Protocol SMC-534-1003: Short Course Thymoglobulin® for Induction Immunosuppressive Therapy in Adult Renal Allograft Recipients

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

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)

INVESTIGATORS AND STUDY CENTER(S)

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

STUDIED PERIOD

March 1998 (first patient enrolled) to
October 1998 (last patient completed)

PHASE OF DEVELOPMENT

Phase II

OBJECTIVES

To compare 3 days of Thymoglobulin® therapy as part of a quadruple, sequential immunosuppressive drug regimen in renal allograft recipients to a historical control group from a previous study (SANG-96-3-K-THY-I) of 7 days of Thymoglobulin® at the same transplant center.

METHODOLOGY

Prospective, nonrandomized, open-label evaluation at a single transplant center for comparison with a historical control group. 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.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)

A total of 40 consecutive renal transplant patients treated with a 3-day regimen were planned and analyzed. They were compared with an historical control group of 48 patients treated with a 7-day regimen of Thymoglobulin® who were enrolled in SANG 96-3-K-THY-I.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and female patients at least 18 years of age receiving renal allografts from any source except living, related donors with identical human leukocyte antigen. Patients who received immunosuppression, except for Thymoglobulin®, cyclosporine, and azathriopin, were excluded.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Thymoglobulin® 3.0 mg/kg intravenously (IV) on day 0, followed by 1.5 mg/kg IV once daily on days 1 and 2.

Cyclosporine and azathioprine doses were determined by the investigator. The patient received prophylaxis with methyl prednisolone prior to the first infusion. Prednisone (1 mg/kg/day) was given orally (PO) on days 1 and 2. Prednisone was tapered over 12 months.

Oral nystatin or mycelex was taken daily for 3 months post transplant. Double-strength trimethoprim/sulfamethoxazole was taken PO. If allergic to sulfonamides, dapsone 50 mg/day or nebulized pentamidine 300 mg/month for 6 months could be substituted. Patients also received either ganciclovir (1 g tid) or acyclovir (200 mg bid PO) for at least 3 months post transplant.

DURATION OF TREATMENT

Three days

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

Not applicable (historical control).

CRITERIA FOR EVALUATION
Criteria for Evaluation – Efficacy
Primary: Incidence of acute rejection 3 months after transplant.
Secondary: Incidence of acute rejection at 1 year; Patient and allograft survival rates at 1 year.

Criteria for Evaluation – Safety
Adverse events (AEs), including tolerability, fever, chills, dyspnea, and hives; leukopenia and thrombocytopenia; infections; and malignancy. Laboratory results also included serum chemistries.

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.

Statistical Methods – Efficacy
The incidence of acute rejection 3 months after transplant among the patients who received the 3-day regimen and those who received the 7-day regimen were compared using Fisher's exact test. Other instances of acute rejection and survival of patients and allografts in the year after transplant were analyzed using the Kaplan-Meier method with confidence intervals (CIs) calculated using Tsiatis variance estimator.

Statistical Methods – Safety
AEs were coded by the modified COSTART dictionary, and AEs of special interest were tabulated by treatment regimen. 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.
Laboratory results were listed.

SUMMARY / CONCLUSIONS
Summary / Conclusions (Patients)
Data were available from all enrolled patients (n=40 for the 3-day regimen; n=48 for the 7-day regimen). There were no significant differences between treatment regimens in patient demographic or baseline characteristics. The mean age was 50 years for patients on the 3-day regimen, compared with 45 years for patients on the 7-day regimen. Approximately 63% of the patients were male. Between 70% and 73% of transplants in both treatment regimens were cadaveric.

Thirty-four patients completed the study of the 3-day regimen. Among those who terminated early, 2 died and 4 discontinued because of graft loss. There were no premature withdrawals from the study of the 7-day regimen.

Summary / Conclusions (Efficacy)
All patients were evaluable for efficacy. In a few instances where the published data differ from what is presented in the study report on the 3-day regimen (because of corrections in the original database prior to preparation of the publication), footnotes are included to explain the differences.

There was no difference between the treatment regimens in terms of the primary endpoint: 2 of 40 patients (5%) on the 3-day regimen had experienced acute rejection at 3 months, compared with 2 of 48 patients (4%) on the 7-day regimen.

One year after transplant, the treatment regimens were also similar in terms of patient survival, graft survival, and acute rejection rates as shown below.

Secondary endpoint	3-day Regimen; n=40 n (%)	7-day Regimen; n=48 n (%)	P-value
1-Year patient survival	38 (95)	47 (98)	0.464
1-Year graft survival	34 (85)[1]	47 (98)	not available
1-Year acute rejection	3 (8)	2 (4)	1.0
[1]The publication stated that graft survival was 95%; this difference is because the published analysis excluded the 3 technical failures (thrombosis) and the present analysis did not.			

The average length of hospital stay after transplantation was 6.1 days for patients on the 3-day regimen, compared with 8 days for patients on the 7-day regimen (p=0.002).

Summary / Conclusions (Safety)
All patients were evaluable for safety. For patients on the 3-day regimen (n=40), the median number of Thymoglobulin® doses received was 3 (range: 1 to 4 doses). For patients on the 7-day regimen (n=48), the median number of full doses of Thymoglobulin® received was 6 (range: 0 to 8 doses).

The safety profiles were generally similar for the 2 treatment regimens. Fever, thrombocytopenia, and CMV were more common among patients on the 3-day regimen and leukopenia was more common among those on the 7-day regimen.

All patients on the 3-day regimen had at least 1 AE, as did all patients on the 7-day regimen.

Most of the AEs among patients on the 3-day regimen were mild and unlikely or not related to study drug.

The incidences of AEs of special interest are summarized below by treatment regimen in order of decreasing frequency on the 3-day regimen.

Adverse event	3-day Regimen; n=40 n (%)	7-day Regimen; n=48 n (%)
Infection	23 (58)	27 (56)
Fever	21 (53)	9 (19)
Thrombocytopenia	14 (35)	5 (10)
Cytomegalovirus	11 (28)[1]	6 (13)
Leukopenia	8 (20)	27 (56)
Malignancy	2 (5)	1 (2)
Chills	0	0
Dyspnea	0	6 (13)
Hives	0	0
[1]The publication showed only 7 instances.		

Among patients on the 3-day regimen, there were 44 SAEs, including 2 deaths. There was also 1 death among the patients on the 7-day regimen. All of these deaths were judged to be unrelated to study treatment.

One patient on the 3-day regimen died of adenocarcinoma of the colon on day 95, and one died of cardiac arrest on day 94.

One patient on the 7-day regimen suffered a fatal pulmonary embolus on day 74.

There were no laboratory abnormalities of note.

Based on Report Prepared on: 12 March 2004
Synopsis Prepared on: 05 June 2006