. of Patients</th>
<th>Active Group, No. of Responders/Total</th>
<th>Placebo Group, No. of Responders/Total</th>
<th>OR (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral methoxsalen plus sunlight</td>
<td>Pathok et al., 1984 31</td>
<td>47 + 24</td>
<td>15/47</td>
<td>0/24</td>
<td>23.37 (1.33 - 409.93)</td>
</tr>
<tr>
<td>Oral trioxsalen plus sunlight</td>
<td>Pathok et al., 1984 31</td>
<td>39 + 24</td>
<td>7/39</td>
<td>0/24</td>
<td>11.31 (0.62 - 201.64)</td>
</tr>
<tr>
<td></td>
<td>Ruiz-Maldonado and Tamayo Sanchez, 1975 32</td>
<td>25 + 22</td>
<td>16/25</td>
<td>8/22</td>
<td>3.11 (0.94 - 10.25)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects (Oral trioxsalen plus sun)</td>
<td>23/64</td>
<td>8/46</td>
<td>3.75 (1.24 - 11.29)</td>
<td></td>
</tr>
<tr>
<td>Oral PS plus sunlight</td>
<td>Farah et al., 1967 33</td>
<td>9 + 27</td>
<td>2/9</td>
<td>0/27</td>
<td>18.33 (0.79 - 424.37)</td>
</tr>
<tr>
<td></td>
<td>Pathok et al., 1984 31</td>
<td>37 + 24</td>
<td>11/37</td>
<td>0/24</td>
<td>21.26 (1.19 - 380.41)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects (Oral PS plus UV-A)</td>
<td>97</td>
<td>13/46</td>
<td>19.87 (2.37 - 166.32)</td>
<td></td>
</tr>
<tr>
<td>Phenylalanine plus UV-A</td>
<td>Antoniou et al., 1989 34</td>
<td>11 + 10</td>
<td>5/11</td>
<td>0/10</td>
<td>17.77 (0.84 - 377.40)</td>
</tr>
<tr>
<td></td>
<td>Orecchia and Perfetti, 1992 35</td>
<td>12 + 6</td>
<td>0/12</td>
<td>0/6</td>
<td>0.52 (0.01 - 29.34)</td>
</tr>
<tr>
<td></td>
<td>Siddiqui et al., 1994 34</td>
<td>8 + 6</td>
<td>0/8</td>
<td>0/6</td>
<td>0.76 (0.01 - 43.93)</td>
</tr>
<tr>
<td></td>
<td>Al-Khawajah, 1996 37</td>
<td>13 + 10</td>
<td>0/13</td>
<td>0/10</td>
<td>0.78 (0.01 - 42.55)</td>
</tr>
<tr>
<td></td>
<td>Pooled random effects (Phenylalanine plus UV-A)</td>
<td>76</td>
<td>5/44</td>
<td>2.24 (0.35 - 14.28)</td>
<td></td>
</tr>
<tr>
<td>Oral khellin plus sun</td>
<td>Abdel Fattah et al., 1982 36</td>
<td>30 + 30</td>
<td>5/30</td>
<td>0/30</td>
<td>13.16 (0.69 - 249.48)</td>
</tr>
</tbody>
</table>

PS indicates unsubstituted psoralen; OR indicate odds ratio; CI, confidence interval, L-R: left-right double blind placebo controlled comparative study; and NA, not applicable

* As a standard option, the computer program Meta- Analyst (Joseph Lau, Boston, MA, USA) corrects a 0 value by 0.5.
Effectiveness.

The OR versus placebo was significant for oral methoxsalen plus sunlight (OR, 23.37; 95% CI, 1.33 to 409.93), oral PS plus sunlight (pooled OR, 19.87; 95% CI, 2.37 to 166.32) and oral trioxsalen plus sunlight (pooled OR, 3.75; 95% CI, 1.24 to 11.29). For therapies that used phenylalanine plus UV-A and oral khellin plus sunlight no significant differences were found between the active drug and the placebo (Table 6).

Patient Series

Literature Search.

A total of 231 patient series were identified. Of these, 46 series were included, reporting on 1866 patients (Table 7).

The exclusion criterion “obsolete drug or dosage scheme” was applied for studies that used daily instead of the currently advised twice-to thrice-weekly intake of psoralens. Daily psoralens intake followed by daily UV exposure is not recommended because of the risks of cumulative phototoxic events. Furthermore, studies on oral PUVA performed in the 1950's were excluded because of the use of an obsolete drug containing 8-methoxypsoralen plus 8-isoamyleneoxypsoralen. Other reasons for exclusion are listed

Table 7. Therapy for generalized vitiligo: Reasons for exclusion of patient series *

<table>
<thead>
<tr>
<th>Methoxsalen +UV-A</th>
<th>Trioxsalen +UV-A</th>
<th>Bergapten +UV-A</th>
<th>PS +UV-A</th>
<th>Phenylalanine +UV-A</th>
<th>Khellin +UV-A</th>
<th>UV-B Broadband</th>
<th>UV-B Narrowband</th>
<th>Oral Corticosteroids</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients series identified</td>
<td>70</td>
<td>39</td>
<td>9</td>
<td>20</td>
<td>30</td>
<td>17</td>
<td>2</td>
<td>9</td>
<td>35</td>
</tr>
</tbody>
</table>

No. (% of series) of series

- Included
  - Methoxsalen +UV-A: 6 (9)
  - Trioxsalen +UV-A: 8 (21)
  - Bergapten +UV-A: 4 (44)
  - PS +UV-A: 1 (5)
  - Phenylalanine +UV-A: 15 (50)
  - Khellin +UV-A: 5 (30)
  - UV-B Broadband: 1 (50)
  - UV-B Narrowband: 1 (11)
  - Oral Corticosteroids: 5 (14)
  - Total: 46 (20)

- Excluded series
  - Methoxsalen +UV-A: 64 (91)
  - Trioxsalen +UV-A: 31 (79)
  - Bergapten +UV-A: 5 (56)
  - PS +UV-A: 19 (95)
  - Phenylalanine +UV-A: 15 (50)
  - Khellin +UV-A: 12 (70)
  - UV-B Broadband: 1 (50)
  - UV-B Narrowband: 8 (89)
  - Oral Corticosteroids: 30 (86)
  - Total: 185 (80)

Reasons for exclusion of patient series, No.

- Double publication: 5
- Combined with another (experimental) drug: 10
- Obsolete drug or dosage scheme: 20
- Compared or placebo treated patient series: 24
- Series of fewer than 5 patients: 0
- Inadequate or insufficient data on effectiveness: 5

* PS indicates unsubstituted psoralen
in Table 7. In cases in which several criteria of exclusion were applicable, only the most important one was listed. For the effectiveness and safety analysis, studies on oral corticosteroids were further divided into studies that described daily intake of corticosteroids and studies on “oral minipulse therapy (OMT)”.

**Effectiveness.**

Figure 2 shows that phototherapy with narrowband UV-B had the highest percentage of patients who achieved more than 75% repigmentation (63%; 95% CI, 50% to 76%), followed by broadband UV-B (57%; 95% CI, 29% to 82%). Only one study of each was included. Oral methoxsalen plus UV-A and oral bergapten plus UV-A had success rates of 51% (95% CI, 46% to 56%) and 43% (95% CI, 38% to 48%) respectively. The differences between the mean success rates of narrowband UV-B, broadband UV-B and oral methoxsalen plus UV-A were not significant.

![Figure 2 Effectiveness of therapies for generalized vitiligo. Analysis was based on patient series (sample size-weighted averages and 95% confidence intervals). PS indicates unsubstituted psoralen; OMT, oral minipulse therapy](image)

**Side Effects.**

Of the 46 included series, 40 (87%) reported side effects (Table 8 and Table 9). Of the oral photochemotherapeutic modalities, methoxsalen had the highest proportion of patients who developed nausea (and vomiting) as a side effect (29%; 95% CI, 24% to 35%), followed by PS (9%; 95% CI, 2% to 15%) and khellin (9%; 95% CI, 2% to 16%). Nausea was caused least often by bergapten and trioxsalen (1%; 95% CI, 0% to 2% and 2%; 95% CI, 0% to 3% respectively). Phototoxic reactions were seen mostly in patients who ingested methoxsalen (25%; 95% CI, 20% to 30%) followed by bergapten (6%; 95% CI, 4% to 8%). In patients using trioxsalen and PS plus UV-A, phototoxic reactions only rarely occurred (1%; 95% CI, 0% to 3% and 0% respectively). Abnormal liver function tests were observed mostly in patients using khellin (17%; 95% CI, 8% to...
### Table 8. Photo(chemo)therapy for generalized vitiligo: Side effects *

<table>
<thead>
<tr>
<th>Drug</th>
<th>Methoxsalen + UV-A</th>
<th>Trioxsalen + UV-A</th>
<th>Bergopten + UV-A</th>
<th>PS + UV-A</th>
<th>Phenylalanine + UV-A</th>
<th>Khellin + UV-A</th>
<th>UV-B Broadband</th>
<th>UV-B Narrowband</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of included series</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>15</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treatment duration, range (mean), months</td>
<td>2-24 (15)</td>
<td>4-28 (19)</td>
<td>3-22 (14)</td>
<td>24 (24)</td>
<td>2-24 (9)</td>
<td>3-24 (10)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>No. of series with side effects reported</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>15</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>277</td>
<td>308</td>
<td>368</td>
<td>72</td>
<td>392</td>
<td>65</td>
<td>14</td>
<td>51</td>
</tr>
</tbody>
</table>

#### Patients with side effects †

- **Nausea (and vomiting)**
  - Trioxsalen: 6 (2) [0-3]
  - Bergopten: 3 (1) [0-3]
  - PS: 2 (2) [1-3]
  - Phenylalanine: 17 (6) [1-4]
  - Khellin: 86 (31) [26-37]
  - UV-B Broadband: 27 (10) [6-13]
  - UV-B Narrowband: 3 (9) [1-5]

- **Phototoxic reactions (erythema to burns)**
  - Methoxsalen: 6 (8) [2-15]
  - Trioxsalen: 22 (6) [4-8]
  - Bergopten: 3 (1) [0-2]
  - PS: 6 (2) [0-3]
  - Phenylalanine: 18 (6) [3-8]
  - Khellin: 10 (5) [2-7]
  - UV-B Broadband: 9 (3) [0-3]
  - UV-B Narrowband: NA

- **Abnormal liver function test results**
  - Trioxsalen: 6 (2) [0-3]
  - Bergopten: 3 (1) [0-3]
  - PS: 2 (2) [1-3]
  - Phenylalanine: 17 (6) [1-4]
  - Khellin: 86 (31) [26-37]
  - UV-B Broadband: 27 (10) [6-13]
  - UV-B Narrowband: 3 (9) [1-5]

- **Miscellaneous systemic (headache, dizziness)**
  - Methoxsalen: 6 (8) [2-15]
  - Trioxsalen: 22 (6) [4-8]
  - Bergopten: 3 (1) [0-2]
  - PS: 6 (2) [0-3]
  - Phenylalanine: 18 (6) [3-8]
  - Khellin: 10 (5) [2-7]
  - UV-B Broadband: 9 (3) [0-3]
  - UV-B Narrowband: NA

- **Miscellaneous cutaneous (pruritus)**
  - Trioxsalen: 6 (2) [0-3]
  - Bergopten: 3 (1) [0-3]
  - PS: 2 (2) [1-3]
  - Phenylalanine: 18 (6) [3-8]
  - Khellin: 86 (31) [26-37]
  - UV-B Broadband: 27 (10) [6-13]
  - UV-B Narrowband: 3 (9) [1-5]

- **Increased contrast between normal and depigmented skin**
  - Methoxsalen: 6 (8) [2-15]
  - Trioxsalen: 22 (6) [4-8]
  - Bergopten: 3 (1) [0-2]
  - PS: 6 (2) [0-3]
  - Phenylalanine: 18 (6) [3-8]
  - Khellin: 86 (31) [26-37]
  - UV-B Broadband: 27 (10) [6-13]
  - UV-B Narrowband: 3 (9) [1-5]

* PS indicates unsubstituted psoralen; NA, Data not available
† Data are reported as number of patients with sample size weighted average percentages in parentheses and 95% confidence intervals between brackets.

### Table 9. Side effects of oral corticosteroids given Daily vs Oral Minipulse Therapy (OMT)

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of included series</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Treatment duration range (mean), months</td>
<td>4-6 (5)</td>
<td>6-24 (15)</td>
</tr>
<tr>
<td>No. of series with side effects reported</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>34</td>
<td>72</td>
</tr>
</tbody>
</table>

#### Patients with side effects †

- **Moonface**
  - Daily: 7 (21) [7-34]
  - OMT: 1 (1) [0-8]

- **Weight gain**
  - Daily: 5 (15) [5-31]
  - OMT: 5 (7) [2-16]

- **Acne**
  - Daily: 1 (3) [0-15]
  - OMT: 2 (3) [0-10]

- **Miscellaneous (systemic)**
  - Daily: 3 (9) [2-24]
  - OMT: 11 (15) [7-24]

† Data are reported as number of patients with sample size weighted average percentages in parentheses and 95% confidence intervals in brackets.

26%). Miscellaneous systemic reactions (headache, dizziness) were reported mostly in patients taking oral PS (23%; 95% CI, 14% to 33%). Pruritus, as one of the miscellaneous cutaneous effects was most frequently seen with the use of methoxsalen (31%; 95% CI, 26% to 37%). An increased contrast between normal and depigmented skin was also reported mostly with the use of methoxsalen (10%; 95% CI, 6% to 13%). Studies on
phenylalanine plus UV-A, broadband UV-B and narrowband UV-B did not report any systemic or local side effects. In 1 patient series with oral khellin, 7 of the 25 (28%) patients dropped out of the study because of (asymptomatic) elevation of liver transaminase levels. In the remaining 7 photochemotherapeutic modalities, the side effects reported were all mild and transient and did not lead to discontinuation of the therapy in any of the patients described. The mean treatment duration of photo(-chemo-) therapies varied between 9 months for phenylalanine plus UV-A and 24 months for oral PUVA.

In comparison with daily intake of corticosteroids, oral minipulse therapy (OMT) with corticosteroids was associated with a lower mean proportion of patients with systemic and cutaneous side effects (Table 9). The differences among the rates of various side effects between daily therapy and OMT were, however, not significant. The treatment duration for OMT varied between 6 and 24 months depending on the number of courses given (each course lasted 5 weeks).

COMMENT

Analysis of the available RCTs on therapies for localized vitiligo showed that only class 3 corticosteroids had significantly better results than placebo. Analysis based on patient series revealed that topical class 3 corticosteroids and class 4 corticosteroids had the highest mean proportion of patients with more than 75% repigmentation. Treatment specific side effects were reported mostly with topical psoralens and intralesional and class 4 corticosteroids. In generalized vitiligo, the OR versus placebo was significant for oral methoxsalen plus UV-A and oral PS plus UV-A. In the series, the highest mean success rates were achieved with narrowband UV-B, broadband UV-B and oral methoxsalen plus UV-A therapy. Oral methoxsalen plus UV-A was associated with the highest rates of side effects. No side effects were reported with narrowband UV-B or broadband UV-B therapy.

Databases are known to be only partially successful in identifying relevant studies. Therefore, other sources were screened manually to optimize the results of the search. In addition, leading authorities and pharmaceutical firms were contacted to minimize publication bias. However, publication bias cannot be excluded in our data set despite extensive efforts to gain all of the performed studies. Only a few studies reporting
“negative findings” of a therapy were found\textsuperscript{28,37}.

We have separated treatment modalities indicated for patients with localized vitiligo from those indicated for patients with generalized vitiligo. Nevertheless, selection bias is likely to influence our findings, since between studies, patients may have suffered from different severity of disease. Smaller lesions may have responded better to therapy than larger ones. Some studies using oral PUVA, also included patients with only localized vitiligo lesions. It is likely that the way of assessing repigmentation also differed between studies. Most studies did not mention which and how many observers were involved in scoring of the repigmentation. For this reason, we have excluded studies that used ratings such as “repigmentation or no repigmentation” as outcome measures without giving percentages of the observed repigmentation. Perhaps, in the future, “computer image analysis” may reflect more accurately the percentage of repigmentation or percentage of depigmentation in patients with vitiligo\textsuperscript{43}.

Other factors that may have influenced treatment outcome are differences between patient populations in age and skin type. Although some authors had the impression that younger and dark-skinned patients gained better results, no definitive controlled study was performed to support this observation. It was also disappointing to note that patient compliance was not reported in any of the studies that used phototherapy. Monitoring of compliance is relevant, since phototherapy in vitiligo is time consuming and requires continuous high motivation of the patients. Furthermore, the issue of whether the treatment had improved quality of life was not addressed in any of the studies.

We therefore propose that future clinical trials in vitiligo should evaluate treatment outcome in relation to such variables as localization and duration of the lesions, skin type, age, quality of life and compliance of the patients. In addition, we support the performance of follow-up studies on the permanency of therapy-induced repigmentation, in particular for photo(chemo)therapy. So far, only 3 studies have addressed this issue. However, all three studies described oral PUVA therapy with the use of a daily dosage scheme that is now considered obsolete\textsuperscript{44-46}.

Only a few RCTs that included both localized and generalized vitiligo could be included in this analysis. No RCT was found on topical PUVA, oral bergapten and broadband UV-B and narrowband UV-B therapy. Therefore, caution is needed in the interpretation of the data. In RCTs on therapies for generalized vitiligo, only a small number of the patients treated with placebo had achieved successful repigmentation. A possible explanation may be that in vitiligo, spontaneous repigmentation rarely occurs and is
Meta-analysis of nonsurgical repigmentation therapies

never complete. Some even believe that “spontaneous” repigmentation does not exist and is in fact UV induced repigmentation. In therapies for localized vitiligo, repigmentation observed in patients treated with placebos can therefore also be attributed to either sun exposure (studies with class 4 corticosteroid and intralesional corticosteroid) or combined UV-A irradiation (studies with topical 2%-5% kheollin plus UV-A).

Analysis of RCTs and of the patient series showed that class 3 corticosteroid was the most effective and safest therapy for localized vitiligo. We do not advise topical class 4 corticosteroids and intralesional corticosteroids because of the significantly higher rates of atrophy. Topical PUVA was shown to be associated with a high risk of phototoxic events (erythema, blistering) and is therefore to be prescribed under strict precautions. Despite the absence of side effects with the use of topical kheollin plus UV-A, we do not recommend this option because the drug is not shown to be effective in the analysis of RCTs and the analysis of patient series.

The choice of therapy in generalized vitiligo can also be made after consideration of the reported effectiveness and safety profiles. Most studies on photochemotherapy concluded that more than 75% repigmentation could be achieved only when patients were treated on a regular basis and for longer periods. For photochemotherapy, at least one year of continuous treatment was required. These observations indicate that only well-motivated, highly compliant patients are suitable for photochemotherapy. “Complete” repigmentation was rarely reported with the use of oral photochemotherapeutic modalities. Most authors attributed this to the observation that certain skin areas, such as the distal dorsal surfaces of the hands and feet, tips of fingers and toes, areas of bony prominence, palms, soles, nipples and lips scarcely repigment at all. Estimation of the response that was judged by overall body repigmentation might have led to lower response rates because the above-mentioned nonresponding areas were included in the calculations. broadband UV-B- and narrowband UV-B therapy were described in only one study each. Narrowband UV-B therapy is considered a novel phototherapy in vitiligo. More studies are needed to confirm the good results and to establish its long-term side effects.

Analysis of the side-effect profiles in the patient series showed that treatment with psoralens (both orally and topically) is not easy to perform. Severe phototoxic reactions can be avoided by careful monitoring of UV exposures. Nausea can be avoided by concomitant ingestion of low fat food or milk. The use of oral kheollin was associated with elevated transaminase levels in a high proportion of the patients. Moreover, in 1 series, 28% of the patients terminated the therapy, because of this adverse effect.
Therefore, we do not advise khellin as 1 of the drugs of choice. On the other hand, no side effects were reported with the use of phenylalanine plus UV-A, broadband UV-B or narrowband UV-B. Figure 2 shows that phenylalanine plus UV-A is a relatively ineffective therapy. However, one may prefer UV-B (narrowband or broadband) therapy over oral methoxsalen plus UV-A therapy, when comparing the side effects. Other advantages of UV-B therapy over oral PUVA include no need for oral intake of psoralens, shorter treatment sessions, and applicability in pregnant women and children younger than 12 years.

Guidelines on the use of photochemotherapeutic modalities in vitiligo should also give recommendations on maximum treatment duration. Both PUVA and UV-B (broadband and narrowband) therapies need not be continuous since these modalities are well known for their carcinogenic properties. In patients with psoriasis, long term PUVA therapy was found to be associated with an increased risk for skin cancer, especially squamous cell carcinoma. To date, only 2 patients with vitiligo have been described with squamous cell carcinoma after prolonged PUVA therapy. This relatively low incidence may be explained by the fact that, in contrast to patients with psoriasis, those with vitiligo receive lower cumulative PUVA dosages, do not expose themselves to “extra” sunrays and do not use tar preparations, cystostatic drugs (methotrexate) or immunosuppressive drugs (cyclosporine). Nevertheless, we suggest that guidelines for maximum cumulative PUVA doses in vitiligo should follow those recommended for psoriasis. With regard to UV-B therapy (both broadband and narrowband) there are presently still insufficient epidemiological data available on humans to provide evidence-based advice regarding a safe maximum dose. However, by means of a dose-response model it has been calculated that long term narrowband UV-B therapy may carry substantially less risk for skin cancer than PUVA therapy.

The use of oral corticosteroids is still considered controversial by many authors since systemic side effects (such as moonface and weight gain) are associated with this therapy. Our results are in agreement with those of these authors, since the drug is relatively ineffective and is related with a high rate of side effects.

On the basis of the results of this review, the following recommendations can be made concerning the choice of the most effective and safest therapy. For patients with localized vitiligo, class 3 corticosteroid is advised as first choice therapy. When patients exhibit generalized vitiligo, UV-B (broadband or narrowband) therapy or oral methoxsalen plus UV-A is recommended. This review may be used as a basis for the development of evidence-based guidelines for the treatment of vitiligo.
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REFERENCES

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A complete list of all studies identified is available on request from the authors.