Phase I Clinical Trial of Serotherapy in Patients with Acute Myeloid Leukemia with an Immunoglobulin M Monoclonal Antibody to CD15[1]

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ABSTRACT

Sixteen patients with acute myeloid leukemia (AML) were treated with a continuous i.v. infusion of mAb PM-81, an IgM mAb directed against the cellular differentiation antigen CD15, which is expressed on leukemia cells of >95% of patients with AML. MAb PM-81, also referred to as MDX-11, is capable of activating human and rabbit complement and lysing CD15-positive AML cells. In this Phase I study, patients were treated with 0.5, 1.0, or 1.5 mg/kg MDX-11 delivered over a 24-h period followed by conventional chemotherapy. Transient decreases in circulating blast cells postinfusion (prior to chemotherapy) were observed at all doses. We were able to show MDX-11 binding to bone marrow blasts in those patients who achieved stable serum levels of MDX-11. Serum MDX-11 was detectable at the 1.0- and 1.5-mg/kg doses. Doses of 0.5 and 1.0 mg/kg were generally well tolerated, with no toxicities greater than grade II (Eastern Cooperative Oncology Group) reported. However, two of five patients receiving the 1.5-mg/kg dose experienced grade IV toxicities that resolved with treatment (one of these patients completed the infusion). Common toxicities reported included fever, chills, and hypotension. Only one patient developed human antimouse antibodies at 4 weeks posttreatment. This study determined that 1.0 mg/kg is a biologically effective dose that can be administered safely with little toxicity. Based on these results, we are pursuing a Phase I/II study of MDX-11 infusion following chemotherapy for patients with relapsed AML.

INTRODUCTION

mAbs have been used in the treatment of malignancies expressing tumor-associated antigens. It is necessary for the mAb to have an effector mechanism, such as the ability to activate complement (C′) or mediate antibody-dependent cellular cytotoxicity, or to carry a cytotoxic agent, such as a radioisotope, drug, or toxin, to allow for killing of tumor cells. mAbs which regulate ligand/receptor interactions that lead to cell death through indirect mechanisms or stimulate programmed cell death (such as apoptosis) could also be used therapeutically. In one of the early and most encouraging trials of *in vivo* mAb therapy, a patient with B-cell non-Hodgkin's lymphoma achieved complete remission, lasting for several years after treatment with an antiidiotype mAb (1). Studies in patients with AML[3] using the mAb M195 (reactive with CD33) labeled with iodine-131 have also met with success in transient reductions of tumor cells. In some cases, cytoreduction was significant enough for patients to proceed to bone marrow transplant. Whole-body imaging for radiolocalization and bone marrow biopsies showed M195 uptake in the bone marrow, liver, and spleen as early as 1 h after infusion (2, 3). Many researchers have also used chimeric and humanized mAbs to reduce toxicities and promote antibody-dependent cellular cytotoxicity in various malignancies (4–6).

We have previously described the mAb PM-81 (anti-CD15), subsequently referred to as MDX-11, which is reactive with leukemia cells from >95% of patients with AML. The epitope recognized by anti-CD15 antibodies is a trisaccharide structure within the pentasaccharide LNF-III (also referred to as LNFP-III, Lewis x, or SSEA-1). CD15 is found on neutrophils, eosinophils, and monocytes, and is present in embryonic tissues, adenocarcinomas, and myeloid leukemias. Thus, MDX-11 is reactive with normal granulocytes and monocytes. MDX-11 is not reactive with lymphocytes or the colony-forming unit-granulocyte-monocyte or burst-forming unit-erythroid (7, 8). This mAb is an IgM antibody capable of activating both rabbit and human complement (9). Although MDX-11 is cytotoxic to early malignant myeloid leukemia precursors and some normal myeloid precursors, pluripotent stem cells are unaffected (9, 10).

Studies exploring the use of MDX-11 as a therapeutic agent are in progress. An early Phase I clinical trial was performed in which three patients with AML with resistant disease in relapse were given up to 500 mg MDX-11 *in vivo*. All

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[3] The abbreviations used are: AML, acute myeloid leukemia; ABMT, autologous bone marrow transplantation; gam, goat antimouse; NHS, normal human serum; HAMA, human antimouse antibodies; PBA, phosphate-buffered saline/bovine serum albumin/sodium azide; LNFP-III, lacto-*N*-fucopentaose III; ECOG, Eastern Cooperative Oncology Group.

patients experienced an approximate 25% transient decrease in leukemic blast counts with little toxicity (11). MDX-11 has also been used, along with an anti-CD14 mAb (AML-2–23), for *ex vivo* treatment of bone marrow for ABMT for patients with AML (12, 13). The results of this study have been encouraging and a randomized trial is being planned.

Despite successes with ABMT in the treatment of AML, it is important to note that up to 50% of patients with transplants eventually relapse, implying that the ablative therapies used to prepare patients for transplant fail to remove all leukemia cells. And while most of the *in vivo* mAb serotherapies used in leukemias to date have shown promise in transient reductions of tumor burden, few cases of complete or partial remissions have been reported (14, 15). With this in mind, and because of the limited toxicities associated with mAb serotherapies, we are evaluating the role of MDX-11 mAb serotherapy for the treatment of AML as an adjunct to standard chemotherapy and for post-ABMT immunotherapy. The objectives of this Phase I study were to establish safety, feasability, and optimal biological dose of MDX-11. The study design included treating patients with relapsed or secondary AML with escalating doses of MDX-11 using a continuous i.v. infusion over 24 h followed by conventional chemotherapy.

MATERIALS AND METHODS

mAb

MDX-11 (Medarex, Inc., Annandale, NJ) was prepared for clinical use under the United States Food and Drug Administration IND 4362. MDX-11 is manufactured using a hollow fiber bioreactor and purified by ion exchange using HPLC. Supernatant is filtered during the manufacturing process and at the end of purification following buffer exchange by column. Final purified antibody is monitored for quality control using HPLC and SDS gels for identity and purity, for activity using binding and specificity assays (flow cytometry) and cytotoxicity assays, and for general safety by determining DNA levels, endotoxin levels, performing viral testing, and general animal safety.

HL60 Cells

HL60, a CD15-positive leukemia cell line, was obtained from the American Type Culture Collection (Bethesda, MD). The cells were cultured in RPMI 1640 (GIBCO-BRL, Life Technologies, Grand Island, NY) with 10% FCS (Hyclone, Logan, UT), and L-glutamine, penicillin, streptomycin, and gentamicin.

Serum MDX-11 Determination

Serum MDX-11 levels were determined using a sandwich ELISA which incorporated gam-IgM in the solid phase, patient sera as the intermediate step, and alkaline phosphatase-conjugated gam-IgM as the final labeled antibody. Blood samples were obtained from patients at screening, and before, during, and after infusion. Briefly, 96-well plates were coated overnight at 4°C with 1 μg gam-IgM, washed with PBS, and blocked with 5% PBA for 45 min to 2 h at 37°C. Standard curve dilutions of IgM (30–0.003 mg/ml) were made in 10% NHS. Patient sera were diluted 1:10 in 1% PBA; higher dilutions of patient serum were made in 10% NHS diluted in PBA. Plates were washed after blocking, and 100 μl of negative control, standard curve, and patient serum dilutions were added to the appropriate wells. Plates were incubated at 37°C for 1.5 to 3 h. After washing, alkaline phosphatase-conjugated gam-IgM was added for 1.5 to 3 h at 37°C. The plate was then washed and developed with *p*-nitrophenyl phosphate disodium. The reaction was stopped with 1 N sodium hydroxide after 20 min, and the plates were read in an ELISA reader (Dynatech MR660) using a 410A filter, blanking on the negative control wells. Standard curve was performed in duplicate, patient samples in triplicate. This assay was able to detect levels as low as 0.1 μg/ml; levels of MDX-11 above 0.5 μg/ml were able to be quantified.

Serum CD15 Determination

Sera from patients in this study were assayed for soluble CD15 using a blocking assay which incorporated LNFP-III (Oxford Glycosystems, Inc., Rosedale, NY). Blood samples were obtained from patients before infusion and at $t = 24$ h (end infusion). The CD15 antigen-positive cell line HL60 was harvested, washed, resuspended to 2×10^7/ml in PBA, and stored on ice until blocking. The first part of the assay was carried out in duplicate in 96-well round-bottomed plates. MDX-11 was diluted to 0.75 units/ml in PBA, and 10 μl (0.0075 units) were added to each well. A standard curve of LNFP-III, 2.0 mg/ml in PBS, was made by adding 0.5–10 μl LNFP-III to the microtiter wells containing MDX-11. For patient samples and NHS, 10 μl of undiluted, 1:5, and 1:10 dilutions were added to wells containing MDX-11. Final volumes were brought to 20 μl with PBA. For negative controls, 5 μl irrelevant mouse IgM (Coulter, Hialeah, FL) and 15 μl PBA were added to the MDX-11. The plate was then incubated at room temperature with shaking for 30 min. After 15 min, Fc receptors on HL60 cells were blocked by adding ½ volume of human blocking IgG (10 mg/ml) and incubating for 10 to 15 min at 4°C (this incubation coincided with the end of the antigen/antibody binding incubation). After the incubations, 75 μl (10^6) Fc-blocked HL60 cells were added to each microtiter well. The plate was incubated for 60 min at 4°C. The contents of the microtiter wells were then transferred to appropriately labeled tubes. All tubes were washed with PBA twice, and 25 μl FITC-labeled gam-IgM were added to each cell pellet and incubated in the dark for 30 to 40 min at 4°C. After washing, the cell pellets were resuspended in 0.5 ml 1% paraformaldehyde and allowed to fix in the dark at 4°C for 1 h. Samples were analyzed by flow cytometry using histogram overlays with appropriate controls. Standards curves of $r^2 \geq 0.98$ were used for determining the amount of soluble CD15 in patient serum.

Patients who were in first remission greater than 1 year and then relapsed were treated with 1-β-D-arabinofuranosylcytosine (100 mg/m^2/day) i.v. for 7 days and daunorubicin (45 mg/m^2/day) i.v. for 3 days as an induction regimen. Patients who relapsed in less than 1 year or were in second or third relapse received high-dose 1-β-D-arabinofuranosylcytoside (3 g/m^2 every 12 h) i.v. for 12 doses unless they had prior treatment with this regimen. Etoposide (100 mg/m^2/day) given i.v. for 5 days and mitoxantrone (10 mg/m^2/day) given i.v. for 5 days were

used in patients who had already been treated with prior regimens listed.

Determination of Total CD15-positive Cells and Cell-bound MDX-11

Total percentage of positive CD15 cells was determined by indirect staining for CD15 on the patient cells using MDX-11 and a secondary FITC-labeled antibody. Cell-bound MDX-11 was determined by using the secondary antibody to directly stain for MDX-11 already bound to the cell surface. Blood samples for determination of total CD15-positive cells and cell-bound MDX-11 were taken from the patients at screening (bone marrow), before, during, and after infusion. In addition, a bone marrow sample was taken for determination of cell-bound MDX-11 at the termination of the infusion. Leukemic cells were isolated by Ficoll-Hypaque gradient centrifugation within 12 h of collection. Separated cells were kept in RPMI 1640 on ice until ready for use. Prior to assay cells were washed with cold PBA and resuspended to 2×10^7/ml in PBA. Each assay tube received 10^6 (50 μl) cells. For determination of total CD15-positive cells, cells were blocked with 25 μl human IgG (10 mg/ml) for 15 min on ice. Autofluorescence control tubes received 25 μl PBA, negative control tubes received 25 μl irrelevant IgM, positive control tubes received 25 μl W632 supernatant (anti-HLA), and test tubes (assayed in duplicate) received 25 μl MDX-11 (200 μg/ml). Cells were incubated with the primary antibody for 60 min on ice and washed. For cell-bound MDX-11 determination and after washing following incubation of primary antibody for total CD15-positive cells, 50 μl PBA were added to autofluorescence tubes, and 50 μl of $F(ab')_2$ gam-IgG + IgM (H + L) FITC-labeled were added to the remaining tubes and incubated for 30 min on ice (dark). Cells were washed, resuspended in 1.0 ml 1% paraformaldehyde, stored in the dark at 4°C, and allowed to fix for 1 h before analysis by flow cytometry. For cell-bound MDX-11 determination, staining with FITC-labeled secondary antibody occurred simultaneously with the incubation of the primary antibody for total CD15-positive cells. The negative control used for calculating cell-bound MDX-11 was the highest of either the $t = 0$ cell-bound MDX-11 or the autofluorescence tube prepared for that time point.

HAMA Determination

Human antimouse antibodies were assayed using a sandwich ELISA in which the plate was coated with MDX-11. Patient serum was incubated as the intermediate step and goat antihuman IgG alkaline phosphatase was the final antibody. Briefly, the plates were coated overnight at 4°C with 1 μg/well of MDX-11. After washing, the plate was blocked with 5% PBA for 1 to 2 h at 37°C and washed. Patient sera and NHS (negative control) were diluted in duplicate 1:20, 1:40, 1:80, and 1:160 using 1% PBA. Positive control serum from an individual who exhibited a HAMA titer of 1:240 (after repeated treatment with a bispecific antibody consisting of PM-81 and an anti-Fc receptor antibody) was diluted to 1:20–1:480. One hundred ml of all dilutions were added to the plates; blank wells received 100 μl 1% PBA. The plate was incubated for 1.5 h at 37°C and washed. A working dilution of goat antihuman IgG alkaline phosphatase was added to all wells and incubated for 1.5 h at 37°C. After washing, the substrate was added and allowed to develop for 20 min at room temperature. The reaction was stopped with 1 N NaOH, and the plate was read at 405 nm within 20 min.

Flow Cytometry

Flow cytometry was performed using a Becton Dickinson FACScan with Lysis II software. For acquiring antibody-stained leukemia cells from patients, forward scatter and side scatter settings were standardized with fixed, FITC-labeled HL60 cells, and fluorescence settings were standardized using a standard bead mixture. Both HL60 cells and the standard bead mixture were provided by Medarex, Inc. Typically, 10,000 cells were acquired for each sample. All on-site analyses were monitored by Medarex, Inc., for consistency.

Study Design

Patient Eligibility. Patients of any French-American-British subclass of relapsed AML and secondary AML after a myelodysplastic phase or prior cytotoxic drug therapy were eligible. Age eligibility included patients 18 years or older. Karnofsky performance status was required to be >70%. Leukemic blast cells were required to be >20% positive for MDX-11. The criteria for cardiopulmonary, liver, and renal function were delineated as left ventricular ejection fraction >0.4, forced expiratory volume (one second) >70% predicted, hepatic transaminases < three times normal values, and creatinine clearance >50 ml/h.

mAb Administration. Patients were hydrated with normal saline for 4 h prior to administration of MDX-11 to increase intravascular volume in hopes of minimizing allergic reactions and/or toxicities. Patients were also premedicated with diphenhydramine and acetaminophen. The mAb was administered i.v. through either a peripheral or central line. Three patients received doses of 0.5 mg/kg, 8 patients received 1.0 mg/kg, and 5 patients received 1.5 mg/kg. The infusion rate was 10 ml/h (240 ml/24 h). Patients received conventional chemotherapy immediately following completion of the MDX-11 infusion.

Tests Performed. Before and during the MDX-11 infusion, complete blood counts and electrolytes were performed. Serum complement, lactate dehydrogenase with isoenzymes, and uric acid levels were checked before, during, and after infusion. Pharmacokinetic parameters included complete blood counts with differential and platelet counts, cell-bound MDX-11, total CD15-positivecells, serum CD15, and serum MDX-11. These parameters were studied before, during, and after MDX-11 infusion. Bone marrow aspirates were obtained for cytology, and flow cytometry assays were obtained at patient screening and at the end of the mAb infusion (24 h). Complete blood counts were performed weekly for 12 weeks after infusion. Physical examination, performance status, serum chemistry, serum electrolytes, routine urinalysis, and PT/PTT were done at 4, 8, and 12 weeks after MDX-11 infusion. HAMA assays were done at 2, 4, 8, and 12 weeks after infusion.

Toxicity Measurements. Toxicity during and after the infusion was assessed and graded according to the Eastern Cooperative Oncology Group (ECOG) toxicity grading scale.

Table 1 Patient characteristics

Patient	Age/sex	Diagnosis	No. of relapses	Initial blood cell counts		
				WBC (× 1000)	% Blast	Hemoglobin *P*
101	24/M	AML	1	27.2	21	9.5
102	38/F	AML	4	22.6	98	8.4
103	67/M	AML	2	1.3	34	9.9
104	62/M	AML	1	66	5	10.1
105	26/F	AML	2	1.7	4	8.7
106	56/M	MDS[a] converted to AML	0	9.2	84	8.4
107	22/M	AML (secondary to Hodgkin's disease)	0	21.9	75	9.3
108	61/M	MDS converted to AML	0	7.8	13	7.6
109	52/M	AML	1	16.3	24	8.6
110	60/F	AML	3	0.4	24	9.6
301	24/F	AML	4	9.4	83	12.1
302	37/M	AML	1	2.9	0	10.9
303	27/M	AML	1	10.6	0	12
304	46/M	MDS converted to AML	0	73.1	84	8.5
401	48/M	AML	3	6.9	36	9.9
402	67/M	AML	2	3.4	5	10.5

[a] MDS, myelodysplastic syndrome.

RESULTS

With the exception of HAMA results, the following results and discussion are based on data obtained before infusion of MDX-11, during infusion of MDX-11, and immediately after the infusion (infusion end, $t = 24$) prior to receiving chemotherapy. Thus, decreases in cell counts and pharmacokinetics results are due to the effects of MDX-11 immunotherapy and not the subsequent chemotherapy.

Patients

Sixteen patients between the ages of 22 and 67 (median age, 47) years were treated in this Phase I study. Each had a Karnofsky status >80%, and all met the criteria for leukemic blast cells >20% positive for MDX-11. Exceptions for cardiopulmonary status were made for two patients who had pulmonary function test results that were suboptimal or had decreased left ventricular function. Table 1 lists individual patient characteristics.

Toxicity

Thirteen patients received the intended dose of MDX-11. Three patients (patients 104, 303, and 401) experienced serious reactions necessitating termination of the infusion. Another patient (patient 106) experienced milder reactions necessitating infusion delays that resulted in the complete infusion taking 33.5 h rather than the intended 24 h. Patient 109 also experienced minor problems leading to interuption of the infusion for 45 min. This patient's results were still included in the pharmacokinetic analyses. Pharmacokinetic data for other patients are incomplete due to insufficient numbers of cells for analysis. The majority of toxicities were common side effects experienced during mAb infusions or minor allergic reactions that resolved upon treatment (Table 2).

All three patients treated at the 0.5-mg/kg level tolerated the MDX-11 infusion without experiencing adverse reactions to the mAb. Of the eight patients treated at the 1.0 mg/kg level, four completed the MDX-11 infusion with no adverse reactions. Two reported adverse reactions of mild fever and mild hypotension, National Cancer Institute toxicity grade 2. One patient (patient 109) experienced hypotension and reported dizziness, nausea, vomiting, back pain, aching, shortness of breath, and fever. The mAb infusion was stopped, and the patient was treated for the symptoms and infused with normal saline. The mAb infusion was restarted after the symptoms subsided (approximately 45 min). The adverse events were considered to be mild (ECOG grade II or less). The eighth patient (patient 104) treated at the 1.0-mg/kg level experienced an acute respiratory episode and reported nausea, vomiting, dizziness, and fever. The infusion was stopped after 20 min, and the symptoms resolved within 3 h after treatment. Although the adverse events were grade II or less, the infusion was not restarted.

Three of the five patients receiving 1.5 mg/kg MDX-11 completed the infusion. One reported no adverse events related to the infusion. Two patients experienced grade II (ECOG) events. One of these patients (patient 401) experienced hypotension, chest pain, diaphoresis, and nausea. The infusion was stopped and not restarted. The symptoms resolved upon treatment. The second patient with grade II toxicities experienced hypotension, fever, chills, sinus congestion, and sneezing. Two of the patients treated at 1.5 mg/kg experienced grade IV (ECOG) events. One patient (patient 105) reported fatigue, chills, hypotension, fever, respiratory distress, and tachycardia, but completed the MDX-11 infusion. This patient died 4 days after infusion due to an underlying Gram-negative sepsis (*Escherichia coli*). The second patient (patient 303) with a grade IV event experienced severe back pain, facial burning, shortness of breath, and nausea 7 min into the infusion. The infusion was halted, and the patient subsequently developed tachycardia, fever, disseminated intravascular coagulation, rhabdomyolysis, and respiratory distress. These symptoms all resolved upon treatment. The infusion was not restarted.

Table 2 Toxicities experienced by patients during PM-81 infusion[a]

Dose (mg/kg)	Symptom	Patient count	Severity			Relation to MDX-11		
			Mild	Moderate	Severe	Possible	Probable	Highly probable
0.5	Headache	1/3	0	1	0	1	0	0
	Chest pain	1/3	0	1	0	1	0	0
	Nausea	1/3	0	1	0	1	0	0
	Rash	1/3	1	0	0	1	0	0
1.0	Dyspnea	3/8	1	1	1	2	0	1
	Chills	2/8	1	1	0	0	1	1
	Hypotension	2/8	0	2	0	0	1	1
	Nausea	2/8	0	2	0	1	0	1
	Vomiting	2/8	2	0	0	1	0	1
	Bronhospasm	1/8	0	0	1	0	0	1
	Asthenia	1/8	1	0	0	0	0	1
	Headache	1/8	1	0	0	0	0	1
	Back pain	1/8	0	1	0	0	0	1
	Vasodilation	1/8	0	1	0	0	0	1
	Hypoxia	1/8	1	0	0	0	0	1
	P uritus	2/8	2	0	0	1	1	0
	Fever	2/8	1	1	0	2	0	0
	Tachycardia	1/8	0	1	0	1	0	0
	Myalgia	1/8	1	0	0	1	0	0
1.5	Fever	4/5	0	4	0	2	1	1
	Nausea	3/5	1	2	0	2	0	1
	Chest pain	2/5	0	2	0	0	1	1
	Tachycardia	2/5	0	2	0	1	0	1
	Dyspnea	2/5	0	2	0	1	0	1
	Back pain	1/5	0	0	1	0	0	1
	Vasodilation	1/5	0	1	0	0	0	1
	Hypoxia	1/5	0	0	1	0	0	1
	Bilirubinemia	1/5	0	0	1	0	0	1
	Myopathy	1/5	0	0	1	0	0	1
	Pruritus	1/5	0	1	0	0	0	1
	Hypotension	3/5	0	2	1	1	2	0
	Chills	2/5	0	2	0	2	0	0
	Asthenia	1/5	1	0	0	1	0	0
	Blood pressure instability	1/5	0	0	1	1	0	0

[a] Toxicities listed in order of dose and probable relation to MDX-11.

HAMAs

Only one patient developed HAMAs noted 4 weeks after infusion (titer, 60). This patient was treated with the 0.5-mg/kg dose of MDX-11.

HAMA assays for IgM and IgE (along with the usual assay for HAMA IgG) were performed on all three patients who experienced severe adverse reactions. Titres for all three patients were within the normal range as compared to pooled human sera. The screening sera and 1-week postinfusion sera from the patient experiencing the most severe reaction were also tested for elevated levels of IgE antibody but were found to be within normal ranges.

Effect of Infusion on WBC and Blast Counts

Nine (75%) of 12 patients had a decrease in total WBC count at the completion of the MDX-11 infusion. Seven of the nine patients with decreased WBCs had a 50% or greater transient decrease in their WBC. Blast counts at the infusion end decreased for 8 (67%) of the 12 patients, with as many patients experiencing a 50% or greater transient decrease in their blast counts (Table 3). Significant transient decreases of WBCs and blast counts were seen at all three MDX-11 doses.

Table 3 Patient blast counts (×1000) before MDX-11 infusion, during infusion, at infusion end, and after infusion during chemotherapy

Patient	Infusion start $t = 0$	$t = 12$ h	Infusion end $t = 24$ h	Postchemotherapy start $t = 48$ h
101	5.71	2.09	10.91	2.34
102	22.15	1.25	8.46	33.25
103	0.44	0.14	0.41	0.40
105	0.07	0.00	0.01	0.02
107	16.43	ND[a]	3.04	4.06
108	1.01	ND	0.00	1.17
109	3.91	3.61	1.37	1.15
110	0.10	0.00	0.00	0.00
301	7.80	12.32	11.19	9.49
302	0.00	0.00	0.00	0.00
304	70.18	93.12	65.14	33.07
402	0.00	0.00	0.09	0.06

[a] ND, not done.

Pharmacokinetics

Serum MDX-11 Levels. The dose of MDX-11 received, along with the initial reservoir of CD15, whether cell-bound (on

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