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Immunogenicity of engineered antibodies

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Abstract

Administration of a therapeutic antibody can lead to an anti-antibody response (AAR). Much effort has been applied to engineering antibodies with as little as possible non-human structure to minimize such responses. Here, we review reported AAR to murine, mouse–human chimeric, and humanized antibodies. Replacement of mouse immunoglobulin constant regions with human ones effects the largest immunogenicity reduction. Humanization of variable domains effects a further decrease.
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1. Introduction

Murine monoclonal antibodies (mAbs) have proved tremendously useful in diagnostics. However, when used in the treatment of patients with various ailments, their effect is not always sustained. This is often due to the development of human anti-mouse antibodies (HAMA), leading to clearance of the murine mAb and adverse events that are sometimes fatal.

HAMA have been the impetus for efforts over the last 20 years to reduce the murine content of therapeutic mAb. Chimeric mAb, with human constant regions, humanized mAb, retaining only murine CDRs, and "fully human" mAb made from phage libraries or transgenic mice have progressively reduced the murine content of therapeutic mAb to nil. Publication of this volume on engineered mAb offers an opportunity to review the degree to which the methods for replacement of murine content with human has translated to a corresponding reduction in incidence of anti-antibody response (AAR).

Comparison of the relative immunogenicity of any two antibodies is rife with logical flaws. In general, one would be comparing two structurally different mAb, recognizing different Ag, used for different indications, among different patient groups, on different dosing regimens, with immunogenicity scored by different procedures. Indeed, a landmark study of a humanized anti-tumor necrosis factor α mAb in healthy volunteers [1] demonstrated human anti-humanized antibody (HAHA) activity in *all* subjects in a low dose cohort and *no* subjects in a high dose cohort. While acknowledging the intellectual hazard of AAR's profound dependency on treatment context, we embarked on a review of the literature on AAR to attempt to discern any broad trends in immunogenicity that may distinguish therapeutic antibodies' molecular format.

2. Methods

To review HAMA responses, a Medline search for the period January 1984 to December 2003 using the unrestricted keywords "human AND anti-mouse AND antibodies" or "HAMA" was done. Similarly, review of HACA responses utilized the keywords "human AND

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anti-chimeric AND antibodies" or "HACA" while review of HAHA responses utilized the keywords "human AND anti-human AND antibodies" or "HAHA". Full-length articles were selected for review based on the contents of their published abstracts. Criteria used to select reports for our database analysis were a clear description of AAR, sufficient numbers of patients for analysis and consistency of data between reports. Where there was more than one paper reporting AAR, the paper with either more patients or most representative data were chosen for inclusion in our database for analysis. We also examined prescribing information posted on-line by mAb manufacturers. Additional Medline searches were focused on the keywords "immunogenicity AND antibodies" and "humanization AND immunogenicity." Relevant publications referenced in the reviewed literature were further included for review, if not present in the original Medline search. For antibodies that had obtained approval by the United States Food and Drug Administration (FDA), the relevant company product information was preferentially used.

3. Findings

The results of this study were limited by varied sensitivity and specificity of assays used for the assessment of AAR and varied methods of sample handling and timing of sample collection. We chose to use AAR incidence figures quoted in the literature at face value, without trying to parse patient subsets or intensity of AAR in individual patients. We grouped incidence into three operational categories: *negligible*, *tolerable*, and *marked*. Abs were classified as having *negligible* immunogenicity when AAR was reported in less than 2% of patients. We adopted this classification because immunogenicity this low represents an ideal, with hardly any need for concern about safety. We classified immunogenicity as *tolerable* if detectable in 2–15% of patients. When classified as tolerable, the mAbs were essentially flawed, though use was arguably warranted for catastrophic or life-limiting disease. We classified immunogenicity as *marked* if present in more than 15% of patients. Products with *marked* AAR were usually clinical failures and regulatory concerns were likely to preclude clinical use except for one time use as radioimmunoconjugates. We used these operational classifications to bin the immunogenicity of mAb in the clinic or in clinical development.

3.1. Are mouse mAb immunogenic?

The immunogenicity of mouse antibodies is well known. The compilation of results in Table 1 represents our attempt to define a baseline from which the effect of chimerization or humanization can be compared. Forty-four murine mAb were included in our analysis (Table 1). As seen in Fig. 1, 84% of mAbs had *marked* HAMA reactions, and 7% had *tolerable* HAMA, while 9% had *negligible* HAMA. Of those with negligible HAMA, two of four were used for imaging, not therapy. Of these 44 murine mAb, three (Muromomab-CD3, Ibritumomab, and Tositumomab) were approved by the FDA for marketing. Ibritumomab (Zevalin) and Tositumomab (Bexxar) are both labeled with radioactive isotopes. One other murine antibody (Edrecolomab) was approved for use in Germany and four others are in late stage development/phase III clinical trials. Of the four antibodies approved for marketing, AAR was on the high end for those approved earlier (88% for muromonab-CD3 and 100% for edrecolomab, approved in 1986 and 1995, respectively). For the ones approved in more recent years, AAR was in the lower range for those that obtained approval (<2% for Y90 ibritumomab and 8% for I131 tositumomab, approved in 2002 and 2003, respectively). In view of the high incidence of AAR with murine mAb, the substantial degree of immunogenicity of mouse mAbs is unequivocal. It is very rare for a murine mAb to show negligible immunogenicity, and very common for 100% of patients to show HAMA.

3.2. Are chimeric mAb less immunogenic than mouse mAb?

Fifteen chimeric Abs with clearly reported AAR were included in our analysis (Table 2). We found that 40% had HACA defined as *marked*, 27% *tolerable*, and 33% *negligible* (Fig. 1). Clearly, when the Fc regions of murine mAbs are substituted with human sequences, the incidence of human AAR is much reduced. Of these 15 chimeric mAbs, four have been approved by the FDA for marketing (rituximab, infliximab, cetuximab, and basiliximab) and two more are in phase II clinical trials (SGN30 (no AAR data found) and G250).

3.3. Are humanized mAb less immunogenic than chimeric mAb?

Twenty-two humanized mAb had clearly reported AAR and were included in our analysis (Table 3). Nine percentage had HAHA defined as *marked*, 36% had *tolerable* AAR, and 55% had *negligible* AAR (Fig. 1). Where two versions of the mAb were used the one reporting the higher AAR was used in our analysis. Six of these mAbs (30%) were approved by the FDA for marketing and four more are in late stage development. Two findings emerge from these data. First, the low immunogenicity of humanized antibodies cannot be assumed. For example, humanized mAb A33, used in colon cancer patients [2], had a HAHA incidence of 66%, a value that would be typical for a fully murine mAb. Second, the main impact of humanizing on immunogenicity is reduction of the *marked* category. Humanized mAb with *marked* immunogenicity are notably less

Table 1
Reported human anti-mouse antibody (HAMA) responses

Antibody (synonyms)	Indication	% of patients with AAR	References
2H4 and 5D3	Nasopharyngeal carcinoma	100	[8]
Anti-Lym1 mAb	B-cell malignancies	38	[9]
10-3D2	Breast tumor	14/indium-111-labeled	[10]
131I-labeled anti-HCC mAb/Hepama-1	Hepatocellular carcinoma	34	[11]
131I-T101	Cutaneous T-cell lymphoma	100/I131-labeled	[12]
14G2a	Refractory melanoma, neuroblastoma, or osteosarcoma	89	[13]
16H5	Rheumatoid arthritis	50	[14]
17-1A	Colorectal CA	100	[15]
A7-NCS	Colorectal carcinoma, pancreatic carcinoma	100	[16]
Anti-CEA antibody fragments (A5B7-F(ab′)2), conjugated to bacterial enzyme, carboxypeptidase G2 (CPG2) followed by a galactosylated anti-CPG2 mAb (SB43)	CEA-bearing tumors	100	[17]
Anti-CEA, anti-In-DTPA bispecific Fab′–Fab	Colorectal carcinoma (imaging)	64	[18]
Anti-melanoma or anti-CEA mAbs	Melanoma, colorectal carcinoma (imaging)	83	[19]
Arcitumomab	Colorectal carcinoma for imaging	0	[20]
B43-Genistein	B-lineage acute lymphoblastic leukemia	33	[21]
B72.3	Colorectal carcinoma	44% with 111In-SCN-Bz-diethylenetriaminepenta-acetic acid (DTPA)-labeled. 26% with In-111 (In-111) B72.3 glycyl-tyrosyl-*n*-diethylenetriaminepenta-acetic acid lysine (GYK-DTPA)-labeled	[22,23]
B-C7	Septic shock	100	[24]
B-E8	Myeloma, renal cell carcinoma	75	[25]
BrE-3, 111In-MX-DTPA	Human ductal breast cancer	83	[26]
BW 250/18399mTc-labeled	Detection of inflammatory lesions (imaging)	1	[27]
BW 431/2699mTc-labeled	Colorectal and lung adenocarcinoma (imaging)	33	[28]
BW 494/BI 51.011	Pancreatic cancer	94	[29]
CCR086 indium-111-labeled	Detection of colorectal carcinoma metastases (imaging)	80	[30]
CYT-103 111In-labeled anti-TAG-72 mAb	Colorectal carcinoma (imaging)	42	[31]
D612	Metastatic gastrointestinal cancer	86	[32]
E5/Edobacomab	Gram negative sepsis	20	[33]
HMFG1, HMFG2, H17E2, B72.3	Ovarian cancer radioimmunotherapy	100	[34]
HRS-3/A9	Hodgkin's disease	46	[35]
Ibritumomab-Tiuxetan/Zevalin	Non-Hodgkin's lymphoma	<2	[36]
IgM mAbs,WM63(CD48)and WM66	Chronic lymphocytic leukemia	0	[37]
Ior EGF/r3	Gliomas or meningiomas	89	[38]
LL2	Non-Hodgkins lymphoma	19	[39]
L6	Adenocarcinoma	64	[40]
M195	Myeloid leukemias, myelodysplastic syndromes	37	[41]
MAb with high human immunodeficiency virus type 1 (HIV-1) neutralizing titers	Human immunodeficiency virus	73	[42]
OC/TR bispecific mAb	Intraperitoneal (i.p.)treatment of ovarian cancer	100	[43]
OC125	Ovarian cancers	100	[44]
OKB7 I131-labeled	CD21-positive, non-Hodgkin's lymphoma	75	[45]
OKT3	Graft rejection	86	[46]
OV-TL 3	Ovarian cancer	40	[47]
T101	Cutaneous T-cell lymphoma or chronic lymphocytic leukemia	100	[12]
I131-tositumomab/Bexxar	Non-Hodgkin's lymphoma	8	[48]
YTH 24.5 and YTH 54.12	Pretreatment of donor organs for transplantation	5	[49]
ZCE 025	Colorectal carcinoma	64/up to 100% with 111In-ZCE 025-labeled form	[50]
ZME 018 and 96.5	Melanoma or basal cell carcinoma	88	[51]

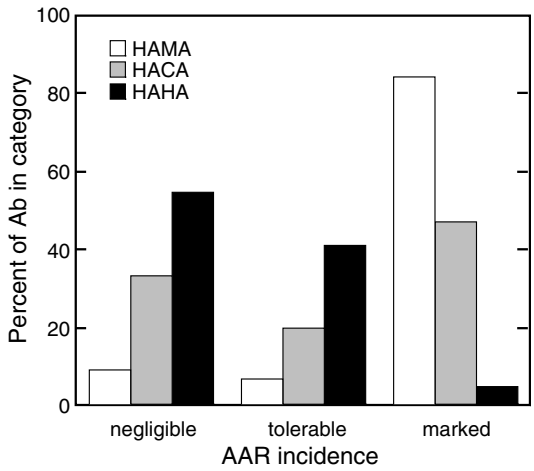

Fig. 1. AAR incidence compared to molecular format. Antibody and immunogenicity incidence data pairs from each clinical study were sorted according to molecular format (mouse, chimeric, and humanized) and binned according to immunogenicity level (negligible, tolerable, and marked) as defined in the text. Bars in the histogram mark the percentage of antibodies, of those of a particular format, whose immunogenicity falls within the indicated level.

common than chimeric mAb in this operational category. However, if the marked category is discounted, humanized and chimeric mAb both have about equal proportions of *tolerable* and *negligible* examples (Fig. 1).

3.4. Does immunosuppression reduce AAR?

Very few studies report controlled comparisons between AAR with concomitant immunosuppression and without. Humira (adalimumab), a phage-derived human anti-TNFα antibody, was immunogenic in 12% of patients, whereas a cohort treated additionally with methotrexate showed 1% AAR [3]. Remicade (infliximab), a chimeric antibody to the same antigen, dosed repeatedly gave AAR in 75% of patients treated with mAb alone, versus 43% of patients concurrently taking immunosuppressive drugs [4]. In a study of Humicade, a humanized anti-TNFα, concomitant use of immune modifiers was incorporated into a complex study design, and was not observed to affect the incidence of AAR [5]. Simulect (basiliximab), a chimeric anti-CD25, gave a contrasting result: 1.4% of transplant patients showed HACA, but this incidence jumped to 12% among patients who also received the murine anti-CD3 antibody muronomab-CD3. In this case, the mouse antibody, though immunosuppressive, may potentiate latent reactivity with murine structures on the chimeric antibody. Immunosuppression of HACA or HAHA, though in keeping with immunological theory, is not necessarily a certainty, and indeed formally, the exceptions are as numerous as the positive examples.

3.5. Is AAR less with anti-B-lymphocyte antibodies?

Since anti-B-cell antibodies would be expected to attenuate the cells responsible for the humoral AAR, immunological theory predicts that mAb to B-cell markers would be inherently less immunogenic than other therapeutic mAb. Clinical immunogenicity data support this hypothesis. Among chimeric and humanized antibodies, evidence is anecdotal. Rituximab and Campath-

Table 2
Reported human anti-chimeric antibody (HACA) responses

Antibody/synonyms	Antigen; indication	% of patients with AAR	References
Rituximab/Rituxan	CD20; B-cell non-Hodgkin's lymphoma	0	[52]
Abciximab	β3integrin of the GPIIb/IIIa and $\alpha_v\beta_3$ receptors on human platelets; adjunct to percutaneous transluminal coronary angioplasty or atherectomy (PCTA) for the prevention of acute cardiac ischemic complications	4.8. After a first readministration, an additional 19.0% became HACA-positive	[53]
Basiliximab/Simulect	CD25; prophylaxis/treatment of organ/hematopoietic stem cell transplant or graft versus host disease	11.8% with OKT3, 1.4% without OKT3	[54]
Infliximab/Remicade	TNFα; Crohn's disease, rheumatoid arthritis	61	[4]
111In-labeled c-Nd2	Pancreatic cancer (imaging)	0	[55]
131I-labeled chimeric L6	Breast cancer	67%. None if concomitant cyclosporin	[56]
cG250	Clear cell renal cancer	0%. 12.5% with I-131-labeled Ab	[57,58]
ch14.18	Ganglioside GD 2; neuroblastoma	0	[59]
chA7Fab	CEA expressing tumors	71	[60]
Chimeric OC/TR	Bispecific F(ab′)2 against CD3 and human folate-binding protein (FBP) on non-mucinous ovarian carcinomas; ovarian carcinoma	50	[61]
cMOv18	Ovarian carcinoma	0	[62,63]
cM-T412	CD4; rheumatoid arthritis	60	[64]
Anti-CEA mAb/cT84.66	Metastatic CEA-producing malignancies	7	[65]
(186)Re-labeled chimeric U36	CD44v6; head and neck cancer	40	[66]
Cetuximab/Erbitux	Epidermal growth factor receptor; colorectal cancer	5	[67]

Table 3
Reported human anti-humanized antibody (HAHA) responses

Antibody/synonyms	Antigen; indication	% of patients with AAR	References
Alemtuzumab/Campath-1H	CD52; B-cell chronic lymphocytic leukemia (B-CLL)	1.9	[68]
Daclizumab/Zenapax	CD25; prophylaxis of acute organ rejection in patients receiving renal transplants, to be used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids	14% low titer anti-idiotype Ab, 34% in pediatrics	[69]
Palivizumab/Synagis	Respiratory syncytial virus; prophylaxis in pediatric patients at high risk of RSV disease	1	[70]
Trastuzumab/Herceptin	HER2/neu (human epidermal growth factor 2); metastatic breast cancer with tumors overexpressing the HER2 protein	0.1	[71]
16.88/CTA 16.88	CTA 16.88-bearing epithelial-derived tumors including carcinomas of the colon, pancreas, breast, ovary, and lung	0	[72]
88BV59/CTA 16.88	CTA 16.88-bearing epithelial-derived tumors (different epitope)	3.7% low titer after a single administration of 88BV59. 0.3% with Tc99m version	[72,73]
hu-A33	"A33" colonic epithelium Ag; colon cancer	Early onset (49%) peaked at 2 weeks, then declined. Later onset (17%) continued building	[2]
Bivatuzumab/BIWA 4	CD44v6; head and neck squamous cell carcinoma (HNSCC)	0% with Tc-99m version. 10% with (186)Re-labeled version	[74,75]
Humicade/CDP571	TNFα; Crohn's disease	7	[5]
Gemtuzumab Ozogamicin/Mylotarg	CD33; acute myeloid leukemia	2.9	[76]
Hu23F2G	CD11/CD18; acute non-infectious inflammatory disorders mediated predominantly by neutrophils, e.g., multiple sclerosis	0	[77]
Hu2PLAP	Placental alkaline phosphatase	0	[78]
Hu5c8	CD154 (CD40 ligand); hemophilia (by suppressing anti-factor VIII antibodies)	0	[79]
HuBrE-3	Breast cancer	14	[80]
HuM291	CD3; renal transplant and graft versus host disease	0	[81]
Adalimumab/Humira	TNFα; developed by phage display of a human antibody library	5% low titer neutralizing antibodies. 1% with methotrexate, versus 12% without	[3]
Natalizumab	α4 integrin; Crohn's disease	7	[82]
Omalizumab	Allergic asthma	0	[83]
Efalizumab/Raptiva	CD11a; psoriasis	6.3	[84]
Bevacizumab/Avastin, rhu anti-VEGF mAb	VEGF expressing solid tumors	0	[85,86]
Cantuzumab Mertansine	CanAg glycoform of MUC1; colorectal cancer; humanized by "resurfacing" technology	0	[87]
Vitaxin	integrin $\alpha_v\beta_3$ (vitronectin receptor); metastatic cancer	0	[88,89]

1H give 0 and 2% AAR, respectively, in the lower echelon of incidence data. Among anti-B-cell mouse mAb, the median incidence is 34%, whereas the median incidence among mAb with non-B-cell targets is 75%. The biological activity of anti-B-lymphocyte mAb thus may yield a low AAR that masks their intrinsic antigenicity.

4. Discussion

4.1. Immunogenicity vs. molecular format

The data tables and histogram in Fig. 1 make clear that the largest step in reducing immunogenicity of therapeutic mAb comes from replacement of murine constant regions with human ones. Humanization of variable regions appears to decrease immunogenicity further. However, the overlap between HAHA and HACA incidence is extensive and blurs the advantage of humanization. Nevertheless, the frequency of marked HACA and the infrequency of marked HAHA suggest that a choice not to humanize entails a ponderable business risk. A parallel question, whether "fully human" mAb are less immunogenic than humanized mAb cannot be answered at present, because full immunogenicity data are available for just one mAb developed from phage-displayed human libraries. Repetitively dosed Humira showed AAR in 12% of patients—at the higher end of AAR incidence of the humanized antibodies listed in Table 3 [3].

4.2. Toward standardization of immunogenicity analysis

In the evaluation of the immunogenicity of humanized, chimeric, and human antibodies, we encounter a lack of a rational quantitative scale for immunogenicity, inability to compare relative immunogenicity between molecules, incomplete clinical data on immunogenicity, and failure to relate immunogenicity to molecular structure/properties such as mutational differences away from germline and anti-allotype reactivity. Emerging technologies and trends may repair this situation.

Biosensor technology provides a means of converting serum reactivity to an absolute scale of the anti-antibody content of individual sera [2]. The traditional method of analyzing antigen binding by polyclonal antisera is to fit binding data to a Sips distribution [6]. A Sips analysis gives the quantity of specific antibody in a sample, its average avidity, and spread of avidity constant. This approach has not been applied to AAR, but its application could facilitate inter-study comparisons.

Anti-allotype reactions are predicted to occur during therapy of a genetically diverse population with a single antibody reagent, but with some exceptions [7], anti-allotype AAR has not been measured. Anti-allotype AAR may be of future significance because in principle it can be circumvented by "personalized" medicine in which a patient receives an allotype-matched therapeutic mAb.

Lastly, the recent announcement by a major pharmaceutical manufacturer that it will publicize the results of all clinical trials of marketed products—both unsuccessful and successful—may portend a similar trend throughout the industry. Reporting of failed trials of therapeutic antibodies may well alter a future version of the histogram in Fig. 1.

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