The Development of Practice Guidelines for the Treatment of Severe Plaque Form Psoriasis

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Objective: To develop and introduce evidence-based guidelines for the selection of 5 commonly used treatment modalities—UV-B, photochemotherapy, methotrexate, acitretin, and cyclosporine—for adult patients with severe plaque form psoriasis.

Patients and Setting: Patients, residents, and dermatologists from the Department of Dermatology of the Academic Medical Center of the University of Amsterdam, Amsterdam, the Netherlands, were involved in this process.

Design: The development process started with a questionnaire to evaluate how patients with severe psoriasis were treated. A systematic literature review was set up to provide evidence-based estimates of effectiveness, adverse effects, and dropout rates. In 2 meetings, the opinion leaders and intended users discussed the results of the questionnaire and systematic review as well as the clinical considerations in the treatment choices. Guidelines were then made regarding the sequence of selection of 5 modalities in the concept of rotational therapy. These guidelines were introduced. Their use was analyzed for 6 months.

Results: Before the guidelines, there was no uniform approach. In the systematic review, 665 studies concerning the treatments were found. Exclusion rates were high. No studies of methotrexate therapy could be included. Photochemotherapy showed the highest average proportion of patients with clearance (70% [6947/9925]) and good response (83% [8238/9925]), followed by UV-B (67.9% [620/913]) and cyclosporine (64% [1030/1609]) therapy. In the second internal meeting, the following sequence for the treatments was defined: UV-B, photochemotherapy, methotrexate, acitretin, and cyclosporine. In 78% (69/88) of patients treated after the introduction, the guidelines were followed to determine the treatment choice.

Conclusions: Guidelines for treating severe plaque form psoriasis can be successfully developed, introduced, and implemented and were considered to improve clinical care.

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CLINICAL GUIDELINES are becoming more prominent in medical practice. The increasing tendency to develop guidelines may be explained by the increase of clinical knowledge and literature, the rising complexity of clinical decisions, and the ongoing awareness of the medical community to improve the quality and efficiency of care. Practice guidelines, defined as systematically developed statements to assist the physician and patient in deciding about appropriate health care for specific clinical circumstances, may give physicians instructions for rational, effective, and cost-conscious decision making. To maximize the potential effect and use of practice guidelines, they should be consistent with the available scientific evidence and with clinical judgment, and should be adapted for local use.

In this study, we developed guidelines for the treatment of severe plaque form psoriasis, translated these guidelines into a flowchart for practical use, and evaluated their use in daily practice.

Psoriasis is a chronic skin disease that may require lifelong intermittent treatment. Recommendations have been published on how the available treatment modalities should be applied. Yet, there is no consensus about the choice of therapy for different clinical circumstances. Some introductory suggestions have been made by Kingston and Lowe in a clinical algorithm for selecting psoriasis therapy based on personal preference and to produce maximum improvement or clearance for the patient. In 1993, Weinstein and White introduced the concept of rotational therapy, an alternation of treatments based on considerations regarding effectiveness and adverse effects on a long-term ba-
METHODS

The project started with a questionnaire to evaluate how patients with severe psoriasis were treated before development of the guidelines. Then, a first internal meeting was organized to gain more insight into the current views concerning the modalities. A systematic literature review was performed. During a second internal meeting, the results of the evaluation of the initial status and the results of the systematic review were presented, and preliminary guidelines were discussed. Thereafter, revised guidelines were introduced, and the introduction was evaluated for 6 months.

RESULTS

EVALUATION OF INITIAL STATUS

The Department of Dermatology of the Academic Medical Center of the University of Amsterdam comprises 8 residents and 7 dermatologists; it is a dermatology department for the city of Amsterdam (30.2% [1308/4332]) and the regional area around Amsterdam (26.3% [1141/4332]) and acts as a referral center for the rest of the Netherlands (43.3% [1883/4332]). In 1994, 195 new patients with psoriasis were diagnosed, 4.5% of all diagnoses. In total, 178 patients with psoriasis were treated, 60% it was moderate. In 19 (22%) patients, 1 of these treatments was prescribed for the first time. Sixty-four (74%) patients had a history of psoriasis of more than 10 years. The most frequently prescribed treatment modality was UV-B (48% [42/87]), followed by PUVA (26% [23/87]), methotrexate (19% [16/87]), cyclosporine (5% [4/87]), and acitretin (2% [2/87]).

The questionnaire did not reveal a general uniform approach or consistent motives for specific treatment choices based on considerations of relative effectiveness and adverse effects.

FIRST INTERNAL MEETING

Ten staff members and residents (opinion leaders and intended users) of the department involved in scientific research in psoriasis and a clinical epidemiologist participated in the first meeting. The goals of this meeting were to discuss the results of the questionnaire, to gain more insight into the current views concerning the modalities and the way of handling severe psoriasis, to keep the clinicians informed about the development of the guidelines, and to create a basis for the introduction of the guidelines. Views about effectiveness and adverse effect profiles of the 5 main treatments of severe plaque form psoriasis were discussed. The participants were requested to give, for the 5 main treatments (after an induction of remission treatment for 8-12 weeks), their estimated opinions about the percentages of patients with a good response (>75% improvement compared with baseline), a moderate response (50%-75% improvement), and a poor response (<50% improvement) and the percentage of patients who reached total clearance (95%-100% improvement). These percentages are listed in Table 1. Apart from acitretin, all therapies were considered to be effective in their ability to induce a remission.

The estimated duration of remission after treatment cessation was 3 to 12 months for PUVA, 3 to 6 months for UV-B, 5 months for acitretin, 3 to 6 weeks for methotrexate, and 3 to 4 weeks for cyclosporine. In general, the duration of remission after photochemo-
therapy was considered to be considerably longer than after use of the oral modalities. Furthermore, it was established that factors that may pose a burden to the patient, as indicated in the results of the questionnaire, may strongly affect the positive or negative choice for a specific modality.

**SYSTEMATIC REVIEW**

By means of a systematic review of the literature, we compared the capacity to induce remission in adult patients with severe plaque form psoriasis and the adverse effect profiles of the 5 most commonly used modalities (whole-body UV-B and PUVA, oral methotrexate, retinoids [etretinate and acitretin], and cyclosporine). Results of this systematic review are reported elsewhere.

With the search, 665 studies were found reporting on 821 patient series. Randomized and nonrandomized patient series formed the units of this analysis. A total of 129 patient series could be included, reporting on 13,677 patients. Exclusion rates were high, mainly because of concomitant antipsoriatic therapy, outdated dosages, or inadequate documentation. No studies on methotrexate therapy could be included. Therapy with PUVA showed the highest average proportion of patients with clearance (70% [6947/9925]) and the highest proportion of patients with good response (83% [8238/9925]), followed by UV-B (67.9% [620/913]) and cyclosporine (64% [1030/1609]) therapy. Therapy with acitretin showed lower proportions of patients with good treatment results (56% [139/248]) (Table 1). Treatment with UV-B and PUVA is stressed to obtain complete remission results (56% [139/248]) (Table 1). Treatment with cyclosporine showed most adverse effects categorized in the miscellaneous group. Use of etretinate and cyclosporine was associated with the highest adverse effect–related dropout rates (9% and 13%, respectively), and therapy with UV-B and PUVA was associated with the lowest dropout rate (2%). With acitretin therapy, 4% of the dropouts were as a result of adverse effects.

**SECOND INTERNAL MEETING: DEVELOPMENT OF PRELIMINARY GUIDELINES**

The second meeting was attended by the same staff members, residents, and epidemiologist as the first meeting. During this meeting, participants commented on the comparison of current views on risk-benefit profiles of the different treatments as expressed during the first meeting and the results of the systematic review. The expected estimates in the first meeting of patients with good results and complete remission seemed to be too optimistic for most treatments compared with the results of the literature review (Table 1). Therapy with PUVA was more effective based on the literature compared with participants’ views.

Based on the results of the questionnaire, the first meeting, and the literature review, preliminary guidelines for the treatment of severe plaque form psoriasis were drafted by the investigators. The proposed sequence of treatments started with UV-B, followed by PUVA, methotrexate, acitretin, and cyclosporine. In this guideline, 1 course of photo(chemo)therapy was considered to be as effective as continuous oral therapy with methotrexate, acitretin, or cyclosporine, with a better risk–benefit ratio. Therefore, it was concluded that therapy should start with photo(chemo)therapy. Although PUVA therapy was the most investigated modality of all 5 investigated treatments, and seemed to be the most effective in inducing remission, it was considered as second choice because of the need for systemic psoralen therapy with potential adverse effects, such as nausea and skin burns, together with the need to wear sunglasses. With comparable effectiveness profiles, use of UV-B was considered to have fewer adverse effects, with less burden for the patient. Because use of small-spectrum UV-B lamps (Waldman lamps, Erbe) seems to be more effective than conventional UV-B therapy, with less induction of erythema, this modality was presented as the therapy of choice.

Superiority of methotrexate treatment to acitretin and cyclosporine treatment has never been established in comparative trials and could not be determined by methods of systematic review of the current literature. However, based on studies of methotrexate therapy in combination with topical therapies and studies of methotrexate therapy in outdated dosages, it was concluded that methotrexate therapy should be given priority over other oral treatments. The participants believed that the prominent position of methotrexate in the oral treatment of psoriasis has to be confirmed in prospective comparative research. Such a trial has just begun in our department.

Although therapy with acitretin seemed to be less effective than therapy with methotrexate and cyclosporine with most subjective, merely mucocutaneous adverse effects, it was not considered last choice. When given on a long-term basis, acitretin may cause fewer adverse effects than cyclosporine, especially with regard to hypertension, kidney function, and immunosuppression. Because a group of patients respond satisfactorily to ac-

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**Table 1. Effectiveness: Patients With Good Response and Clearance as Mentioned in the First Expert Meeting and the Results From the Systematic Literature Review**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>UV-B</th>
<th>PUVA</th>
<th>MTX</th>
<th>Acitretin</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with good response, %†‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First meeting</td>
<td>75</td>
<td>75</td>
<td>80‡</td>
<td>60-70</td>
<td>75‡</td>
</tr>
<tr>
<td>Systematic review§</td>
<td>68</td>
<td>83</td>
<td>…</td>
<td>56</td>
<td>64</td>
</tr>
<tr>
<td>Patients with clearance, %†</td>
<td>&gt;70</td>
<td>&gt;70</td>
<td>65</td>
<td>35</td>
<td>55-75</td>
</tr>
<tr>
<td>Systematic review§</td>
<td>44</td>
<td>70</td>
<td>…</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

*PUVA indicates psoralen–UV-A, MTX, methotrexate, and CsA, cyclosporine. †Good response is greater than 75% improvement compared with baseline; clearance is 95% to 100% improvement. ‡Dose dependent. §Sample size–weighted averages were calculated.
The preliminary flowchart was presented to all the physicians in the inpatient and outpatient clinic of our department and to the members of the Dermatology

INTRODUCTION OF THE GUIDELINES

The preliminary flowchart was presented to all the physicians in the inpatient and outpatient clinic of our department and to the members of the Dermatology
Society of Amsterdam. Taking into account all comments received, a prefinal version of the flowchart was designed.

All physicians in our department were requested to use the flowchart for each patient with severe psoriasis for whom 1 of the 5 treatments was considered. For 6 months, all flowcharts were collected. With a questionnaire, the physicians were requested to indicate whether the flowchart had been adhered to. If not, the reasons for not adhering to the flowchart were documented. All physicians were asked to inform us of their views about the usefulness of the flowchart in present-day practice. They were asked whether use of the flowchart gave support during the process of clinical decision making and whether it would fit in with current practice. Suggestions for improvement were documented, and the final version of the flowchart was drafted (Figure).14

Ten physicians used the flowchart and completed the second questionnaire. During the 6 months, 88 patients with psoriasis (35 females and 53 males; age range, 15-74 years; mean age, 48 years) received 1 of the 5 treatments. Seventeen patients (19%) received 1 of these treatments for the first time for psoriasis. In 37 (42%) patients, the psoriasis was diagnosed as severe, and in 51 (58%) it was moderate. Sixty-nine percent of patients had a history of psoriasis for more than 10 years. In 69 patients (78%), the flowchart was adhered to. The reasons for not adhering to the flowchart in 19 patients are listed in Table 2. One or more reasons for a single patient could be given for not following the flowchart. In most patients, the flowchart was not adhered to because PUVA therapy was chosen instead of UV-B therapy, mainly because of familiarity and good experience with PUVA and for practical reasons (our department has flat-beded equipment for PUVA but not for UV-B therapy).

Table 2. Analyses of the Introduction of the Flowchart: Reasons the Flowchart Was Not Followed in 19 Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Not able to tolerate (PUVA instead of UV-B)</th>
<th>Quick remission required (PUVA instead of UV-B)</th>
<th>Twice weekly instead of 3 times a week</th>
<th>Preference for other therapy, not specified</th>
<th>Good experience by patients with this therapy</th>
<th>Bad experience by patients with this therapy</th>
<th>Thick plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV-B</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PUVA</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MTX</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acitretin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CsA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* More than 1 reason was possible for a single patient. PUVA indicates psoralen–UV-A; MTX, methotrexate; and CsA, cyclosporine.

In this study, we developed guidelines for the treatment of severe plaque form psoriasis, translated these guidelines into a flowchart for practical use, and evaluated their use in daily practice. To maximize the potential effect and use of practice guidelines, they should be consistent with the available scientific evidence and with clinical judgment and should be adapted for local use. The validity and acceptability of guidelines can be improved by involving clinicians who will be using the guidelines in the development process, thus motivating clinicians to use these guidelines.15-18

We, therefore, combined a systematic review of the literature with 2 questionnaires among the physicians in our department, 2 meetings with clinicians in our department and an epidemiologist, and 2 presentations—1 in the department and 1 in the region—during which the guidelines were discussed and commented on. During these meetings, current views concerning the treatment choices could be discussed. This process was the basis for the development and subsequent implementation and evaluation of the clinical guidelines.

The systematic review of the literature, performed in the spirit of evidence-based medicine,10 focused on studies in which the induction of remission and the adverse effect profiles of the main monotherapeutic modalities given according to the current treatment strategies in severe plaque form psoriasis were analyzed. Because of the small number of good randomized controlled trials, the estimates obtained are almost certainly subject to selection bias. Therefore, the summary estimates of effectiveness should be compared and interpreted with caution. It is unfortunate that well-designed, randomized, comparative studies are lacking for the most often used therapies in this condition. For this reason, the guidelines could not be truly evidence based.

Expected duration of remission after discontinuation of therapy, dropout rates as a result of adverse effects (short and long term), and patient burden were factors considered to play an important role. These aspects were mainly based on the clinical experience of the experts. Therefore, the following sequence was adapted: UV-B, PUVA, methotrexate, acitretin, and cyclosporine.

Evaluation of the use of the flowchart showed that in 69 (78%) patients in the Department of Dermatology with severe plaque form psoriasis adhered to the flowchart. The treating physicians in the department con-
cluded that the flowchart helped them improve the daily care of these patients.

We conclude that guidelines for treating severe plaque form psoriasis can be successfully developed and introduced in a department of dermatology. However, the implementation of guidelines is an ongoing process, which has to be evaluated regularly to optimize their use. This, and whether the guidelines will reduce inappropriate practice and improve efficiency and clinical outcomes, and quantitative measures of patient preferences, as described by Zug et al., should be further investigated. Furthermore, objective data on treatment with methotrexate, the duration of remission, and the long-term risk-benefit ratios of the different modalities should be the subject of future research. Finally, to optimize their usability in everyday practice, these guidelines may be extended to other therapies or combinations.

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