A Meta-Analysis of the Placebo Rates of Remission and Response in Clinical Trials of Active Ulcerative Colitis

CHINYU SU,* JAMES D. LEWIS,*‡ BRITTANY GOLDBERG,* COLLEEN BRENSINGER,‡ and GARY R. LICHTENSTEIN*

*Division of Gastroenterology, Department of Medicine, Hospital of the University of Pennsylvania and University of Pennsylvania Presbyterian Medical Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; ‡Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania

See Sparrow MP et al on page 209 and Yacyshyn B et al on page 215 in the February 2007 issue of CGH.

Background & Aims: Knowledge of the placebo outcomes and understanding specific study features that influence these outcomes is important for designing future clinical trials evaluating therapy of ulcerative colitis (UC). The aims of this study were to estimate the placebo rates of remission and response in placebo-controlled, randomized clinical trials for active UC and to identify factors influencing these rates. Methods: We performed a systematic review and meta-analysis of placebo-controlled, randomized clinical trials evaluating therapies for active UC identified from MEDLINE from 1966 through 2005. Results: Forty studies met the inclusion criteria. The pooled estimates of the placebo rates of remission and response were 13% (95% confidence interval, 9%–18%; range, 0%–40%; median, 12%) and 28% (95% confidence interval, 23%–33%; range, 0%–67%; median, 30%), respectively, both with significant heterogeneity. Studies that used more stringent definitions of outcomes had lower placebo rates of remission and response. Study duration, number of study visits, disease duration, baseline composite and rectal bleeding scores of the disease activity index, and inclusion of endoscopic mucosal healing as the remission definition all were associated with the placebo remission rate. Conclusions: Rates of remission in the placebo arm of UC clinical trials ranges from 0% to 40%. The placebo remission rates are influenced by the trial length, number of study visits, use of stricter remission definitions, and design features that enroll patients with more active disease. These factors should be considered when designing future placebo-controlled clinical trials in patients with active UC.

Ulcerative colitis (UC) is an idiopathic inflammatory disorder of the colon that is characterized clinically by intermittent episodes of acute exacerbation alternating with quiescence. Patients with UC may experience spontaneous clinical improvement or even remission in the absence of any medical intervention. Thus, establishing efficacy of medical therapies for UC requires proof of superiority to placebo via placebo-controlled, randomized clinical trials (PC-RCTs). In this regard, understanding the outcomes of placebo-treated patients and factors influencing these outcomes in clinical trials of active UC is important for designing and interpreting results of open-label and randomized clinical trials. In addition, the disease course of placebo-treated patients in these studies may help clinicians in decision making by predicting the likelihood of achieving remission in patients without changing existing therapy.

We have shown previously that the study duration, number of study visits, and baseline scores of a standardized disease activity index all were predictors of attaining placebo remission in clinical trials of active Crohn’s disease (CD).1 A prior systematic review of placebo-controlled trials for active UC only included studies before 1995 and reported a placebo clinical remission rate of 9.1% and a placebo benefit rate of 26.7%.2 That analysis suggested that studies with 3 or more follow-up visits tend to have higher rates of improvement in patients treated with placebo than studies with fewer than 3 study visits. However, heterogeneity in the definitions of outcomes among clinical trials of UC makes interpretation of those results difficult. In this study, we performed a systematic review and meta-analysis of PC-RCTs for active UC through 2005 to estimate the rates of remission and response among patients receiving placebo and to identify factors that influence these rates, including different outcome definitions.

Materials and Methods

Study Identification and Inclusion

PC-RCTs for the treatment of active UC were identified from the MEDLINE electronic database. We searched this database from January 1966 through May 2005 using

Abbreviations used in this paper: CI, confidence interval; OR, odds ratio; PC-RCT, placebo-controlled, randomized-controlled trials; UCDAI, Ulcerative Colitis Disease Activity Index.

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the following medical subject headings: “ulcerative colitis” or “UC” or “colitis” or “inflammatory bowel disease,” AND “placebo” or “double-blind” or “clinical trial.” The search was limited to “human and English language” studies, and excluded “comment or editorial or letter or review.” The bibliographies of all the review articles were identified and all meta-analysis studies were searched manually to identify other potential studies.

Studies that fulfilled all the following criteria were included for analysis: (1) the study was a placebo-controlled trial, (2) all patients in the study had active disease at entry unless the study was designed specifically with an induction and a maintenance therapy arm separately, (3) the study reported the methodology of defining clinical response or remission, and (4) the proportion of patients achieving response or remission was available. For studies in which results were reported for multiple time points, the results of the primary end point defined in the studies were recorded. However, if the primary end point was not defined, the results from the final time point were recorded. Studies reported solely as abstracts were not included in the meta-analysis.

**Data Abstraction**

Data abstraction was conducted by 2 independent reviewers (C.S. and B.G.). The definition and the proportions of patients achieving the following outcomes were recorded: clinical remission, clinical response, endoscopic remission, and histologic remission. Unless otherwise specified, remission and response in the remainder of this article refer to clinical remission and clinical response, respectively. In addition, data on features of study design, patient characteristics, and study outcomes were abstracted. These included the publication year, the study location, the sample size, the inclusion criteria, the active treatment modalities and their route of administration, the duration of follow-up evaluation, the number and frequency of study visits, the duration and distribution of disease, prior and concurrent medical therapies, and, when applicable, the entry disease activity scores and the results on the individual components of the disease activity index. Outcomes were dichotomized into remission vs no remission, and response vs no response based on the outcome definition. In studies in which endoscopic data were reported but endoscopic remission was not defined, an endoscopic score of zero was chosen arbitrarily as the definition of remission.

**Statistical Analyses**

Pooled estimates of the placebo remission and response rates and stratum-specific rates for different categories of study designs were calculated using random-effects logistic regression analysis, after applying sample weights according to the placebo sample size, as implemented using STATA’s (STATA Corp, College Station, TX) xlogit command. Heterogeneity among studies was assessed with the Pearson \( \chi^2 \) test. In addition, the medians and ranges of the placebo rates were reported to complement interpretation of the pooled estimates. The effect of study design on the placebo remission rate was estimated using univariate logistic regression models with a random study effect. Analyses also were performed to limit studies to those using the same definition of outcomes. Multivariate models could not be performed because of the limited number of studies using the same definitions for remission or response and collinearity of several variables.

The most commonly used disease activity indices among all the trials in this study were the Mayo Score or the Sutherland Index (Appendix). Both instruments use a 12-point scale incorporating 4 components of disease activity: stool frequency, rectal bleeding, mucosal appearance on sigmoidoscopy, and physician’s global assessment. Although the precise definitions of these 2 metrics differ slightly, they are sufficiently similar for the purpose of this study and thus were considered one scale, Ulcerative Colitis Disease Activity Index (UCDAI), in our analyses.

The correlation between placebo rates of outcomes based on different definitions was assessed with the Spearman correlation coefficient. For all the analyses, a \( P \) value of less than .05 was considered statistically significant. All analyses were completed using STATA version 9.0 (STATA Corp) and SAS version 9.1 (SAS Institute, Cary, NC).

**Results**

**Description of the Studies**

Our search strategy identified 480 potentially relevant articles. Reviewing their titles and abstracts allowed us to exclude 377 articles that were not clinical trials of active UC. Of the 102 articles selected for full article review, 39 fulfilled the inclusion criteria.3–41 One study included 2 independent placebo-controlled trials for the same therapy administered via 2 different routes, and thus was considered 2 separate studies in all our analyses and in this report.6 Of the 63 excluded articles, 30 studies did not clearly define clinical response or remission and/or report placebo rates of clinical outcomes, and 21 studies did not contain a placebo arm. Other reasons for exclusion included lack of clinical data (6 studies), inclusion of both patients with active and inactive disease (5 studies), cross-over study design precluding abstraction of relevant data (2 studies), and duplication of results reported in another article (2 studies). Some studies fulfilled multiple exclusion criteria.

Among the 40 studies that fulfilled the inclusion criteria, 27 studies reported data on placebo remission rates (Table 1).3,9,12–16,18,20–23,26–31,33–41 Six studies3,9,21,26,27,34 defined remission as a UCDAI of 0, and 6 studies22,23,31,35,36,38 defined remission as a UCDAI of less than 3. Other remission definitions included a score of...
1 on the 6-point Physician’s Global Assessment (2 studies, 30, 37), and Rachmilewitz Index (42) of 4 or less (2 studies, 30, 37, including 1 study requiring a decrease of the Index by 2 points as an additional criterion) (Appendix). Thirty-four studies reported data on placebo response rates (Table 1). 3–8, 10–19, 21–25, 27–29, 31–34, 36, 37–41 The most commonly used definition of response was a decrease in the UCDAI score by 3 or more points in 5 studies. 21, 22, 27, 34, 36 Three studies defined response as a decrease in the UCDAI score by 2 or more points, and 2 studies defined response as a Physician’s Global Assessment score of 2 or less. Endoscopic and histologic placebo remission rates were reported in 14 and 8 studies, respectively. 12–14, 18, 21, 23, 26–30, 33–35, 41 All studies were conducted in an outpatient setting, except for 2 studies that reported the placebo response rates. 19, 32

**Placebo Remission Rates**

The pooled estimate of the placebo remission rate combining all 27 studies reporting remission data was 13% (95% confidence interval [CI], 9%–18%) (Table 1). There was statistically significant heterogeneity among studies (range, 0%–40%; test of heterogeneity, $P < .001$). The pooled estimate of the placebo remission rate remained the same with significant heterogeneity when the analysis excluded 1 study in which steroid refractoriness was among the inclusion criteria and all patients received concurrent steroid therapy during the study (12%; 95% CI, 8%–18%; $P$ for heterogeneity < .001). The pooled estimates of the placebo remission rate were 5% (95% CI, 2%–16%) and 17% (95% CI, 10%–28%) among 6 studies that defined remission as a UCDAI score of 0 and among 6 studies that defined remission as a UCDAI score of less than 3, respectively. With the exception of 2 outliers from a total of 12 studies using the UCDAI, the different criteria for remission perfectly discriminated studies with higher and lower placebo remission rates (Table 2). The placebo rates of endoscopic and histologic remission were estimated to be 18% and 8%, respectively.

Other study design factors that influence the placebo remission rates were identified using the univariate logis-

### Table 1. Placebo Rates of Remission and Response Based on Various Definitions of Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>% Pooled estimate (95% CI)</th>
<th>$P$ for heterogeneity</th>
<th>Range, %</th>
<th>Median, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All definitions</td>
<td>27</td>
<td>13 (9–18)</td>
<td>&lt;.001</td>
<td>0–40</td>
<td>12</td>
</tr>
<tr>
<td>UCDAI = 0</td>
<td>6</td>
<td>5 (2–16)</td>
<td>.025</td>
<td>0–21</td>
<td>5</td>
</tr>
<tr>
<td>UCDAI &lt; 3</td>
<td>6</td>
<td>17 (10–28)</td>
<td>.08</td>
<td>4–33</td>
<td>21</td>
</tr>
<tr>
<td>PGA = 1</td>
<td>2</td>
<td>13 (9–19)</td>
<td>.70</td>
<td>12–14</td>
<td>13</td>
</tr>
<tr>
<td>Rachmilewitz Index ≤ 4</td>
<td>2</td>
<td>39 (29–50)</td>
<td>.67</td>
<td>35–40</td>
<td>38</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>14</td>
<td>18 (13–24)</td>
<td>.001</td>
<td>0–37</td>
<td>19</td>
</tr>
<tr>
<td>Histologic</td>
<td>8</td>
<td>8 (3–19)</td>
<td>&lt;.001</td>
<td>0–44</td>
<td>6</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All definitions</td>
<td>34</td>
<td>28 (23–33)</td>
<td>&lt;.001</td>
<td>0–67</td>
<td>30</td>
</tr>
<tr>
<td>↓ UCDAI ≥ 3</td>
<td>5</td>
<td>30 (15–50)</td>
<td>.004</td>
<td>9–56</td>
<td>36</td>
</tr>
<tr>
<td>↓ UCDAI ≥ 2</td>
<td>3</td>
<td>52 (40–65)</td>
<td>.45</td>
<td>47–67</td>
<td>48</td>
</tr>
<tr>
<td>PGA ≤ 2</td>
<td>2</td>
<td>32 (25–39)</td>
<td>.26</td>
<td>27–36</td>
<td>32</td>
</tr>
</tbody>
</table>

PGA, Physician’s Global Assessment.

*One study also included a decrease of the index by 2 points for defining remission.

### Table 2. Placebo Remission Rates of the 12 Studies Defining Remission as a UCDAI of 0 or a UCDAI of Less Than 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo sample size</th>
<th>Study duration, wk</th>
<th>Entry UCDAI score</th>
<th>Definition of remission, UCDAI score</th>
<th>Placebo remission rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nikolaus et al34</td>
<td>7</td>
<td>N/A</td>
<td>8.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sandborn et al27</td>
<td>33</td>
<td>4</td>
<td>7.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vernia et al38</td>
<td>27</td>
<td>6</td>
<td>6.1</td>
<td>&lt;3</td>
<td>3.7</td>
</tr>
<tr>
<td>Schroeder et al35</td>
<td>38</td>
<td>6</td>
<td>7.7</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Sandborn et al21</td>
<td>20</td>
<td>4</td>
<td>8</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Williams et al26</td>
<td>13</td>
<td>6</td>
<td>7.4</td>
<td>0</td>
<td>7.7</td>
</tr>
<tr>
<td>Sandborn et al36</td>
<td>28</td>
<td>4</td>
<td>7.5</td>
<td>&lt;3</td>
<td>11</td>
</tr>
<tr>
<td>Steinhart et al23</td>
<td>19</td>
<td>6</td>
<td>7.4</td>
<td>&lt;3</td>
<td>16</td>
</tr>
<tr>
<td>Roberts et al26</td>
<td>44</td>
<td>8</td>
<td>6.8</td>
<td>0</td>
<td>20.5</td>
</tr>
<tr>
<td>Scheppach22</td>
<td>16</td>
<td>8</td>
<td>7.6</td>
<td>&lt;3</td>
<td>25</td>
</tr>
<tr>
<td>Probert35</td>
<td>20</td>
<td>6</td>
<td>8.5</td>
<td>&lt;3</td>
<td>30</td>
</tr>
<tr>
<td>Vernia31</td>
<td>15</td>
<td>6</td>
<td>6.1</td>
<td>&lt;3</td>
<td>33.3</td>
</tr>
</tbody>
</table>

N/A, not applicable.

*Variable.
Table 3. Predictors of the Placebo Remission Rates in PC-RCTs Among Studies Using the Same Outcome Definition

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Remission: UCDAI = 0 (6 studies)</th>
<th>Remission: UCDAI &lt; 3 (6 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year (per 1-year increment)</td>
<td>1.0 (0.8-1.2)</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>Study location (Europe vs North America)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size ratio of active treatment vs placebo group (&gt;1 vs ≤1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up visits (per 1-week increment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of follow-up visits (per 1-visit increment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of placebo patients with extensive colitis (per 10% increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of placebo patients with distal disease (per 10% increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of placebo patients with proctitis (per 10% increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean/median duration of disease in placebo patients (per 1-year increase)</td>
<td>1.4 (1.1-1.7)</td>
<td>1.0 (0.6-1.6)</td>
</tr>
<tr>
<td>Concurrent oral/intravenous steroid therapy during the study (yes vs no)</td>
<td>0.2 (0.03-1.10)</td>
<td>1.4 (0.4-5.2)</td>
</tr>
<tr>
<td>Concurrent immunomodulators during study (yes vs no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent oral mesalamines during study (yes vs no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent topical mesalamines during study (yes vs no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of drug administration (topical vs oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal inclusion criteria of UCDAI (DAI ≥ 6 vs DAI ≥ 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean/median entry UCDAI of placebo group (per 1-point increase)</td>
<td>1.0 (0.4-4.9)</td>
<td>1.4 (0.7-2.7)</td>
</tr>
<tr>
<td>Baseline score in rectal bleeding component of the UCDAI in placebo group (per 1-unit increase)</td>
<td>0.004 (&lt;.001-25)</td>
<td></td>
</tr>
<tr>
<td>Endoscopic mucosal healing used as criterion for remission (yes vs no)</td>
<td></td>
<td>1.1 (0.3-4.0)</td>
</tr>
</tbody>
</table>

aAll studies were conducted in North America, except 1 study that was conducted in both North America and Europe.
bOnly 1 study had 4 follow-up visits; all 5 other studies had 3 follow-up visits.
cAll except 1 study had 0% placebo patients with proctitis.
dAll 6 studies did not allow concurrent immunomodulators.
eOnly 1 study did not permit concurrent oral mesalamines.
fOnly 1 study allowed concurrent topical mesalamines.
gOnly 1 study had an oral administration route.
hOnly 1 study had DAI ≥ 3 as minimal inclusion criteria, and only 1 study had DAI ≥ 6 as minimal inclusion criteria.
iOnly 2 studies had data available for the baseline rectal bleeding score.
jAll 6 studies used endoscopic mucosal healing as a criterion for remission.

Tic regression analysis. The results of these analyses for studies with a remission definition of a UCDAI of 0 and a remission definition of a UCDAI of less than 3 are summarized in Table 3. In studies using the more stringent definition of remission (UCDAI = 0), factors positively associated with the placebo remission rate include the duration of follow-up evaluation, the number of follow-up visits, and the duration of disease in the placebo group. Factors associated negatively with the placebo remission rate include baseline UCDAI scores in the placebo patients for studies reporting UCDAI data and baseline scores for the rectal bleeding component of the UCDAI in the placebo patients. Permission for concurrent oral or intravenous steroid therapy and permission for concurrent oral mesalamine therapy during the study were also negative predictors of the placebo remission rates, although the association did not reach statistical significance. In the 6 studies defining remission as a UCDAI of less than 3, no predictors were associated positively with the placebo remission rate, whereas permission for concurrent topical mesalamine therapy during the study was associated negatively with the placebo remission rate. When all 27 studies were included, the only statistically significant predictors of placebo remission rate were the geographic location of the study and the inclusion of complete endoscopic mucosal healing, defined as having an endoscopic score of 0, as part of the definition for remission. Studies conducted in Europe were more likely to have a higher placebo remission rate than North American studies (odds ratio [OR], 2.9; 95% CI, 1.5-5.4; P = .001). The inclusion of endoscopic mucosal healing for defining remission was associated with a lower placebo remission rate (OR, 0.4; 95% CI, 0.2-7; P = .002).

Among studies using a UCDAI score of 0 as the definition of remission, we also calculated pooled estimates of the placebo remission rate within each stratum of those variables found to be statistically significant predictors of placebo remission rate in the univariate analysis. Studies that had 4 weeks or fewer of follow-up evaluation also had 2 or fewer follow-up visits. The pooled estimate of the placebo remission rate for these studies was 2% (95% CI, 0.3%-12%; test for heterogeneity, P = .20) (Table 4). The pooled estimate of the placebo
remission rate for studies with more than 4 weeks of follow-up evaluation and more than 2 follow-up visits was 11% (95% CI, 5%–24%; test for heterogeneity, $P = .10$). The test for heterogeneity was no longer statistically significant in many of the strata after stratifying across various categories of study features, suggesting that these study design factors at least partially account for the heterogeneity among studies. Stratification on entry UCDAI scores in the placebo group did not eliminate the heterogeneity among studies with baseline mean UCDAI scores of less than 8. Of the 4 studies with baseline UCDAI scores of less than 8, 3 had remission rates of less than 8%. In contrast, 1 study26 with a placebo remission rate of 20.5% had other features of study design associated with a high placebo remission rate, including a long follow-up duration (8 wk), many study visits (5 visits), and a long mean disease duration among the placebo group (11 y). Multivariate logistic analyses incorporating all of these factors may be useful in elucidating the relative contributions of each variable. However, the small number of studies limited our ability to conduct such models.

**Placebo Response Rates**

The pooled estimate of the placebo response rates in the 34 studies reporting data on this outcome was 28% (95% CI, 23%–33%) (Table 1). The placebo response rates ranged from 0% to 67% (test for heterogeneity, $P < .001$). Excluding the 2 inpatient studies for severe, steroid-refractory UC,19,32 the pooled estimate of the placebo response rates was 29% (95% CI, 24%–34%; test for heterogeneity, $P < .001$). The rate was similar among the 5 studies that defined response as a decrease in the UCDAI score by 3 points or more (30%; 95% CI, 15%–50%; test for heterogeneity $P = .004$).21,22,27,34,36 However, the pooled estimate of the placebo response rate was 52% (95% CI, 40%–65%) in the 3 studies that used a less stringent definition of a decrease in the UCDAI of 2 or more points,23,31,38 without significant heterogeneity ($P = .45$).

Univariate logistic regression analysis was used to examine the association between study features and the placebo response rates (Table 5). In studies reporting response data excluding 2 inpatient studies for severe, steroid-refractory UC, both the publication years and European studies were associated positively with the placebo response rate, whereas the baseline UCDAI score in the placebo group was associated negatively with the placebo response rate. When the analysis was limited to the 5 studies using a decrease in the UCDAI of 3 or more points as the definition of response, only the duration of disease in the placebo group was associated negatively with the placebo response rate (Table 5).

**Comparison of Placebo Remission and Response Rates**

There was a relatively strong correlation between placebo remission and placebo response rates among the 21 studies that reported both sets of data ($r = .57$, $P = .007$) (Table 6). As expected, the placebo response rate was always equal to or higher than the placebo remission rate (median difference, 25%; interquartile range, 11%–31.0%). The clinical remission rates were correlated strongly with the endoscopic remission rates ($r = .77$, $P = .001$), but not the histologic remission rates in the placebo group ($r = .36$, $P = .38$) (Table 6). Of the 6 studies that incorporated endoscopic remission into their definition for clinical remission,26–28,33–35 4 studies had identical placebo rates for clinical and endoscopic remission.26,27,34,35 Among the 8 studies that did not include endoscopic remission as part of the criteria for clinical remission,12–14,18,23,29,30,41 the placebo clinical remission rate was greater than the placebo endoscopic remission rate in 4 studies,13,14,23,30 whereas the reverse was true in 3 studies.18,29,41 In 1 study, the placebo clinical and endoscopic remission rates were identical.12

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**Table 4. Stratum-Specific Placebo Remission Rates According to Study Features in Studies Defining Remission as a UCDAI of 0**

<table>
<thead>
<tr>
<th>Stratum</th>
<th>No. in stratum</th>
<th>% Remission rate (95% CI)</th>
<th>$P$ for heterogeneity</th>
<th>Range, %</th>
<th>Median, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6</td>
<td>5 (2–16)</td>
<td>.03</td>
<td>0–21</td>
<td>5</td>
</tr>
<tr>
<td>Study duration, wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>2</td>
<td>2 (0.3–12)</td>
<td>.20</td>
<td>0–5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;4</td>
<td>3</td>
<td>11 (5–24)</td>
<td>.10</td>
<td>5–21</td>
<td>7.7</td>
</tr>
<tr>
<td>Number of study visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>2</td>
<td>2 (0.3–12)</td>
<td>.20</td>
<td>0–5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;2</td>
<td>3</td>
<td>11 (5–24)</td>
<td>.10</td>
<td>5–21</td>
<td>7.7</td>
</tr>
<tr>
<td>Duration of disease in the placebo group, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>3</td>
<td>3 (1–10)</td>
<td>.41</td>
<td>0–5</td>
<td>5</td>
</tr>
<tr>
<td>&gt;7</td>
<td>2</td>
<td>18 (9–31)</td>
<td>.19</td>
<td>0–21</td>
<td>10.3</td>
</tr>
<tr>
<td>Entry UCDAI in the placebo group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>4</td>
<td>6 (2–20)</td>
<td>.01</td>
<td>0–21</td>
<td>6.4</td>
</tr>
<tr>
<td>≥8</td>
<td>2</td>
<td>4 (0.5–22)</td>
<td>.55</td>
<td>0–5</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Table 5. Predictors of the Placebo Response Rates in PC-RCTs in All Studies Except 2 Inpatient Studies for Severe, Steroid-Refractory Disease and in Studies Defining Response as a Decrease in the UCDAI by at Least 3 Points

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>All definitions (32 studies)</th>
<th>Response: ↓ UCDAI ≥ 3 (5 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Publication year (per 1-year increment)</td>
<td>1.04 (1.002–1.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Study location (Europe vs North America)</td>
<td>2.0 (1.2–3.3)</td>
<td>.005</td>
</tr>
<tr>
<td>Sample size ratio of active treatment vs placebo group (&gt;1 vs ≤1)</td>
<td>.9 (.6–1.5)</td>
<td>.69</td>
</tr>
<tr>
<td>Duration of follow-up period (per 1-week increment)</td>
<td>1.0 (.97–1.1)</td>
<td>.31</td>
</tr>
<tr>
<td>Number of follow-up visits (per 1-visit increment)</td>
<td>1.0 (.8–1.2)</td>
<td>.98</td>
</tr>
<tr>
<td>% of placebo patients with extensive colitis (per 10% increase)</td>
<td>.9 (.8–1.1)</td>
<td>.26</td>
</tr>
<tr>
<td>% of placebo patients with distal disease (per 10% increase)</td>
<td>1.1 (.9–1.2)</td>
<td>.26</td>
</tr>
<tr>
<td>Mean/median duration of disease in placebo patients (per 1-year increase)</td>
<td>1.0 (.9–1.3)</td>
<td>.61</td>
</tr>
<tr>
<td>Concurrent oral/intravenous steroid therapy during the study (yes vs no)</td>
<td>.7 (.4–1.2)</td>
<td>.23</td>
</tr>
<tr>
<td>Concurrent immunomodulators during study (yes vs no)</td>
<td>.9 (.3–2.9)</td>
<td>.81</td>
</tr>
<tr>
<td>Concurrent oral mesalamines during study (yes vs no)</td>
<td>1.3 (.6–2.5)</td>
<td>.49</td>
</tr>
<tr>
<td>Concurrent topical mesalamines during study (yes vs no)</td>
<td>1.5 (.9–2.4)</td>
<td>.14</td>
</tr>
<tr>
<td>Route of drug administration (topical vs oral)</td>
<td>1.2 (.8–2.0)</td>
<td>.38</td>
</tr>
<tr>
<td>Minimal inclusion criteria of UCDAI (DAI ≥ 6 vs DAI ≥ 3)</td>
<td>.6 (.4–9.5)</td>
<td>.22</td>
</tr>
<tr>
<td>Mean/median entry UCDAI of placebo group (per 1-point increase)</td>
<td>.5 (.3–9.5)</td>
<td>.22</td>
</tr>
<tr>
<td>Baseline score in rectal bleeding component of the UCDAI in placebo group (per 1-unit increase)</td>
<td>.5 (.5–1.2)</td>
<td>.28</td>
</tr>
</tbody>
</table>

*aExcluding 2 studies that were conducted in an inpatient setting and had severe, steroid resistance as an inclusion criterion.
*bOnly 1 study was conducted entirely in Europe.
*cOnly 1 study had an 8-week follow-up period; the remaining studies had 4-week follow-up periods.
*dAll except 1 study had 0% placebo patients with proctitis.
*eAll 5 studies allowed concurrent steroids, and concurrent oral mesalamine use.
*fOnly 1 study allowed concurrent immunomodulators.
*gNo studies had an oral administration route.
*hOnly 1 study had a DAI ≥ 6 as minimal inclusion criterion.
*iOnly 2 studies had data available.
*jOnly 1 study had a baseline rectal bleeding score available.
{kOnly 1 study did not use endoscopic mucosal healing as a criterion for remission.

Table 6. Spearman Correlation Coefficients (r) Between Various Placebo Outcomes

<table>
<thead>
<tr>
<th>Placebo outcomes</th>
<th>Remission</th>
<th>Response</th>
<th>Endoscopic remission</th>
<th>Histologic remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Remission</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Response</td>
<td>.57</td>
<td>.007</td>
<td>.43</td>
<td>.19</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>.77</td>
<td>.001</td>
<td>.43</td>
<td>.19</td>
</tr>
<tr>
<td>Histologic remission</td>
<td>.36</td>
<td>.38</td>
<td>.13</td>
<td>.76</td>
</tr>
</tbody>
</table>

Discussion

Randomized, controlled trials are the most objective means of evaluating drug efficacy, and the inclusion of placebo arms is particularly important in diseases characterized by intermittent periods of acute exacerbation alternating with remission such as UC. In this regard, knowledge of the outcomes of patients receiving placebo therapy and factors influencing these outcomes is important for the design and conduct of clinical trials in UC. In this study, the pooled estimates of the placebo remission and response rates of all prior PC-RCTs for active UC were 13% and 28%, respectively. There was significant heterogeneity among these studies, with the placebo rates ranging from 0% to 40% (median, 12%) for remission, and from 0% to 67% (median, 30%) for response.

The overall remission and response rates estimated from our meta-analysis were comparable with previous estimates. However, use of these estimates without consideration of other study design features can be mis-
leading. In particular, we showed important differences in remission rates and response rates when different outcome definitions were used. The pooled estimate of placebo remission rates in studies defining remission as having a UCDAI score of 0 was 5%, lower than the 17% in studies defining remission as having a UCDAI score of less than 3. The highest placebo remission rates were reported in studies using a different instrument, Rachmilewitz Index of 4 or less, as the definition of remission (pooled estimate, 39%). Similarly, studies defining response as a 3-point or greater decrease in the UCDAI had lower placebo response rates than studies defining response as a 2-point or greater decrease in the UCDAI score. Thus, studies with the stricter definitions had lower placebo rates of outcomes. As such, some of the heterogeneity observed in our pooled analyses may be explained by the choice of outcome definitions. Therefore, we believe that our stratified analyses are more informative than the overall pooled analyses.

In this study, we also identified several features of study design that influenced the likelihood of achieving remission in patients receiving placebo therapy. In contrast to the findings of a previous meta-analysis, we observed that study duration was associated positively with the placebo remission rate in both sets of univariate analyses limited to studies using the same definition of remission. This variable is likely an important predictor of achieving placebo remission, and has been shown to be such in clinical trials of active CD. This positive correlation between study duration and the placebo remission rate is intuitively plausible because the probability of spontaneous remission increases over time. These PC-RCTs of active UC overall had a relatively short study duration. All of the studies had 8 weeks or fewer of follow-up evaluation, except for 3 studies that were 12 weeks in duration.

We also showed that studies with a greater number of study visits were more likely to have higher placebo remission rates (OR per 1-visit increment, 2.2; 95% CI, 1.3–3.7; P = .003). This observation was consistent with the results reported by Ilnyckyj et al, in which placebo-treated patients with 3 or more study visits had higher rates of clinical response but not clinical remission. This association between the number of study visits and placebo outcomes supports the notion that the act of participating in a clinical trial, regardless of the treatment received, may impart a certain effect on the outcomes. This finding has been observed previously in clinical trials of active CD and irritable bowel syndrome, suggesting that the influence of study visits on the placebo outcome is not disease-specific.

It generally is accepted that patients with more severe disease are less likely to experience spontaneous remission. We indeed showed that studies with higher disease activity scores at study entry for the placebo group had lower placebo remission rates (OR per 1-point increase, 1; 95% CI, 0.04–0.49; P = .002). Similarly, studies with higher baseline scores on the rectal bleeding component of the disease activity index had lower placebo remission rates (OR per 1-point increase, 0.04; 95% CI, <.001 to .25; P = .008). It is possible that rectal bleeding is a more objective measure of the disease activity than factors such as abdominal pain and bowel frequency. Thus, the rate of placebo remission may be minimized by selecting patients with more severe disease severity as determined by the composite score on the DAI and the individual score for rectal bleeding. Obviously, such an inclusion strategy must be balanced against the potential downside of insufficient enrollment caused by overly stringent inclusion criteria and a lack of generalizability.

It is of interest to note that when all studies were considered, those that included complete endoscopic mucosal healing as one criterion for the definition of remission had lower placebo remission rates. This is intuitively plausible because the inclusion of endoscopic mucosal healing most certainly translated to increased stringency of the definition of remission. Placebo-treated patients would be less likely to achieve spontaneous remission under these strict definitions.

In examining the placebo remission rates of PC-RCTs for active UC, we found significant heterogeneity among these studies. This observation could be the result of several variables, including the outcome definition, the study duration, and baseline disease activity, among other characteristics of the study population (eg, concomitant use of corticosteroids and aminosalicylates). The definition of outcome appears to be an important factor. With the exception of 2 studies, all the studies defining remission as a UCDAI score of 0 had lower placebo remission rates than studies using a UCDAI score of less than 3 to define remission (Table 2). Of the 2 outliers, 1 study had a high placebo remission rate of 20.5% despite using a UCDAI of 0 to define remission. This study also had many other features of study designs that may contribute to a high placebo remission rate, such as a long follow-up duration and many study visits. The other study had a low placebo remission rate of 3.7%, despite using a UCDAI score of less than 3 to define remission. Although no specific study feature could be identified that likely contributed to the low placebo remission rate in this study, it is of interest to note that this study evaluated a topical therapy and that all patients were on concurrent topical mesalamines. Certainly, chance also could contribute to the placebo remission rates in these 2 outlier studies.

Among studies using a single definition of outcome, there still may be other factors that influence the placebo remission rates. This may be more relevant among studies using less stringent definitions of remission because with more stringent definitions (eg, UCDAI = 0) the placebo remission rates generally are low. Intuitively, baseline disease severity would be expected to be an
imported predictor of placebo remission rates. Unfortunately, the mean baseline disease severity was very similar across studies, thereby preventing assessment of this potential association. Ultimately, the evaluation of placebo response rates within subgroups of individual trials or in a meta-analysis incorporating data from individual patients may help to determine the importance of other factors such as disease severity and study duration. Given the study heterogeneity, caution must be exercised when interpreting our pooled results. When there is significant heterogeneity, more meaningful information often is obtained from stratified analyses. As such, we believe that the results from our stratified analyses (Table 4) and the reported median values and ranges provide more meaningful information than the overall pooled estimates. However, the applicability of these pooled estimates from our stratified analyses across studies with similar study features still may be limited by the remaining heterogeneity.

We found fewer variables that significantly predicted the placebo outcomes as defined by response. This is most likely owing to the heterogeneity of the response definition. The concept that patients with more severe disease were less likely to spontaneously achieve favorable outcomes again was shown here. Studies with higher mean disease activity scores among the placebo patients at baseline were associated with lower placebo response rates (OR per 1-point increase, 0.4; 95% CI, 0.2–0.8; P = .006).

In our study, we showed a relatively strong correlation between placebo rates of remission and response. This is to be expected because all patients with a clinical remission also would have achieved a clinical response. Although there was substantial variability in the definitions for endoscopic and histologic remissions in these PC-RCTs, the placebo remission rates based on endoscopic and histologic criteria were relatively comparable with those based on clinical definitions. However, although the placebo rates of clinical remission correlated well with the placebo rates of endoscopic remission, the correlation between clinical and histologic remission was weak. There are several potential explanations for this. Certainly, greater differences among studies in the definitions for histologic remission than endoscopic remission may account for this finding. Endoscopic and histologic assessments of disease activity are both subject to interobserver variability. However, physicians may incorporate the endoscopic findings into their overall assessment of disease activity, whereas histologic findings are generally not available at the time of the clinical assessment. Finally, it is possible that histologic healing takes longer to occur than macroscopic mucosal healing. Because histologic features may predict future relapse, further research is needed to define which of these outcome measures is clinically the most important.

Some have argued that the use of invasive measures adds little to the assessment of disease activity in UC. If this is the case, there would be little justification for the use of sigmoidoscopy, which adds cost, is invasive, and may decrease patient recruitment. The counter argument suggests that it is important to document mucosal healing because this likely is associated with the subsequent relapse rate. That we observed poor correlation between clinical remission and histologic remission suggests that this issue requires further exploration. It is possible that better noninvasive clinical measures would correlate better with mucosal healing.

There were several limitations to our study. First, the aggregate nature of data collection in this type of meta-analysis may not completely reflect the true relationship between placebo outcomes and characteristics of individual patients. Thus, our results should be interpreted in the appropriate context. Similarly, we were not able to examine whether certain factors may be associated with the achievement of placebo remission based on clinical, endoscopic, and histologic definitions in the same patients. In addition, some additional variables that may influence the placebo outcomes, such as prior response to certain medical therapies and smoking status, were not available for analysis. Despite these limitations, our findings that the placebo outcome was influenced by the duration of follow-up evaluation and design features that included patients with more active disease are conceptually plausible and are important considerations when designing future trials.

We also cannot exclude the possibility that a publication bias exists in the reported medical literature. Studies showing a significant benefit to active treatment may be more likely to be published than those failing to show a benefit. Studies showing a positive outcome with treatment in turn may be more likely to have lower placebo rates of outcomes, whereas the reverse may be true for studies with a negative outcome. Presumably, small studies with low placebo response rates and greater drug effect measured by response were preferentially published over small studies with high placebo response rates and less drug effect based on response. It is not possible to know with certainty how this bias would affect our results, but presumably our estimate of the pooled placebo response rates may be slightly lower than that observed if all studies were published. The magnitude of this difference likely is small because the large studies contribute most of the weight to the pooled estimates. More importantly, the utility and clinical significance of using response as an outcome measure remains controversial for clinical trials of UC. Our results on the placebo outcomes based on remission likely provide the most meaningful data.

In summary, the placebo rates of remission and response in clinical trials of active UC are influenced by features of the study design. The variability in the placebo outcomes cannot be explained by any design feature alone, and no
single estimate is precise for all studies of active disease. The definition of outcome, duration of the trial, number of study visits, and severity of disease being treated are important factors related to outcomes among patients receiving placebo. As such, these factors will influence the statistical power of the study and should be considered in designing future placebo-controlled trials of active UC. Finally, the large variability in the selection of outcome measures and the poor correlation observed between clinical definitions of remission and the histologic findings highlights the important need for further research to define an optimal outcome measure for UC trials.

**Appendix**

**Mayo Score**

**Stool frequency**

0 = Normal number of stools for this patient
1 = 1–2 stools more than normal
2 = 3–4 stools more than normal
3 = 5 or more stools more than normal

**Rectal bleeding**

0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed

**Findings of flexible proctosigmoidoscopy**

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

**Physician’s global assessment**

0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

**Sutherland Index**

**Stool frequency**

0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = More than 4 stools/day more than normal

**Rectal bleeding**

0 = None
1 = Streaks of blood
2 = Obvious blood
3 = Mostly blood

**Mucosal appearance**

0 = Normal
1 = Mild friability
2 = Moderate friability
3 = Exudation, spontaneous bleeding

**Physician’s rating of disease activity**

0 = Normal
1 = Mild
2 = Moderate
3 = Severe

**Physician’s Global Assessment Scale**

1 = Complete relief of symptoms
2 = Marked improvement of symptoms
3 = Moderate improvement of symptoms
4 = Slight improvement of symptoms
5 = No change in symptoms
6 = Worsening of symptoms

**Rachmilewitz Index**

1. Number of stools weekly

0 = <18
1 = 18–35
2 = 36–60
3 = >60

2. Blood in stools (based on weekly average)

0 = None
2 = Little
4 = A lot

3. Investigator’s global assessment of symptomatic state

0 = Good
1 = Average
2 = Poor
3 = Very poor

4. Abdominal pain/cramps

0 = None
1 = Mild
2 = Moderate
3 = Severe

5. Temperature owing to colitis

0 = 37°C–38°C
3 = >38°C

6. Extraintestinal manifestations

3 = Iritis
3 = Erythema nodosum
3 = Arthritis

7. Laboratory findings

1 = Sedimentation rate >50 mm in first hour
2 = Sedimentation rate >100 mm in first hour
4 = Hemoglobin <100 g/L

**References**

1. Su C, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A meta-analysis of the placebo rates of remission and response in


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Address requests for reprints to: Chinyu Su, MD, Division of Gastroenterology, University of Pennsylvania School of Medicine, University of Pennsylvania Presbyterian Medical Center—Presbyterian, 218 Wright-Saunders Building, 39th and Market Streets, Philadelphia, Pennsylvania 19104. e-mail: chinyu.su@uphs.upenn.edu; fax: (215) 662-0950.