Treatment of vitiligo

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The development of guidelines for the treatment of vitiligo

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ABSTRACT

Objective: To develop and introduce evidence-based guidelines for the treatment of vitiligo in children and in adults

Patients and Setting: Patients, residents and dermatologists from the Department of Dermatology, Academic Medical Center, University of Amsterdam and the Netherlands Institute for Pigmentary Disorders in Amsterdam.

Design: Scientific evidence obtained from 3 systematic reviews of the literature was combined with the results of 2 questionnaires and interviews of potential users of the guidelines, 3 internal expert meetings and 1 local expert meeting during which preliminary guidelines were presented and commented on. A final version of the guidelines was synthesized and disseminated among potential users. Six months after the introduction of these guidelines, their use was evaluated.

Results: Before the development of the guidelines there was no uniformity in treatment selection and there was variability in estimates of treatment outcome. The meta-analysis showed that treatment with class 3 ("potent") corticosteroids and narrowband UV-B were the most effective and safest therapies for localized and for generalized vitiligo, respectively. From another systematic review it was concluded that patients with segmental, stable or lip-tip vitiligo could be successfully treated with most autologous transplantation methods. For vitiligo universalis, results of the systematic review showed that depigmentation using monobenzylether of hydroquinone or Q-switched ruby laser was equally effective. The final version of the guidelines consisted of a treatment scheme together with detailed treatment protocols. Implementation of the guidelines was evaluated in 5 physicians. After the introduction of these guidelines, they were followed in most adult cases with vitiligo (71% of patients with localized vitiligo, 82% with generalized vitiligo, 100% with stable or segmental vitiligo and 80% with universal vitiligo). In children with vitiligo, the physicians adhered to the guidelines for 52% of the cases.

Conclusion: Guidelines for the treatment of vitiligo can be successfully developed and disseminated for daily clinical practice. The results of the implementation of these guidelines should be confirmed in other centers involving more clinicians.
INTRODUCTION

Vitiligo is a common idiopathic pigmented skin disorder for which there is no definite cure available. Treatment in vitiligo aims to achieve repigmentation in the lesions and to stabilize the depigmenting process. Repigmentation leads to an improvement of the cosmetic appearance and of the skin tolerance for sunburns. Each year, many articles are published about the effectiveness and safety of various different repigmentation therapies. Because of the increasing clinical knowledge and literature it is essential to create strategies that may facilitate therapeutic decision making.

There is a growing interest in the use of clinical guidelines for the practice of medicine. Guidelines contain systematically developed statements that assist the clinician in choosing the most appropriate therapy for a specific condition. Guidelines are regarded as tools to reduce inappropriate care, control geographic variations in practice patterns and make the use of health care resources more effective. Several guidelines and review articles have been published on categories of patients with vitiligo that should receive therapy and, if so, which treatment should be applied. Unfortunately, many of these recommendations were based on personal preferences. Some were the product of informal or formal institutional consensus meetings, which were at best supported by a limited number of references to the scientific literature. Personal and institutional experience can be misleading since the numbers of observations is usually small and there are no controls. Furthermore, decisions about intervention made by patients and physicians are far from random; follow-up is usually limited, incomplete and short-term, and memory can be highly selective. Consequently, there is a wide variation in the therapeutic histories of comparable patients.

Since the early 1980s, more evidence-based guidelines are being developed. Evidence-based guidelines link recommendations directly to scientific evidence of effectiveness. Rules of evidence are emphasized over expert opinion in making recommendations. Within this movement, the explicit method specifies the benefits, harms and costs of potential interventions to derive explicit estimates of the probability of each outcome and compares the desirability of the outcomes from the patient's perspective. This approach enhances the accuracy and diminishes the subjectivity of treatment recommendations. When sufficient scientific proof is lacking, estimates may also be generated by expert opinion, provided that the source of the estimate is adequately documented.

Many skin diseases, such as vitiligo, are chronic in nature and have an unknown cause.
Guidelines for treatment of vitiligo

Therefore, the choice for treatment varies with certain patient and disease characteristics. Recent clinical evidence has shown that many traditional vitiligo treatments are ineffective, harmful, or have been replaced by more effective and less toxic therapeutic modalities. A more systematic approach using practice guidelines can be valuable in the treatment of vitiligo, since it incorporates new information into existing strategies of therapeutic decision making.

In this article, we describe the development and implementation of evidence-based guidelines for the treatment of vitiligo at the Netherlands Institute for Pigmentary Disorders (NIPD) and the Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands.

METHODS

At the start of the project, a guideline-development group was composed, consisting of 1 main investigator (M.D.N.), 2 staff members of the Department of Dermatology (W.W. and J.D.B.), a clinical epidemiologist (P.M.M.B.), a clinical librarian (H.D.), and an external expert on pigmentary disorders who did not work at either of the 2 institutions (S.P.).

An evaluation was made of the existing strategies for the treatment of vitiligo using a questionnaire and a structured interview. A meta-analysis of the literature was performed concerning the most currently studied and applied nonsurgical repigmentation therapies, and the most current autologous transplantation methods and depigmentation therapies.

During a first internal meeting, the results of the evaluation of initial status and the results of the literature studies were presented. A draft of the guidelines was discussed. Subsequently, preliminary guidelines were developed and discussed in a second internal meeting. At a final expert meeting the preliminary guidelines were revised. After its acceptance, the final version of the guidelines was disseminated. Their use was evaluated 6 months after the introduction.
RESULTS

EVALUATION OF TREATMENT POLICY BEFORE THE DEVELOPMENT OF THE GUIDELINES

The NIPD is a specialized national outpatient clinic for patients with pigmented skin diseases. In 1997, 1951 new patients were seen at this institute. Of these, 8.3% (162/1951) were patients from the city of Amsterdam and its surrounding areas, and 91.7% (1789/1951) came from outside this region. Seven hundred forty-one patients with vitiligo were diagnosed in 1997 (38% of all diagnoses). In 1997, 5751 new patients visited the outpatient clinic of the Department of Dermatology of the Academic Medical Center of the University of Amsterdam. Patients came from the city of Amsterdam and its surrounding areas (65%; [3738/5751]) as well as from outside this region (35% [2013/5751]). In 1997, 43 patients (0.7% of all diagnoses) were diagnosed as having vitiligo, of which 90% were referred to the NIPD. At the beginning of the study in September 1997, the NIPD consisted of 1 dermatologist and 2 residents. The Department of Dermatology comprised 9 dermatologists and 12 residents.

To detect variations in current treatment policy and disagreements in estimates of treatment outcome and adverse effects, an evaluation was made of the existing strategies for the treatment of vitiligo. The evaluation consisted of a questionnaire and a structured interview. An inventory was made of the therapy choices and regimens for the treatment of vitiligo using a questionnaire. All physicians were asked for their definition of a successful event in vitiligo therapy. Subsequently, all participants were interviewed by one of the investigators (M.D.N.) and asked to comment on their own therapy selection. For each therapeutic option, their opinion was solicited regarding the expected percentage of patients achieving a successful event and the expected rates of adverse effects.

Of the 23 questionnaires sent, 14 were filled in and returned. Nine physicians (all from the Department of Dermatology) reported that they had too little experience with the treatment of vitiligo, since they had treated no more than 5 patients with vitiligo over the past year. These physicians did not complete the questionnaire.

The first-choice therapies of the remaining 14 respondents are listed in Table 1. The results show that the respondents were not unanimous in their selection of a first-choice therapy. For children younger than 12 years, topical corticosteroid therapy was chosen by 79% (11/14) of the respondents for localized vitiligo, 79% (11/14) for generalized vitiligo, and 86% (12/14) for stable vitiligo. In children with generalized vitiligo, phototherapeutic
Guidelines for treatment of vitiligo

Table 1: Evaluation of first-choice therapies *

<table>
<thead>
<tr>
<th>Clinical Type of Vitiligo</th>
<th>No. (%) of Patients</th>
<th>Children &lt; 12 years</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (≤ 2% depigmentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>11 (79)</td>
<td>9 (64)</td>
<td></td>
</tr>
<tr>
<td>Autologous transplantation</td>
<td>0</td>
<td>4 (29)</td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>3 (21)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Generalized (&gt; 2% depigmentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>11 (79)</td>
<td>10 (71)</td>
<td></td>
</tr>
<tr>
<td>Narrowband UV-B</td>
<td>2 (14)</td>
<td>2 (14)</td>
<td></td>
</tr>
<tr>
<td>Oral psoralen-UV-A</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>0</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous transplantation</td>
<td>0</td>
<td>10 (71)</td>
<td></td>
</tr>
<tr>
<td>Narrowband UV-B</td>
<td>0</td>
<td>2 (14)</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>12 (86)</td>
<td>2 (14)</td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>2 (14)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lip-Tip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>3 (21)</td>
<td>11 (79)</td>
<td></td>
</tr>
<tr>
<td>Autologous transplantation</td>
<td>0</td>
<td>2 (14)</td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>11 (79)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Therapy-resistant and/or vitiligo universalis (&gt; 80% depigmentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depigmentation therapy</td>
<td>1 (7)</td>
<td>9 (64)</td>
<td></td>
</tr>
<tr>
<td>Oral psoralen-UV-A</td>
<td>0</td>
<td>5 (36)</td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>13 (93)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Results are based on 14 returned questionnaires

modalities, such as narrowband UV-B and oral psoralen and UV-A (PUVA) were prescribed by 14% (2/14) and 7% (1/14) of the respondents, respectively. Children with lip-tip vitiligo or universal vitiligo were not given any therapy by 79% (11/14) and 93% (13/14) of the physicians, respectively. Autologous transplantation methods were not chosen as first-choice therapy for children by any of the respondents.

For adults, topical corticosteroid therapy was prescribed by 64% (9/14) of the physicians for localized vitiligo, 71% (10/14) for generalized vitiligo and 79% (11/14) for lip-tip
vitiligo. In patients with generalized vitiligo, other treatment choices were narrowband UV-B therapy (14% [12/14]) and oral PUVA (7% [1/14]). In patients with stable vitiligo, most respondents (71% [10/14]) recommended autologous transplantation as the first-choice therapy. There was also no consensus regarding the therapy for patients with universal vitiligo; 64% (9/14) would offer depigmentation therapy, whereas 36% (5/14) would prescribe repigmentation therapy with oral PUVA.

During the interviews it appeared that most respondents (12 of 14) regarded “more than 75% repigmentation” as a cosmetically acceptable level of repigmentation. Therefore this was defined as a successful event of vitiligo therapy. Table 2 shows that physicians working at the NIPD are generally more optimistic towards treatment outcome than those working at the Department of Dermatology. The expected rates of adverse effects were more or less consistent among the respondents (results not shown). Many respondents questioned whether therapy-induced repigmentations were permanent. They did not agree on the maximum recommended dosage for phototherapies, in view of the long-term carcinogenic risks.

Table 2. Mean estimated percentages of patients with vitiligo who achieved repigmentation greater than 75% induced by first-choice therapies*

<table>
<thead>
<tr>
<th>First-Choice Therapy</th>
<th>Dept of Dermatology (n=12)</th>
<th>NIPD (n=2)</th>
<th>Meta-Analysis14 Systematic Review15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>15</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Oral psoralen-UV-A</td>
<td>30</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Narrowband UV-B</td>
<td>30</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Minigrafting</td>
<td>30</td>
<td>80</td>
<td>68</td>
</tr>
</tbody>
</table>

* Dept of Dermatology indicates, the Department of Dermatology, Academic Medical Center, University of Amsterdam, the Netherlands; NIPD, Netherlands Institute for Pigmentary Disorders, Amsterdam, the Netherlands

SYSTEMATIC REVIEWS OF THE LITERATURE

We have performed a meta-analysis and a systematic review of the available literature (last update December 1997) on the most applied forms of non-surgical repigmentation therapy and autologous transplantation methods respectively, with regard to both effectiveness and safety. The methods and results of these studies have been reported elsewhere14-15. In addition, a systematic review was performed on the effectiveness and
Guidelines for treatment of vitiligo

safety on depigmentation therapies for vitiligo (unpublished study, M.D., W.W., J.D.B., P.M.M.B., 1997). Data sources consisted of computerized searches of bibliographic databases (using MEDLINE [National Library of Medicine, Bethesda, Maryland] and EMBASE [Elsevier Science BV, Amsterdam]), a complementary manual literature search and contacts with researchers and pharmaceutical firms. Predefined selection criteria were applied to both randomized controlled trials (RCTs) as well as nonrandomized controlled trials. 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. A preliminary search revealed that only a minor number of RCTs were performed on vitiligo therapies. Therefore, analysis was also performed on the available patient series. Because comparative or placebo-controlled trials can contain a description of at least 2 patient series, the total number of patient series could exceed the total number of studies included.

A. Meta-analysis of nonsurgical repigmentation therapies

Sixty-three studies were found on therapies for localized vitiligo. Of these, 10 of 11 RCTs and 29 of 110 patient series were included. One hundred seventeen studies on therapies for generalized vitiligo were found. Of these 10 of 22 RCTs and 46 of 231 patient series were included. Most studies were excluded because they described combination therapies or an obsolete drug or dosage scheme and because there were inadequate or insufficient data on effectiveness.

Among RCTs on localized vitiligo, the pooled OR vs placebo for treatment with topical class 3 corticosteroids was 14.32 (95% confidence interval [CI], 2.45 to 83.72). In the patient series, therapies with topical class 3 corticosteroids and class 4 corticosteroids had the highest mean success rates (56%; [95% CI, 50% to 62%] and 55% [95% CI, 49% to 61%] respectively). Topical 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 unsubstituted psoralen (25%; 95% CI, 12% to 38%). Atrophy was the most common adverse effect for local corticosteroid therapy, occurring most commonly in patients receiving treatment with intralesional corticosteroids (33%; 95% CI, 22% to 43%) followed by patients treated with class 4 corticosteroids (14%; 95% CI, 10% to 18%) and class 3 corticosteroids (2%; 95% CI, 1% to 5%).

In the RCTs on generalized vitiligo, the OR vs placebo for treatment with oral methoxsalen and sunlight was 23.37 (95% CI, 1.33 to 409.93), for treatment with oral unsubstituted psoralen and sunlight it was 19.87 (95% CI, 2.37 to 166.32) and for treatment with oral
trioxsalen and sunlight the pooled OR was 3.75 (95% CI, 1.24 to 11.29). In the series, the best mean success rates were reported for narrowband UV-B (63%; 95% CI, 50% to 76%), broadband UV-B (57%; 95% CI, 29% to 82%) and oral methoxsalen and UV-A (51%; 95% CI, 46% to 56%) therapies. Treatment with oral methoxsalen and UV-A was associated with the highest rates of adverse effects including nausea and vomiting in 29% (95% CI, 24% to 35%) and phototoxic reactions in 25% (95% CI, 20% to 30%) of the cases. No adverse effects were reported with narrowband or broadband UV-B therapy.

The results of this study allowed us to conclude that treatment with class 3 corticosteroids and UV-B therapy were the most effective and safest therapies for localized and for generalized vitiligo, respectively.

B. Systematic review of autologous transplantation methods

Sixty-three studies were found, of which 16 reported on minigrafting, 13 on split-thickness skin grafting, 15 on grafting of epidermal blisters, 17 on grafting of cultured melanocytes and 2 on grafting of noncultured epidermal suspension. Of these, 39 patient series were included in our analysis. Autologous transplantation methods were performed in cases of stable and segmental vitiligo. Patients with lesions on sites that did not respond to non-surgical therapies, such as lips, hands, feet, fingers (so-called “lip-tip vitiligo”), and genital areas, were also treated with these methods.

The highest mean success rates were achieved with split-thickness skin (87%; 95% CI, 82% to 91%) and epidermal blister (87%; 95% CI, 83% to 90%) grafting. The average success rate for 5 culturing techniques varied from 13% to 53%. However, for 4 of the 5 culturing methods, fewer than 20 patients were reported. Minigrafting had the highest rate of adverse effects. Scar formation of the donor site occurred in 40% of the cases (95% CI, 34% to 47%) and cobblestoning appearance of the grafts at the acceptor site was seen in 27% of the cases (95% CI, 21% to 33%). Nevertheless, minigrafting was shown to be the easiest, fastest, and least expensive method.

Because no comparative controlled trials were included, the treatment recommendations for transplantation should be viewed with caution. Split-thickness skin or epidermal blister grafting can be recommended as the most effective and safest techniques. No definite conclusions can be drawn with regards to the effectiveness of culturing techniques, since only a small number of patients have been studied. The choice of transplantation method also depends on disease characteristics as well as on the availability of specialized personnel and equipment.
C. Systematic review of depigmentation therapies for vitiligo universalis

Two studies were found on the use of monobenzzone (or monobenzylether of hydroquinone). One was a case report and had to be excluded. The second was an open retrospective study on 18 patients. One patient dropped out of this study. Eight of the remaining 17 patients (47%; 95% CI, 23% to 72%) who treated with monobenzzone achieved 100% depigmentation.

Only 1 study was found on depigmentation therapy using the Q-switched ruby (QSR) laser. In 3 (38%; 95% CI, 9% to 76%) of 8 patients who received treatment with QSR laser, 100% depigmentation was observed.

Burning, erythema, contact dermatitis and pruritus occurred most commonly in patients treated with depigmenting cream. Patients who were treated with laser therapy experienced pain in 50% of the cases and erythema in all cases. These adverse effects disappeared after 2 or 3 days.

Treatment recommendations regarding the most effective and safest depigmenting therapy for vitiligo universalis can only be made with caution, since only 1 study has been found for the 2 different modalities. For now, no large differences in the levels of effectiveness can be inferred from the 2 trials included in the analysis. One may prefer the use of a cream over laser therapy since cream is less expensive and easier to apply. A major disadvantage however, is that bleaching with cream may take months or years to result in evident signs of depigmentation. In contrast, laser therapy is faster, and it is possible to treat larger areas of residual pigment at once, but one must keep in mind that patients with a negative Koebner phenomenon will not respond to laser therapy.

THE DEVELOPMENT OF PRELIMINARY GUIDELINES

Nine dermatologists and 12 residents from the Department of Dermatology and 1 dermatologist and 1 resident from the NIPD and a clinical epidemiologist participated in the first internal meeting. During this meeting, the results of the questionnaires, interviews and literature studies were presented and discussed.

Based on the results of the questionnaire, the literature studies and the first internal meeting, preliminary guidelines for the treatment of vitiligo were synthesized. These guidelines were distributed by internal mail to all potential users (staff dermatologists and residents of both target institutions).

In the second internal meeting, which was attended by the same personnel as the first, participants gave their comments on the preliminary guidelines. At the same time, a draft of the preliminary guidelines was mailed to the external expert for critical review.
THE FINAL VERSION OF THE GUIDELINES

Comments from the staff members and the residents of both institutions and comments from the external expert were incorporated in a new draft of the guidelines.

The final version was then synthesized in the form of a treatment scheme (Table 3).

Table 3. Treatment scheme for vitiligo

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Type of Vitiligo</th>
<th>First-Choice Therapy *</th>
<th>Alternative Therapies *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &lt; 12 yrs</td>
<td>All</td>
<td>Class 3 corticosteroids (and UV-A); course, 6-9 mo (aged &lt; 6 yrs, no UV-A)</td>
<td>Local UV-B (311 nm); course, 6-12 mo</td>
</tr>
<tr>
<td>Adults</td>
<td>Localized (≤ 2% depigmentation)</td>
<td>Class 3 corticosteroids (and UV-A); course, 6-9 mo</td>
<td>Local UV-B (311 nm); course, 6-12 mo</td>
</tr>
<tr>
<td></td>
<td>Generalized (&gt; 2%)</td>
<td>UV-B (311 nm); course, 6-24 mo</td>
<td>Oral psoralen-UV-A; course, 6-24 mo</td>
</tr>
<tr>
<td></td>
<td>Segmental or stable</td>
<td>Autologous transplantation (until 100% repigmentation)</td>
<td>Class 3 corticosteroids (and UV-A); course, 6-9 mo UV-B (311 nm); course, 6-24 mo</td>
</tr>
<tr>
<td></td>
<td>Lip-Tip</td>
<td>Autologous transplantation (until 100% repigmentation)</td>
<td>Micropigmentation (until 100% repigmentation)</td>
</tr>
<tr>
<td></td>
<td>Therapy-resistant and/or generalized (&gt; 80% depigmentation)</td>
<td>Depigmentation with bleaching creme and/or laser (until 100% depigmentation)</td>
<td>None</td>
</tr>
</tbody>
</table>

* The course is expressed as a range from minimum to maximum.

Recommendations regarding first and alternative choices were given according to the age of the patient, clinical type, severity of disease, and disease activity. For this purpose, a slightly modified version of the classification of vitiligo according to Nordlund and Ortonne is used (Table 4). Recommendations on the minimum and maximum treatment duration were made during a consensus meeting with a smaller group of experts, consisting of members of the guideline development group, an expert on phototherapeutic therapies, and a photobiologist. When sufficient scientific evidence was lacking, recommendations on the selection of therapy and dosage schemes were made during this same consensus meeting.
Guidelines for treatment of vitiligo

Table 4. Classification of vitiligo *

<table>
<thead>
<tr>
<th>Localized vitiligo</th>
<th>Generalized vitiligo</th>
<th>Segmental vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focalis:</strong></td>
<td><strong>Vulgaris:</strong></td>
<td>-One or more macules in a (quasi) dermatomal pattern</td>
</tr>
<tr>
<td>- Extent not more than 2% of the body surface</td>
<td>- Extent more than 2% of the body surface</td>
<td>- Extent is variable</td>
</tr>
<tr>
<td>- Only one or more macules in maximally 2 anatomical sites</td>
<td>- More than 2 anatomical sites involved</td>
<td>- Usually unilateral</td>
</tr>
</tbody>
</table>

**Vulgaris:**
- Extent not more than 2% of the body surface
- Maximally 2 symmetrical anatomical sites involved

**Universalis:**
- Extent more than 80% of the body surface

* Modified from Classification by Ortonne

For children younger than 12 years, treatment with class 3 topical corticosteroids (e.g., fluticasone propionate or betamethasone valerate) were recommended as the first-choice therapy. This choice was made regardless of the clinical type. When no repigmentation was observed after 6 months, localized UV-B therapy or topical PUVA therapy could be prescribed and the “skin saving principle” applied (i.e. parts of the body where no lesions were present, especially the face, should be shielded during treatments). Additionally, parts of the body that had repigmented satisfactorily during the course of the therapy should, if possible, be shielded during subsequent treatments (e.g. trousers should be worn). In children, genital areas should always be protected during UV exposures. Treatment with topical corticosteroid may be combined with UV-A radiation. In a recent left-right comparative study, it was shown that the combined treatment with fluticasone propionate and UV-A therapy led to a higher repigmentation grade than treatment with treatment with either fluticasone propionate alone or UV-A. A facial tanner or a sun bed can be used as the UV-A source.

In adult patients, treatment choice was guided by clinical type. Patients with only localized vitiligo could be treated with class 3 corticosteroids combined with UV-A therapy. If there is no response after 6 months, localized UV-B or topical PUVA therapy can be given as an alternative. Narrowband UV-B therapy was recommended as the most effective and safest therapy for generalized vitiligo. A minimum treatment duration of 6 months was recommended for narrowband UV-B therapy. Responsive patients could be given...
this treatment for a maximum of 24 months. After the first course of 1 year, a resting period of 3 months was recommended to minimize the annual cumulative dose of narrowband UV-B.

The therapy selected as the first choice for segmental, stable, or lip-tip vitiligo was autologous transplantation. In the NIPD, split-thickness skin grafting and minigrafting are performed on a routine basis for these conditions. For patients who do not desire a surgical intervention, alternatives may be considered.

For patients with extensive areas of depigmentation (more than 80%) and/or disfiguring lesions on the face, who do not respond to repigmentation therapies, depigmentation of the residual melanin should be considered. During and upon completion of the therapy, patients are permanently at risk for acquiring sunburn from acute solar irradiation. Patients should therefore be advised to minimize sun exposure and to apply broad-spectrum sunscreens. The use of a potent bleaching cream and/or laser therapy (e.g. the Q-switched ruby laser) are considered to be the cornerstones of depigmentation therapy for these patients.

In all cases, advice regarding the use of camouflage and sunblocking agents should always be given. If necessary, psychological counseling may be recommended.

These guidelines were distributed together with detailed treatment protocols (not included in this article).

DISSEMINATION AND IMPLEMENTATION OF THE FINAL VERSION OF THE GUIDELINES

The guidelines were mailed to all potential users. A copy of the guidelines was placed on the desk of every treatment room as a reminder. The guidelines were incorporated into the specific dermatological treatment protocol index to which every dermatologist and resident has access. Furthermore, the guidelines was presented and commented on during an internal meeting and again during a local symposium on pigmented disorders. The implementation of the guidelines was discussed once a week during regular staff meetings and their use was encouraged.

EVALUATION

After 6 months, use of the guidelines was evaluated by means of a questionnaire. Since during this period almost all patients with vitiligo had been referred to the NIPD for treatment, evaluation of the use of the guidelines took place primarily at the NIPD.
Guidelines for treatment of vitiligo

The second questionnaire was also sent to physicians working at the Department of Dermatology; physicians were asked to evaluate whether dissemination and implementation of the guidelines had also succeeded there.

Information was obtained from NIPD patient record forms regarding the therapy given to patients with vitiligo between June 1998 and January 1999. In addition, in individual cases the reasons for not adhering to the guidelines were noted.

In the questionnaire, all physicians were asked to indicate whether they were familiar with the guidelines and how many new patients with vitiligo they saw during the past 6 months. They were also asked to indicate what sources of information they used to make a first choice of therapy. All physicians were also asked to give their opinion regarding the context and content of the guidelines and their usefulness in daily practice.

Twenty-three questionnaires were sent to the physicians working at both institutions. In the introduction period, 2 new part-time staff members and 1 new resident were employed at the Department of Dermatology and at the NIPD, respectively.

Eighteen staff members and residents of the Department of Dermatology had seen fewer than 5 patients with vitiligo during the introduction period. These physicians did not report responses regarding the context and content of the guidelines. However, all 18 physicians reported that they were familiar with the guidelines.

Table 5. First-choice therapies in 302 patients with vitiligo evaluated over a period of 6 months

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Type of Vitiligo</th>
<th>First-Choice Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (&lt; 12 yrs) (n = 44)</td>
<td>Localized (n = 8)</td>
<td>Class 3 corticosteroids and UV-A (n = 23)</td>
</tr>
<tr>
<td></td>
<td>Generalized (n = 33)</td>
<td>Local UV-B (311 nm) (n = 18)</td>
</tr>
<tr>
<td></td>
<td>Stable (n = 0)</td>
<td>Autologous transplantation (n = 3)</td>
</tr>
<tr>
<td></td>
<td>Segmental (n = 3)</td>
<td>No therapy (n = 0)</td>
</tr>
<tr>
<td>Adults (n = 258)</td>
<td>Localized (n = 21)</td>
<td>Class 3 corticosteroids and UV-A (n = 15)</td>
</tr>
<tr>
<td></td>
<td>Generalized (n = 207)</td>
<td>UV-B (311 nm) (n = 170)</td>
</tr>
<tr>
<td></td>
<td>Segmental (n = 10) or stable (n = 14)</td>
<td>Class 3 corticosteroids and UV-A (n = 33)</td>
</tr>
<tr>
<td></td>
<td>Lip-Tip (n = 1)</td>
<td>No therapy (n = 4)</td>
</tr>
<tr>
<td></td>
<td>Therapy-resistant and/or generalized (&gt; 80% depigmentation) (n = 5)</td>
<td>Autologous transplantation (n = 24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autologous transplantation (n = 0); No therapy (n = 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depigmentation therapy (n = 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No therapy (n = 1)</td>
</tr>
</tbody>
</table>
The questionnaire was completed by 2 respondents from the Department of Dermatology and by 3 respondents from the NIPD. All 5 reported that they had used the guidelines during therapeutical decision making. They also agreed that the guidelines gave clear directions for which patient group and clinical types the treatments were recommended. Treatment recommendations as presented in the guidelines were found to be reader-friendly and comprehensive. Furthermore, the respondents believed that the objectives were clearly defined and that dosage schemes were adequately adapted for clinical use. Finally, they found that circumstances in which exceptions might be made and patient’s preferences were clearly defined in the treatment protocols that were attached to the guidelines.

In the introduction period, 302 patients with vitiligo had visited the NIPD (Table 5). Among them were 44 children with vitiligo who were younger than 12 years. The clinical type of their vitiligo is also shown in Table 5. In 23 cases (52%), therapy with class 3 corticosteroids and UV-A was the first choice, which is in accord with the guidelines. In 18 children, localized narrowband UV-B therapy was prescribed. The reasons for not adhering to the guidelines in these cases were “fast stabilization required” (14 cases) and “on specific request of the parents” (4 cases). Three patients (1 was aged 9 years, and 2 were aged 11 years) received autologous transplantation by minigrafting technique because they had localized and stable vitiligo patches.

There were 258 adults patients with vitiligo. Of the 21 patients with localized vitiligo, the guidelines were followed in the treatment of 15 patients (71 %), 3 were given localized narrowband UV-B therapy (all on specific request of the patient) and 3 did not desire therapy. Two hundred seven patients had generalized vitiligo of which 82% (170/207) received narrowband UV-B, according the guidelines. In 33 patients, class 3 corticosteroid and UV-A therapy was prescribed because patients specifically requested this therapy (11 cases), or because they found the distance to the hospital too great (13 cases), lacked time (2 cases) or wanted only to treat facial lesions (7 cases). The remaining 4 patients with generalized vitiligo did not wish to be treated. There were 21 patients with segmental and stable vitiligo, all of whom received autologous transplantation, a choice that was in accord with the guidelines. There was 1 patient with lip-tip vitiligo who did not want any treatment. Five adult patients were diagnosed as having vitiligo universalis, 4 of whom (80%) had started with depigmentation therapy and 1 of whom did not desire depigmentation therapy.
The successful introduction of clinical guidelines depends on the strategies for developing, disseminating and implementing these guidelines into daily practice. The introduction of guidelines for the treatment of vitiligo, as described in this study, has taken into account all 3 crucial stages. Guidelines are more likely to achieve the desired health effects if they are consistent with the available scientific evidence or, in the absence of such evidence, with the best clinical judgements. Compliance with guidelines has been shown to be enhanced if these guidelines are developed and adopted by those who will use them. Therefore, we have linked scientific evidence from 3 literature studies with the results of 2 questionnaires and interviews among the potential users of the guidelines, 3 internal expert meetings and 1 local expert meeting during which the guidelines were presented and commented on. After the guidelines were accepted and introduced in daily practice, the final version was evaluated.

The results of the first questionnaire showed that there was no uniformity in treatment choices and in estimates of treatment outcome. In view of the potential long-term carcinogenic risks of UV-B and oral PUVA, many physicians asked the guideline development group to come up with recommendations on the maximum treatment duration for these phototherapeutic modalities. The literature review therefore focused on clinical trials in which the percentage of repigmentation, adverse effect profiles and treatment duration were all adequately reported and analyzed. The best available evidence is delivered by RCTs and summarized in systematic reviews and meta-analysis. However, our own systematic reviews of the available literature showed that only a small number of properly designed RCTs has been performed for both nonsurgical repigmentation therapies and autologous transplantation methods in vitiligo. The systematic review of depigmentation therapies in vitiligo showed that no RCT has yet been performed. In such analyses, calculated weighted estimates on treatment outcome and safety from uncontrolled studies cannot be considered as measures of effectiveness, since these studies are prone to selection bias. Such summary estimates should therefore be interpreted with caution. Furthermore, only a few studies were found on the treatment of vitiligo in children. In most trials, both children and adults were included in the study and treatment outcome was not analyzed separately. Recommendations for children could therefore not be entirely evidence-based. The additional input from experts that was generated during the internal and expert meetings was needed to develop explicit guidelines.
Six months after their introduction, the dissemination of the guidelines had succeeded both in the Department of Dermatology and at the NIPD. All 23 participating physicians were familiar with the guidelines. However, implementation was only partly successful, since only 5 of these physicians had treated a substantial number of patients with vitiligo during this period (more than 5 patients). These 5 physicians considered the guidelines to be an easy, practical and useful tool for making a specific treatment choice.

Analysis of first treatment choices made for 302 new patients with vitiligo revealed that the guidelines were followed for most adults (n= 258). In children with vitiligo, the physicians adhered to the guidelines for 52% of the cases. This relatively low compliance rate compared with adults may be explained by the way that the treatment scheme was formulated for children (i.e. no further distinction was made in the several clinical types or the disease activity). The effectiveness and safety of narrowband UV-B therapy for children with generalized vitiligo is currently being investigated. In the future, the data from this trial could lead to an evidence-based adjustment of the treatment scheme for children.

The finding that the guidelines were not followed in all cases confirms the general belief that guidelines should not be regarded as rigid criteria, but that they are intended to be flexible. Guidelines should guide action in most cases. Depending on the patient, the setting, the circumstances, or other factors, any part of the guidelines can and should be adjusted to fit individual needs.

The results of this study show that clinical guidelines for the treatment of vitiligo can be successfully developed and disseminated for daily clinical practice. Implementation of these guidelines was only partly successful, however, since the number of physicians using the guidelines was low. Therefore, the results of the implementation of these guidelines should be confirmed in other centers involving more clinicians who see more patients with vitiligo. Guidelines are not static and should regularly be updated to take into account changes in medical knowledge and practice and particularly the results of randomized trials and meta-analyses. Future studies in vitiligo treatment should also focus on the permanence of therapy induced repigmentations and on the long-term risk-benefit ratios of the different modalities.
Guidelines for treatment of vitiligo

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