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Safety and Pharmacokinetics of a Human IgM anti-Lipid A Monoclonal Antibody in Primary Immune Deficient Patients

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Abstract

A phase I clinical study of a human IgM anti-lipid A monoclonal antibody was conducted in 24 patients with a primary immunodeficiency syndrome. Six patients each were evaluated at one of four dosage levels: 50 mg, 75 mg, 100 mg or 150 mg. Subjects were observed for both acute adverse events as well as various laboratory parameters over 28 days. In addition, a pharmacokinetic study was done on the single antibody infusion at each dosage level assessing half-life, peak concentration and 24 hr concentration. The results indicated that the infusion may be safely given at all four dosage levels and that the pharmacokinetics of this antibody is probably linear.

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INTRODUCTION

The rate of nosocomial as well as community acquired septicemia has increased over the past decade [1, 2]. Gram negative organisms play a major etiologic role in these infections [3], with Gram negative bacteremia being associated with a mortality rate higher than 20% [4]. For those patients who go on to develop septic shock this mortality rate has been shown to climb over 50% [5, 6].

Lipid A, a subunit of the core lipopolysaccharide (LPS) moiety of gram negative bacterial cell walls, is believed to be the trigger in the development of what has come to be known as the sepsis syndrome, which leads to and often culminates in septic shock [7, 8].

Over the past two decades, clinical as well as animal and basic data have been accumulating which strongly suggest that antibody to the core LPS structure could be protective against the sequelae of the sepsis syndrome. The first study supporting this theory was published in 1982 by Ziegler and colleagues [7]. Subsequent studies have provided support for this hypothesis [4, 9, 10, 11].

The purpose of this study was to determine the safety and pharmacokinetics of a human IgM anti-Lipid A (with a murine J chain) monoclonal antibody in patients with primary immunodeficiencies 24 hours before and 24 hours after they received their intravenous immunoglobulin (IVIG) replacement.

METHODS

PATIENT POPULATION

Twenty four patients over 13 years of age with a primary immunodeficiency (as defined by the World Health Organization criteria), on maintenance IVIG replacement therapy, were enrolled to participate in the study. At entry, they all signed an informed consent that had been approved by the Committee on Clinical Investigation at Children's Hospital in Boston. They all had normal renal function and no clinical evidence of active infection for 1 month prior to infusion. Patients with a history of allergy to blood or blood products or to mouse protein, and patients who had been on antibiotic treatment for an active infection over the 2 weeks prior to the monoclonal antibody infusion were not eligible to enter the study.

RANDOMIZATION

Patients were infused with the anti-Lipid A monoclonal antibody in an open label, uncontrolled single infusion fashion. Six patients were randomized to each one of four dosage levels: 50 mg, 75 mg, 100 mg and 150 mg. Within each of the dosage levels, patients were stratified into two categories: half were infused with the anti-Lipid A monoclonal antibody 24 hours prior to their scheduled IVIG infusion, and the other half were infused with it 24 hours after their scheduled infusion of IVIG. Each dosage level, beginning with the lowest, was completed sequentially.

MONOCLONAL ANTIBODY PREPARATION

The antibody was originally derived from spleen cells from an individual who had been immunized with Salmonella minnesota (Re595 mutant), whole killed vaccine, prior to undergoing splenectomy for idiopathic thrombocytopenic purpura. This particular antibody was chosen for development based upon its ability to cross-react with the LPS of various Gram negative genera, and it has been shown to react with the Lipid A moiety of LPS in vitro. The antibody was originally isolated from a human-human hibridoma. The antibody genome was then genetically engineered into a murine myeloma cell line. The resulting cell line produced a human IgM antibody. No human J chain was engineered into the cell line, therefore being of murine origin. The engineered antibody behaved identically in in vitro assays as did the original human monoclonal antibody.

MONOCLONAL ANTIBODY ADMINISTRATION

The IgM anti-Lipid A monoclonal antibody is a liquid preparation at a concentration of 1 mg/ml. The material was infused intravenously at a rate of 1 ml/minute for the first half hour; then the rate was doubled every half hour to no more than 4 ml/minute.

MEASUREMENT OF SPECIFIC IGM ANTI-LIPID A ANTIBODY LEVELS

Blood samples were drawn at the following times for the pharmacokinetics study: baseline, 0.25, 0.5, 1, 3, 6, 12, 18, 24, 48, and 72 hours and at 7, 10, 14, 21 and 28 days post-infusion.

The samples were batched and tested at a central laboratory (Applied Sciences Safety and Efficacy Assessment Center, Baxter Healthcare Corporation; Round Lake, Illinois).

MONITORING PARAMETERS

Patients had chemistry panel, liver function tests, complete blood count, factor VIII related antigen (von Willebrand Factor), complement studies (C4 and CH50) and urinalysis done at baseline, and repeated at regular intervals over the first 24 hours and then at days 2, 3, 7 and 28 after the infusion of the human IgM monoclonal antibody.

A complete physical examination was done at baseline and 28 days post infusion, with the recording of all abnormal findings. Patients were closely monitored for clinical signs of adverse reactions at frequent intervals for the first 24 hours and then 28 days after the infusion. Vital signs (respiratory rate, pulse rate, blood pressure and temperature) were obtained pre-infusion, every half hour or more frequently if clinically indicated during the infusion, as well as prior to each blood draw.

DATA ANALYSIS

Pharmacokinetic data were analyzed for half-life determination using the method of Lee, Poon and Kingdon [12].

The various numeric results were summarized according to means, medians, and standard deviations in the case of quantitative data and percentages and counts in the case of qualitative data.

For the chemistry, hematology and immunology data collected over time, the results at each time point were compared to baseline using the Wilcoxon signed-rank test. To allow for the multiplicity of testing within each variable, the usual significance level of 0.05 was adjusted by the simplest Bonferroni [13] inequality according to the number of comparisons, k, performed, i.e. 0.05/k.

RESULTS

All 24 patients met eligibility criteria for the study, and they all completed the study as planned. The patients' demographic characteristics are shown in Table 1.

Figure 1

Table 1: Patients' demographic characteristics

	50 mg (n = 6)	75 mg (n = 6)	100 mg (n = 6)	150 mg (n = 6)
Age (mean ± standard dev.)	29.3 ± 8.9	30.8 ± 12.0	24.5 ± 12.0	23.5 ± 10.1
Males	3	1	4	2
Females	3	5	1	4

Every enrolled patient completed the infusion of the anti-lipid A monoclonal antibody. Five participants experienced adverse events with their anti-lipid A monoclonal antibody infusion. Of these, only two were of possible relationship to the infusion. A study subject reported moderate chills, and a second one presented with mild edema of the upper lip.

In addition, the vital signs observed during and after the infusions did not change in any clinically appreciable fashion. There were no notable changes in the physical examinations conducted at baseline and on day 28.

There were no significant changes in the chemistry, liver function, hematologic or urinary testing. There were no significant changes in the C4, CH50 and von Willebrand Factor levels either.

The pharmacokinetics at the different dosage levels are shown in Table 2. The peak concentration achieved after infusion of 50 mg of the monoclonal antibody was 10.4 ± 3.3 µg/ml, and it reached 44.2 ± 9.1 after infusion of the highest dose. The time required to reach the peak concentration was 0.4 ±0.3 hour. The half-life of the infused monoclonal antibody varied from 95.0 ± 149.1 to 194.7 ± 258.7 hours at different dose levels. The lipid A monoclonal antibody's serum level was obtained at regular intervals in all patients. The mean serum level for each dosage group at the different intervals is shown in the Figure.

There was no significant difference in the pharmacokinetics of the antibody whether it was given either before or after an IVIG infusion (p>0.05).

Figure 2

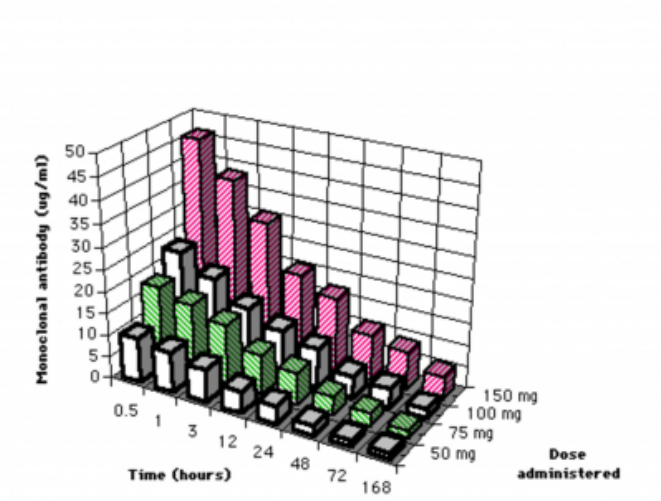
Table 2: Pharmacokinetic analysis

	50 mg (n = 6)	75 mg (n = 6)	100 mg (n = 6)	150 mg (n = 6)
Half-life (hr)	95.0 ± 149.1	150.1 ± 311.4	194.7 ± 258.7	129.5 ± 122.5
Median (hr)	27.8	27.2	54.1	83.0
Peak conc. (µg/ml)	10.4 ± 3.3	20.8 ± 7.4	22.7 ± 6.7	44.2 ± 9.1
24 hr conc. (µg/ml)	3.5 ± 1.9	7.0 ± 2.1	7.6 ± 2.0	16.6 ± 2.3

Half -life, peak concentration. and 24 hr concentration expressed in mean ± standard deviation for each dosage group.

Figure 3

Figure: Mean serum levels of Lipid A monoclonal antibody at different time points in all 4 dosage groups



DISCUSSION

This was the first administration to human subjects of the human IgM anti-Lipid A monoclonal antibody developed by Baxter Healthcare Corporation, Hyland Division. The primary objectives of the study were to determine the safety and pharmacokinetics of this product.

We chose to administer it to patients with primary immunodeficiencies because they would be less likely to develop antibodies against the monoclonal antibody. As these patients received IVIG replacement on a regular basis, it was also possible to assess the changes in the pharmacokinetics of the human IgM anti-Lipid A monoclonal antibody in relation to a concomitant infusion of IVIG.

The product was well tolerated by all 24 patients at the four different dosage ranges used. Two patients developed mild symptoms while receiving the highest dosage used in the study. The chills observed in one of the subjects were successfully treated with acetaminophen, and the mild edema of the upper lip observed in the other study subject resolved spontaneously while still receiving his infusion.

It was also possible to determine the pharmacokinetics of this human IgM antibody. The average half-life was 142.3 hours, although the standard deviation of 210.4 was large since there were some extreme results (values ranged from 12 to 786 hours). As a result, the median was only 48 hours. Using a different human IgM anti-lipid A monoclonal antibody, Khazaeli et al. [$_{14}$] observed a half life, in 7 of his

patients studied, of 31.5 ± 9.7 hours. The half-life of normal human IgM is of approximately 5 days [15]. Our monoclonal antibody, though originally isolated from a human-human hibridoma, had its genome engineered into a murine myeloma cell line. The resulting human monoclonal antibody had a J chain of murine origin. Therefore, our monoclonal antibody is likely to have some subtle alterations in its structure that may explain why it does not have a similar half-life to normal human IgM.

There does not appear to be any notable difference in the half-lives at different doses, indicating that the pharmacokinetics of this antibody is probably linear.

Further studies now need to be undertaken to assess the safety, pharmacokinetics and clinical effectiveness of this monoclonal antibody in septic patients.

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