Are Cytotoxic Agents Beneficial in Idiopathic Membranous Nephropathy? A Meta-Analysis of the Controlled Trials1,2

Thomas F. Imperiale, Stanley Goldfarb, and Jeffrey S. Berns3

1,2 T.F. Imperiale, Department of Medicine, Case Western Reserve University at MetroHealth Medical Center, Cleveland, OH

3 S. Goldfarb, J.S. Berns, Department of Medicine, Division of Nephrology and Hypertension, The Graduate Hospital, Philadelphia, PA

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ABSTRACT

The use of cytotoxic agents for the treatment of idiopathic membranous nephropathy is controversial. Although several controlled trials have been published, both the comparison groups and the study findings have varied, resulting in clinical uncertainty. To explore this uncertainty, a meta-analysis of controlled trials of treatment with cyclophosphamide or chlorambucil was performed in patients with idiopathic membranous nephropathy and nephrotic-range proteinuria. Patients in the control groups received only symptomatic treatment or corticosteroids. Descriptive and quantitative data from each trial were abstracted independently. Outcomes included effects of treatment on renal function and proteinuria, with a complete remission (CR) or partial remission (PR) defined as the complete or partial resolution of proteinuria without deterioration of renal function. For patients having either any response (CR or PR) or only a CR, both the relative risk (RR) and the number needed to be treated were calculated. The five trials that satisfied criteria for inclusion in the analysis were clinically and statistically homogeneous. There were no placebo-controlled trials that met the criteria for inclusion. Among the 228 patients in these studies, the RR of achieving any response with cytotoxic agents was 2.3 (95% confidence interval, 1.7 to 3.2) and the RR for a CR was 4.6 (95% confidence interval, 2.2 to 9.3), with respective numbers needed to be treated of 2.9 and 4.7, meaning that between three and five patients would need to be treated with cytotoxic agents to achieve one response. Exclusion of the only nonrandomized trial had no significant effect on the results. Both chlorambucil and cyclophosphamide showed similar beneficial effects. This meta-analysis demonstrates that treatment with cytotoxic agents benefits patients with idiopathic nephrotic syndrome due to membranous nephropathy by bringing about the resolution of nephrotic-range proteinuria. The published results of these five trials do not allow a conclusion to be drawn regarding the effects of cytotoxic drug therapy on renal function, highlighting the need for studies of the long-term benefits and risks of therapies for idiopathic membranous nephropathy.

Key Words: Membranous nephropathy, immunosuppressive agents, meta-analysis, nephrotic syndrome

The best treatment of idiopathic membranous nephropathy remains an area of clinical controversy (1–5). Attempts to define appropriate therapeutic regimens for this relatively common glomerular disease have been complicated by its variable clinical course, with some patients following a benign course and others progressing to end-stage kidney failure (1.6–9), the absence of uniformly reliable prognostic indicators that might allow treatment of only those at greatest risk for a poor outcome (1.6–10), the inconsistent results of clinical trials, and concern about treatment-related toxicities.

Because of persistent uncertainty regarding the utility of corticosteroids alone in the treatment of nephrotic syndrome due to idiopathic membranous nephropathy (1–3,11–14), there has been increasing interest in the use of the cytotoxic agents cyclophosphamide and chlorambucil for the treatment of this disorder (1,5). However, despite many reports of the use of these drugs, their proper therapeutic role remains controversial. To further explore this issue and to determine which areas of clinical uncertainty remain and merit further study, we performed a meta-analysis of published controlled trials of these agents in the treatment of nephrotic syndrome due to idiopathic membranous nephropathy.
METHODS

Study Identification and Selection

We searched the medical literature using the MEDLINE database from 1976 to 1993 with the search headings of "membranous glomerulonephritis" (with the subheadings therapy, drug therapy), "English," and "human" and limited this set of studies to randomized controlled trials, clinical trials, and review articles. In addition, a manual search was done with the references from each retrieved report. The following criteria were used in selecting studies for inclusion: study design—clinical trial; target population—adults with idiopathic membranous nephropathy and nephrotic-range proteinuria; intervention—cytotoxic agents (cyclophosphamide, chlorambucil) with or without corticosteroids; and outcome—improvement in proteinuria and change in renal function. We excluded case reports and case series, abstracts, review articles, editorials, and studies containing duplicate data or reports of data later presented in full.

Appropriateness of Pooling the Trials

We reviewed the trials to determine their clinical comparability, looking for similarity in the baseline state of subjects in each trial and for similarity in treatment regimens. Treatment groups of subjects receiving only symptomatic therapy (i.e., low-sodium diet, diuretics, antihypertensives, as clinically indicated), corticosteroids, or placebo were considered to be control groups. The statistical validity of aggregating the trials was addressed with a statistical test of homogeneity (15), which assumes that differences in the results of individual trials are the result of chance alone (that is, that all trial results are homogeneous). This test provides a Q statistic with a χ² distribution and N – 1 degrees of freedom, where N is the number of trials. A P value greater than 0.05 suggests that the assumption of homogeneity is not violated and that standard statistical techniques can be applied.

Quantitative Analysis

Two of us (T.F. Imperiale, J.S. Berns) independently abstracted quantitative data regarding the number of subjects in treatment and control groups and of subjects with either complete or partial resolution of proteinuria, as defined in the individual studies. Nephrotic syndrome was defined in all studies by the occurrence of proteinuria ≥3.5 g/day. Assessment of changes in renal function was sought by determining the number of patients in each study group with an increase of serum creatinine by 50% or more above baseline levels or a requirement for dialysis or transplantation.

We began the analysis with all trials (the most sensitive or powerful result), then conducted secondary subgroup analyses of only randomized clinical trials, of trials with the individual cytotoxic agents, and of trials in which cytotoxic agents were compared with symptomatic treatment only (i.e., excluding trials in which control patients received corticosteroids). The effect of treatment was computed by the use of relative risks (RR) or risk ratios for the outcomes of complete remission and any (complete or partial) remission of proteinuria. Summary point estimations of effect were computed by the use of precision-based weighted averages of RR, with the weights derived from the reciprocals of the variances (16). Ninety-five percent confidence intervals (CI) were calculated by the Taylor series method (16). For those RR demonstrating a clear benefit (i.e., the RR and lower 95% CI were greater than one), the "number needed to be treated" (NNT) was calculated. The NNT represents a clinically meaningful measure of the consequences of treatment (17). For this analysis, the NNT represents the number of subjects who need to be treated with cytotoxic agents to result in complete or partial remission for one patient. It is calculated by taking the reciprocal of the absolute difference in event rates between the control and treatment groups. Ninety-five percent CI values for the NNT were calculated by inverting the CI values for the absolute difference by the method of Fleiss for a proportion (18). All analyses and calculations were performed on SuperCalc spreadsheets (SuperCalc, Version 5.0; Computer Associates International Inc., San Jose, CA).

RESULTS

Twenty-eight references were obtained from MEDLINE; 23 reports were excluded: cytotoxic agents were not used in 6 reports; 13 reports were case series, editorials, or correspondence; 2 studies were follow-up reports of previously published data; and 2 reports contained insufficient data on proteinuria. Abstracts were also excluded. Manual searching produced one additional report that was excluded because it combined patients with both non-nephrotic and nephrotic-range proteinuria. Of 10 published clinical trials, 5 trials were excluded: 2 were excluded because they were long-term follow-up reports of previously published data (19,20); 1 contained insufficient data on proteinuria (21); one contained insufficient data on proteinuria and included only subjects with a long latency period before treatment, all of whom had failed treatment with corticosteroids (22); and one combined both non-nephrotic and nephrotic patients (23).

Of the five trials (24–28) included in the analysis and described in Table 1, four were randomized. One study was a nonrandomized controlled trial (25). None was placebo controlled. Two studies were from a single center (27,28); there were not any overlapping patients between the two studies (C. Ponticelli, personal communication, 1994). In three trials, patients in the control group received symptomatic treatment only without placebo (24,26,27), whereas in the other two trials, the control group received corticosteroids (25,28). In one study, patients also received warfarin and dipyradimole for 2 yr (25). In four studies, none of the patients had received prior cytotoxic drug treatment, whereas in one study (26), the use of immunosuppressives within the prior 12 months was an exclusion criterion. In two studies (24,25), some patients were receiving corticosteroids at the time treatment with cyclophosphamide was begun. The numbers of subjects in the trials ranged from 22 to 92 and totaled 228. The interval between randomization and mean follow-up varied from 1 yr to over 4 yr. Complete remission of proteinuria was defined in the studies as a reduction in proteinuria to ≤0.2 g/day (24,26–28) or to ≤0.5 g/day (25). Partial remission was defined as a reduction in proteinuria to between 0.2 and 2 g/day (24,27,28), to ≤3 g/day (28), or to between 0.6 and 3.4 g/day with a 50% reduction in proteinuria (25). The test of homogeneity had a P value >0.05 for each
TABLE 1. Descriptive characteristics of included trials

<table>
<thead>
<tr>
<th>Author, Yr. (Ref. No.)</th>
<th>No. of Subjects</th>
<th>Treatment Regimen</th>
<th>Control Regimen</th>
<th>Mean Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donadio et al., 1974 (24)</td>
<td>22</td>
<td>Cyclophosphamide, 1.5 to 2.5 mg/kg per day for 1 yr</td>
<td>Symptomatic treatment</td>
<td>1 yr</td>
</tr>
<tr>
<td>Ponticelli et al., 1984 (27)</td>
<td>62</td>
<td>Chlorambucil, 0.2 mg/kg per day alternating with MP for 6 months</td>
<td>Symptomatic treatment</td>
<td>31 ± 18 months, Rx 37 ± 22 months, Cont</td>
</tr>
<tr>
<td>West et al., 1987 (25)</td>
<td>26</td>
<td>Cyclophosphamide, ≤2.0 mg/kg per day for 23 ± 4 months (range 8 to 34 months) ± prednisone</td>
<td>Prednisone for 20 ± 4 months (range 5 to 78 mo.) in 15 of 17 patients</td>
<td>33 ± 5 months, Rx 36 ± 4 months, Cont</td>
</tr>
<tr>
<td>Murphy et al., 1992 (26)</td>
<td>26</td>
<td>Cyclophosphamide, ≤1.5 mg/kg per day for 6 months</td>
<td>Symptomatic treatment</td>
<td>2 yr</td>
</tr>
<tr>
<td>Ponticelli et al., 1992 (28)</td>
<td>92</td>
<td>Chlorambucil, 0.2 mg/kg per day alternating with MP for 6 months</td>
<td>MP for 6 months</td>
<td>54 ± 16 months, Rx 54 ± 17 months, Cont</td>
</tr>
</tbody>
</table>

a MP, methylprednisolone; Rx, treated group; Cont, control group.
b Also received warfarin and dipyridamole for 2 yr.

analysis, supporting the assumption of homogeneity of the evaluated studies and indicating that combining the studies was appropriate from a statistical standpoint.

QUANTITATIVE ASSESSMENT

Results for the outcome of complete resolution of proteinuria are shown in Table 2. Among all trials, cytotoxic agents increased the chance of achieving a complete remission of proteinuria by a factor of 4.6 (95% CI, 2.2 to 9.3). The NNT, i.e., the number of subjects with idiopathic membranous nephropathy and nephrotic-range proteinuria who would need to be treated with cytotoxic agents to achieve one complete remission was 4.7 (95% CI, 3.2 to 8.4). Exclusion of the only nonrandomized trial from the analysis had little effect on the main results (Table 2). Subgroup analyses for the specific cytotoxic agents were consistent with the main results, as was analysis of the four studies comparing cytotoxic agents with a non-steroid-treated control group. All subgroup analyses (Table 2) demonstrated clinically impressive increases in the likelihood of achieving complete remission of nephrotic-range proteinuria, with small NNT. Analysis excluding the study of Murphy et al. (26), which included treatment with warfarin and dipyridamole, did not significantly alter the overall results (data not shown).

Results for the outcome of any response (i.e., complete or partial remission) are shown in Table 3. Among all trials, the RR of achieving any response with cytotoxic agents was 2.3 (95% CI, 1.7 to 3.2), with an NNT of 2.9 (95% CI, 2.1 to 4.4). The four secondary analyses shown in Table 3 of randomized trials only, of the individual cytotoxic agents, and of studies without corticosteroid-treated control patients demonstrated consistent results, again showing impressive increases in the likelihood of achieving any response.

TABLE 2. Outcome: complete resolution

<table>
<thead>
<tr>
<th>Trial Subgroup</th>
<th>Trial N</th>
<th>Total No. of Subjects</th>
<th>P (Rx)</th>
<th>P (Control)</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Trials</td>
<td>5</td>
<td>228</td>
<td>0.29</td>
<td>0.07</td>
<td>4.6 (2.2–9.3)</td>
<td>4.7 (3.2–8.4)</td>
</tr>
<tr>
<td>All RCT</td>
<td>4</td>
<td>202</td>
<td>0.27</td>
<td>0.08</td>
<td>3.4 (1.6–7.1)</td>
<td>5.2 (3.4–11.0)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>2</td>
<td>154</td>
<td>0.30</td>
<td>0.08</td>
<td>4.0 (1.7–8.2)</td>
<td>4.4 (2.9–9.5)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3</td>
<td>74</td>
<td>0.25</td>
<td>0.06</td>
<td>4.5 (1.2–17)</td>
<td>5.3 (2.8–35)</td>
</tr>
<tr>
<td>Cytotoxics versus Symptomatic Treatment Only</td>
<td>3</td>
<td>110</td>
<td>0.29</td>
<td>0.07</td>
<td>3.0 (1.5–11.0)</td>
<td>4.7 (2.9–14)</td>
</tr>
</tbody>
</table>

a RCT, randomized controlled trial; P (Rx), proportion of patients with complete response in treatment group; P (Control), proportion of patients with complete response in control group.
The role of glucocorticoid and cytotoxic drugs in the treatment of idiopathic membranous nephropathy with nephrotic syndrome remains uncertain. The authors of a recent cohort study of 100 untreated patients suggested that symptomatic treatment only, rather than glucocorticoids and immunosuppressive drugs, was indicated for most patients with membranous nephropathy (9). An accompanying editorial largely supported this position (4). However, only 37% of the patients in that study had nephrotic syndrome (9); the fact that the initial level of proteinuria in that study was not predictive of subsequent renal function may reflect the multiple categories of proteinuria the authors analyzed, with the resulting lack of power to detect clinically important differences. Attempts to favorably alter the prognosis of idiopathic membranous nephropathy focused initially on the use of glucocorticoids (1,11–14,29,30). Although a course of daily or alternate-day glucocorticoid therapy still appears to be common, most prospective controlled studies have failed to demonstrate a significant benefit from this treatment (1,2,12–14). Aside from glucocorticoids, cyclophosphamide and chlorambucil have been evaluated most extensively in both controlled and uncontrolled observations (19,20,22–28,30–33). The role of these cytotoxic agents remains controversial, however, both because of concerns of toxicity and because of uncertainty regarding the efficacy of these drugs.

We conducted a meta-analysis of prospective studies in which cytotoxic agents were compared with glucocorticoids, placebo, or symptomatic treatment. Studies were evaluated to determine the response to therapy as assessed in two ways: by the efficacy in achieving a complete or partial remission of proteinuria and by the influence on the risk of developing progressive renal insufficiency. Although the first type of response may be observed in relatively short-term studies, the latter can only be evaluated confidently with studies that are properly designed to assess long-term changes in kidney function. Although some previous studies have found a benefit of cytotoxic drug therapy on renal function, others have not, although treatment protocols and patient populations have been variable and none of the studies included enough patients to provide adequate statistical power (5,34). A recent decision analysis supported a role for cytotoxic drug therapy (methylprednisolone combined with chlorambucil) in patients with idiopathic membranous nephropathy (35).

We were unable to address the question of the effects of cytotoxic drug therapy on long-term renal function on the basis of the available literature. Aside from the two studies of Ponticelli et al. (27,28), the number of patients evaluated in the other two studies for which individual patient renal function outcome data were provided (24,26) was too small to apply meta-analysis. Additionally, several of these studies had "zero" events (doubling of serum creatinine or need for dialysis or transplantation), making estimates of RR and CI statistically invalid and unreliable. The only large-scale, controlled, prospective studies that provide information on the long-term effects of cytotoxic drug therapy on renal function outcomes are those of Ponticelli et al. included in our analysis (27,28) and a follow-up report (20). In their first study

### TABLE 3. Outcome: any response (complete or partial resolution) \(^{a}\)

<table>
<thead>
<tr>
<th>Trial Subgroup</th>
<th>Trial N</th>
<th>Total No. of subjects</th>
<th>P (Rx)</th>
<th>P (Control)</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Trials</td>
<td>5</td>
<td>228</td>
<td>0.64</td>
<td>0.29</td>
<td>2.3 (1.7–3.2)</td>
<td>2.9 (2.1–4.4)</td>
</tr>
<tr>
<td>All RCT</td>
<td>4</td>
<td>202</td>
<td>0.62</td>
<td>0.28</td>
<td>2.2 (1.6–3.2)</td>
<td>3.0 (2.2–4.9)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>2</td>
<td>154</td>
<td>0.67</td>
<td>0.31</td>
<td>2.0 (1.4–2.9)</td>
<td>3.3 (2.2–6.4)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3</td>
<td>74</td>
<td>0.69</td>
<td>0.35</td>
<td>2.2 (1.4–2.9)</td>
<td>3.2 (1.8–7.5)</td>
</tr>
<tr>
<td>Cytotoxic versus Symptomatic Treatment Only</td>
<td>3</td>
<td>110</td>
<td>0.66</td>
<td>0.31</td>
<td>2.2 (1.4–3.3)</td>
<td>2.9 (1.9–5.9)</td>
</tr>
</tbody>
</table>

\(^{a}\) RCT, randomized controlled trial; P (Rx), proportion of patients with any response in treatment group; P (Control), proportion of patients with any response in control group.
(27), after a mean follow-up of about 31 months in the treatment group (steroids plus chlorambucil), none of 32 patients experienced an increase in the serum creatinine, compared with 8 of 32 control patients (symptomatic treatment only) after a mean follow-up of 37 months. With longer follow-up (mean duration of follow-up, 5 yr in both groups), 19 of 39 control patients, but only 4 of 42 treated patients, had worsening renal function, with 4 patients in the control group but only 1 in the treated group requiring dialysis (20). In a separate study comparing methylprednisolone alone with methylprednisolone plus chlorambucil (28), 6 (13%) of 45 patients who received chlorambucil had worsening of renal function, compared with 10 (21%) of 47 patients who received steroids alone.

In other glomerular diseases, the presence of nephrotic-range proteinuria may be associated with poorer renal survival compared with that in patients with lesser degrees of proteinuria or remission of the nephrotic syndrome (36). Although most reports have found nephrotic syndrome to be a risk factor for the progression of renal insufficiency in patients with idiopathic membranous nephropathy (6-8,10,36-38), whether treatment-related remissions will be predictive of the long-term preservation of renal function remains conjectural (38). Other potential benefits of a reduction in proteinuria, such as increased serum albumin, improvement in nutrition, and reduced risk of infection, atherosclerotic disease, and renal vein thrombosis (39,40) may, however, be worthwhile goals of drug therapy, even in the absence of a well-documented beneficial effect on long-term renal function.

Two other meta-analyses of treatment of idiopathic membranous have appeared in preliminary reports (41,42). One combined eight randomized controlled trials of either glucocorticoid or cytotoxic immunosuppressive agents compared with placebo or symptomatic treatment and concluded that drug therapy was associated with less impairment of renal function and a greater reduction in proteinuria (41). An analysis of only studies of cytotoxic drug therapy was not reported. Hogan et al. pooled the results of 35 studies, apparently combining retrospective and prospective studies, both controlled and uncontrolled (43). They reported that treatment with alkylating agents was associated with a better preservation of renal function compared with no treatment or corticosteroids (which was not better than no treatment) and a greater likelihood of remission of proteinuria during the first or second year after therapy compared with no treatment, although the latter benefit was not sustained at 3 yr (42).

Two issues important to the validity of meta-analysis are the inclusion of all relevant reports and the "combinability" of studies. Regarding the first issue, our analysis was limited to clinical trials of adults with idiopathic membranous nephropathy and nephrotic syndrome, most of whom had received only supportive therapy before the trial. One nonrandomized trial was included in which cyclophosphamide was compared with prednisone. Analyses with and without this trial did not show clinically important or statistically significant differences in the results. Likewise, analysis without the study of Murphy et al. (26), which included extended treatment with warfarin and dipyridamole, did not alter the results of our analysis. Abstracts were excluded because of limitations in reporting. The issue of combinability is more difficult to address. Although statistical homogeneity existed for all trial subgroups, the power to detect heterogeneity was limited by the small number of trials. Clinical homogeneity of the trial population is more a judgment based on study inclusion and exclusion criteria and the clinical characteristics of the different study groups. The preliminary reports of Couchoud et al. (41) and Hogan et al. (42) discussed above were more inclusive of studies with varying designs, patient populations, and treatment protocols than was the meta-analysis presented here. The inclusion and exclusion criteria we used clearly resulted in an analysis of fewer studies and patients, but which is more rigorous methodologically, resulting in clinical conclusions that therefore may be more valid and reliable.

Only large-scale, long-term studies will allow us to address the question of a beneficial effect on long-term renal function outcome. Additional unanswered questions are the specific roles of the different cytotoxic agents, the benefits and risks of different drug administration protocols, and the utility (or lack thereof) of combining cytotoxic agents with glucocorticoids.

REFERENCES