A Systematic Review of Autologous Transplantation Methods in Vitiligo

M. D. Njoo, MD; W. Westerhof, MD, PhD; J. D. Bos, MD, PhD; P. M. M. Bossuyt, MD, PhD

Objective: A systematic review of the effectiveness, safety, and applicability of autologous transplantation methods in vitiligo.

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 all studies found.

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

Data Synthesis: Sixty-three studies were found, of which 16 reported on minigrafting, 13 on split-thickness 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. The highest mean success rates (87%) were achieved with split-skin grafting (95% confidence interval, 82%-91%), and epidermal blister grafting (87%) (95% confidence interval, 83%-90%). The mean success rate of 5 culturing techniques varied from 13% to 53%. However, in 4 of the 5 culturing methods, fewer than 20 patients were studied. Minigrafting had the highest rates of adverse effects but was the easiest, fastest, and least expensive method.

Conclusions: Because no controlled trials were included, treatment recommendations should be formulated with caution. Split-thickness and epidermal blister grafting can be recommended as the most effective and safest techniques. No definite conclusions can be drawn about the effectiveness of culturing techniques because only a small number of patients have been studied. The choice of method also depends on certain disease characteristics and the availability of specialized personnel and equipment.

Arch Dermatol. 1998;134:1543-1549

VITILIGO is a common hypopigmentary disorder occurring in about 1% of the world’s population, regardless of age, sex, and skin color. The disorder is primarily treated by medical therapies. However, these therapies are not successful in every patient. In patients who do respond, complete repigmentation is rarely achieved. Certain areas such as lips, nipples, genitals, eyelids, and distal extremities are areas that are known to respond poorly.1,2

Several methods of autologous transplantation of melanocytes have been developed to repigment lesions that are stable and those that are refractory to medical therapies. Autologous skin grafts can be obtained from the uninvolved skin using several techniques.3,4 When using the minigrafting (or punch grafting) technique, 1- to 2-mm full-thickness punch grafts are harvested from normally pigmented donor sites and are then transplanted to depigmented acceptor sites from which similar punch grafts have been removed. Epidermal blister grafting involves the formation of epidermal blisters by application of a negative pressure to the normally pigmented skin. Two days before transplantation, blistering of the depigmented lesion is induced using liquid nitrogen or topical psoralen plus UV-A therapy. After blister formation, the depigmented epithelium is removed and the roofs of the pigmented donor blisters are transplanted to the denuded lesional areas. Split-thickness grafting involves removal of the depigmented epithelium by superficial dermabrasion or dermatome. A thin split-thickness skin graft is then harvested from a normally pigmented donor area with a dermatome and placed into the denuded achromic area. Transplants

From the Netherlands Institute for Pigmentary Disorders (Drs Njoo and Westerhof), and the Departments of Dermatology (Drs Westerhof and Bos) and Clinical Epidemiology and Biostatistics (Dr Bossuyt), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

©1998 American Medical Association. All rights reserved.
METHODS

DATA SOURCES

The computerized bibliographical databases MEDLINE (National Library of Medicine, Bethesda, Md, updated December 15, 1997) and EMBASE (Elsevier Science BV, Amsterdam, the Netherlands, updated December 15, 1997) were screened for clinical trials from January 1966 to December 1997. No language restrictions were applied. As main keywords (including analogues and derivatives) we used “vitiligo,” “surgery,” “skin transplantation,” and “transplantation autologous.” Other sources were abstract books of symposia and congresses, dissertations, textbooks, monographs, reviews, editorials, letters to the editor, free or rapid communications (short papers), and the reference lists from all the articles retrieved. Also, we contacted 21 leading authorities in the field of vitiligo and 9 pharmaceutical companies to provide us with any additional published and unpublished data.

STUDY SELECTION: INCLUSION AND EXCLUSION CRITERIA

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

We included clinical trials on minigrafting, split-skin grafting, grafting of epidermal blisters, grafting of cultured melanocytes, and grafting of noncultured epidermal suspension performed in patients with vitiligo. Excluded were double publications (reports of the same study published in different journals or languages), studies describing combination with another (experimental) technique, methodological studies, studies reporting on fewer than 3 patients, and studies with insufficient data on effectiveness. The exclusion criterion “methodological study” was used for studies describing only the technique. In cases of double publications only, the most detailed publication was selected.

DATA EXTRACTION

Patient Series Analysis

Because no randomized controlled trials were found, analysis was needed on the available patient series. Because comparative trials can contain a description of 2 or more patient series, the total number of patient series can exceed the total number of studies included. Success rates were presented as sample size–weighted averages, which were calculated for each modality by dividing the total number of patients achieving more than 75% repigmentation by the total number of patients in the included series. The 95% confidence intervals (CIs) of these averages were calculated using CIA for MS-DOS, version 1.0, 1989, using the “Exact Method.”

Adverse Effects

The treatment duration (range and mean values) was also determined for each treatment modality. Treatment-specific adverse effects were estimated by dividing the number of patients experiencing adverse effects by the total number of patients in the included series. For each study, sample size–weighted averages for these frequencies and their 95% CIs were calculated with the same software used for the calculation of the success rates. Imperfect color matching as an adverse effect of the acceptor site was defined as the occurrence of hyperpigmentation and/or hypopigmentation of the grafts giving a variegated appearance of the pigment in the treated area.

Other Factors Relevant for Choice of Transplantation Method

Because every grafting method has its specific advantages and disadvantages, other aspects of treatment were included such as clinical types treated, maximum treatable lesion size, required size of the donor skin, duration of the procedure, and need for special equipment or personnel.

RESULTS

LITERATURE SEARCH

In total, 63 studies were obtained, of which 42 could be identified in the databases (Table 1). The mean hit rate of the databases was 67%, with a range of 33% to 100%. Fifteen of the 21 leading authorities and 7 of the 9 pharmaceutical firms contacted replied and provided us with relevant references. No study required a third reviewer to resolve disagreements about selection.

The number of studies ranged from 2 to 17 for the 5 different modalities. Most studies reported on results with grafting of cultured melanocytes (17/63 [27%]). No controlled clinical trials were found. One Korean study on epidermal blister grafting was not yet available when this manuscript was submitted.14

A total of 64 patient series could be identified, varying from 2 to 17 series among the different modalities. After ap-
plication of the exclusion criteria, 25 series were excluded. A total of 39 series (61%) could be included,15-53 reporting on the results in 1035 patients.

The reasons for exclusion are summarized in Table 1. In cases with more than one exclusion criterion, only the most important one is listed.

Effectiveness

The highest success rates were achieved with split-thickness grafting (87% [95% CI, 82%-91%]) and epidermal blister grafting (87% [95% CI, 83%-90%]) (Figure 1). The lowest success rate was reported with grafting of noncultured epidermal suspension (31% [95% CI, 11%-59%]). However, of the latter, a total of only 16 patients were studied.

Figure 1 shows the effectiveness of different transplantation methods using cell culturing techniques. Studies using the same culture medium were combined. Studies A, B, and E described in vitro culturing techniques of epidermis containing both keratinocytes and melanocytes (“co-cultures”). In study E, only 1 publication was included reporting the results in 15 patients. In study B, only 4 patients were treated. Study A was associated with the highest percentage of patients with more than 75% repigmentation (53% [95% CI, 27%-78%]) in a total of 15 patients. Studies C and D used melanocytes alone in the cultures. However, with study C only 1 publication was found to report the results of 18 patients. Study D reported a mean success percentage of 48% (95% CI, 39%-56%) in a total of 130 patients.

Adverse Effects

Of the 39 included series, 35 (90%) reported adverse effects (Table 2). Scar formation at the donor site, considered to be the most undesirable adverse effect, was most frequently reported with minigrafting (40% [95% CI, 34%-47%]), followed by split-thickness grafting (12% [95% CI, 7%-16%]). No scar formation was observed with the other techniques. Hyperpigmentation at the donor site

Table 1. Results of the Literature Search and Reasons for Exclusion of Patient Series*

<table>
<thead>
<tr>
<th>Results</th>
<th>Minigrafting</th>
<th>Split-Thickness Grafting</th>
<th>Grafting Epidermal Blister</th>
<th>Grafting Cultured Epidermis/Melanocytes</th>
<th>Grafting Noncultured Epidermis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies obtained</td>
<td>16</td>
<td>13</td>
<td>15</td>
<td>17</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>Through databases (hit rate database, %)</td>
<td>7 (44)</td>
<td>9 (69)</td>
<td>12 (80)</td>
<td>13 (76)</td>
<td>1 (50)</td>
<td>42 (67)</td>
</tr>
<tr>
<td>Patient series identified</td>
<td>17</td>
<td>13</td>
<td>15</td>
<td>17</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>Excluded series (patient series identified, %)</td>
<td>9 (56)</td>
<td>8 (62)</td>
<td>10 (67)</td>
<td>10 (59)</td>
<td>2 (100)</td>
<td>39 (61)</td>
</tr>
<tr>
<td>Reasons for exclusion of series</td>
<td>Double publication</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Compared with another (experimental) technique</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Methodological study</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Series of &lt;3 patients</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Inadequate/insufficient data on effectiveness</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, all values are given as number.

Figure 1. Effectiveness of autologous noncultured transplantation methods in vitiligo. Analysis based on patient series; sample size–weighted averages; range of 95% confidence intervals (CIs) in brackets.

Figure 2. Effectiveness of autologous cultured transplantation methods in vitiligo. Analysis based on patient series; sample size–weighted averages; range of 95% confidence intervals (CIs) in range brackets. Mel indicates melanocytes; ker, keratinocytes.
was mostly reported with epidermal blister grafting (28% [95% CI, 23%-33%]). In patients receiving noncultured epidermal suspension grafts, no adverse effects were reported at the donor sites.

At the acceptor sites, a cobblestone appearance of the grafts was a specific adverse effect of the minigrafting technique and occurred in 27% of the cases (95% CI, 21%-33%). Milia and partial loss of grafts were the 2 most common adverse effects with split-thickness grafting (13% [95% CI, 8%-18%] and 11% [95% CI, 7%-15%], respectively). In all 5 techniques, imperfect color matching occurred in less than 10% of the cases. Thick margins of the grafts occurred exclusively in split-thickness grafting (in 5% of the cases [95% CI, 2%-9%]). Scar formation and infection were less common adverse effects (<3% each) at the acceptor sites.

**Other Factors Relevant for Choice of Transplantation Method**

Table 3 shows that all clinical types of vitiligo have been treated with these 5 techniques. Most experience was gained with generalized vitiligo (415/1035 [40%]), followed by segmental vitiligo (190/1035 [18%]). Areas commonly resistant to medical therapies have also been treated with these transplantation methods, including lips, nipples, eyelids, genitals, and fingers. The best results have been achieved with split-thickness grafting and epidermal blister grafting. Minigrafting caused the highest proportion of adverse effects at the donor and acceptor sites.

**Comment**

A review of the available literature was performed to assess the effectiveness, safety, and applicability of different forms of autologous transplantation methods in vitiligo. The results indicated that the highest success rates were achieved with split-thickness grafting and epidermal blister grafting. Minigrafting caused the highest proportion of adverse effects at the donor and acceptor sites. On the other hand, minigrafting was the easiest, fastest, and least expensive transplantation method.

The data presented here should be interpreted with caution. As there were no comparative studies, only average success and adverse-effect rates could be studied, which only allows for indirect comparison. Furthermore, of the 9 different studies on grafting techniques, 5 reported on fewer than 20 patients, 4 of these on culturing techniques (studies A, B, C, and E) and 1 on grafting of noncultured epidermal suspension. Because of the low numbers of patients studied, conclusions about effectiveness and safety of these therapies must be drawn with caution.

Despite our attempts to obtain all relevant studies, we cannot exclude the possibility that publication bias...
has interfered with our data. Some leading authorities provided us with unpublished articles already accepted for publication.

In all studies, patients fulfilled certain selection criteria before they were admitted for transplantation. Their conditions had been refractory to treatment for at least 6 to 12 months and had stabilized for at least 1 to 2 years. Patients with a tendency for scar or keloid formation and patients younger than 12 years were excluded. We agree with existing guidelines that patients should first meet the above-mentioned selection criteria before transplantation can be applied; however, these criteria have not been used consistently by all investigators. Moreover, the definition of “stabilized disease” differed among the studies. For example, the disease was considered stable when there were no new lesions or when old lesions had not grown in 2 years according to Savant and in 6 months according to Boersma et al. Not all authors used the minigrafting test to select stable cases. These differences in selection procedure may explain some of the variations in treatment outcome. When vitiligo is still active, there is a higher risk for treatment failure and for the development of the Koebner phenomenon at the donor site. The relatively lower success rate achieved with minigrafting can be explained by variations in the size of pigment spread of the depigmented lesions (up to 100% repigmentation grade more accurately).

In this review, the effectiveness of only monotherapies is summarized. However, the combination of 2 techniques may increase the repigmentation grade. Falabella et al have shown that the minigrafting method can be used as an effective additional procedure to restore completely the depigmented lesions (up to 100% repigmentation) when, after epidermal blister grafting or grafting of cultured cells, residual achromic areas are still present.

Among the noncultured transplantation methods, split-thickness grafting and epidermal blister grafting were shown to be the most effective methods. The relatively lower success rate achieved with minigrafting can be explained by variations in the size of pigment spread of the punch grafts. Racial factors and skin type may play an important role in this matter. Postoperative radiation therapy may improve the repigmentation grade in minigrafting. A facial tanner or a sunbed can be used as UV sources. Just as it has been shown in epidermal blister grafting test as an objective parameter to select stable cases and on the patient’s history.

Variations in the method of assessing repigmentation grade may also have influenced treatment outcome. One study used “digital image analysis” to assess repigmentation grade more accurately.

In this review, the effectiveness of only monotherapies is summarized. However, the combination of 2 techniques may increase the repigmentation grade. Falabella et al have shown that the minigrafting method can be used as an effective additional procedure to restore completely the depigmented lesions (up to 100% repigmentation) when, after epidermal blister grafting or grafting of cultured cells, residual achromic areas are still present.

Among the noncultured transplantation methods, split-thickness grafting and epidermal blister grafting were shown to be the most effective methods. The relatively lower success rate achieved with minigrafting can be explained by variations in the size of pigment spread of the punch grafts. Racial factors and skin type may play an important role in this matter. Postoperative radiation therapy may improve the repigmentation grade in minigrafting. A facial tanner or a sunbed can be used as UV sources. Just as it has been shown in epidermal blister grafting test as an objective parameter to select stable cases and on the patient’s history.
grafting that pigment spreading can be enhanced by pre-operative radiation therapy of the donor sites using psoralen plus UV-A; this modification may be useful with minigrafting.

The question arises whether the repigmentation induced by grafting methods is permanent. Since transplantation of melanocytes does not treat the underlying cause in vitiligo, reactivation of the disease may lead to a secondary failure of the treated skin and to the development of the Koebner phenomenon at the donor sites. Follow-up studies are therefore needed to address this issue.

Analysis of adverse-effect profiles indicate that mini-grafting had the highest proportion of patients with adverse effects at the donor and acceptor sites. The risks of minigrafting are well known and are generally acceptable. A cobblestone appearance may resolve spontaneously but can also be prevented by punching the holes much deeper at the acceptor area and by using more superficial donor grafts. However, superficial scar formation at the donor sites still remains the main limitation of this method.

Adverse effects have also been encountered in many patients undergoing split-thickness grafts. Milia, however, are temporary phenomena, and thick margins can be treated with repeated dermabrasion. Scar formation at the donor sites can be prevented by using a very thin graft, and the risk of graft loss can be minimized by adequate postoperative care (immobilization of the treated area).

In all techniques, imperfect color matching of the grafts was caused by hypopigmentation and/or hyperpigmentation. Hypopigmentation of the grafts can be explained by reactivation of the disease or, as in culturing techniques, by an insufficient concentration of grafted melanocytes. Hyperpigmentation of the grafts may be related to overstimulation of melanocytes by growth factors or cytokines during the reepithelialization phase. To minimize hyperpigmentation, any form of postoperative radiation therapy should be halted when sufficient color matching is achieved.

Grafting of cultured autologous melanocytes was originally a promising procedure to repigment large acrochordal areas using relatively small donor areas. However, culturing methods are still in a developmental stage since relatively low numbers of patients have been studied. There is also concern regarding the tumorigenic risks of culturing techniques because certain culture media contain tumor promoters and grafted areas are postoperatively treated with UV radiation. To date, melanoma has not been reported in patients treated with these techniques. Nevertheless, we do not recommend the supplementation of culture media with tumor promoters and the prolonged use of postoperative UV therapy.

Because no randomized controlled trials were included in our analysis and because of the low numbers of patients studied in some modalities, the following treatment recommendations in this study should be viewed with caution. Among the uncultured transplantation methods, split-thickness and epidermal blister grafting can be recommended as the most effective techniques. No definite conclusions can be drawn with regard to the effectiveness of culturing techniques, since only small numbers of patients were studied. Most adverse effects of grafting techniques are temporary and can be easily prevented or treated. The choice of transplantation method also depends on certain disease characteristics (ie, size and localization of the lesions) and the availability of specialized personnel and equipment. Further studies involving a statistically significant number of patients are required to substantiate our treatment recommendations.

Accepted for publication July 24, 1998.

This project was supported by a grant from the Commission for Guidelines for Clinical Practice, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

Presented at the Second Stichting Nederlands Instituut Voor Pigmentstoornissen Symposium, Amsterdam, November 21, 1997.

We would like to thank Helene Dyserinck, clinical librarian, for her assistance with the bibliographical database searches and Phylis Spuls, MD, for her help at various stages of this work.

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

Corresponding author: M. D. Njoo, MD, Netherlands Institute for Pigmentary Disorders, IWO Building, Academic Medical Center, Meibergdreef 35, 1105 AZ, Amsterdam, the Netherlands (e-mail: snip-ww@knoware.nl).

REFERENCES