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NAME OF SPONSOR/COMPANY:

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
SangStat Medical Corporation, Menlo Park, CA 94025 (SangStat Medical Corporation was acquired by Genzyme Corporation September 2003)

TITLE OF STUDY:

SANG-96-3-K-THY-I: a Randomized, Double-Blinded Compaison of Thymoglobulin® vs Atgam for Induction Immunosuppressive Therapy in Adult Renal Transplant Recipients

INVESTIGATORS AND STUDY CENTERS:

This was a single-center study conducted in the United States.

STUDIED PERIOD:

11 May 1996 (first patient enrolled) to
10 March 1998 (last patient completed)

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

To compare the efficacy and safety of 2 antithymocyte globulins the investigational drug Thymoglobulin (derived from rabbits) and the commercially available drug Atgam (derived from horses) for induction immunosuppression in adult renal transplant recipients, from transplantation through 1 year of follow up.

METHODOLOGY:

Single-center, double-blind, parallel-group study. Adult renal transplant patients were enrolled and randomly assigned in a 2:1 ratio to receive Thymoglobulin or Atgam. All patients received quadruple sequential immunosuppressive therapy consisting of induction with Thymoglobulin or Atgam followed by triple immunosuppressive therapy. Maintenance immunosuppression consisted of cyclosporin with dose adjustments after 1-3 months in conjunction with azathioprine and corticosteroids. For viral prophylaxis, 200 mg acyclovir was administered 2x/day for 3 months after transplant. When either the donor or recipient had prior risk of exposure, oral ganciclovir was given at 1000mg 3x/day.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

90 patients were planned and 72 were enrolled, dosed, and analyzed for efficacy and safety.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and female adult recipients of cadaveric renal transplants, who had no known contraindication to the administration of horse or rabbit anti-thymocyte globulin, were willing to practice contraception for ≥ 90 days post-transplantation, and provided written informed consent were eligible. Women who were pregnant or nursing were excluded.

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 intraoperatively and once daily thereafter for ≥ 6 days (ie, for at least 7 days) but no more than 14 days total.

CRITERIA FOR EVALUATION:

Change In The Plan:
The protocol was originally designed to show equivalence of Thymoglobulin and Atgam, with equivalence defined as failure to reject the null hypothesis that Thymoglobulin patients had a 1-year incidence of acute rejection ≥ 35% more than that of Atgam patients. Subsequently, it was deemed important to test whether Thymoglobulin reduced the incidence of acute rejection, including acute rejection at 1 year.

Criteria for Evaluation – Efficacy:
Primary: Incidence of acute rejection 6 months after renal transplant. (Acute episodes of rejection were suggested by clinical signs, such as fever, graft tenderness, and increase in serum creatinine, and confirmed by biopsy evidence of rejection as defined by the Banff criteria.)

Secondary:
-Acute rejection at 12 months
-Patient and graft survival at 6 and 12 months
-Event-free survival (defined as freedom from death, graft failure, or acute rejection) at 6 and 12 months

Criteria for Evaluation – Safety:
Primary: Incidence of cytomegalovirus (CMV) disease and serious adverse events (SAEs).
Secondary: Delayed graft function and duration of transplant hospitalization.

Criteria for Evaluation - Other:
Hospital costs were to be documented but those results are not summarized.

STATISTICAL METHODS:

Statistical Methods - Patients:
Demographic information and baseline characteristics were summarized using descriptive statistics. For continuous variables, treatment groups were compared using the standard 2-sample t test. For highly skewed data, the Wilcoxon rank sums test was used. For categorical variables, treatment groups were compared using Fisher's exact test. All tests were 2-tailed, and p-values < 0.05 were considered statistically significant.

Statistical Methods - Efficacy:
Time-to-event analyses (time to rejection, time to graft failure, time to patient death, and time to either rejection, graft failure, or death) were based on the log-rank test. Event-free rates were calculated using the Kaplan-Meier method. For the purposes of evaluating graft survival rate, death with a functioning graft was considered an event in order to estimate the percent surviving with a functioning graft and included all cases in the intent-to-treat analysis.

A Cox Proportional Hazards model was used to compute the relative risk (RR) of acute rejection (Thymoglobulin versus Atgam) and the 95% confidence interval (CI). This approach allows for varying lengths of patient follow up and simultaneous control for the effect of patient confounders on outcome.

Statistical Methods - Safety:
All adverse events (AEs) were tabulated by treatment group, and SAEs were listed and described in narratives. Prospectively selected AEs of special interest were summarized with group comparisons based on the Wilcoxon rank sums test. The change from baseline in laboratory values at 7, 14, 30, 90, 180, 270, and 360 days after transplant within treatment was tested using the Wilcoxon rank sums test. For this analysis, a p-value < 0.007 was considered statistically significant (Bonferroni correction = 0.05/7).

The difference between the treatments in the incidence of CMV disease and delayed graft function was analyzed using Fischer's exact test. A Wilcoxon rank sums test was used to assess whether Thymoglobulin treatment prolonged hospitalization.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Patients:
Seventy-two consecutive patients were enrolled and randomized: Thymoglobulin, n=48; Atgam, n=24.

There were no statistically significant differences between treatment groups in the demographic or baseline characteristics of transplant recipients or donors. The mean age of recipients was 45 years in the Thymoglobulin treatment group and 52 years in the Atgam treatment group; approximately 20% of patients in both treatment groups were ≥ 60 years of age. Females made up 38% of patients in both treatment groups.

All patients had end-stage renal disease (ESRD), and the distributions of causes of ESRD were similar for the 2 treatment groups. There was no difference in the overall CMV status or in the substratification of donor and recipient CMV seropositivity at the time of transplantation. The majority of transplants in both treatment groups were cadaveric (Thymoglobulin 73%; Atgam 79%). First transplants accounted for 92% of procedures in the Thymoglobulin group and 90% of procedures in the Atgam group.

There were no premature withdrawals from the study, and all patients were followed up for at least 12 months (mean, 17.2 months; range, 12 to 23 months).

Summary / Conclusions - Efficacy Results:
The rate of rejection was lower for patients receiving Thymoglobulin compared with Atgam. At 6 months after transplantation, 2 of 48 (4%) Thymoglobulin patients versus 4 of 24 (17%) of Atgam patients had an acute rejection episode (*P*=0.038). By 1 year after transplantation, no additional Thymoglobulin patients had an acute rejection episode, but 2 additional Atgam patients had an acute rejection episode. Thus, at 12 months after transplantation, 2 of 48 (4%) Thymoglobulin patients versus 6 of 24 (25%) Atgam patients had an acute rejection episode (*P*=0.014). The RR for acute rejection (Thymoglobulin vs. Atgam) was 0.14 (95% CI=0.03 to 0.68). Thus, there was an 86% reduction in the rate of acute rejection over the course of followup. The first rejection episodes were also less severe among Thymoglobulin patients compared with the Atgam patients (*P*=0.02).

None of the Thymoglobulin patients experienced a recurrent rejection episode, compared with 2 of 6 (33%) Atgam patients who experienced organ rejection; this difference was not statistically significant.

Graft survival was superior with Thymoglobulin compared with Atgam (98% vs 83%; *P*=0.020, log rank test) when graft loss from all causes was considered. Excluding death, no graft loss occurred in the Thymoglobulin patients. However, 3 of 24 (13%) Atgam patients lost their allografts: 2 lost allografts because of thrombosis (1 immediately after the initial transplant surgery and the other immediately after repair of a urinary leak 6 weeks after transplantation) and the third patient lost the allograft 11.5 months after transplantation secondary to recurrent rejection.

The rate of event-free survival was greater for Thymoglobulin patients compared with the Atgam patients. At 6 months the event-free survival rate was 94% ± 4% for Thymoglobulin versus 71% ± 9% for Atgam, and at 1 year 94% ± 4% for Thymoglobulin versus 63% ± 10% for Atgam (*P*=0.0005, log rank test).

Summary / Conclusions - Safety Results:
One patient in each treatment group received 8 days of induction therapy; all others were dosed for shorter durations. The median number of full doses of Thymoglobulin administered was 6 (range, 0 to 8) compared with 7 (range, 1 to 8) for Atgam (*P*=0.008). The median number of half-doses administered was 1 (range, 0 to 7) for Thymoglobulin and 0 (range, 0 to 4) for Atgam (*P*=0.001). Study drug was held or reduced most commonly because of leukopenia occurring during the period of induction therapy. Leukopenia was more common among Thymoglobulin patients than among Atgam patients (56% versus 4%, $P < 0.0001$).

There were over 400 AEs during the study and 89 SAEs, including 2 deaths.

• The only difference between treatments in terms of AEs was the incidence of acne, reported by 19% of Thymoglobulin patients compared with none of the Atgam patients.

• The median number of SAEs per patient was significantly lower (*P*=0.013, Wilcoxon rank sums test) among Thymoglobulin patients (median: 0 and range: 0 to 11) compared with Atgam patients (median: 1.0 and range: 0 to 5). However, because of the wide range in the number of SAEs among the Thymoglobulin patients, the mean number of SAEs did not differ between the groups: 1.2 ± 2.3 (Thymoglobulin) compared with 1.8 ± 1.5 (Atgam). Serious pancytopenia in an Atgam patient was considered drug-related and hypotension in a Thymoglobulin patient was probably drug-related. Most other SAEs were judged possibly related or not related to study drugs.

• There were 2 deaths during the follow-up period. One Thymoglobulin patient suffered a fatal pulmonary embolus at day 74 post-transplant, and 1 Atgam patient suffered a cerebral vascular accident at day 34 post-transplant. These deaths were considered by the investigator to be unrelated to study treatment.

No patient developed any post-transplant lymphoproliferative disorder, but 1 patient, who was randomized to the Thymoglobulin treatment arm, was diagnosed with colon cancer at 8 months post-transplant. He underwent surgical resection and remained without evidence of residual cancer at the last follow up.

Serum creatinine levels declined rapidly in both groups following transplant and there were no statistically significant differences in between-treatment comparisons at any time point. At 7 days post-transplant, the mean serum creatinine levels were 2.3 ± 2.0 mg/dL (Thymoglobulin) and 2.5 ± 3.1 mg/dL (Atgam). Among patients with functioning allografts, at 6 months post-transplant the mean serum creatinine levels were 1.6 ± 0.4 mg/dL (Thymoglobulin) versus 1.5 ± 0.4 mg/dL (Atgam); at 1 year post-transplant the mean serum creatinine levels were 1.6 ± 0.5 mg/dL (Thymoglobulin) versus 1.8 ± 1.5 mg/dL (Atgam).

The mean duration of transplant hospitalization did not differ between the 2 treatment groups (Thymoglobulin 8.1 ± 2.9 days; Atgam 7.8 ± 1.7 days; p=0.630).

Thymoglobulin provided more profound and more prolonged lymphopenia than did Atgam. Absolute lymphopenia developed rapidly upon administration of study drug and persisted for almost a full year among Thymoglobulin patients, compared with resolution by 14 days post-transplant among Atgam patients.

Leukopenia (white blood cells < 3000 cells/mm^3) occurred almost exclusively during the induction period and more commonly among Thymoglobulin patients (56%) than Atgam patients (4%) (*P*<0.0001).

During the first year after transplantation, thrombocytopenia (<100,000 platelets/mm^3) was documented in 10% of Thymoglobulin patients and 8% of Atgam patients. This was not a statistically significant difference.

Despite the fact that leukopenia was more common among the Thymoglobulin patients, there was no statistically significant difference in the incidence of infections between the treatment groups. Among patients who received Thymoglobulin, 27 of 48 (56%) developed infection at any time during the study, compared with 18 of 24 (75%) Atgam patients.

The incidence of CMV disease 6 months post-transplant was lower among Thymoglobulin patients (5 of 48, 10%) compared with Atgam patients (8 of 24, 33%, *P*=0.025). During the first year after transplantation, CMV disease continued to be less common among Thymoglobulin patients (6 of 48, 13%) compared with Atgam patients (8 of 24, 33%, *P*=0.056). Pertinently, all CMV disease reported in this study developed after discontinuation of prophylactic oral ganciclovir.

One patient experienced delayed graft function requiring dialysis. This patient, who received Thymoglobulin, was anuric before the transplant procedure and had nonoliguric (>500 cc urine volume) delayed graft function. The patient required only 1 dialysis treatment, for hyperkalemia, after transplantation. The hyperkalemia was believed to have resulted from transient limb ischemia secondary to clamping of the iliac artery for an endarterectomy performed during the transplant operation.

Based on report prepared on: 25 September 1998
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