CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 1994, p. 365–372 Vol. 1, No. 4
1071-412X/94/$04.00+0
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MINIREVIEW

Will Immunogenicity Limit the Use, Efficacy, and Future Development of Therapeutic Monoclonal Antibodies?

KRISTINE KUUS-REICHEL,* LANA S. GRAUER,[1] LINDA M. KARAVODIN,[1] CHRISTINE KNOTT,[1] MELINDA KRUSEMEIER,[1] AND NEIL E. KAY[2]

Hybritech Incorporated, San Diego, California 92196-9006,[1] and College of Medicine, University of Kentucky, Lexington, Kentucky 40506-0084[2]

INTRODUCTION

Monoclonal antibodies have been under investigation for more than 10 years for use in a variety of clinical applications. These include immunosuppression of allograft rejection; cancer therapy; and treatment of autoimmune diseases, lymphoproliferative disorders, and infectious diseases (14, 17, 71, 74). A potential major barrier in the effective use of monoclonal antibodies for the treatment of human disease is the production of anti-antibodies in response to monoclonal antibody administration (10, 31, 35, 64). Patients who receive monoclonal antibodies exhibit varying degrees of immune responsiveness to the antibodies. This has been measured by assays for human anti-mouse antibody (HAMA) or human anti-human antibody (HAHA). The effects of HAMA and HAHA production on the efficacy of monoclonal antibody therapy are unclear. In this minireview we detail the HAMA and HAHA results of clinical trials in which murine, chimeric (mouse-human), or human monoclonal antibodies were administered to patients and, when possible, summarize the data. We discuss the implications of this information on the potential use of monoclonal antibodies for the diagnosis and treatment of human disease.

HUMAN ANTIBODY RESPONSE TO MOUSE MONOCLONAL ANTIBODIES

The HAMA responses of patients to 38 antibodies in 48 clinical studies are given in Table 1. The clinical protocols were highly variable regarding the dose of antibody per injection, the total dose of injected antibody, the timing of antibody administration, the antibody formulation, and the patient population. The total dose of antibody given to an individual patient ranged from approximately 10 μg to 12 g. Individual patients received from 1 to 47 injections of antibody. As shown in Table 2, 46% of the patients who received one injection of mouse monoclonal antibody developed HAMAs. HAMA responses increased to 75 and 55% among patients who received two to five and more than five injections of mouse monoclonal antibody, respectively.

In general, the total percentage of patients who develop HAMA increases with the number of injections. However, there are exceptions. Weiner et al. (75) reported that administration of 16 injections of 500 mg of 17-1A did not induce a HAMA response, while administration of 1 to 4 injections of 400 mg of 17-1A resulted in HAMA development in 84% of the patients (75). In another study, patients who received eight injections of T101 did not develop HAMAs (21). Conversely, all of the patients who received only one injection of G250 developed HAMAs at all doses of antibody injected (52).

When the data were analyzed to evaluate the effect of the total dose of mouse antibody on HAMA responses, there was little difference in the percentage of patients who developed HAMAs (Table 3). HAMA responses ranged from 49 to 62% in patients who received from less than 1 to 200 mg of antibody. In contrast, 93% of patients who received more than 200 mg of mouse antibody developed HAMA responses.

The form of the antibody injected may also influence the HAMA response. Of patients who received intact mouse antibody, $F(ab')_2$ fragments, and Fab fragments, 57, 83, and 2% of patients, respectively, developed HAMA responses (Table 4). These data show no advantage of $F(ab')_2$ fragments in the elimination of HAMA responses in comparison with intact mouse antibodies. However, Fab fragments appear to be less immunogenic than either intact mouse antibodies or $F(ab')_2$ fragments. Additional studies need to be done to verify these conclusions. To date, results of studies with even smaller and potentially less immunogenic antibody fragments (Fv) have not been reported.

There was great variation between the clinical protocols that were reviewed to obtain the data shown in Tables 1 through 4 and described above. As expected, HAMA responses increased with an increasing number of injections (Table 2). The dosage of antibody appears to be less influential on HAMA development except when the dosage is greater than 200 mg (Table 3).

Another factor that could influence the induction of HAMAs is the immune status of the patients who received mouse antibodies. Many patients tested in these protocols were potentially under drug-mediated immunosuppression or were immunocompromised because of their disease state. Therefore, it is reasonable to assume that if the same studies were done on immunocompetent patients, the percentage of patients who develop HAMA would be even greater. Unfortunately, it was not possible to assess the immune status of each of the patients used in the trials referenced here.

HAMA measurements themselves are not necessarily comparable between different centers. There is no standardization of HAMA testing or an established program for proficiency testing for HAMA. Both commercially available assays and those developed at individual centers were used to measure HAMA reactivity. For example, Kimball et al. (35) distributed a large set of serum samples for correlative testing of HAMA. Serum samples were obtained from transplant recipients who

* Corresponding author. Mailing address: Hybritech Incorporated, P.O. Box 269006, San Diego, CA 92196-9006. Phone: (619) 535-8613. Fax: (619) 457-5308.

TABLE 1. HAMA responses in patients who received mouse monoclonal antibodies

Disease and antibody[a]	Total dose[b]	No. of injections	No. of patients who tested HAMA positive/total no. tested	% Positive[c]	Reference
Colon cancer					
MN-14[d,e,f]	5 mg	1	5/6	83	63
MN-14[d,e,f]	1 mg	1	3/10	24	63
XOMAZYME −791[d,e,f]	0.2–0.4 mg/kg	10	9/9	100	41
B72.3[d,f]	0.2 mg	1	2/12	17	37
	2 mg	1			
	20 mg	1			
B72.3[f]	—[g]	—	31/103	30	42
B72.3[d,e,f]	1 mg	1	3/3	100	65
B72.3[d,e,f]	1 mg	1	6/23	26	78
Anti-CEA[d,f]	—	>8	19/24	79	15
CCR086[d,e,f]	5 mg	1	0/4	0	1
A5B7[d,e,f]	10–30 mg	2–4	6/6	100	39
CCR086[d,e,f]	20 mg	1	4/5	80	1
17-1A[e,f]	200–2,000 mg	1–4	41/43	95	22
17-1A[d,e,f] + gamma interferon	1,600 mg	4	13/14	93	58
17-1A[d]	12 g	16	0/28	0	75
1083-17-1A[d,f]	<360 mg	1	8/16	50	62
	366–1,000 mg	2 or 5	1/2	50	
17-1A[d,f]	—	1	8/11	73	28
		1	8/22	36	
		1	5/9	45	
		2	13/14	93	
		3–5	4/4	100	
		6–8	3/4	75	
Immu-4[f] (Fab′)	—	—	0/109	0	55
CC49[d,f]	—	18	18/18	100	18
HMFG1, HMFG2, H1732, B72.3[f,h]	1–51 mg	1–3	10/10	100	65
Ovarian cancer					
AUA1, HMFG2, HMFG1, H1732[d,f]	10–30 mg	2–4	36/36	100	66
AUA1, HMFG1[d,e,f]	20–30 mg	1	5/22	23	67
OVB3-PE[d,e,f]	2–20 μg/kg	2–4	11/11	100	53
OC-125 [F(ab′)$_2$][f]	—	—	18/18	100	43
OC-125 [F(ab′)2][d,f]	10–70 mg	1	16/23	69	49
OC-125[d]	—	—	6/10	60	29
Melanoma					
ZME018[d,e,f]	21 mg	1	3/8	38	34
96.5[d,e,f]	—	2	5/6	83	34
9.2.27[d,e,f,i]	361 mg	5	3/7	43	2
9.2.27[d,e,f,i]	860 mg	5	0/2	0	2
14G2a[d,f]	—	4	12/12	100	59
Adenocarcinoma					
BW494[f]	2–490 mg	2–14	17/18	94	61
L6 + subcutaneous interleukin-2[d,e,f]	1,400 mg	7	9/14	64	81
Lung cancer					
Anti-GRP[d,f]	47–4,200 mg/m^2	36–47	4/12	33	3
NR-LU-10 (Fab)[f]	—	—	2/35	6	60
T lymphocytes					
T101[d,e,f]	20 mg	2	2/3	67	82
T101[d,e,f]	20–30 mg	2–3	5/5	100	23
T101[d,f,j]	6–400 mg	8	4/14	29	2
T101[d,f]	—	8	0/13	0	21
T101[d,f]	—	4	1/4	25	6
		3	1/3	33	
		4	1/4	25	
T101[f]	—	1–4	5/16	31	64
4DC6[d,e,f]	6 mg	6	1/1	100	77
16H5[d,e,f]	105–140 mg	14	3/4	75	30
OKT4A[d,f]	2.4 mg/kg	12	6/6	100	27
M-T151/VIT4[d,e,f]	70 mg	7	6/8	75	12
M-T151[d,e,f]	140 mg	7	6/10	60	12
B-F5[d,e,f]	70 mg	7	0/1	0	76
	105 mg		1/2	50	
	140 mg		1/7	14	

Continued on following page

TABLE 1—*Continued.*

Disease and antibody[a]	Total dose[b]	No. of injections	No. of patients who tested HAMA positive/total no. tested	% Positive[c]	Reference
B-F5[d,e,f]	200 mg	10	9/10	90	12
	300 mg				
16H5[d,e,f]	105–175 mg	7	5/10	50	30
B-cell lymphoma					
CD19[d,f]	—	5	25/43	58	25
RFB4 (Fab')[f]	—	2–6	1/15	7	72
Other or mixed targets					
L6[d,f]	35–2,800 mg/m^2	7	13/18	72	24
HMFG1[f]	16–240 mg	1–3	6/6	100	69
CYT-356[f]			0/23	0	68
RG83852[d,f]	50–400 mg/m^2	5	2/11	18	54
G250[d,f]	0.2 mg	1	8/8	100	52
	2 mg	1			
	10 mg	1			
	25 mg	1			
Fibriscint (Fab)[f]	0.5 mg	1	16/806	2	79
Myoscint (Fab)	0.5 mg	1	0/>1,000	0	79

[a] Antibody(s) used in each study. Data are categorized by disease target and not necessarily specificity. In studies in which multiple antibodies were used, total dose reflects the sum of all antibodies. All studies were performed with whole antibodies except where indicated.
[b] Total dose of antibody administered as cited in the reference or calculated from the dose and number of injections.
[c] Percentage of patients positive for HAMA was calculated from the data in the previous column.
[d] Data were used to construct Table 2.
[e] Data were used to construct Table 3.
[f] Data were used to construct Table 4.
[g] —, data not given.
[h] In that study, the relative amounts of different antibodies were not stated.
[i] Escalating dose schedule.
[j] Number of injections stated in the clinical protocol, although it appears that some patients received less than eight injections.

received OKT3. Patient samples were sent to seven testing centers for independent analysis of the immunoglobulin G (IgG) anti-OKT3 antibody. The seven laboratories yielded widely disparate estimates of the number of HAMA-positive serum samples. Since HAMA assays are clearly variable, reliable and consistent measurement of HAMAs from center to center should be required.

HUMAN ANTIBODY RESPONSE TO HUMAN OR "HUMANIZED" MONOCLONAL ANTIBODIES

The rationale behind the development of human or humanized monoclonal antibodies is the assumption that the patient's humoral immune response to human antibodies would be significantly reduced compared with that to mouse monoclonal antibodies (31, 74). Several human or humanized antibodies have undergone clinical trials. Unfortunately, in many cases, anti-human antibodies were not measured.

Clinical trials that report the analysis of HAHA or human anti-chimeric antibody responses are detailed below (Table 5).

TABLE 2. HAMA responses in patients who received mouse monoclonal antibodies by number of injections of antibody

No. of injections	No. of studies[a]	No. of patients who tested HAMA positive/no. of patients tested	% Positive[b]
1	13	84/182	46
2–5	15	141/187	75
>5	18	117/213	55

[a] The data used to derive this table are indicated in Table 1.
[b] Percentage of patients positive for HAMA was calculated from data in previous column.

In all cases cited here, the anti-antibody responses against the whole antibody were measured. In the case of chimeric antibodies, anti-antibody responses to the whole antibody, without discrimination between human and mouse regions, were measured. In the majority of the studies, there was no measurable immune response against the injected antibodies (Table 5). In some studies, multiple injections and/or a highly immunogenic antibody were predictably influential in the development of an anti-human or an anti-chimeric antibody response (32, 45, 46).

The relationship between multiple injections and immune response is summarized in Table 6. Fifty-two percent of patients who received more than one injection of chimeric antibody developed anti-antibody responses, whereas 12% of patients who received a single injection of antibody developed anti-antibody responses. Only 0.6% of the patients who received one injection of human antibodies developed anti-antibody responses. Data were not available on multiple injections of human antibodies. Thus, after one injection,

TABLE 3. HAMA responses in patients who received mouse monoclonal antibodies by total dose of antibody

Total dose (mg)	No. of studies[a]	No. of patients who tested HAMA positive/no. of patients tested	% Positive[b]
<1	4	23/47	49
2–10	3	6/11	55
11–50	7	39/64	61
51–200	5	20/32	62
>200	6	84/90	93

[a] The data used to derive this table are indicated in Table 1.
[b] Percentage of patients positive for HAMA was calculated from data in previous column.

TABLE 4. HAMA responses in patients who received mouse monoclonal antibodies by form of antibody

Antibody	No. of studies[a]	No. of patients who tested HAMA positive/no. of patients tested	% Positive[b]
Intact	52	441/774	57
$F(ab')_2$	2	34/41	83
Fab	4	19/965	2

[a] The data used to derive this table are indicated in Table 1.
[b] Percentage of patients positive for HAMA was calculated from data in previous column.

human antibodies appear to be even less immunogenic than chimeric antibodies.

A dose- or injection-related anti-chimeric antibody response was seen with the humanized monoclonal antibody CAM PATH-1H, an IgG1 monoclonal antibody specific for the glycoprotein CDw52 (32). Four patients were given 1 injection of antibody (4 mg) and four patients received 10 injections of antibody (60 mg). There was no measurable anti-CAM PATH-1H antibody response with one injection, but three of four patients generated anti-antibody responses after multiple injections. The investigators concluded that humanization reduced the immunogenicity of the antibody but anti-idiotypic responses may still be generated with repeated injections, even in patients who share an Ig allotype with the humanized antibody (32).

In addition to or in the absence of a humoral immune response, cellular immunoregulatory pathways can be activated (57). A single dose of human 105AD7 anti-idiotypic antibody was given to six patients with colorectal cancer in a phase I clinical trial (57). Lymphocyte proliferation to 105AD7 and increased interleukin-2 production were measured in four of five patients. However, no anti-idiotypic antibodies or anti-tumor antibodies were detected.

EFFECT OF HAMA ON IMAGING AND THERAPEUTIC EFFICACY

The development of HAMA in patients following injection of murine monoclonal antibodies resulted in diminished imaging and therapeutic efficacy in some clinical trials (13, 39, 40, 44, 56, 64, 70) but not in others (4, 34, 78). The reduced efficacy reported in patients who develop HAMA responses has been attributed to the rapid clearance of the murine antibody because of complex formation and the blocking of the murine antibody-binding domain by human anti-idiotypic antibody.

In one study (56) in which patients received multiple courses of ^{131}I-labelled antibody, all patients developed HAMA within 1 month. The authors stated that HAMA reduced the efficacy of the radiotherapy by the development of immunocomplexes that resulted in increased clearance of the antibody and decreased tumor uptake of the murine antibody. It has been suggested that even in studies in which clearance of murine antibodies through complex formation is not present, the anti-mouse Ig response may interfere with antibody-mediated effector cell functions, deplete complement, or block critical effector cell function (70).

HAMA has interfered with imaging efficacy, especially in repeat-use protocols. One study was designed to examine the effectiveness of cyclosporine A (CsA) in suppressing HAMA. Serial nuclear scan images showed that when HAMA levels were maintained at less than 6 μg/ml by the administration of

TABLE 5. Anti-antibody responses in patients who received human or humanized antibodies[a]

Disease and antibody	Total dose[b]	No. of injections	No. of patients who tested HAHA positive/no. of patients tested[a]	% Positive[c]	Reference
Colon cancer					
Human 105AD7	100 μg	1	0/6	0	57
Chimeric B72.3	Varied	1	8/9	88	46
		2	8/9	88	46
Chimeric 17-1A	—[d]	1	0/6	0	47
Chimeric B72.3	2–3 mg	1	4/5	80	45
Adenocarcinoma					
Human 88BV59	8–10 mg	1	2/53	4	14
Human 16.88	5 mg	1	0/16	0	26
T lymphocytes					
Chimeric anti-CD4	50–300 mg	>1	—	10	79
Chimeric anti-Tac	0.5–1.5 mg/kg	1	0/15	0	8
Chimeric anti-CD7 (SDZCHH380)	180 mg	6	0/10	0	38
Chimeric CAMPATH-1H	4 mg	1	0/8	0	32
	60 mg	10	3/4	75	
	260 mg	15	3/4	75	
Ovarian cancer, chimeric MOV18 [Fab, $F(ab')_2$]	1 mg	1	0/14	0	11
Platlets, chimeric 7E3-IgG1	5–20 mg	1	0/47	0	79
Lipopolysaccharide, human HA1A	100 mg	1	0/198	0	79
Colon or breast cancer, human MCA	10 mg	1	0/24	0	48

[a] Anti-antibody responses to the whole antibody were measured. Mouse versus human activity was not determined in patient responses to chimeric antibodies.
[b] Total dose of antibody administered as cited in the reference or calculated from the dose and number of injections.
[c] Percentage of patients positive for HAHA was calculated from data in previous column.
[d] —, data not available.

TABLE 6. Anti-antibody responses in patients who received human or chimeric monoclonal antibodies[a]

Antibody and no. of injections	No. of studies[b]	No. of patients who tested HAHA positive/no. of patients tested	% Positive[c]
Chimeric			
1	7	12/104	12
>1	4	14/27	52
Human			
1	5	2/297	0.6
>1	—[d]	—	—

[a] Anti-antibody responses to the whole antibody were measured. Mouse versus human activity was not determined in patient responses to chimeric antibodies.
[b] Data used to derive this table are given in Table 5.
[c] Percentage of patients positive for HAHA was calculated from data in previous column.
[d] —, data not available.

CsA, repeated injections led to the further accumulation of radioactivity in the tumor with each dose. In contrast, a patient whose HAMA level rose to 39 μg/ml before administration of the second dose of ^{131}I-labelled A5B7 showed no tumor localization, although localization was acceptable with the first dose of antibody when this patient's HAMA level was 1 μg/ml (39).

In another study (40), ^{99m}Tc-labelled anti-CEA antibody was injected multiple times to image adenocarcinoma of the lung. Good images were obtained following the first injection of antibody, but no tumor imaging was possible after the second injection of antibody. Uptake of antibody in the liver, spleen, and skeleton was observed following the second injection. In addition, second injections of antibody induced serum sickness.

In contrast to these examples, several groups have reported minimal or no impact of HAMA on the ability to image tumors with antibody in HAMA-positive patients (4, 34, 78). In addition, the development of HAMAs may in fact prove to be beneficial in immunotherapy and may be responsible for the delayed efficacy which has recently been reported in several clinical trials of immunotherapy (see below).

MANAGEMENT OF HAMA RESPONSES

Many patients who receive injections of mouse monoclonal antibodies develop HAMA responses. Anti-antibody responses could be decreased or eliminated by blocking the development of the response with immunosuppressant drugs.

Studies by Ledermann et al. (39) and Bjorn et al. (9) show that CsA is effective in decreasing, but does not eliminate, the HAMA response associated with the injection of mouse monoclonal antibodies (9, 39). In spite of the incomplete suppression of HAMA responses, use of CsA allowed for multiple administrations of radiolabelled murine monoclonal antibodies (9).

Dhingra et al. (16) studied the effect of 15-deoxyspergualin (DSG) on HAMA generation to the antibody L6 which induces anti-antibody responses in two-thirds of the patients who receive it (24). Both anti-mouse- and anti-L6-specific antibody responses were measured (16). Anti-mouse antibody responses were not measurable in six of eight patients in the group that received DSG at 50 mg/m^2 and six of seven patients in the group that received DSG at 150 mg/m^2. Production of anti-L6-specific antibody was prevented in three of eight patients in the group that received DSG at 50 mg/m^2 and in three of three patients in the group that received DSG at 150 mg/m^2 (16).

While CsA and DSG were able to decrease HAMA responses in patients who received mouse monoclonal antibodies, they were unable to completely eliminate them. In addition, administration of immunosuppressant drugs is often associated with unacceptable toxicities that will decrease their usefulness in the attenuation of the HAMA response. On the horizon, there are several new drugs that show potential for the management of anti-antibody responses via their abilities to block the generation of primary antibody responses in vivo. These include brequinar sodium (33, 80), mycophenolic acid (20), and leflunomide (5).

RELATIONSHIP OF MONOCLONAL ANTIBODIES TO THERAPEUTIC BENEFIT OF TUMOR PATIENTS

Recently, several groups have suggested that the immune response generated by injection of monoclonal antibodies may invoke a cascade of anti-idiotypic antibodies that produce beneficial effects in tumor patients. There is no direct proof that the idiotypic network is the operative mechanism in human tumor regression after the infusion of murine monoclonal antibodies. However, several trials report results that strengthen this hypothesis. Ovarian cancer patients were given murine monoclonal antibody reactive for CA125 antigen, a commonly expressed surface antigen in nonmucinous epithelial ovarian adenocarcinoma (73). There was a correlation between a vigorous HAMA response, induction of the idiotypic network, and patient prognosis (73). Recently, it has been shown that two of these patients, who had high HAMA levels in their sera, may have had enhanced cytotoxic lymphocyte activities over those in patients with low HAMA levels in their sera (19). A separate study demonstrated that patients with gastrointestinal cancer treated with mouse monoclonal antibodies reactive with colorectal membrane antigens can generate anti-idiotypic antibodies and have improved tumor regression (36).

Thus, it appears that murine monoclonal antibodies are capable of activating the idiotypic network which may generate anti-tumor activity through both humoral and cellular responses (7, 50). The likelihood of cross-reactive anti-idiotypes (7) should also increase the spectrum of tumor patients who will benefit from therapy that activates the idiotypic network.

SUMMARY

While monoclonal antibodies show promise for use in the treatment of a variety of disease states, including cancer, autoimmune disease, and allograft rejection, generation of anti-antibody responses still remains a problem. For example, 50% of the patients who receive OKT3 produce blocking antibodies that interfere with its binding to T cells, thus decreasing the therapeutic effect (51). HAMA responses have also interfered with tumor imaging (39, 40) and radioimmunotherapy (56).

The generation of an anti-antibody response is dependent on many factors. These include the dose of antibody, the number of injections of antibody, the immunogenicity of the antibody, the form of the antibody, and the immunocompetence of the recipient. Predictably, both the number of injections of antibody and the dosage are influential in the generation of an anti-antibody response. It is apparent that human antibodies, chimeric antibodies, and mouse Fab fragments are much less likely to induce anti-antibody responses than intact mouse monoclonal antibodies or mouse F(ab')$_2$ fragments

when one injection is administered. Injection of human or chimeric antibodies appears to reduce immunogenicity, but the probability that anti-antibody responses can still be induced on multiple injections must be considered and appropriately evaluated.

Several areas demand extensive investigation to enhance the clinical utility of monoclonal antibodies. First, results of thorough clinical trials with human or chimeric antibodies need to be evaluated for the induction of anti-antibodies after multiple injections of antibodies. Second, less immunogenic forms of antibodies (Fab, Fv) need to be studied for their clinical efficacies and for their abilities to induce anti-antibody responses. Finally, it is possible that human antibodies, chimeric antibodies, and/or antibody fragments will still not eliminate anti-antibody responses, especially when multiple administrations are required and patients produce anti-antibodies that block effector cell function. In this case, immunosuppression should be considered as an adjunct therapy to eliminate deleterious anti-antibody responses.

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