Effect of Anti-Lymphocyte Induction Therapy on Renal Allograft Survival: A Meta-Analysis

LYNDA ANNE SZCZECH,*† JESSE A. BERLIN,* SHREERAM ARADHYE,*† ROBERT A. GROSSMAN,*† and HAROLD I. FELDMAN*†
*Center for Clinical Epidemiology and Biostatistics and the Department of Biostatistics and Epidemiology, and †Renal Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Abstract. Induction immunosuppression with antilymphocyte antibodies has not been shown to improve cadaveric kidney allograft survival in randomized, controlled trials despite widespread use. This meta-analysis of randomized, controlled trials assessed the effectiveness of induction therapy in prolonging allograft survival. Studies of induction therapy were identified in Medline (1986 through 1996), using the terms “monoclonal antibodies” or “antilymphocyte serum,” and “kidney transplantation,” “human,” and “clinical trial.” Bibliographies, pharmaceutical manufacturers, the United Network for Organ Sharing, National Institutes of Health, and study authors were also consulted. Seven of 247 identified studies met the following inclusion criteria: (1) an adult study population; (2) assessment of antilymphocyte antibodies in the immediate posttransplant period; (3) a control arm of cyclosporine, azathioprine, and prednisone in the immediate posttransplant period; and (4) presentation of survival data. Two readers independently extracted protocol and survival data from each study. Summary odds ratios (fixed and random effects) and a rate ratio from proportional hazards regression at 2 yr were estimated to examine the effect of induction therapy on allograft survival. The summary odds ratios were both 0.66 (confidence interval [CI], 0.45 to 0.96; \( P = 0.03 \)), and the rate ratio was 0.69 (CI, 0.49 to 0.97; \( P = 0.03 \)), indicating a beneficial effect of induction therapy on allograft survival. Allograft survival was 79.6% (CI, 75.6 to 83.6%) in the conventional therapy group and 85.6% (CI, 82.1 to 89.1%) in the induction therapy group and 79.6% (CI, 75.6 to 83.6%) in the conventional therapy group. These results were stable in a sensitivity analysis based on study quality. Allograft survival was prolonged with induction therapy compared with conventional immunosuppression. These data indicate a potential role for the routine use of induction therapy in renal transplantation to optimize the survival of cadaveric allografts. (J Am Soc Nephrol 8: 1771-1777, 1997)
All two hundred and forty-seven potentially eligible studies were examined to identify those that met the predetermined inclusion criteria listed in Table 1. Two hundred and forty-six studies were excluded. One hundred and ninety-three did not study antilymphocyte antibodies as induction therapy; 15 were not randomized; 24 did not have a control group that received conventional therapy (i.e., concurrent administration of cyclosporine, azathioprine, and prednisone) in the immediate posttransplant period; three included only pediatric patients; four studies presented duplicate data or reported partial data later published in full; and one randomized trial that met all other inclusion criteria did not present survival data in the published report (17). This RCT of 30 patients studied ALG and was principally focused on rejection episodes during a median follow-up of approximately 1 yr. After all exclusions, seven randomized trials remained eligible for study.

Data Collection and Statistical Analyses

Two researchers (L. Szczek, S. Aradhye) independently extracted the following data from each reported study: year of publication, type of antibody therapy, number of patients randomized, and the proportion of allografts surviving in each treatment group at 6, 12, and 24 mo. Differences in interpretation of the specific language in published articles were resolved in a conference.

Scores describing the methodologic quality of each study were computed using an instrument developed to examine the quality of drug studies (18). These scores fall between 0 and 1, with a score of 1 representing the highest quality. The instrument measures numerous characteristics of studies regarding design (use of blinding and complete follow-up) and analysis (power calculations, confounding).

The number of patients alive and at risk for allograft failure at the beginning of each time period (6, 12, or 24 mo) and the number of allograft failures occurring during each period were abstracted from each study. For some studies (8,9,13), this information was estimated from survival curves; for others (10–12,14), it was taken directly from survival data presented in tabular form.

As an initial analysis, two-by-two contingency tables were constructed for each trial comparing treatment group assignment (induction therapy versus no induction therapy) by outcome (failed versus functioning) at the end of 2 yr of follow-up. The odds ratio for each study was calculated, and homogeneity of the odds ratios across studies was tested. This examined the hypothesis that the studies were estimating a single treatment effect that was common to all studies. A lack of statistical significance indicated, within the statistical limits of the test, that the differences in results across studies were explicable based on sampling variation and that pooling of results was justifiable. The Mantel-Haenszel summary odds ratio (fixed-effects model) and the 95% confidence interval (CI), using the Robins-Breslow-Greenland variance formula (19), were calculated. This summary odds ratio is a weighted average of the study-specific odds ratios, with weights proportional to the inverse of the variance of the odds ratio within each study (20). A summary odds ratio using a random-effects model adapted from DerSimonian and Laird (21) was also estimated. The random-effects model takes into account variability in odds ratios across studies when calculating the weighted average and the CI.

When there is heterogeneity (excessive variability) of odds ratios across studies, the random-effects model produces wider CI than the usual Mantel-Haenszel procedure (22).

To confirm the results of the analyses based on the odds ratio, we also fit fixed- and random-effects models of the risk difference at 2 yr. The results of these analyses were very similar to those based on the odds ratio and are, therefore, not presented.

As an additional analysis, a discrete time version of the proportional hazards regression model that estimated the rate ratio of allograft failure was also implemented. This approach accounted for time period (0 to 6, 6 to 12, or 12 to 24 mo) and allowed testing of homogeneity across studies and across time periods. Using this model, the survival data were viewed as discrete, with the potential for allograft failures and censoring to occur at some time during each of the three time periods. The error distribution was defined as binomial, with the number of patients at risk at the beginning of each interval as the denominator of the binomial proportion. The model was fit using the complementary log–log link (23–26) with generalized linear interactive model 3.77 software.

Time period was included as a set of indicator variables in the models to allow pooling of comparable time periods across studies. Six indicator variables identifying the seven studies were also included. The main variable of interest, treatment with induction therapy, was tested in a model into which indicators for time period and study were forced.

We performed a sensitivity analysis of the Mantel-Haenszel summary odds ratio, using only studies whose quality scores exceeded 0.73. This cutoff represents the mean plus 1 SD of the scores obtained during the development of the methodologic quality instrument (18).

The interactions between treatment effect across time and treatment effect based on type of induction therapy (OKT3 versus polyclonal antilymphocyte globulin) were investigated by comparing a model including the main effects of treatment, study, and time period, with a model that also included each interaction term of interest. These comparisons were accomplished using likelihood ratio chi-squared tests. Testing the treatment by time period interaction examined the constancy of treatment effect across time. Similarly, testing the treatment by type of induction therapy interaction examined the consistency of the benefit from induction therapy between OKT3 and ALG.

Goodness-of-fit of all models was assessed using the deviance statistic that tests the fit of a given model against a fully saturated ("perfect-fitting") model. A P value for this test below 0.05 is an indication of a poor fit of the model to the observed data, whereas P values greater than 0.05 indicate an acceptable fit. A P value below 0.05 was regarded as significant for assessing interaction terms. All P values reported are two-sided, and all CI reported are 95% intervals.

Results

Description of Studies

Seven RCT with a combined total of 794 patients were selected for analysis. Descriptions of the individual study de-

Table 1. Study inclusion criteria*

| Randomized trial studying adult recipients of cadaveric renal transplants |
| Assessed the use of OKT3, MALG, ALG, or ATG with sequential use of cyclosporine as prophylaxis against rejection in the immediate posttransplant period |
| Control arm of conventional therapy (concurrent use of cyclosporine, azathioprine, and prednisone) in the immediate posttransplant period |
| Survival data provided for both treatment arms |

* MALG, Minnesota antilymphoblast globulin; ALG, antilymphoblast globulin (Lyphoglobuline); ATG, antithymocyte globulin (Thymozytenglobuline).
signs, characteristics of the treatment and control groups, and quality scores are provided in Table 2.

Three studies examined OKT3 and, combined, studied 397 patients in whom 76 allografts failed over 2 yr. Follow-up ranged from 2 yr in the study by the Spanish Monotherapy Study Group (14) to 5 yr in the study by Norman et al. (12). Although each of these trials used OKT3 at a dose of 5 mg/d, the duration of therapy ranged from 4 d (14) to 14 d (11). The Spanish Monotherapy Study Group (14) restricted randomization to recipients of first cadaveric transplants who were more than 50 yr of age. This trial included three treatment arms: cyclosporine monotherapy, OKT3 with cyclosporine begun on day 4, and cyclosporine with prednisone; however, only the last two met the criteria for inclusion. Neither Abramowicz et al. (11) nor Norman et al. (12) used similar exclusion criteria.

Four studies examined antilymphocyte globulins and, combined, studied 397 patients in whom 62 allografts failed over 2 yr. Michael et al. (8) and Slakey et al. (13) used Minnesota antilymphoblast globulin as the induction agent, whereas Belitsky et al. (9) used the antilymphoblast globulin Lymphoglobulin and Banhegyi et al. (10) used the antithymocyte globulin Thymozytenglobulin. Michael et al. (8) restricted inclusion to patients with delayed graft function defined as the need for dialysis in the first week posttransplant, whereas Slakey et al. (13) restricted inclusion to patients with immediate allograft function. Three studies, Belitsky et al. (9), Banhegyi et al. (10), and Slakey et al. (13), limited inclusion to first transplant recipients. Additionally, Banhegyi et al. (10) limited study inclusion to recipients with a panel-reactive antibody level of less than 40%.

Quality scores ranged from 0.69 (9, 10) to 0.86 (11, 12), all of which exceeded the mean quality score (0.60) among the studies used to develop the quality score instrument. Four of the seven studies included in this meta-analysis had a score more than 1 SD above this mean (8, 11–13).

Quantitative Assessment

The odds ratios indicating the odds of allograft failure in the group receiving induction therapy compared with the group receiving conventional immunosuppression are shown for each individual study in Figure 1. Each study, with the exception of Belitsky et al. (9), had an odds ratio of less than one, indicating a beneficial effect of induction therapy on allograft survival, but none reached statistical significance. The test for heterogeneity of odds ratios across all seven studies was not significant (P = 0.75), justifying the pooling of their results.

The pooled results of the seven studies revealed a greater allograft survival rate at 24 mo with the use of induction therapy compared with conventional therapy (summary odds ratio, 0.66 [CI, 0.49 to 0.96]; P = 0.03), using both the fixed- and random-effects models. Translated into survival proportions, 85.6% (CI, 82.1 to 89.1%) of the allografts in the group receiving induction therapy were still functioning at 24 mo compared with 79.6% (CI, 75.6 to 83.6%) of the allografts in the group receiving conventional therapy.

Induction therapy was again shown to be beneficial to allograft survival, using the discrete time survival analysis. The proportional hazards model demonstrated a good fit to the data (P = 0.49). The rate ratio, which summarizes the ratio of the rates of allograft failure in the treatment group versus the control group, was 0.69 (CI, 0.49 to 0.97; P = 0.03). The estimated survival probabilities from this model at 24 mo for the average of the seven studies were very similar to the crude survival rates reported above (84.8% treatment group, 78.9% control group).

No interactions were found between treatment with induction therapy and either time period (P = 0.60) or type of induction therapy (OKT3 or polyclonal antilymphocyte globulin) (P = 0.42).

The sensitivity analysis, using the four studies with the highest-quality scores, revealed results similar to our principal analysis. The use of induction therapy compared with conventional therapy was associated with a greater allograft survival at 24 mo (summary odds ratio, 0.55 [CI, 0.35 to 0.86]; P = 0.01).

Discussion

This meta-analysis demonstrates an increase in cadaveric renal allograft survival in recipients of antilymphocyte antibody induction therapy. Patients who received induction therapy had a 6% greater 2-yr allograft survival rate compared with those who received conventional therapy. This is the first study using data from RCT to show this benefit, and it suggests that induction therapy may have an important role in kidney transplantation. Each of the trials, with the exception of one, demonstrated a trend toward improved allograft survival with induction therapy, consistent with the results of this meta-analysis. These results were stable in a sensitivity analysis.

Induction therapy has been widely used and actively investigated over the past decade, but the majority of cohort studies (27–30) and all RCT (8–14) have failed to demonstrate a benefit in allograft survival. Before this meta-analysis, the only studies to show a benefit of induction therapy were the retrospective cohort studies published by Cecka et al. (31) in 1993 and Opelz et al. (32) in 1995. Each study examined a large number of transplant patients reported to registries. Cecka et al. (31) reported an 8.1% greater 1-yr allograft survival rate in the group receiving induction therapy compared with the group receiving conventional therapy. Opelz et al. (32) similarly reported a 3.9% survival difference in the two groups at 3 yr. Additionally, a review of randomized clinical trials using antibody induction therapy concluded that it may improve long-term allograft survival (33).

One prior meta-analysis (34) failed to find a significant benefit from induction therapy on allograft survival. It included 11 studies examining OKT3 published between 1985 and 1991. Its results were difficult to interpret because it included primarily cohort studies and studies in which cyclosporine was not a part of the maintenance immunosuppression. In addition, recent randomized trials (8–14) were not included.

The benefit of induction therapy can be explained by several potential mechanisms. T lymphocytes play a prominent role in antigen recognition and allograft rejection (35), and antilymphocyte antibodies inhibit the generation of functional effector
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Michael et al. (8)</th>
<th>Belitsky et al. (9)</th>
<th>Banhegyi et al. (10)</th>
<th>Abramowicz et al. (11)</th>
<th>Norman et al. (12)</th>
<th>Slakey et al. (13)</th>
<th>Spanish Monotherapy Study Group (14)</th>
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<tbody>
<tr>
<td>No. in treatment group b</td>
<td>21</td>
<td>57</td>
<td>55</td>
<td>56</td>
<td>105</td>
<td>61</td>
<td>41</td>
</tr>
<tr>
<td>No. in control group</td>
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<td>53</td>
<td>60</td>
<td>52</td>
<td>102</td>
<td>60</td>
<td>41</td>
</tr>
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<td>Agent for induction therapy</td>
<td>Minnesota ALG</td>
<td>ALG</td>
<td>ATG</td>
<td>OKT3</td>
<td>OKT3</td>
<td>Minnesota ALG</td>
<td>OKT3</td>
</tr>
<tr>
<td>Dose of agent</td>
<td>20 mg/kg per d</td>
<td>0.5 ml/kg per d</td>
<td>200 mg/d (100 mg/d if weight &lt; 50 kg)</td>
<td>5 mg/d (increased to 10 mg/d if level was &lt; 500 ng/ml)</td>
<td>5 mg/d</td>
<td>day 1: 5 mg/kg</td>
<td>day 2: 10 mg/kg days 3 to 7:20 mg/kg</td>
</tr>
<tr>
<td>Duration of induction therapy</td>
<td>Continued until urine output was &gt; 700 cc/d and creatinine fell by 25%</td>
<td>Continued until serum creatinine was &lt; 300 μmol/L</td>
<td>Administered on days 1, 2, 4, 6, and 8</td>
<td>14 d</td>
<td>10 to 14 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Patients with delayed graft function</td>
<td>First cadaver transplant recipients</td>
<td>PRA was &lt; 40% and first cadaver transplant recipients</td>
<td>None</td>
<td>Recipients of donor kidneys ≥ 2 yr of age</td>
<td>First cadaver transplant recipients, immediate graft function</td>
<td>Recipients were &gt; 50 yr of age and without diabetes or HUS as primary disease</td>
</tr>
<tr>
<td>Recipient age</td>
<td>Not given</td>
<td>Stated as no significant difference</td>
<td></td>
<td>Mean</td>
<td>49.7 yr</td>
<td>34.3 yr</td>
<td>43 yr</td>
</tr>
<tr>
<td>control group</td>
<td>Not given</td>
<td>Stated as no significant difference</td>
<td></td>
<td>Median</td>
<td>47.3 yr</td>
<td>35.3 yr</td>
<td>40 yr</td>
</tr>
<tr>
<td>Recipient sex (% male)</td>
<td>Not given</td>
<td>Stated as no significant difference</td>
<td></td>
<td>Mean</td>
<td>59</td>
<td>70</td>
<td>63.8</td>
</tr>
<tr>
<td>History of prior transplant (%)</td>
<td>Not given</td>
<td></td>
<td></td>
<td>58</td>
<td>60</td>
<td>62.7</td>
<td>55</td>
</tr>
<tr>
<td>treatment group control group</td>
<td>0</td>
<td>0</td>
<td>19.6</td>
<td>10.5</td>
<td>0</td>
<td>0</td>
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<td>control group</td>
<td>0</td>
<td>0</td>
<td>15.4</td>
<td>16.7</td>
<td>0</td>
<td>0</td>
<td>Not given</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
<td>21.9</td>
<td>36.0</td>
<td>29.4</td>
<td>26.7</td>
</tr>
<tr>
<td>treatment group control group</td>
<td>25</td>
<td>Not given</td>
<td>Not given</td>
<td>29.4</td>
<td>26.7</td>
<td>29.4</td>
<td>26.7</td>
</tr>
<tr>
<td>% PRA</td>
<td>Not given</td>
<td>Not given</td>
<td>mean PRA c</td>
<td>All patients had PRA &lt; 50%</td>
<td>74.3% with PRA &lt; 10%</td>
<td>93.4% with PRA &lt; 50%</td>
<td>93.3% with PRA &lt; 50%</td>
</tr>
<tr>
<td>treatment group control group</td>
<td>0% with &gt; 50% PRA c</td>
<td>53%</td>
<td></td>
<td>77.5% with PRA &lt; 10%</td>
<td>93.3% with PRA &lt; 50%</td>
<td>93.3% with PRA &lt; 50%</td>
<td>93.3% with PRA &lt; 50%</td>
</tr>
<tr>
<td>control group</td>
<td>8% with &gt; 50% PRA</td>
<td>29%</td>
<td></td>
<td>77.5% with PRA &lt; 10%</td>
<td>93.3% with PRA &lt; 50%</td>
<td>93.3% with PRA &lt; 50%</td>
<td>93.3% with PRA &lt; 50%</td>
</tr>
<tr>
<td>HLA-DR mismatch treatment group</td>
<td>Not given</td>
<td>No significant difference</td>
<td>0.6/recipient 0.5/recipient</td>
<td>0.82/recipient 0.56/recipient</td>
<td>0.97/recipient 0.95/recipient</td>
<td>Not given 0.6/recipient 0.7/recipient</td>
<td></td>
</tr>
<tr>
<td>control group</td>
<td>Not given</td>
<td>No significant difference</td>
<td>0.6/recipient 0.5/recipient</td>
<td>0.82/recipient 0.56/recipient</td>
<td>0.97/recipient 0.95/recipient</td>
<td>Not given 0.6/recipient 0.7/recipient</td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time</td>
<td>29.8 h</td>
<td>Not given</td>
<td>24.2 h</td>
<td>26.7 h</td>
<td>19.5 h</td>
<td>20.2 h</td>
<td>24.0 h</td>
</tr>
<tr>
<td>treatment group control group</td>
<td>30.7 h</td>
<td></td>
<td>23.2 h</td>
<td>26.2 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>36 mo</td>
<td>Range, 3 to 34 mo</td>
<td>Mean, 9.0 mo</td>
<td>60 mo</td>
<td>Mean, 32.3 mo</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>Methodologic quality score (18)</td>
<td>0.82</td>
<td>0.69</td>
<td>0.69</td>
<td>0.69</td>
<td>0.86</td>
<td>0.82</td>
<td>0.73</td>
</tr>
</tbody>
</table>

a ALG, antilymphoblast globulin; ATG, antithymocyte globulin, PRA, panel-reactive antibody; HUS, hemolytic-uremic syndrome.
b Discrepancies in size between treatment and control groups were due to chance during randomization.
c P < 0.05.
T cells and the activity of mature cytotoxic effector lymphocytes (36). Early modulation of recipient lymphocytes may, therefore, result in a relative immune unresponsiveness (37). Additionally, the passenger leukocyte theory, first proposed in 1957, suggests that blocking the interaction between recipient lymphocytes and donor antigen presenting cells during the finite lifespan of donor lymphocytes may remove an important source of immune stimulation (38-40). Acute rejection has been shown to be a negative prognostic factor in allograft survival (41-43). The use of induction therapy may also benefit recipients by: (1) providing effective prophylaxis against rejection; (2) treating early subclinical rejection; or (3) treating rejection that has been masked by early allograft dysfunction from acute tubular necrosis. Supporting the biological plausibility of these hypotheses, each of the studies included in this meta-analysis showed a decreased rate of acute rejection in the induction therapy groups (8-14). Finally, with the use of induction therapy, the administration of cyclosporine may be delayed, thereby avoiding the potentially deleterious vasoconstrictive effects of this medication in the immediate posttransplant setting (44).

The benefit of induction therapy detected in this meta-analysis is based on pooled results of RCT, in which the patients studied and the immunosuppressive protocols used, varied. Despite these variations in patient exclusion criteria and antilymphocyte induction agents, we detected no differences in the efficacy of induction therapy across trials. Although tests of heterogeneity may be limited in power, they suggest that these studies can be pooled for analysis and that the beneficial effect of induction therapy is not specific to any one antibody preparation.

Publication bias, the selective publication of studies based on outcome, may represent one of the most important limitations of a meta-analysis. Although the appropriateness of inclusion of unpublished data in a meta-analysis has been debated (45,46), it has been shown that a bias often exists in that studies published may not be representative of all studies performed (47-49). As a result of this bias, a meta-analysis may not represent the true effect of a treatment, but rather only a summary of a nonrepresentative sample. We limited the likelihood of publication bias through extensive efforts to identify all published and unpublished studies. In addition, because none of the published RCT reported a statistically significant benefit from induction therapy on allograft survival, it is unlikely that large, unpublished negative trials exist.

Another potential limitation of meta-analysis is the influence of studies using methodology of poor quality. Each of the studies included in this analysis was of high quality, in large part because of their randomized, controlled design. Nonetheless, we performed a sensitivity analysis among the highest-quality studies. The results were similar to our principal findings and suggested a more potent association between induction therapy and allograft survival.

Finally, the studies included in this meta-analysis did not examine the effect of antibody induction therapy in immunosuppressive regimens that include newer agents such as tacrolimus (Prograf, Fujisawa USA, Deerfield, IL) and mycophenolate mofetil (CellCept, Roche). In the absence of RCT with this aim, recent results from the U.S. (50) and Tricontinental (51) Mycophenolate Mofetil Renal Transplant Study Groups may provide some opportunity to assess the efficacy of antibody induction used with mycophenolate mofetil (MMF) in different cohorts. The U.S. study group reported a 3-yr allograft survival of 86.0% among patients receiving a regimen including MMF and antithymocyte gamma-globulin. The Tricontinental Study Group patients received MMF without antibody induction and experienced a similar 3-yr allograft survival of 83.1%. Despite these similarities, it is difficult to conclude that antibody induction therapy has no impact on allograft survival when used with MMF. Notably, the U.S. and Tricontinental study popu-
lations differed with respect to race and comorbidities, both of which are highly related to allograft survival. For example, in the U.S. study, 24% of patients were African-American and 22% had diabetes mellitus in contrast to 0 and 10%, respectively, in the Tricontinental study.

In conclusion, this meta-analysis is based on data from RCT and is the first demonstration of an improvement in allograft survival among adult cadaveric renal transplant recipients who received antilymphocyte antibody as induction therapy. There are, however, additional questions to be explored. In addition to examining the role of antibody induction therapy in combination with newer immunosuppressive drugs, clinical subgroups that may derive particular benefit from induction therapy (e.g., those patients with increased sensitization, a history of failed transplant, or delayed graft function) need to be examined. These subgroups of patients could not be examined using data from the published reports. The benefit derived from induction therapy needs to be balanced against its substantial toxicities, which include an increased risk of infection and lymphoid neoplasia (15,16). Side effect profiles were not presented in sufficient detail in the published reports to allow their inclusion in this analysis. Finally, given the high costs and morbidity associated with its use, the role of induction therapy will depend, in part, on re-evaluation and confirmation of its cost-effectiveness. If the previously estimated, favorable cost-effectiveness of antilymphocyte induction therapy can be confirmed (52), it would further emphasize the potential role of antilymphocyte antibody induction therapy in renal transplantation.

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