Human Anti-Murine Immunoglobulin Responses in Patients Receiving Monoclonal Antibody Therapy[1]

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ABSTRACT

Human anti-murine immunoglobulin responses were assessed in serum from three groups of patients receiving murine monoclonal antibody therapy. Each of the three patient groups responded differently. Chronic lymphocytic leukemia patients demonstrated little or no preexisting murine immunoglobulin G-reactive antiglobulin prior to treatment, while the cutaneous T-cell lymphoma and melanoma patients demonstrated preexisting antiglobulin levels in the same range as those demonstrated in healthy controls. None of 11 chronic lymphocytic leukemia patients receiving the T101 monoclonal antibody demonstrated an antiglobulin response, whereas all four of the cutaneous T-cell lymphoma patients receiving the same antibody developed increased levels of antiglobulins. Three of nine malignant melanoma patients receiving the 9.2.27 monoclonal antibody showed an increase in antiglobulin titers. In patients developing antiglobulin responses, the response was rapid, typically being detectable within 2 weeks. The antiglobulins were primarily immunoglobulin G and, with the exception of a single melanoma patient in whom the response appeared to have a substantial 9.2.27-specific component (i.e., antiidiotype), were cross-reactive with most murine immunoglobulin G preparations tested. This pattern of results suggested that the antiglobulin was a secondary immune reaction with elevation of the levels of preexisting antiglobulin which was cross-reactive with the mouse antibody administered. While the presence of serum antiglobulin would be expected to present major complications to monoclonal antibody therapy, no clinical toxicity related to antiglobulin responses was observed in these patients, and no inhibition of antibody localization on tumor cells was seen.

INTRODUCTION

Attempts at serotherapy of human tumors date back to the treatment of chronic myelogenous leukemia with antisera by Lindstrom (6) in 1927. However, due to the difficulty in obtaining large quantities of antisera of sufficient specificity, and the many side effects of crude antisera, this form of therapy has not come into general use. The development of monoclonal antibodies of defined specificity and unlimited availability has rekindled interest in the use of passively administered antibody as a form of cancer therapy (13).

The development of host antibodies against passively administered immunoglobulin, with possible neutralization of the administered immunoglobulin and anaphylactic or other immune reactions, has been viewed as a potential major complication to serotherapy. Recent reports of clinical trials with murine monoclonal antibodies have confirmed that human anti-mouse immunoglobulin antibodies may be induced (1, 2, 10, 14, 17). Miller et al. (10) reported development of anti-mouse immunoglobulin antibodies in 4 of 7 T-cell lymphoma patients treated with the anti-Leu-1 monoclonal antibody. In 3 of these 4 patients, the development of anti-mouse immunoglobulin antibodies appeared to contribute to tumor escape from therapy. Similarly, Dillman et al. (1) attributed the lack of response to therapy, in 2 of 4 cutaneous T-cell lymphoma patients receiving the T101 monoclonal antibody, to the presence of human anti-mouse immunoglobulin antibodies. Sears et al. (17) also reported the presence of human anti-mouse immunoglobulin antibodies in 9 of 18 gastrointestinal tumor patients receiving the monoclonal antibody 1083-17-1A. However, other studies did not report that human antiglobulin responses presented major problems in monoclonal antibody therapy (3, 7–9, 15). The relatively small number of reports in the literature of monoclonal antibody clinical trials, the variety of diseases treated, and the lack of uniformity in the design of these trials makes it difficult to draw general conclusions as to the conditions under which host anti-mouse immunoglobulin responses would be expected to develop.

The Biological Therapeutics Branch of the National Cancer Institute has recently completed Phase I clinical trials with the IgG2a monoclonal antibody T101 in patients with CLL[3] and CTCL and the IgG2a monoclonal antibody 9.2.27 in patients with malignant melanoma (2, 3, 14). The T101 antibody recognizes the T65 antigen present on the cell surface of both normal and malignant T-cells, as well as some B-cell cancers, including CLL (16). The 9.2.27 antibody recognizes a M_r 250,000 glycoprotein-proteoglycan associated with melanoma (11). In this paper, the host anti-mouse immunoglobulin responses observed during these trials are summarized, with a comparison of the differences and similarities in the responses elicited within the 3 disease groups, and an analysis of the specificity of the detected antibodies.

MATERIALS AND METHODS

Patients. Patients considered for the clinical trial with T101 were adults with histologically confirmed diagnosis of CLL or CTCL. Patients with malignant melanoma were considered as candidates for treatment with the 9.2.27 antibody. Patients received no radiation or immunosuppressive drugs for at least 4 weeks prior to entry into these trials. Prior to treatment, all patients were fully ambulatory and had no serious unrelated disease, and their tumor cells were positive for reactivity with the antibody to be used in therapy. The mean and range of age of each patient population was: CLL, 59, 43 to 81; CTCL, 56, 42 to 68; melanoma, 48, 23 to 72 years.

[3] The abbreviations used are: CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; ELISA, enzyme-linked immunosorbent assay.

The control population used in this study consisted of 11 healthy individuals with no history of cancers and no previous therapy with murine-derived agents and ranged in age from 20 to 45 years, with a mean of 31 years.

Study Plan. Patients were treated with either T101 or 9.2.27 monoclonal antibody. Details of the design and clinical findings of each trial have been reported elsewhere (3, 14). Briefly, patients with CLL or CTCL received T101 antibody i.v. at fixed-dose levels of 1, 10, 50, or 100 mg. Patients were treated twice weekly for 4 weeks. Initially, patients received the total dose of antibody in 100 ml of 0.9% NaCl solution (saline) with 5% human albumin over 2 hr. Due to pulmonary toxicity associated with the rapid rate of infusion, this was later amended so that antibody was administered at a rate of no more than 1 to 2 mg of T101 antibody per hr. Melanoma patients received the 9.2.27 antibody by i.v. infusion in 100 ml of saline with 5% human serum albumin over 2 hr. Each patient received single doses of antibody twice weekly on an escalating dose schedule of 1, 10, 50, 100, and 200 mg or 10, 50, 100, 200, and 500 mg. A summary of the number of patients treated and the amount of antibody administered is presented in Table 1.

Assay for Human Anti-Mouse Antibody. Sera used in all assays were separated from peripheral blood and stored at $-20°$ until use. Antiglobulins in dilutions of serum were measured using solid-phase T101 or 9.2.27 antibodies dried at $37°$ overnight onto polyvinyl plates at 100 ng of antibody per well and washed with 0.1 M tris (pH 8.3)-0.02% NaN_3-0.5% Tween 20 (Sigma Chemical Co., St. Louis, MO). Dilutions of serum were incubated on the plates at room temperature for 45 min. Bound human immunoglobulin was detected with heavy chain-specific (γ or μ) goat anti-human immunoglobulin conjugated with alkaline phosphatase (Sigma) during a 45-min incubation. For comparison, standard curves were generated against solid-phase human IgM myeloma proteins or pooled normal human IgG (Cappel Laboratories, Cochranville, PA), and antiglobulin expressed as μg of protein bound to plates per ml of serum.

For assays of antiglobulin specificity, plates were coated with T101 Fab or 9.2.27 F(ab')$_2$ preparations (100 ng/well); the mouse myeloma proteins MOPC-21 (IgG1), RPC-5 (IgG2a), UPC-10 (IgG2a), MOPC-141 (IgG2b), and FLOPC-21 (IgG3) (Litton Bionetics, Kensington, MD); mouse IgG (Sigma); mouse IgM (Pel Freeze Biologicals, Rogers, AR); rabbit IgG (Dako, Denmark); or whole T101 or 9.2.27 antibodies. Inhibition of binding to T101 or 9.2.27 target antigen was assessed by performing the ELISA in the presence of a 1000-fold-greater concentration (100 μg/well) of the soluble inhibitor murine IgG2a antibodies 9.2.27, T101, D3, or RPC-5 as compared to the solid-phase target immunoglobulin.

Assay for Mouse Immunoglobulin. Murine immunoglobulin in dilutions of serum was assayed using affinity-purified goat anti-mouse immunoglobulin (KPL, Gaithersburg, MD) adsorbed onto polyvinyl plates at 100 ng/well and washed as above. Bound mouse immunoglobulin

was detected with a goat anti-mouse immunoglobulin conjugated with alkaline phosphatase (Sigma) and compared against a standard curve of either T101 or 9.2.27 antibody.

Assay for Human Serum Immunoglobulin. Serum IgG and IgM levels were determined by radial immunodiffusion utilizing Endoplate immunoglobulin test kits obtained from Kallestad Laboratories, Austin, TX.

Immunofluorescent Staining of Melanoma Specimens. Tumor cells were prepared as single-cell suspensions by teasing tissues which were obtained from skin lesions. To assess *in vivo* localization of the murine 9.2.27 antibody, the cell suspensions were incubated with fluorescein isothiocyanate-conjugated goat anti-mouse IgG (Tago, Inc., Burlingame, CA) for 30 min at $4°$. The cells were then washed by centrifugation and analyzed on a Cytofluorograf 50H (Ortho Diagnostic Systems, Westwood, MA). A similar goat antibody directed against mouse IgM (Tago) was used as a negative control, and incubation in the presence of excess 9.2.27 antibody served as a positive control. All biopsy specimens were obtained 24 hr following infusion of the 9.2.27 antibody.

Statistical Evaluation. Serum antiglobulin levels for a given patient were considered significantly increased at antiglobulin levels greater than 2 S.D.s above the mean of the healthy control group.

RESULTS

Development of Antiglobulin Responses. In order to determine the level of mouse-reactive antiglobulins which could be detected in healthy individuals by our ELISA, antiglobulin levels were assessed in 11 normal donors. As illustrated in Chart 1, the control population demonstrated detectable levels of IgG and IgM antiglobulin reactive with both the T101 and 9.2.27 antibodies. These preexisting antiglobulin levels in the CLL patients prior to therapy were significantly lower ($p < 0.005$ by Student's t test) than those demonstrated by the healthy controls. Serum immunoglobulin levels were determined on the same specimens. Both serum IgG and IgM levels were significantly lower in the CLL group as compared to the control group. However, CLL serum immunoglobulin levels were roughly one half that of controls, while CLL antiglobulin levels were less than one tenth that of control antiglobulin levels.

To substantiate that the assay used was in fact detecting human anti-mouse immunoglobulin antibody, 2 control experiments were performed. To demonstrate that the binding of human immunoglobulin to the ELISA plate was not nonspecific, control and patient specimens were incubated on plates coated with either the T101 or 9.2.27 antibodies, or left uncoated. Table 2 demonstrates that binding did not occur in the absence of mouse immunoglobulin on the plates and that binding was roughly equivalent irrespective of the antibody used to coat the plates. To further substantiate that the preexisting human antibody activity was indeed reactive with mouse immunoglobulin, we performed the ELISA for human anti-mouse immunoglobulin activity in the presence of a 1000-fold-greater concentration of a variety of murine IgG2a preparations. As indicated in Table 3, roughly 50% of the activity could be inhibited in such a manner. The percentage of inhibition represents the decrease in titer due to the presence of the inhibitor immunoglobulin. While there was substantial variability between titers of antiglobulin in the 5 individuals examined, the percentage of inhibition in each case was quite similar, as indicated by the relatively low S.D. The inhibition was not restricted to the mouse immunoglobulin preparation used as the solid-phase antigen. The remaining 50% of the activity is most likely attributable to the weak affinity of antiglobulins for soluble immunoglobulin (12) as compared to the

Table 1
Summary of monoclonal antibody therapy

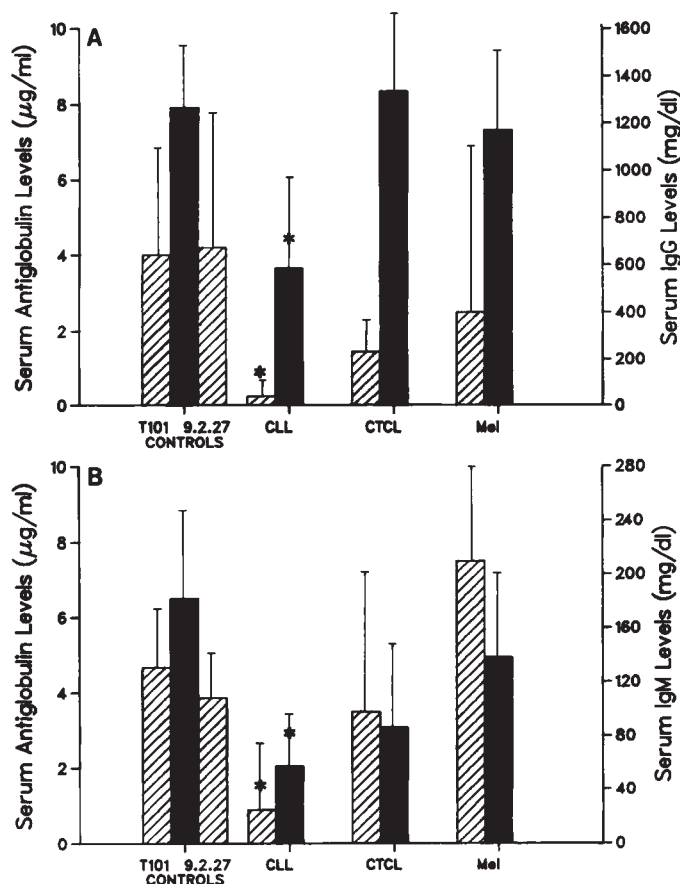| No. of patients treated	Disease	Total dose received (mg)
1	CLL	6
2	CLL	8
1	CLL	50
2	CLL	80
1	CLL	150
1	CLL	300
2	CLL	400
1	CTCL	8
1	CTCL	66
1	CTCL	80
1	CTCL	162
7	Melanoma	361
2	Melanoma	860

Chart 1. Antiglobulin and serum immunoglobulin levels in healthy controls and patients prior to therapy. Serum IgG (A) or IgM (B) antibody levels to both T101 and 9.2.27 antibodies in controls and the appropriate treatment antibody in patients [T101 for CLL and CTCL patients, 9.2.27 for melanoma (Mel) patients] are shown (▨). Serum immunoglobulin levels are indicated for comparison (■). Columns, mean of each group; bars, S.D. The number of individuals in each group was: control, 11; CLL, 11; CTCL, 4; melanoma, 9. *, levels in patient groups which were significantly lower than those of the appropriate control group ($p < 0.005$ as determined by the Student t test).

Table 2

Specific binding of human serum immunoglobulin in solid-phase ELISA IgG antiglobulin assay

Serum specimen	Solid-phase target antigen	Serum dilution			
		1:10	1:50	1:250	1:1250
Melanoma Patient K. G. prior to 9.2.27 treatment	None[a]	0.07[b]	0.00	0.00	0.00
	T101	0.55	0.33	0.26	0.14
	9.2.27	0.47	0.31	0.24	0.11
Melanoma Patient K. G. following 9.2.27 treatment	None	0.04	0.00	0.00	0.00
	T101	0.56	0.43	0.42	0.19
	9.2.27	0.53	0.49	0.41	0.20
Normal control	None	0.08	0.00	0.00	0.00
	T101	0.64	0.35	0.30	0.10
	9.2.27	0.70	0.37	0.25	0.09

[a] No target antigen or control protein bound to plates.
[b] Mean of duplicate absorbance determinations at 405 nm.

solid-phase immunoglobulin, or to nonspecific interactions (4) such as Fc-Fc interactions between the human immunoglobulin and solid-phase murine immunoglobulin.

Antiglobulin levels were assessed in patients over the period of treatment with either T101 or 9.2.27 antibodies as the target

Table 3

Inhibition of 9.2.27-reactive human antiglobulin activity in normal human serum with murine IgG2a

Values represent the mean of 5 healthy control specimens.

Monoclonal antibodies	Inhibitor	
	Titer[a]	% of inhibition
None	70 ± 45[b]	
9.2.27	42 ± 30	42 ± 5
T101	43 ± 36	41 ± 9
D3	34 ± 27	51 ± 10
RPC-5	35 ± 36	57 ± 17

[a] Reciprocal of the dilution yielding an absorbance at 405 nm of 0.3.
[b] Mean ± S.D.

antigens. In the T101 trial, serum specimens were obtained before the third, fifth, and seventh doses. These specimens were obtained immediately prior to doses in order to minimize the possibility of circulating free mouse IgG being present in the specimen. To confirm that serum mouse IgG levels were low, mouse IgG levels were quantitated in all serum samples. Specimens from CLL and CTCL patients all demonstrated mouse IgG levels of less than 1 μg/ml. Specimens from melanoma patients demonstrated somewhat higher levels of mouse IgG but, in all cases, were less than 25 μg/ml. As depicted in Chart 2, CLL patients treated with T101 failed to develop detectable antiglobulin levels over the period of therapy. In contrast, while CTCL patients demonstrated rather low antiglobulin levels prior to receiving T101 antibody, a significant increase in IgG levels of antiglobulin developed over the course of therapy in all 4 patients (Chart 3). Three of these 4 patients also demonstrated rises in IgM antiglobulin levels over the course of therapy, but not to the same magnitude as IgG responses.

Of the 9 melanoma patients in the 9.2.27 trial, 3 developed significant levels of IgG antiglobulin (Chart 4). These same 3 patients demonstrated lower, but yet significant, levels of IgM antiglobulin during the course of therapy. All 3 individuals who developed antiglobulin levels received a total of 361 mg of 9.2.27 antibody.

Specificity of Antiglobulin Response. In order to determine the specificity of the antiglobulin responses elicited, sera from patients who demonstrated significant elevations in antiglobulin levels were tested against a variety of immunoglobulins (Table 4). Specimens from the 4 CTCL patients were assessed for reactivity against whole T101 and a Fab fragment of T101, as well as 5 IgG murine myeloma proteins, the IgG and IgM components of normal mouse serum, and a rabbit IgG preparation. Specimens from the 3 melanoma patients who demonstrated antiglobulin responses were tested against a similar panel, with the exception that the F(ab')₂ fragment of 9.2.27 was substituted for the Fab fragment of T101.

Sera from all 4 CTCL patients and the 3 melanoma patients demonstrated substantial reactivity with whole T101 or 9.2.27, most murine myeloma proteins of the different IgG subclasses, and mouse IgG (Table 4). Little or no reactivity was observed against the Fab or F(ab')₂ fragments or to mouse IgM. These results suggest that the antiglobulin response elicited in these patients was directed to determinants common to murine IgG and was not specific for either the T101 or 9.2.27 antibody. Further, the lack of reactivity to Fab or F(ab')₂ fragments suggests that the reactivity is directed against determinants on the Fc region of the immunoglobulin molecule and not determinants,

Chart 2. Antiglobulin levels in CLL patients. Serum IgG (*A*) or IgM (*B*) antibody levels to the T101 antibody are indicated. *Points*, determinations on serum specimens from 9 patients obtained either prior to therapy (Dose 0) or immediately preceding the indicated dose.
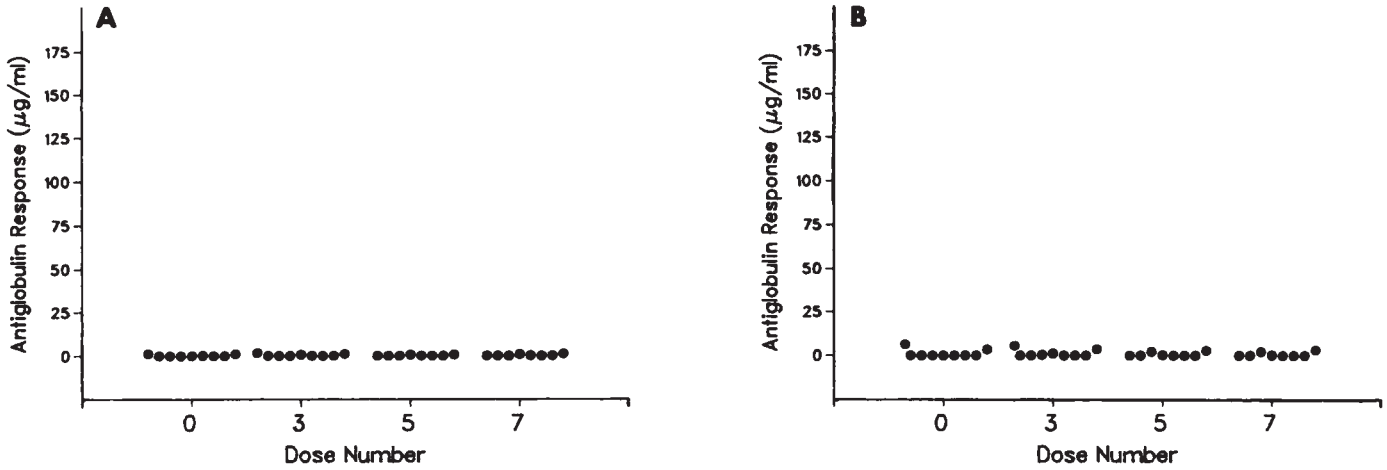

Chart 3. Antiglobulin levels in CTCL patients. Serum IgG (*A*) or IgM (*B*) antibody levels to the T101 antibody are indicated. *Points*, determinations on serum specimens from patients receiving total T101 doses of 8 (●———●), 66 (●····●), 80 (●–––●), or 162 (●——●) mg. Specimens were obtained either prior to therapy (Dose 0) or immediately prior to the indicated dose.
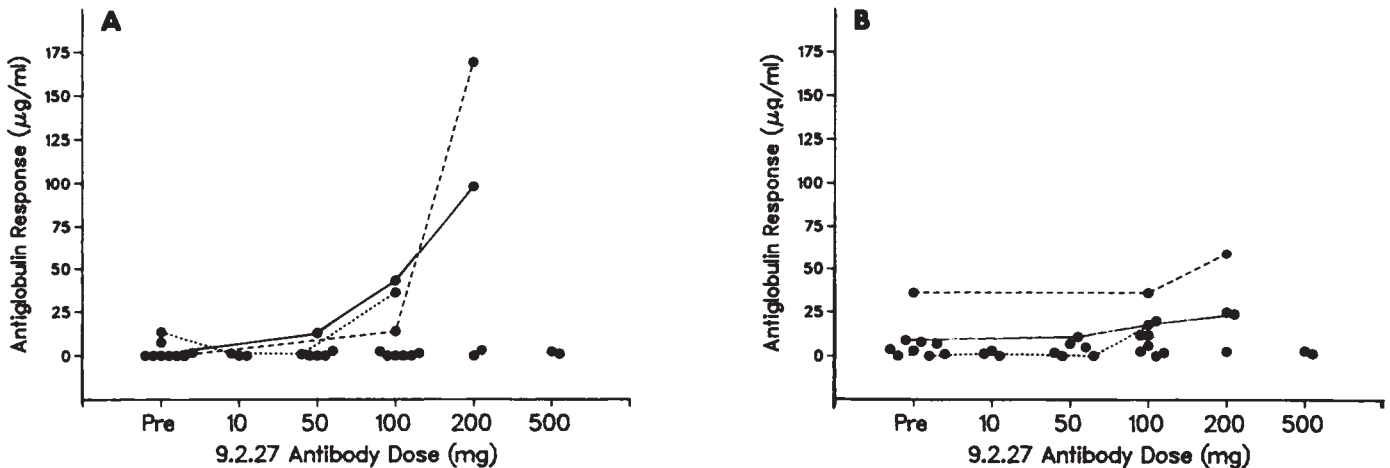
Chart 4. Antiglobulin levels in melanoma patients. Serum IgG (*A*) or IgM (*B*) antibody levels to the 9.2.27 antibody are indicated. *Points*, determinations on serum specimens from 9 patients obtained either prior to therapy (*Pre*) or i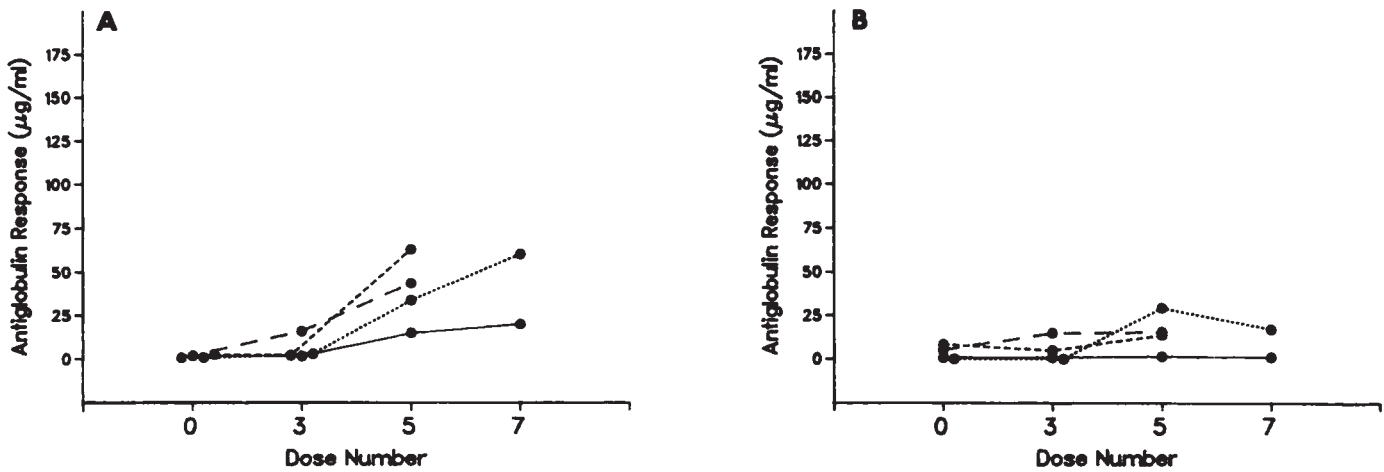mmediately preceding the indicated dose. *Points* from the 3 patients with significant (>2 S.D. above mean of normal controls) responses are connected to indicate the progression of the response.

Table 4

Specificity of posttherapy antiglobulin responses

Values represent μg/ml of serum of human IgG or IgM antiglobulin reactive with the indicated target antigen. Specimens were obtained immediately prior to the final dose of antibody.

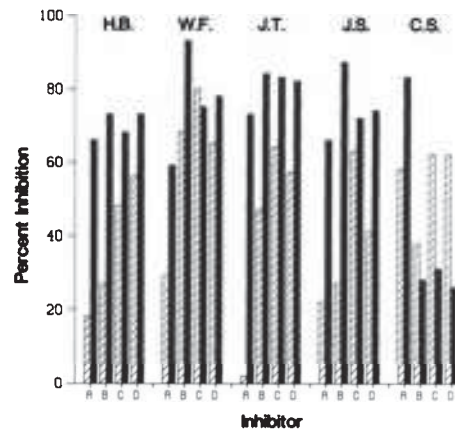| Antibody preparation	CTCL patients				Melanoma patients		
	H. B.	W. F.	J. T.	J. S.	M. F.	C. S.	C. J. S.
T101							
IgG	71.4	91.2	61.2	63.0	40.0	157.5	107.1
IgM	4.9	12.8	14.4	14.4	43.7	58.0	44.1
T101 Fab							
IgG	1.9	1.9	2.7	1.5	ND[a]	ND	ND
IgM	0	0.5	1.2	2.7	ND	ND	ND
9.2.27							
IgG	111.8	55.9	75.0	17.9	25.1	129.4	108.7
IgM	1.6	6.4	6.3	6.8	27.8	189.0	29.1
9.2.27 F(ab′)$_2$							
IgG	ND	ND	ND	ND	1.9	109.5	1.9
IgM	ND	ND	ND	ND	4.7	125.7	12.0
MOPC-21 (γ1)							
IgG	150.9	77.9	61.3	51.4	127.6	236.9	20.8
IgM	2.3	8.2	7.5	5.3	14.8	167.3	36.4
RPC-5 (γ2a)							
IgG	150.9	77.9	61.3	51.4	127.6	236.9	100.8
IgM	2.3	8.2	7.5	5.3	14.8	167.3	22.2
UPC-10 (γ2a)							
IgG	184.2	104.2	104.2	19.8	85.8	256.7	158.6
IgM	1.2	5.7	4.8	2.6	12.8	53.4	13.4
MOPC-141 (γ2b)							
IgG	165.2	180.4	148.0	24.9	116.2	173.3	73.4
IgM	2.2	9.1	11.1	15.2	70.4	162.8	12.8
FLOPC-21 (γ3)							
IgG	185.6	142.4	142.4	2.8	159.1	166.7	50.1
IgM	1.9	3.4	3.6	3.3	182.7	228.8	12.0
Mouse IgG							
IgG	29.2	33.1	41.7	38.2	108.4	297.5	62.9
IgM	0.7	6.2	6.7	8.5	103.2	213.5	75.2
Mouse IgM							
IgG	1.1	0	0	1.5	1.9	3.1	1.5
IgM	0	0	0.5	0.7	1.0	29.2	1.2
Rabbit IgG							
IgG	1.1	0	1.1	1.7	82.2	68.5	12.1
IgM	0.9	0.8	1.6	3.7	13.5	59.9	17.7

[a] ND, not done.

Chart 5. Inhibition of human serum IgG antiglobulin activity with soluble murine IgG2a monoclonal antibody preparations. Specimens obtained prior to antibody therapy (▨) or immediately prior to the final dose of antibody (■) were assessed by solid-phase ELISA for antiglobulin activity against the antibody used in therapy (T101 or 9.2.27). Inhibition of binding of serum antibody to the solid-phase antigen was assessed following addition of a 1000-fold excess of the following IgG2a murine monoclonal antibodies: 9.2.27 (A); T101 (B); D3 (C); or RPC-5 (D). Results are expressed as the percentage of inhibition of titer in the presence of each blocking antibody as compared to the titer in the absence of a blocking antibody. The *patient initials* corresponding to those in Table 4 are indicated over each distribution.

such as the antibody-combining site or idiotype, which reside in the Fab region. Interestingly, the 3 melanoma patients showed reactivity with rabbit IgG, indicating that the antiglobulin response in these patients was not mouse specific. The antiglobulin response in the CTCL patients, however, appeared to be specific for mouse IgG.

One melanoma patient, Patient C. S., demonstrated substantial reactivity against the 9.2.27 F(ab′)$_2$ fragment as well as the whole 9.2.27 antibody (Table 4). However, this reactivity was not restricted to the 9.2.27 antibody but was also present against the murine myeloma proteins and the mouse and rabbit IgG preparations. To further investigate the potential of a 9.2.27 anti-idiotypic component in the antiglobulin response of this and the other patients, a series of blocking studies similar to those described in Table 3 was performed. The results of these studies are presented in Chart 5. Due to insufficient quantities of serum, the 2 melanoma patients other than Patient C. S., who developed significant elevations in antiglobulin levels, could not be examined in this manner. With the exception of Patient C. S., the antiglobulin response was largely inhibitable with all of the murine IgG2a preparations used, with no evidence of an anti-idiotypic component to the antiglobulin response. Patient C. S. demonstrated over 80% inhibition in the presence of soluble 9.2.27 antibody, as compared to roughly 30% inhibition with the other preparations. These data, in combination with the binding studies pre-

sented in Table 4, indicate that this patient developed an anti-globulin response which, although not completely specific for the 9.2.27 antibody, consisted of a substantial component which appears to be specific for the 9.2.27 antibody.

In order to determine the specificity of the preexisting antiglobulin in these patients, pretreatment sera from 3 of the CTCL patients and the 3 melanoma patients with elevated antiglobulin levels during therapy were examined for reactivity against the panel of mouse and rabbit immunoglobulin preparations indicated in Table 4. These analyses demonstrated that the specificity of preexisting antiglobulins was very broad, consistent with the broad specificity of posttherapy antiglobulins in these patients. Data from a representative CTCL patient are presented in Chart 6. This particular patient demonstrated detectable IgG antiglobulin to many, but not all, murine immunoglobulin preparations examined and IgM reactivity against all murine immunoglobulin preparations. Elevated antiglobulin responses posttherapy consisted of IgG antibodies.

Effect of Antiglobulin Responses upon Therapy and *in Vivo* Localization of Antibody. Clinical responses in these Phase I trials were either transient or undetectable (2, 3, 14). The CLL patients all demonstrated transient decreases in leukemia counts but failed to demonstrate lasting effects following cessation of therapy. The CTCL patients had minor regressions of skin lesions that continued throughout the course of therapy regardless of antiglobulin responses. None of the 9 melanoma patients demonstrated any regression of cutaneous nodules during the course of therapy. However, *in vivo* localization of the 9.2.27 antibody was detected in biopsy specimens removed during the course of therapy. The presence of antiglobulin responses did not appear to affect *in vivo* localization in the 3 patients with substantial antiglobulin levels. For example, Chart 7 compares *in vivo* binding of the treatment antibody as detected by immunofluorescence and flow cytometry to the level of serum IgG antiglobulin in one patient. Serum antiglobulin levels as high as

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