The Course of Chronic Plaque-Type Psoriasis in Placebo Groups of Randomized Controlled Studies

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Objective: To determine the outcome in placebo-treated patients with plaque-type psoriasis.

Data Sources: Online search of MEDLINE and EMBASE until January 2001 and the Cochrane Library (2001, issue 1), supplemented by references, reviews, guidelines, and textbooks.

Study Selection: Randomized controlled induction of remission trials of patients with chronic plaque-type psoriasis with systemic treatments with a placebo group not treated with antipsoriatic medication. Identified studies were examined by 2 independent reviewers. Through MEDLINE, 290 studies could be identified. Twenty-seven placebo-controlled studies were included (488 patients).

Data Extraction: Two independent reviewers extracted data on first author, year of publication, design, comparison, placebo treatment, number of patients, treatment duration, type of psoriasis and baseline severity in the placebo group, mean relative change in outcome measures, and/or percentage of patients with worsening of psoriasis; no change; minimal, moderate, or good improvement; or complete clearance.

Data Synthesis: Owing to substantial heterogeneity and differences in the way outcomes were reported, no summary estimates could be obtained. The outcome of placebo treatment was poor in most studies. Some reported a mean relative change of 11% to 47%. The highest percentages of patients ended up in the worsening, no change, or minimal improvement categories. Also, complete clearance was possible. No explanation for the differences in outcome between placebo groups could be found. Description of placebo groups was often insufficient.

Conclusions: The effect of treatment in placebo groups varied across studies in an unpredictable way. To evaluate the variability, improvement of the standardization of study designs, entry criteria, and outcome measures is necessary in psoriasis trials.

Arch Dermatol. 2004;140:338-344

In measuring the specific effects of systemic therapeutic interventions, researchers keep in mind that the natural course of a disease as well as the placebo effects of an intervention can influence therapeutic outcome.1 The natural course of psoriasis varies considerably from patient to patient. Variation may include chronic persistence of the lesions for many years, temporary remissions with or without exacerbation, and persistent or only temporary regression.2 Endogenous and exogenous factors can initiate, aggravate, or provoke the clinical manifestations.

Placebo effects have been reported to influence treatment outcome in general in up to 35% of patients.3 These effects include patient expectations, the attitude and instructions given by the treating physician, the treatment mode, and even the color of drugs.4 The existence of variation in the natural course and the placebo effect are therefore good reasons for the inclusion of placebo control groups in...
clinical trials of new therapies and to blind patients and physicians from treatment allocation.

The influence of natural course and placebo on treatment outcome in psoriasis has been the subject of debate. In chronic plaque-type psoriasis, variations in clinical expression are considered to be limited. The need for placebo control groups is believed by many to be less urgent for this disease than it is for more variable diseases.5

Some data about the natural course of psoriasis and the percentage of patients with self-limiting psoriasis can be obtained from older epidemiologic studies.6,7 Farber and colleagues6,7 reported that nearly 40% of the patients experienced at least once in their life an episode of complete remission. These results were based on patient questionnaires, without specifying the duration and extent of the psoriasis or factors influencing these episodes. In that review, 29% of the patients claimed that their psoriasis went into remission without physician-directed therapy. Krueger wrote that after the onset, psoriasis tends to wax and wane, but spontaneous remission is rare. Greaves and Weinstein8 wrote that psoriasis plaques can regress spontaneously without scarring after weeks, months, or years.

The existence of a placebo effect itself has been challenged by the results of a study conducted by Hrobjartsson and Gotzsche.9 Based on a review of trials comparing placebo with no treatment, these authors concluded that there was little evidence that placebos have powerful clinical effects.

Performing a placebo-controlled trial may be more difficult than performing comparison studies with active treatments for the following reasons: participants must be convinced of the necessity of using a placebo treatment, withholding an accepted treatment may be harmful, there should be an accurate resemblance of the drug, and the blinding procedure must be thorough.

To determine the outcome in the placebo groups in randomized controlled trials, we performed a systematic review of randomized placebo-controlled trials of systemic drugs for chronic plaque-type psoriasis. For that purpose, we tried to identify all placebo-controlled trials and extracted data on treatment outcome in the placebo-treated control groups.

### METHODS

**IDENTIFICATION OF THE STUDIES**

An extensive systematic search was performed for randomized controlled trials of systemic psoriasis treatments. Articles were gathered with the assistance of a clinical librarian through an online search of the MEDLINE computer database from 1966 to January 2001 and EMBASE. As main search terms (including analogues and derivatives), psoriasis, placebos, and placebo effect were used to identify relevant clinical trials and comparative studies. The Cochrane Library (2001, issue 1) was also screened for controlled studies. Additionally, references of articles such as textbooks, reviews, editorials, letters to the editor, free/rapid communications, and guidelines concerning these systemic treatments were screened. Furthermore, international professionals with expertise in psoriasis were consulted and pharmaceutical industries were requested to provide us with additional references of published clinical studies. Finally, abstract books of symposia and congresses were screened to optimize the result of the search.

**INCLUSION AND EXCLUSION CRITERIA**

In our review, we included randomized placebo-controlled studies of systemic drugs concerning adult patients with chronic plaque-type psoriasis, in which induction of remission (maximally, 16 weeks of treatment) was studied in the active treatment groups vs placebo-controlled groups. Studies were excluded from our review when the study design did not allow an evaluation of the outcome of placebo treatment or when antipsoriatic comedication was used in the placebo group. We also excluded studies in which the data were insufficiently documented. Double publications were also excluded.

**STUDY SELECTION AND DATA EXTRACTION**

All articles on eligible placebo groups were independently evaluated by 2 reviewers. In case of disagreement on the criteria for inclusion and exclusion, a third investigator was consulted. The following data were extracted from each included report on a placebo group: year of publication, study design, placebo treatment (if available, substance, dose, frequency, color, and taste) and treatment in the comparison group, number of placebo-treated patients, type of psoriasis and initial severity, treatment duration, outcome measurements, and outcome (final severity).

**DATA ANALYSES**

The outcome in placebo groups was analyzed in 2 ways. In some studies, the outcome of treatment is described in terms of changes in a specific disease severity parameter at the end of the treatment compared with baseline. In those studies, the mean relative change was calculated for each placebo group.

Such changes are not always reported. In studies that did not report average changes, the effect of treatment was summarized in terms of the number of patients with either worsening of psoriasis, no change, or improvement. We used the following categories: patients with worsening of psoriasis, no change, minimal improvement (≤25%), moderate improvement (≤50%), good improvement (>50%), and clearance (complete remission).

Some studies in our review mentioned the outcome of placebo treatment in both ways. These studies were used in both analyses. To explore the reasons for heterogeneity, we examined the study results with respect to the initial severity of the psoriasis, differences in treatments, and study duration.

**RESULTS**

**RESULTS OF THE SEARCH**

Twenty-seven studies could be included in this analysis. All were performed in a double-blind manner except for 1.11 Excluded studies were double publications; studies in which it was not mentioned that the active treatment or placebo was allocated at random; studies concerning topical treatments in which a comedication was used that might have influenced the results in the placebo group; studies in which the design and outcome measures did not allow us to analyze the placebo group; and studies that were named a placebo-controlled study but in which the placebo group did not really exist. Of the
27 studies, 21 mentioned the mean relative change in outcome measure; 15 reported the percentages of patients with worsening of psoriasis, no change, minimal, moderate, or good improvement, or clearance; and 9 mentioned the outcome of treatment in both ways.

OUTCOME OF PLACEBO TREATMENT

The 27 included studies (9% of the identified studies through MEDLINE) reported on 488 placebo-treated patients, with the number of patients per placebo group ranging from 6 to 50. The baseline severity of psoriasis varied from moderate to severe, described in terms such as recalcitrant, chronic, disabling, or resistant to topical drugs. Treatment duration in these studies ranged from 10.3 days to 16 weeks. Most studies mentioned the kind of placebo treatment. Two studies had used identically appearing tablets or tablets with the vehicle only. Nine studies did not mention anything about the kind of treatment used as placebo.

Various outcome measures were used in the included trials, such as medium differences in total body surface area (BSA); erythema, scaling, and induration; mean percentage of PASI (Psoriasis Area and Severity Index) score reduction; decrease in average global score; investigator’s overall assessment; and investigator’s final judgment. The Figure shows the mean relative change in outcome of 21 included placebo groups, relative to sample size. The standard error could not be calculated for all studies. In 5 studies the average change from baseline in outcome parameters in the placebo groups was 0. In 13 studies there was worsening of psoriasis, no change, or minimal improvement (<10%). Three studies reported 11.0% to 18.1% improvement on average, 4 reported 22.0% to 28.7% improvement, 1 reported 36.4% improvement, and 1 reported 47% improvement (Figure). Jakubowicz and colleagues reported on 15 patients who had been treated for 4 weeks with placebo. Their median PASI score changed from 22.72 to 16.51. The European FK 506 Multicentre Psoriasis Study Group reported on 23 patients in whom a mean reduction of PASI score of 47% was observed at the end of week 9. Peeters et al analyzed 14 patients in whom the BSA changed from 2.4% at baseline to 4.8% after 16 weeks. There was no change in the infiltration score, but a worsening could be seen in the mean (SD) scaling score (scale from 0-8), which changed from 1.9 (1.1) to 2.3 (1.2) (a worsening of 21%).

The data in the second group of studies were difficult to summarize. In some cases, the percentages of patients with at least 25% improvement or less than 50% improvement were given. Others used wide ranges of improvement. Altmeyer and colleagues reported that 18% of the patients showed complete to slight improvement. Some studies only mentioned the percentages of patients with moderate to good response, without providing definitions of moderate and good. In all cases, the highest percentages of patients were seen in the minimal improvement, no improvement, or worsening categories. Nevertheless, some studies mentioned that a few patients achieved complete clearance while receiving placebo treatment (Table 1).

No explanation for differences in outcome in placebo groups could be detected in terms of the duration of the study (range, 15 days to 16 weeks), the initial severity of the psoriasis, or the treatments in the placebo groups (frequency, color, and taste). Table 2 gives more details about the studies.

In this systematic review of placebo-treated groups in controlled trials of systemic drugs for chronic plaque-type psoriasis, we found substantial and unpredictable variation in the outcome of treatment in placebo groups. The effects of placebo in 27 included studies varied from worsening or no change to sizable reductions in the severity of psoriasis measured.

In the first group of studies of 21 placebo groups in this review, the average change in outcome parameters ranged from 0% to 47%. In 13 of these studies, the mean change could be categorized as worsening, no change, or minimal improvement. In the second group of studies that mentioned the percentages of patients with or without improvement, the highest percentages of patients were found in the minimal improvement, no change, or worsening categories, although patients with moderate to good improvement and even clearance were also described. We were not able to identify factors that could consistently be associated with the size of the reduction.

As in any systematic review, consideration of the effect of publication bias is appropriate. The researchers’ willingness to submit a study report to a medical journal as well as the editor’s eagerness to publish it can both be influenced by the size of the treatment effect found. If the difference between active treatment and placebo treatment is small, this can be due to either a small effect of the active drug or a large improvement in the placebo-treated patients. If this holds, studies with large improvements in placebo-treated groups would be underreported.

There was a considerable variability in the design of the studies in this review and the way in which the outcome of treatment was documented. Some studies used
more objective measurement for outcome such as BSA and PASI. Others relied on a global impression by the treating physician or the patient. This variability hampers the use of meta-analysis as a tool to obtain more precise estimates of the effects of treatment. The more subjective ways of measuring outcome in psoriasis trials are not free from bias. If both the physician and the patient expect improvement, the effects of treatment will tend to be overestimated. Although this will not so much affect the comparison of active treatment vs placebo, provided treatment allocation was blinded, high expectations can lead to an overestimation of treatment effect in placebo groups. This cannot explain all of the positive results, since improvements of up to 47% were also reported with more objective outcome measures, such as the changes in PASI score.

In most of the studies in this review, the use of emollients was allowed. The fact that the severity of psoriasis remained unchanged in several placebo groups might indicate that a gradual worsening could have happened if emollients had not been used. It is possible that in the studies with no improvement or even worsening of the psoriasis, more patients with exacerbating psoriasis than patients with chronic stable psoriasis had been included. Other explanations for variations in the outcome of placebo treatment are possible. Whether the psoriasis at baseline was in a deteriorating, stable, or improving phase was an important factor in these analyses. Differences between the study centers can also influence treatment outcome.

We can conclude that the outcome in placebo groups in studies on chronic plaque-type psoriasis is variable and unpredictable. This may be due to variations in the natural course of psoriasis in the included placebo-treated patients and/or in the effect of treatment with placebo treatment itself. Chronic stable plaque-type psoriasis is maybe less stable than many of us believe it is, at least in the 16-week treatment period that was analyzed in this review. Open studies may therefore be of limited value. For example, in 2 studies on ranitidine in psoriasis, one (an open prospective study) suggested that 4 months of treatment with ranitidine can result in a mean improvement of 67% in two thirds of the patients,

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<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Treatment; Comparison Placebo Treatment</th>
<th>No. of Placebo-Treated Patients</th>
<th>Treatment Duration, wk</th>
<th>Type and Baseline Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogler and Olansky, 1970</td>
<td>RDB, crossover</td>
<td>Azathioprine: (500-mg tablets) 200 mg/kg per day; identical appearing tablets in adjustable doses</td>
<td>226</td>
<td>6</td>
<td>Generalized plaque-type; refractory to topical agents</td>
</tr>
<tr>
<td>Greaves and Dawber, 1970</td>
<td>RDB</td>
<td>Zinc sulphate: 220 mg; identical capsules containing lactose</td>
<td>10</td>
<td>6</td>
<td>Extent varied from scattered plaques to over half BSA</td>
</tr>
<tr>
<td>Willkens et al, 1984</td>
<td>RDB</td>
<td>Methotrexate: 2.5 mg every 12 h in 3 consecutive doses per week, increase to 5 mg every 12 h in 3 consecutive doses if necessary after 6 wk; identical regimens of placebo tablets</td>
<td>21</td>
<td>12</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ellis et al, 1991</td>
<td>RDB, 3 doses vs placebo</td>
<td>Cyclosporine: oral solution, 3, 5, or 7.5 mg/kg per day; vehicle: olive oil, peglicol 5 oleate, base and bland emollients</td>
<td>25</td>
<td>8</td>
<td>Severe, &gt;25% BSA; chronic, large plaques (n = 83) or disabling (n = 2); no satisfactory response to at least 1 other major treatment</td>
</tr>
<tr>
<td>Van Joost et al, 1988</td>
<td>RDB</td>
<td>Cyclosporine: solution 100 mg/mL (mean, 5.5 mg/kg per day in 2 equal daily doses); cyclosporine vehicle solution (olive oil and polyethyalted oleic glycerin) in 2 equal doses based on body weight</td>
<td>10</td>
<td>4</td>
<td>Severe; recalcitrant; mean PASI score, 30</td>
</tr>
<tr>
<td>Engst and Huber, 1989</td>
<td>RDB</td>
<td>Cyclosporine: 5 mg/kg per day; NS</td>
<td>6</td>
<td>4</td>
<td>Severe; resistant to local therapy; PASI score, minimal of 20 (range, 22.3-29)</td>
</tr>
<tr>
<td>Ellis et al, 1986</td>
<td>RDB</td>
<td>Cyclosporine: tablets of 100 mg/mL; vehicle solution (olive oil and polyethyalted oleic glycerin), identical in appearance and taste, single daily dose</td>
<td>10</td>
<td>4</td>
<td>Severe, &gt;20% BSA; chronic, large plaques; failed to improve satisfactorily on other antipsoriatic treatments</td>
</tr>
<tr>
<td>Meffert et al, 1992</td>
<td>RDB</td>
<td>Cyclosporine: 5 mg/kg per day; NS</td>
<td>18</td>
<td>12</td>
<td>Severe, therapy resistant</td>
</tr>
<tr>
<td>Meffert et al, 1997</td>
<td>RDB</td>
<td>Cyclosporine: 1.25 or 2.5 mg/kg per day; NS</td>
<td>43</td>
<td>10</td>
<td>Moderate to severe; mean ± SD PASI score, 15.6 ± 5.1 (range, 8-25); indication for systemic therapy</td>
</tr>
<tr>
<td>Gupta et al, 1990</td>
<td>RDB</td>
<td>Sulfasalazine: 500-mg tablets 3 times per day for 3 d (if tolerated, increase to 500 mg in 2 consecutive doses 3 times per day—if possible, increase to 500 mg in 2 consecutive doses 4 times per day); placebo tablets containing lactose and starch in similar appearance, same number of tablets</td>
<td>27</td>
<td>8</td>
<td>Moderate to severe; stable plaque type</td>
</tr>
<tr>
<td>Wilkamp et al, 1995</td>
<td>RDB, 3 doses vs placebo</td>
<td>SDZ IMM 125: 40, 100, 200 and 400 mg in 2 separate doses; emollients</td>
<td>15</td>
<td>4</td>
<td>Moderately severe; conventional therapy ineffective or inappropriate; mean ± SD BSA, 21% ± 22%; Global severity score, 6.0</td>
</tr>
<tr>
<td>Gottlieb et al, 2000</td>
<td>RDB 2 doses vs placebo</td>
<td>Anti-CD4: 225 mg per course or 750 mg per course, 3 identical infusions over a 5-d period; NS</td>
<td>9</td>
<td>2</td>
<td>Mean ± SD PASI score, 19.0 ± 4.51 (range, 15.4-29.1)</td>
</tr>
<tr>
<td>Gomez et al, 1979</td>
<td>RDB</td>
<td>Mycophenolic acid: capsules 2 daily doses at 400 mg, increasing if possible until 96 mg/kg per day; identical capsules with starch</td>
<td>12</td>
<td>12</td>
<td>Resistant to topical agent; several patients resistant to methotrexate, several patients with severe psoriasis; severity score 47.6; BSA, 24.8%</td>
</tr>
<tr>
<td>Savery et al, 1976</td>
<td>RDB, crossover</td>
<td>Levodopa: 500 mg in 2 daily doses; NS</td>
<td>20</td>
<td>12</td>
<td>Chronic (&gt;3 mo)</td>
</tr>
<tr>
<td>Siddiqui and Al-Khawajah, 1990</td>
<td>RDB</td>
<td>Vitamin D₃ 1 µg/d; 1 capsule per day; similar presentation in coded vials</td>
<td>21</td>
<td>12</td>
<td>Moderate to severe; PASI score &gt;15</td>
</tr>
<tr>
<td>Meffert et al, 1992</td>
<td>RDB, crossover</td>
<td>Trepidil: 600 mg/d; similar placebo</td>
<td>9</td>
<td>3</td>
<td>Chronic stationary PASI score 13.5</td>
</tr>
<tr>
<td>De Jong et al, 1991</td>
<td>RDB</td>
<td>MK886: 150 mg in 3 daily doses; matching placebo, 31 doses per patient</td>
<td>8</td>
<td>1.5</td>
<td>Chronic plaque</td>
</tr>
<tr>
<td>Basak and Chatterjee, 1993</td>
<td>RCT</td>
<td>Colchicine: 2 mg/d in 2 divided doses; multivitamin tablets in 2 daily doses</td>
<td>25</td>
<td>8</td>
<td>Chronic plaque; ESI score, 9</td>
</tr>
<tr>
<td>Feuerman and Nir, 1973</td>
<td>RDB, crossover</td>
<td>Allopurinol: 100 mg (3 tablets) in 2 daily doses; placebo tablets with identical appearance</td>
<td>7</td>
<td>8</td>
<td>From active lesions to generalized</td>
</tr>
<tr>
<td>Çoban et al, 1997</td>
<td>RDB</td>
<td>Ranitidine: 600 mg; NS</td>
<td>25</td>
<td>16</td>
<td>Chronic severe plaque-type; mean ± SD PASI score, 11.55 ± 1.17</td>
</tr>
</tbody>
</table>

(Continued)
the variability, improvement of the standardization of study design, entry criteria, and outcome measures is necessary in psoriasis trials.

Although it may be ethically more justified to perform a study comparing a new therapy with one of the available therapies in psoriasis (known as an active control clinical trial) than to perform a placebo-controlled trial,\textsuperscript{42,43} placebo-controlled trials are essential in chronic plaque-type psoriasis study designs. In phase 2 trials, such studies can reduce the number of patients that are necessary to participate. Ineffective or minimally effective treatments can be detected more easily if they are compared with a placebo treatment, and highly effective treatments can be identified as such with limited numbers of patients. To combine the investigations about the efficacy and the determination of the accurate dosages or dosage schemes, dose-finding studies may incorporate a placebo arm.

Accepted for publication October 28, 2003.

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REFERENCES


15. Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid: increasing dose after 4 wk in 3 daily doses, 2 mononethyl fumarate tablets or coated tablets with 284 mg of fumaric acid, 5 mg of magnesium salt of mononethylfumaric acid, and 3 mg of zinc salt of this acid; placebo tablets, packages identical.


Table 2. Characteristics of Included Placebo Controlled Trials (cont)

<table>
<thead>
<tr>
<th>Source Design</th>
<th>Treatment and Comparison Placebo Treatment</th>
<th>No. of Placebo-Treated Patients</th>
<th>Treatment Duration, wk</th>
<th>Type and Baseline Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nugteren-Huying et al,\textsuperscript{15} 1990</td>
<td>Fumaric acid: increasing dose after 4 wk in 3 daily doses, 2 mononethyl fumarate tablets or coated tablets with 284 mg of fumaric acid, 5 mg of magnesium salt of mononethylfumaric acid, and 3 mg of zinc salt of this acid; placebo tablets, packages identical</td>
<td>13</td>
<td>16</td>
<td>Stable; BSA &gt;10% (mean, 21.4% [range, 10%-80%])</td>
</tr>
<tr>
<td>Peeters et al,\textsuperscript{16} 1992</td>
<td>Fumaric acid: mononethyl fumarate; placebo tablets</td>
<td>14</td>
<td>16</td>
<td>Mean ± SD years of psoriasis, 12.8 ± 10.6; mean ± SD BSA, 3.3% ± 2.4%</td>
</tr>
<tr>
<td>Altmeyer et al,\textsuperscript{16} 1994</td>
<td>Fumaric acid: mononethyl fumarate; ascending doses; corresponding numbers of placebo tablets</td>
<td>50</td>
<td>16</td>
<td>Chronic plaque; exanthemic, guttate, pustular, or erythroderma; duration longer than 2 y. BSA at least 10%; PASI score, 24</td>
</tr>
<tr>
<td>The European FK 506 Multicentre Psoriasis Study Group,\textsuperscript{14} 1996</td>
<td>FK506 (tacrolimus): initial dose, 0.05 mg/kg per day, increasing to 0.1 or 0.15 mg/kg per day at the end of week 3 and 6, respectively; NS</td>
<td>23</td>
<td>9</td>
<td>Moderate to severe; recallcitant plaque; mean PASI score, 28</td>
</tr>
<tr>
<td>Jakubowicz et al,\textsuperscript{13} 1987</td>
<td>Etretinate: maximum 1 mg/kg per day; NS</td>
<td>20</td>
<td>4</td>
<td>Very severe; widespread; mean ± SD PASI score, 18.48 ± 7.05</td>
</tr>
<tr>
<td>Franco et al,\textsuperscript{29} 1997</td>
<td>Tamoxifen citrate: 40 mg in 2 daily doses; 2 daily doses of corresponding placebo</td>
<td>10</td>
<td>4</td>
<td>Plaque type; BSA maximum, 50%</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, total body surface area; ESI, erythema, scaling, and induration; NS, placebo treatment not specified; PASI, Psoriasis Area and Severity Index; RCT, randomized controlled trial; RDB, randomized double-blind.


The authors of this study use data from the placebo groups in clinical trials to study the natural history of psoriasis by following the outcome of placebo-treated patients. Most patients were in the minimal improvement, no improvement, or worsening categories, although there was considerable variability in the outcome of placebo groups.


Michael Bigby, MD