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TITLE OF STUDY:

SANG-93-3-K-THY-R: A Double-Blinded, Randomized, Multicenter Phase III Clinical Trial of Thymoglobulin® vs. Atgam® in the Treatment of Acute Graft Rejection Episodes Following Renal Transplantation in Adults

INVESTIGATORS AND STUDY CENTERS:

This was a multicenter study conducted at 25 centers in the United States.

STUDIED PERIOD:

23 August 1994 (First Patient Enrolled) To
21 August 1996 (Last Patient Completed)

PHASE OF DEVELOPMENT:

Phase 3

OBJECTIVES:

To compare the safety and efficacy of Thymoglobulin® (derived from rabbits) and Atgam® (derived from horses) in the treatment of acute cellular rejection after renal transplantation.

METHODOLOGY:

Multicenter, double-blind, randomized, parallel-group study. Adult renal transplant patients with biopsy-proven acute rejection were enrolled and randomly assigned to receive Thymoglobulin® or Atgam®. Randomization was stratified according to severity of graft rejection using the Banff criteria (i.e., mild/not responding to steroid therapy, moderate, or severe acute cellular rejection). Patients were given quadruple sequential immunosuppression consisting of induction with Thymoglobulin® followed by maintenance with cyclosporine, azathioprine, and prednisone. Prophylactic anti-infectives were prescribed according to the site's routine. Patients were followed for 90 days. In addition, safety surveillance was conducted for a period of 1 year after study enrollment.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Approximately 200 patients were planned. The overall rate of rejection reversal was higher than anticipated, and the dropout rate was lower than expected. Therefore, with the FDA as an arbitrator, the study sponsor and investigators agreed to end the study early after enrolling 160 patients. That sample size provided adequate power to test the primary hypothesis stated in the protocol. In all, 163 patients were enrolled and dosed; 162 were analyzed for efficacy; and 163 were analyzed for safety.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and female patients at least 18 years of age with biopsy-proven acute rejection after a first or second renal transplant. Patients were eligible if they could have a central line placed for vascular access, had no known contraindication to the administration of horse or rabbit anti-thymocyte globulin, and provided written informed consent.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Thymoglobulin® 1.5 mg/kg/day intravenously (IV).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Atgam® 15 mg/kg/day IV.

DURATION OF TREATMENT:

Administered once daily for 7 to 14 days, starting within 24 hours after the biopsy that established study eligibility. The dose of study drug could be reduced by half if the platelet count fell to 50,000 to 75,000 cells/mm^3 during study treatment. Study drug could be stopped if platelet count was <50,000 cells/mm^3 or white blood cell (WBC) count was <2,000 cells/mm^3.

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Efficacy:
Primary:
Response to study treatment. Success was defined as creatinine levels ≤100% of the baseline serum creatinine on 2 consecutive measurements at least 2 days apart at the end of treatment or 14±3 days after the institution of treatment.

Secondary:
Graft survival at day 30. Success if the patient was alive, without a nephrectomy, and had not returned to permanent dialysis on or before day 30. Failure if the patient had died, had a nephrectomy, or returned to permanent dialysis on or before day 30.

Serum creatinine level on day 30 as a percent of the baseline value. The day-30 creatinine level was defined as the value closest to day 30 within a window from day 25 to day 46. If there were no results within the window, day-30 creatinine was classified as “not done.” The result was classified as “not evaluable” if the patient had died, had a nephrectomy, or returned to permanent dialysis on or before day 30 (whether or not creatinine was assessed within the window).

Improvement in the post-treatment biopsy relative to the baseline biopsy. This was defined as an improvement of ≥1 grade (e.g., severe to moderate or moderate to mild) according to the Banff criteria. Post-treatment biopsies were performed at the end of treatment or within the next 7 days. If there were no results within the window, post-treatment biopsy was classified as “not preformed.” The result was classified as “not evaluable” if the patient had a nephrectomy or returned to permanent dialysis on or before day 30 (whether or not post-treatment biopsy was performed within the window).

Supplementary:
Recurrent rejection. For patients whose study treatment reversed the primary rejection episode, the timing of the next rejection episode (if any) was documented if it occurred on or before day 90. Recurrent acute rejection, death, nephrectomy, or return to permanent dialysis on or before day 90 were all considered to be recurrent rejection for the purpose of the analyses.

Criteria for Evaluation - Safety:
Adverse events (AEs), clinical laboratory results (chemistry and hematology), physical examinations, and vital signs were assessed.

Criteria for Evaluation - Other:
T cell subsets (CD2, CD3, CD4, and CD8) measured at 5 centers.
Anti-rabbit and anti-horse antibody formation in human serum samples.

STATISTICAL METHODS:

Statistical Methods - Patients:
Demographic information and baseline characteristics were summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) for continuous variables, and counts and percents for categorical variables. For continuous variables, treatment groups were compared using the Wilcoxon rank sum test. For categorical variables, treatment groups were compared using Fisher’s exact test.

Statistical Methods - Efficacy:
Response (success or failure) rates in terms of creatinine levels were compared between treatment groups adjusting for baseline rejection severity using a weighted average of proportions. A 1-sided 95% confidence interval (CI) was constructed for the difference in response rates between treatment groups (Thymoglobulin® minus Atgam®), weighted by severity. The 2 treatment groups were considered equivalent in rate of response if the lower 1-sided 95% confidence bound was greater

than -0.20. A lower bound greater than zero would indicate a significantly higher response rate in the Thymoglobulin® group compared with the Atgam® group.

The analyses of the secondary endpoints of day-30 graft survival and improved post-treatment biopsy were similar to the analysis of the primary endpoint. The day-30 serum creatinine as a percent of baseline was analyzed using analysis of variance of the log ratio, including effects for center, treatment, center by treatment interaction, and baseline rejection severity.

Time to first recurrent rejection, measured in days from day 1, was based on the log-rank test stratified for severity group. Only patients initially considered to be successes were included in the analysis. Treatment differences in the rate of rejection-free graft survival were analyzed using the log-rank procedure, and 2-tailed P-values were reported.

Statistical Methods - Safety:
AEs, coded by the modified COSTART dictionary, were tabulated by treatment. Comparisons of incidence were based on a 2-tailed Fisher's Exact test. AEs were also summarized by relationship to treatment and by severity. Serious adverse events (SAEs), AEs leading to treatment interruption or discontinuation, and deaths were summarized. Infections and malignancies were reported separately from AEs.

Clinically important laboratory results were identified based on normal ranges; values were flagged high or low relative to the normal range in computer-generated listings. Summary descriptive statistics were provided for quantitative laboratory parameters. Median changes from baseline to last infusion and day 90 were compared using the Wilcoxon rank sum test. Shifts from baseline to the last infusion and from baseline to day 90 were tabulated by treatment.

Results of physical examinations and vital signs assessments were tabulated.

Statistical Methods - Other:
Summary descriptive statistics were determined for T cell subsets at specified time points. The difference between treatment groups in T cell counts was evaluated using the Wilcoxon rank sum test, and 2-tailed P-values were to be reported; however, the P-values were not included in the final report.

Tests for differences between treatments in the number of patients with positive antibody titers were based on Fisher's Exact test, and 2-sided P-values were reported.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Patients:

A total of 163 patients were enrolled and randomized: Thymoglobulin®, n=82; and Atgam®, n=81.

There were no statistically significant differences between treatment groups in the demographic or baseline characteristics. The mean age was 39.3 years (range: 15 to 73 years) for patients in the Thymoglobulin® group compared with 40.6 years (range: 17 to 68 years) for patients in the Atgam® group. Approximately two-thirds of the patient were male, with a greater percentage of males in the Thymoglobulin® group (57 of 82 or 70%) compared with the Atgam® group (49 of 81 or 61%). Just over half of the patients in each treatment group were Caucasian, and approximately 35% in each group were African-American. Baseline severity of rejection was distributed similarly in the 2 treatment groups with between 70 and 73% of patients in each group having moderate Banff Grade II rejection at baseline.

A total of 78 of 81 (95%) Thymoglobulin® patients completed the 3-month follow-up visit compared with 76 of 81 (94%) of Atgam® patients.

Summary / Conclusions - Efficacy Results:

Data set analyzed for the primary endpoint: the intent-to-treat (ITT) population, including all randomized patients who had a biopsy-proven rejection at the time of enrollment (n=162). One patient in the Atgam® group was omitted from the ITT population because the patient did not have biopsy-proven rejection at the time of study enrollment. While all analyses were based on the ITT population, the number of patients in the secondary analyses, the supplementary analysis of recurrent rejection, and the T cell subsets varied depending on availability and evaluability of the data according to the specifications in the descriptions of the criteria for evaluation of efficacy (above).

The success rate was significantly (P=0.027) higher for patients receiving Thymoglobulin® than it was for those treated with Atgam®: 72 of 82 (88%) Thymoglobulin® patients had successful responses to study treatment compared with 61 of 80 (76%) Atgam® patients. The overall weighted estimate of the difference in response rates was 11% (Thymoglobulin® rate minus Atgam® rate) with a lower confidence bound of 2%. The lower bound greater than zero indicates a significantly higher response rate in the Thymoglobulin® group compared with the Atgam® group.

Thymoglobulin® was similar to Atgam® in terms of the 3 protocol-specified secondary endpoints: day-30 graft survival (Thymoglobulin® 77 of 82 patients or 94% versus Atgam® 72 of 80 patients or 90%), median day-30 serum creatinine as a percent of baseline (Thymoglobulin® median 71% versus Atgam® 72%), and improvement in the follow-up biopsy (Thymoglobulin® 13 of 20 patients or 65% versus Atgam® 9 of 18 patients or 50%).

Among patients who achieved an initial response, recurrent rejection at 90 days occurred in 12 of 72 (17%) Thymoglobulin® patients compared with 22 of 61 (36%) Atgam® patients (P=0.011).

Summary / Conclusions - Safety Results:

Data set analyzed: all randomized patients who had at least 1 follow-up safety observation (n=163).

The median number of doses of Thymoglobulin® administered was 10 (range, 3 to 14) compared with 10 (range, 4 to 14) for Atgam®. The treatment groups did not differ significantly in the distribution of infusions received (P=0.310). Dose reductions or interruptions were more common in the Thymoglobulin® group compared with the Atgam® group. Dose reductions were reported by 28 of 82 (34%) of Thymoglobulin® patients compared with 8 of 81 (10%) Atgam® patients (P<0.001). Dose interruptions were reported by 20 of 82 (24%) of Thymoglobulin® patients compared with 14 of 81 (17%) Atgam® patients. The dose reductions and interruptions were not unexpected because the study agents are polyclonal anti-lymphocytic agents, and the rules for reducing or interrupting study drug were based on falling WBC counts.

All patients had at least 1 AE, and 96 of 163 (59%) had SAEs, including 4 deaths.

• In Thymoglobulin® group 82 patients had 1203 AEs (14.6 events/patient); in the Atgam® group 81 patients had 1160 AEs (14.3 events/patient).

• The most common AEs (reported by at least 25% of patients in either treatment group) were fever, chills, leukopenia, pain, thrombocytopenia, headache, diarrhea, peripheral edema, abdominal pain, hypertension, nausea, asthenia, tachycardia, hyperkalemia, and dyspnea.

• More patients reported leukopenia (P<0.001) in the Thymoglobulin® group compared with the Atgam® group. More patients reported dizziness (P<0.006) and dysuria (P<0.018) in the Atgam® group compared with the Thymoglobulin® group.

• The most common related AEs (reported by more than 15% of patients in either treatment group) were chills, fever, thrombocytopenia, leukopenia, headache, and nausea. Chills (P=0.006), leukopenia (P=0.001), nausea (P=0.030), and vomiting (P=0.027) were each reported more frequently in the Thymoglobulin® group compared with the Atgam® group.

• Many AEs were of moderate intensity and some were severe; however, toxicities were generally not dose-limiting.

• SAEs related to study drug were reported by 15 of 82 (18%) of Thymoglobulin® patients compared with 9 of 81 (11%) Atgam® patients.

• There were 4 deaths during the study, 3 in the Thymoglobulin® group and 1 in the Atgam® group.
In the Thymoglobulin® group, 1 death because of post-transplant lymphoma was possibly related to study drug; 1 death in the setting of abdominal pain, leg pain, convulsion, apnea, rales in left base of lungs, and confusion was unlikely related to study drug; and 1 death because of myocardial infarction and anemia was not related to study drug.
In the Atgam® group, 1 death because of high-grade non-Burkitt's lymphoma was possibly related to study drug.

• None of the patients was recorded as failing to complete the 90-day follow-up visit because of an AE.

The observed elevations in creatinine and blood urea nitrogen were typical for the patient population studied. Changes in hematology parameters showed general trends toward decreased WBC and platelet counts in both treatment groups. Leukopenia was expected in the setting of anti-T cell cytotoxic activity and efficacy of the therapies.

AEs related to over-immunosuppression such as cytomegalovirus infection and herpes infection were infrequent, perhaps because of the broad use of antiviral therapy. The incidence of new malignancies was also low.

There were no notable changes in physical examinations or vital signs.

Summary / Conclusions - Other Results:

During and after therapy, T cell subsets were performed in 12 Thymoglobulin® patients and 14 Atgam® patients. T cell subsets were significantly lower in the Thymoglobulin® group compared with Atgam® at the end of therapy: median CD3 values were 5 cells/mm^3 for Thymoglobulin® and 147 cells/mm^3 for Atgam® (P=0.001). At day 30, CD3 values were 180 cells/mm^3 for Thymoglobulin® and 722 cells/mm^3 for Atgam® (P=0.016). (Source: Gaber AO, First MR, Tesi RJ, et al. Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin® versus Atgam® in the treatment of acute graft rejection episodes after renal transplantation. Transplantation 1998;66[1]:29-37.)

There was no difference in sensitization level to horse IgG after Atgam® treatment or rabbit IgG after Thymoglobulin® treatment. In a separate analysis in which presensitized patients were included as sensitized, sensitization level had no correlation with treatment success or failure.

Based on report prepared on: 5 January 1997
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