Objective: To compare characteristics of patients enrolled in a long-term multicenter cohort trial who had used biological therapies for treatment of psoriasis with those who had not used these agents.

Design: Retrospective analysis of users vs nonusers of biological therapies.

Setting: Database from the PUVA Follow-up Study, a multicenter, 30-year study of patients originally treated with psoralen UV-A (PUVA) for moderate to severe psoriasis.

Patients: A total of 521 patients who completed the last cycle of follow-up of the PUVA Follow-up Study.

Main Outcome Measures: Demographic data, severity data (physician global assessment), type of biological therapy used, patients’ opinions about their therapy, and their best treatment.

Results: Seventy-four of 521 patients (14%) used biological therapies: 65% etanercept (n=48), 22% infliximab (n=16), 11% efalizumab (n=8), and 8% alefacept (n=6). Users of biological therapies were younger, had more formal education, and were more likely to have had a greater extent of psoriasis at entry than the other cohort members. In 1998, those who used biological treatments were more likely than other cohort members to have been assessed as having severe psoriasis. In 2004, no significant difference was noted. Users of etanercept considered this agent to be as effective as methotrexate and more effective in clearing their skin and having fewer adverse effects than PUVA or UV-B. The proportion of patients originally enrolled in the 16 centers who had used biological agents varied greatly (0%-33%).

Conclusion: After short durations of therapy, patients’ opinions about biological agents tended to be positive.

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Since 2003, multiple biological therapies have been approved for treatment of moderate to severe psoriasis. Nearly all public data about those agents comes from company-sponsored studies, and most only assess response over a 3- to 6-month period of standardized doses. A recent report suggests that efficacy observed in clinical practice is less than that observed in clinical trials.

See also pages 912 and 950

The PUVA Study was originally organized as a prospective study of the short-term efficacy and safety of oral psoralens and UV-A (PUVA) for the treatment of moderate and severe psoriasis. Organized in the 1975-1976 period at 16 academic centers, the study recruited 1450 patients, 65% men (mean age at enrollment, 44 years). In 1977, the PUVA Follow-up Study was reorganized as a long-term safety and efficacy study and enrolled 1380 of the 1450 patients treated under the initial protocol of the PUVA Study. For 30 years, the PUVA Follow-up Study has documented health events, treatments, adverse effects, quality of life, and severity of the psoriasis. The study includes 22 cycles of patient interviews, 9 cycles of standardized, study-sponsored dermatologic examinations, and periodic eye examinations. Patients were observed regardless of their continued use of PUVA or continuing care for their psoriasis at the original center. Data collection for the cohort ended in the spring of 2005. This cohort experience provides an opportunity to study the use of biological agents among a diverse spectrum of patients ascertained at many academic practices independent of enrollment in company-sponsored clinical trials. In the last decade, use of PUVA in this cohort
has become infrequent. Cohort patients have used a wide range of therapies, including systemic agents. We determined the frequency of the use of biological agents, compared the characteristics of cohort patients who used and did not use biological agents, and quantified the patients’ opinions about these new therapies.

### METHODS

Detailed descriptions of the methods of the PUVA Follow-up Study and the composition of the cohort have been previously published. The current report includes all data collected through the 22nd and final cycle of the follow-up (FY-22) as of May 2005.

We compared the disease and demographic characteristics for patients who reported use of any biological treatments for psoriasis (biological group) with other cohort patients who had never used these therapies and were interviewed during FY-22. We also compared physicians’ global assessments (PGAs) of patients in 1998, when no biological treatments were available, with those made in 2005, about 2 years after the first licensing of these agents. The PGAs of severity were completed as part of the standardized dermatologic examination (rated clear, mild, moderate, or severe). In addition, during FY-22, we asked all participants to answer the following question: “Over the 28 years of the PUVA study, is there one treatment that has been most beneficial? If yes, specify which treatment.”

We asked only the biological group to rate the biological treatments and other therapies they had ever used on a Likert scale (1, best; 5, worst) with respect to the following questions: (1) “How well did your skin clear?” (2) “How long did your skin stay clear after stopping treatment?” (3) “How easy was the treatment to use?” and (4) “The side effects you may have experienced?” We calculated the percentage of patients who responded 1 or 2 (best or near best) to determine the percentage of patients with a positive opinion. Any evaluation including fewer than 13 patients was excluded from the analysis.

Statistical analysis was performed with SPSS, version 11 for Mac OS (SPSS Inc, Chicago, Illinois), using the t test, Fisher exact test, Mann-Whitney test, and Wilcoxon signed rank test, depending on the characteristics of variables.

### RESULTS

As of May 2005, 521 patients had completed FY-22. Of the original cohort of 1380 patients, 617 had died, 127 had resigned, and 115 were otherwise lost. There were 74 patients (14% of those interviewed in FY-22) reporting use of biological agents, of whom 4 had used multiple agents (3 had used both etanercept and infliximab, and 1 had used infliximab and efalizumab). Overall, 48 patients had used etanercept (Enbrel; Amgen, Thousand Oaks, California) (65% of all users of biological agents), 16 infliximab (Remicade; Centocor, Malvern, Pennsylvania) (22%), 8 efalizumab (Raptiva; Genentech, South San Francisco, California) (11%), and 6 alefacept (Amevive; Biogen-Idec, Cambridge, Massachusetts) (8%). Because some patients used multiple treatments, these percentage add to more than 100.

Members of the biological group were not different from other cohort members in sex distribution, but the biological group was younger and had more formal education (Table 1). There were no statistically significant differences between groups with regard to job, marital status, or general health. The percentage of patients reporting a diagnosis of psoriatic arthritis was also comparable (data not shown).

In 1998, the time of the most recent study-sponsored dermatologic examination prior to the availability of biological therapies, eventual users of biological agents were significantly more likely than nonusers to have moderate to severe PGAs (Table 2). When FY-22 PGA scores for biological users were compared with 1998 scores, a significant increase in the proportion of patients rated as having clear skin or mild psoriasis was observed (57.7% vs 33.3%) (P = .01). Among cohort members who had not used biological agents, the distribution of PGA scores in 1998 and FY-22 was remarkably similar (Table 3).

A higher proportion of patients in the biological agent group than other study participants interviewed during FY-22 previously used methotrexate, retinoids, and cyclosporine. Both total lifetime PUVA treatments and months of use of methotrexate were significantly higher in the biological agent group (Table 3).

In response to the question about their most beneficial treatment over the 28 years of the PUVA study (Table 4), 74% of patients who had not used biological agents and who indicated a single most beneficial therapy chose PUVA as their most beneficial treat-

### Table 1. Demographic and Clinical Characteristics of Users of Biological Therapies and Other Cohort Members

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Biological Agent Users (n=74)</th>
<th>Other Cohort Members (n=447)</th>
<th>All (N=521)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>65</td>
<td>61</td>
<td>61</td>
<td>.54</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>61±10</td>
<td>65±12</td>
<td>64±12</td>
<td>.004</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>17 (24)</td>
<td>150 (35)</td>
<td>167 (33)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>29 (41)</td>
<td>199 (46)</td>
<td>229 (46)</td>
<td></td>
</tr>
<tr>
<td>College or more</td>
<td>24 (34)</td>
<td>81 (19)</td>
<td>105 (21)</td>
<td></td>
</tr>
<tr>
<td>Total c</td>
<td>70 (100)</td>
<td>430 (100)</td>
<td>500 (100)</td>
<td></td>
</tr>
<tr>
<td>Age at psoriasis onset, mean±SD, y</td>
<td>18±9</td>
<td>20±10</td>
<td>19±10</td>
<td>.16</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not determined; NS, not significant.

a Unless otherwise indicated, data are reported as number (percentage) of patients.

b t Test for differences in means; χ² test for differences in proportions.

c May not sum to 100% due to rounding.
ments. Nearly half of all users of tumor necrosis factor α inhibitor gave comparable positive statements about these agents. In Table 5 we summarize the results of pairwise comparisons of opinions of etanercept users about effectiveness and safety of etanercept compared with PUVA, UV-B, and methotrexate in the categories of clearing the skin, durability of remission, ease of use, and tolerability so far experienced. Etanercept was considered more effective in clearing the skin than PUVA or UV-B, and in short-term use appeared to be better tolerated than the 3 drugs with which patients had long-term experience. The number of users of other biological agents was too small for meaningful comparisons. The proportion of patients at the 16 centers who reported using biological agents varied substantially, from 0% to 33% of those interviewed.

By mid 2005, biological therapies for psoriasis had been used by about 1 in 7 members of the PUVA cohort. Most of these patients (82%) used tumor necrosis factor α inhibitors, and most of these used etanercept. Although alefacept and efalizumab were the first to receive US Food and Drug Administration approval for treatment of psoriasis, they were much less frequently used than etanercept. Some of our patients might have been treated as participants in clinical trials, and others might have received the drug by off-label prescription. The limited experience of dermatologists with these drugs might have affected the opinions of users about biological treatments, and some of our cohort might have been treated at doses lower than those currently advocated for etanercept.

In the present study, users of biological agents were younger and more educated than the other cohort members. Younger and more educated persons might be more likely to be early adopters of new therapies. Among the reasons for this might be greater awareness of new drugs, less resistance to new therapies, or better insurance coverage. Also, physicians might be more hesitant to use systemic immunosuppressive agents in older patients, which is supported by our findings that methotrexate users were significantly younger than nonusers (P < .05; data not shown).

Users of biological treatments had used other systemic therapies for treatment of psoriasis more often and for a longer time than other cohort members, including PUVA, methotrexate, oral retinoids, and cyclosporin. For example, the proportion of biological agent users who had also used cyclosporin was more than 3 times that of other cohort members.
of other cohort patients. In addition to being early adopters, users of biological agents might prefer a more aggressive approach to treatment or have better access to new treatments.

Dermatologists in this study assessed a higher proportion of biological agent users as having moderate or severe disease on a standardized examination performed about 5 years before biological agents became available. This finding suggests those who eventually used biological agents had more severe or treatment-refractory disease than other cohort members.

Our data suggest that use of biological agents in our cohort had a modest but significant beneficial effect on the severity of psoriasis. Among users of biological agents, there was a significant improvement in the distribution of PGA scores from 1998 to 2004-2005 (ie, from the era before the introduction of biological agents to roughly 2 years after they were approved). Most of the improvement in PGA scores occurred in the moderate-severity group. The proportion with severe disease did not decrease significantly. At the time of the final assessment, nearly half of biological agent users still had moderate or severe disease.

Patients’ opinions about biological agents were generally positive. Nearly half of the patients who used alefacept, etanercept, or infliximab considered those treatments to be the best they had ever used. In 7 of 10 comparisons to the 3 other systemic therapies most often used by the cohort (PUVA, UV-B, and methotrexate), users of etanercept were significantly more likely to rate this therapy more favorably with respect to clearing, remission, ease of use, and adverse effects than the other treatments they had used. However, this finding should be interpreted with caution. Experience with etanercept spanned at most a few years compared with decades of use for some patients with methotrexate, UV-B, and PUVA. Experience with etanercept was so limited that fewer than 50% of patients answered the questions concerning remission. Given the limited time these agents have been available, patients’ indications of safety at this point are most likely statements about tolerability rather than long-term safety.11,12

Recent analyses have raised concern about the safety of some of these agents in moderate to long-term use for other indications.13 Higher doses of some biological agents are used for psoriasis than for other indications. Robust long-term safety data for biological agents used to treat patients with psoriasis are still lacking.14 Although the manufacturers of these products are committed to long-term safety studies, a recent review of the status of such

### Table 4. Treatments Evaluated by Biological Agent Users and Other Cohort Members as Most Beneficial in Treating Psoriasisa

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Biological Agent Users</th>
<th>Other Cohort Members</th>
<th>All Cohort Members</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ever Used</td>
<td>Thought It Best</td>
<td>Ever Used</td>
<td>Thought It Best</td>
</tr>
<tr>
<td>PUVA</td>
<td>70</td>
<td>14 (20)</td>
<td>352</td>
<td>259 (74)</td>
</tr>
<tr>
<td>UV-B</td>
<td>64</td>
<td>1 (2)</td>
<td>351</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>55</td>
<td>17 (31)</td>
<td>211</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Retinoid</td>
<td>22</td>
<td>0</td>
<td>57</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>11</td>
<td>0</td>
<td>19</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Alefacept</td>
<td>6</td>
<td>3 (50)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Etanercept</td>
<td>44</td>
<td>21 (48)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Infliximab</td>
<td>13</td>
<td>6 (46)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>7</td>
<td>2 (29)</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; ND, not determined; NS, not significant; PUVA, psoralen UV-A.

### Table 5. Pairwise Comparisons of Opinions of Etanercept Users About Effectiveness and Safety of Etanercept Compared With PUVA, UV-B, and Methotrexatea

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PUVA</th>
<th>UV-B</th>
<th>Methotrexate</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>S</td>
<td>E</td>
<td>I</td>
<td>P Value</td>
</tr>
<tr>
<td>Clearing</td>
<td>13</td>
<td>22</td>
<td>4</td>
<td>.03</td>
</tr>
<tr>
<td>Stay clear</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>.002</td>
</tr>
<tr>
<td>Easy to use</td>
<td>27</td>
<td>14</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>24</td>
<td>15</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: E, etanercept equal to other treatment; I, etanercept inferior to the other treatment; PUVA, psoralen UV-A; S, etanercept superior to the other treatment.

a Unless otherwise indicated, data are reported as number of patients who indicated that they had ever used the treatment and number (percentage) of patients who thought that treatment was the most beneficial for treating their psoriasis. Only patients who reported actual use of a therapy were asked to assess whether it was most beneficial. This was an optional section of the interview, and 99 patients chose not to complete this section.

b χ² Test for biological agent users vs other cohort members who reported use of that therapy.

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Author Contributions: Dr Stern had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jones-Caballero and Stern. Acquisition of data: Unaeze and Stern. Analysis and interpretation of data: Jones-Caballero, Unaeze, Peñas, and Stern. Drafting of the manuscript: Jones-Caballero and Peñas. Critical revision of the manuscript for important intellectual content: Jones-Caballero, Unaeze, and Stern. Statistical analysis: Peñas and Stern. Obtained funding: Stern. Administrative, technical, and material support: Stern. Study supervision: Unaeze and Stern.

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Additional Information: Dr Stern has been involved in the PUVA cohort study for more than 30 years and has relationships with manufacturers of phototherapy units. However, he has not had financial support from these manufacturers.

REFERENCES