Safety and Efficacy of Arcitumomab Imaging in Colorectal Cancer After Repeated Administration

William A. Wegener, Nicholas Petrelli, Aldo Serafini, and David M. Goldenberg

Department of Clinical Research, Immunomedics, Inc., Morris Plains, and Garden State Cancer Center, Belleville, New Jersey; Division of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, New York; and Division of Nuclear Medicine, University of Miami School of Medicine, Miami, Florida

In pivotal phase III clinical trials for detecting recurrent or metastatic colorectal cancer, most patients received a single arcitumomab injection. However, the early detection of postsurgical recurrence or metastases with arcitumomab will necessitate serial studies for surveillance. We present immunogenicity, safety, and imaging data supporting the use of multiple administrations of arcitumomab. **Methods:** Human antimouse antibody (HAMA) response, adverse events, clinical laboratory values, and diagnostic imaging results were evaluated in 44 patients (24 men, 20 women; age range, 28–78 y) after repeated arcitumomab administration (44 second and 3 third injections). Most patients initially had Dukes' class B or C colorectal cancer and had known or occult disease recurrence and elevated serum carcinoembryonic antigen levels at the time of the repeated injection. **Results:** At the repeated injection, in no patient did elevated HAMA titers develop, hematology and serum chemistry changes were clinically insignificant, and only 1 adverse event (eosinophilia) was judged at least possibly related to arcitumomab. Arcitumomab imaging results at the second injection were comparable with those obtained in phase III trials after a single injection of arcitumomab, having a 78% per-lesion concordance with CT in the abdomen and pelvis and a 73% sensitivity and 94% specificity based on 9 patients with cancer confirmed surgically at 11 anatomic sites and excluded at 16 sites. **Conclusion:** These data indicate that at least 2 injections of arcitumomab can be given safely to patients with colorectal cancer, without increased immunogenicity and with imaging efficacy equivalent to the first administration.

Key Words: colorectal cancer; immunoscintigraphy; diagnostic imaging; ^{99m}Tc; arcitumomab; monoclonal antibody; immunogenicity; clinical trial

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Arcitumomab is an anticarcinoembryonic antigen (CEA) murine monoclonal antibody Fab′ fragment approved in the United States, Europe, and Canada as a ^{99m}Tc-labeled imaging agent for detection of recurrent or metastatic colorectal carcinoma (*1–3*). More than 500 patients were administered arcitumomab in the clinical trials supporting this approval, but only a limited number of patients were given a second dose. Follow-up studies now indicate that serial studies will be required if arcitumomab is to play a role in postsurgical surveillance for early detection of recurrence or metastases (P Lechner, P Lind, DM Goldenberg, unpublished data, 1999). This report evaluates clinical trial data currently available to show the safety, efficacy, and lack of immunogenicity of repeated arcitumomab administration.

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For correspondence or reprints contact: William A. Wegener, MD, PhD, Immunomedics, Inc., 300 American Rd., Morris Plains, NJ 07950.

MATERIALS AND METHODS

Study Design

Patients received repeated administration of arcitumomab for detection of colorectal cancer in 1 of 2 similar open-label multicenter trials. The study was conducted at 10 institutions in the United States under protocols approved by the institutional review board of each site. All patients had known or suspected colorectal cancer at the time of initial administration and underwent repeated administrations at the time of scheduled follow-up tests or because recurrence was known or suspected. For inclusion in the study, patients had to be more than 21 y old; willing and able to give written informed consent; ambulatory, with good performance status (>60% on the Karnofsky scale or <2 on the Eastern Cooperative Oncology Group scale); and able to return to the hospital at the scheduled intervals. In addition, patients had to stop taking experimental anticancer therapy and radiotherapy for 1 mo before and 1 wk after arcitumomab administration. Pregnant or lactating women, patients with known allergies to mouse proteins, patients currently participating in an immune therapy program, and individuals not mentally responsible were excluded from participation. One trial also required human antimouse antibody (HAMA) titer levels to be <440 ng/mL before repeated administration and excluded patients with serum creatinine > 1.5 mg/dL or who had previously received monoclonal antibodies other than arcitumomab.

Arcitumomab was supplied in 3-mL vials as a lyophilized powder containing 1.25 mg of the anti-CEA antibody Fab′ fragment (CEA-Scan; Immunomedics, Inc., Morris Plains, NJ). For preparation, arcitumomab was reconstituted with 925 ± 185 MBq (25 ± 5 mCi) ^{99m}Tc-sodium pertechnetate solution. After allowing labeling to proceed for at least 5 min, the percentage of free ^{99m}Tc was determined by instant thin layer chromatography. All patients had <10% free ^{99m}Tc required for administration. For each arcitumomab administration, a baseline serum CEA level was obtained, hematology (hemoglobin, hematocrit, white blood cells, and platelets) and serum chemistries (glucose, blood urea nitrogen, creatinine, uric acid, calcium, phosphorus, total protein, total

bilirubin, alkaline phosphatase, and serum glutamic-oxaloacetic transaminase) were collected at baseline, 24 h, and 7 d after injection, and serum samples for HAMA determination were collected at baseline, 4–6 wk, and 3–4 mo after injection.

Planar and SPECT images of the chest, abdomen, and pelvis were obtained after each arcitumomab injection, beginning 2 h after injection, with additional planar imaging at 18–24 h. Arcitumomab imaging studies were evaluated on a regional basis (chest, liver, extrahepatic abdomen, and pelvis) as positive or negative for colorectal cancer, and the location of all positive lesions was recorded (multiple sites could be identified within a region). Arcitumomab results were correlated with results from surgery, biopsy, or laparoscopy or with conventional diagnostic techniques.

Patients were monitored during study participation for adverse events. Hematology and serum chemistry data were categorized as less than, within, or greater than normal values, and changes from baseline value and category were determined at 24 h and at 1 wk after the arcitumomab injection for each patient. The immunogenicity of arcitumomab was evaluated by measuring HAMA titers using ImmuSTRIP HAMA (Immunomedics), an enzyme-linked immunosorbent assay with a sensitivity of 74 ng/mL and a variability of 17 ng/mL (*4*). HAMA responses were classified as either positive (1 or more postinjection values > 74 ng/mL and increased by at least 17 ng/mL from baseline), negative (all postinjection values ≤ 74 ng/mL or, for postinjection values > 74 ng/mL, increased <17 ng/mL from baseline), or nonevaluable (no postinjection serum sample available or 1 postinjection value > 74 ng/mL, with no baseline sample available).

Patients

A total of 44 patients enrolled in this study received 2 (n = 41) or 3 (n = 3) administrations of arcitumomab. At the initial diagnosis, 1 patient had a benign villous adenoma, whereas the others had histologically proven colorectal adenocarcinoma, either locoregional (Dukes' class A, n = 2; B, n = 19; or C, n = 16) or metastatic (n = 6). The site of the primary tumor was the rectum (n = 11), rectosigmoid (n = 8), sigmoid (n = 10), descending colon (n = 1), splenic flexure (n = 3), transverse colon (n = 2), ascending colon (n = 4), or cecum (n = 5). The patients (20 men, 24 women) ranged from 28 to 78 y old at the time of the second injection.

Patients received their second injection at a mean (±SD) of 9.4 ± 6.4 mo after their initial injection, with comparable ^{99m}Tc doses administered each time (914 ± 200 MBq [24.7 ± 5.4 mCi] versus 932 ± 185 MBq [25.2 ± 5.0 mCi], respectively). Between the first and the second injections, 21 patients underwent surgical resection accompanied by chemotherapy (n = 6), chemo- and radiation therapy (n = 5), or no additional therapy (n = 10). Of the 23 nonsurgical patients, 9 also received chemotherapy. Serum CEA levels were 92.4 ± 367.8 ng/mL and 128.3 ± 351.1 ng/mL at the first and second injections, respectively. Three patients received a third injection at 6, 9, and 20 mo after their second injection.

RESULTS

Immunogenicity

HAMA responses at the first, second, and third injections are summarized in Table 1. Five patients at the first injection and 9 patients at the second injection were nonevaluable, having no postinjection samples available. After the first injection, 1 patient had a positive HAMA response (titers nonmeasurable at baseline, 2.5 ng/mL at 3 wk, and 175 ng/mL at 3 mo), which had normalized approximately 1 y later, at which time this patient received a second injection without a HAMA response (titers, 27 ng/mL before the second injection, 24 ng/mL at 4–6 wk, and 7.8 ng/mL at 3–4 mo). No patient had a positive HAMA response after the second injection (0/35 evaluable patients) or the third injection (0/3 evaluable patients).

TABLE 1
HAMA Response Data

HAMA response	Positive	Negative	Nonevaluable
First injection (n = 44)	1	38	5
Second injection (n = 44)	0	35	9
Third injection (n = 3)	0	3	0

Adverse Events

After the first injection, 3 patients had reported 1 adverse event each (orthostatic hypotension, considered possibly related; elevated lactate dehydrogenase and swollen throat glands, each considered only remotely related), but none of these 3 patients reported adverse experiences after their repeated injections. Only 1 patient reported an adverse event after the second injection, and no adverse events were reported after any third injection (1/47 repeated injections, 2%). The single event was an isolated laboratory finding (asymptomatic eosinophilia, 11% maximum differential value) in a 68-y-old man with adenocarcinoma of the colon metastatic to the lung, liver, and axilla. The event was considered not clinically significant but probably related to study drug administration.

Laboratory Results

At the second injection, mean paired laboratory changes from baseline at 24 h and 1 wk were small compared with baseline means, and none differed from 0 (no change) by more than 1 SD. The number of patients with shifts in categoric data were infrequent, and the changes were generally matched, with both increases and decreases occurring. At the third injection, hematology and serum chemistry values were also obtained at baseline, 24 h, and 1 wk for all 3 patients; no significant changes occurred for any parameter.

Imaging Efficacy of Repeated Injections

After the second injection, surgical confirmation was obtained in 9 patients, comprising 27 abdominopelvic sites (9 liver, 18 extrahepatic). Arcitumomab revealed 8 of 11 sites of confirmed cancer (72.7%), including 4 of 6 liver sites and 4 of 5 extrahepatic sites, and correctly excluded 15 of 16 sites in which cancer was excluded at surgery (93.8%), including 3 of 3 liver sites and 12 of 13 extrahepatic sites. A total of 116 sites in the liver, extrahepatic abdomen, and pelvis were evaluated by both arcitumomab imaging and conventional diagnostic modalities ([CDMs] typically CT) after the second injection (Table 2). Arcitumomab imaging identified more sites as positive for cancer than did CDMs

TABLE 2
Arcitumomab Imaging Results After Second Injection*

Finding	Sites evaluated		
	Liver	Extrahepatic (abdomen or pelvis)	Total
Pos. arcitumomab, pos. CDMs	10	5	15
Pos. arcitumomab, neg. CDMs	3	14	17
Neg. arcitumomab, neg. CDMs	24	52	76
Neg. arcitumomab, pos. CDMs	2	6	8
Total	39	77	116

*Per-site correlation with conventional diagnostic modalities (CDMs).
Pos. = positive; neg. = negative.

(32 versus 23), at both hepatic (13 versus 12) and extrahepatic (19 versus 11) locations. Arcitumomab and CDMs agreed at 34 of 39 liver sites (87.2%) and 57 of 77 extrahepatic sites (74.0%), for an overall concordance of 78.4%. Figures 1–3 show typical image findings after the first and second injections.

At the third injection, the 3 patients had 7 sites in the liver, abdomen, and pelvis evaluated by both arcitumomab and CT. Arcitumomab identified 2 sites as positive for cancer that were not identified by CT but was otherwise concordant with CT, which had negative findings everywhere. One patient had surgical confirmation, with a necrotic liver metastasis undetected by either CT or arcitumomab.

DISCUSSION

In the phase III trials of arcitumomab imaging for colorectal cancer, more than 400 patients were evaluated for immunogenicity, and only 3 patients had a positive response, resulting in a <1% HAMA response rate after the first injection (*1*). Because arcitumomab comprises only the Fab′ active binding portion of a murine monoclonal antibody, the low HAMA response rate after a single injection is not surprising. This low immunogenicity is likely attributed to the absence of the more immunogenic Fc portion, the low protein dose injected (approximately 1 mg), and the faster blood clearance that occurs with Fab′ fragments compared with intact antibodies. A high HAMA response may not only limit the usefulness for repeated imaging studies because of HAMA-associated altered clearance and biodistribution but also potentially interferes with murine antibody–based serum immunoassays, including assays for CEA and cancer antigen 125 that are routinely used to follow up colorectal patients for recurrence. The low HAMA response rate after a single injection of arcitumomab represents a significant improvement over the first immunoscintigraphy agent approved in the United States for imaging colorectal cancer (satumomab pendetide), which instead comprises an intact murine monoclonal antibody, has slower plasma clearance, and produces a HAMA response in approximately 55% of patients after a single injection (*5*).

Although the low (<1%) immunogenicity of arcitumomab after the first injection means that a second imaging study can be performed with little likelihood of HAMA-associated interference, the feasibility of routine imaging studies needed to monitor postsurgical patients for recurrence requires that repeated injections of arcitumomab also not provoke immunogenicity. In this study, 35 patients had serum samples available for determination of a HAMA response after a second administration of arcitumomab, and none had a positive response. In addition, 3 patients also received a third injection and were HAMA negative after each injection. Thus, immunogenicity after at least 2 administrations of arcitumomab is not evident. Furthermore, this study includes 1 of the few patients who had a positive response after the first administration. However, the patient's HAMA results were negative at the time of the second administration 1 y later, and no elevation occurred after the second injection, further supporting the lack of immunogenicity from repeated injections of arcitumomab.

In a therapeutic trial using higher protein doses of the intact immunoglobulin G from which arcitumomab is derived, Behr et al. (*6*) found no consistent differences in plasma and whole-body antibody half-lives at HAMA titers less than 300 ng/mL. In our study, the maximum HAMA titer after repeated administrations was 24 ng/mL. Thus, the likelihood that any HAMA titers induced after second

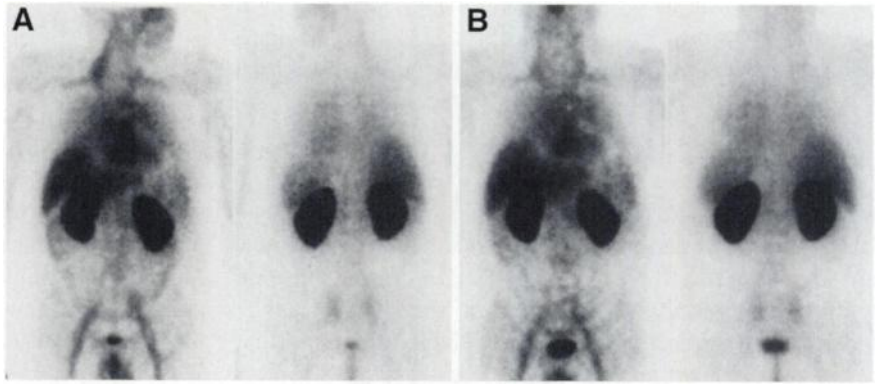

FIGURE 1. Typical biodistribution pattern in composite anterior and posterior planar arcitumomab images obtained 5–8 h after injection. (A) Initial study of patient with history of colon cancer who subsequently underwent low anterior resection for rectosigmoidal recurrence followed by 2 courses of 5-fluorouracil and leucovorin. (B) Study repeated 1 y later.

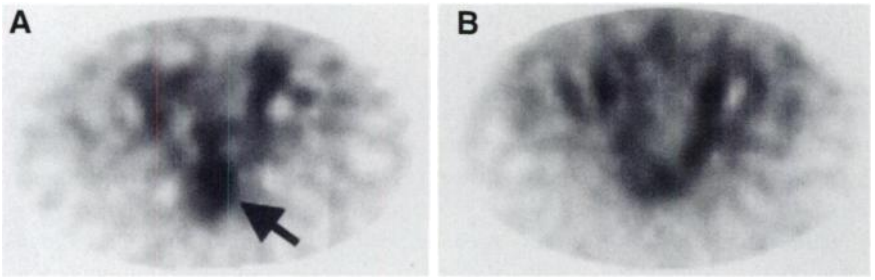

FIGURE 2. SPECT arcitumomab images of patient with rectal cancer. (A) Coronal image shows intense increased uptake in posterior pelvis (arrow). (B) Corresponding image obtained 6 mo later after low anterior resection.

arcitumomab administrations will affect pharmacokinetics appears low.

No clinically significant adverse experiences were reported after repeated administration, and none of 3 patients who had an adverse event after their first injection had an event reported after repeated administration. No adverse events were reported after the third injection, and the only adverse event reported after the second arcitumomab injection (asymptomatic transient eosinophilia) had been reported in the phase III trials, after a single injection in 1 patient. Changes in hematology and serum chemistry laboratory values after repeated administration appeared to be clinically insignificant. Comparison of mean values before and after the second injection showed little change, and shift changes from baseline occurred infrequently and with balanced numbers of increases and decreases, consistent with patient variability or related underlying medical conditions. Thus, repeated administrations appear safe.

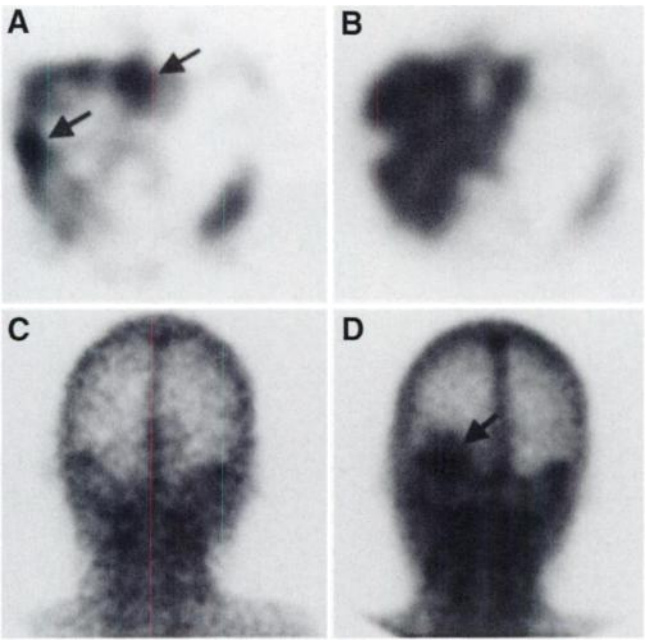

FIGURE 3. Arcitumomab images obtained 5 mo apart of colorectal patient with extensive liver involvement. Transverse SPECT images of liver initially show increased focal uptake at sites of metastases (arrows, A) but show decreased uptake after treatment by infusional ethanol ablation (B). Posterior planar images of head show normal findings initially (C) but disease progression on repeated study involving left occipital and parietal scalp (arrow, D).

Imaging results obtained after second injections supported the ability of repeated administrations to successfully target colorectal disease. Surgical information was available for 9 patients who had surgical confirmation of cancer at 11 sites and exclusion of cancer at 16 sites. On the basis of definitive surgical confirmation, arcitumomab imaging had a 73% sensitivity and a 94% specificity at these sites. In the liver, abdomen, and pelvis, arcitumomab imaging revealed 32 sites as positive for cancer compared with 23 sites revealed by CT and other CDMs. The overall per-site concordance with CDMs was 78%, including both liver (34/39, 87%) and extrahepatic sites (57/77, 74%). These results compare favorably with those obtained in phase III trials after a single injection, in which arcitumomab had a 57% sensitivity and an 83% specificity at surgically confirmed sites in the abdomen, liver, and pelvis; identified more sites as positive for cancer than did CT; and had a 69% per-lesion concordance with CT in surgically explored patients (*1,2*). Thus, repeated administrations maintain the ability of the imaging agent to detect sites of colorectal disease.

Because CT has a low sensitivity for detecting early extrahepatic or pelvic recurrence or metastases of colorectal cancer after presumptive curative surgery (*2,7*), immunoscintigraphic studies may become increasingly important as a surveillance method. Although serial studies with anti-CEA antibodies have been conducted, this approach has previously been limited by a significant HAMA response with ^{111}In-labeled intact antibodies (*8*). The results reported here support the suitability of repeated administrations with ^{99m}Tc-labeled arcitumomab, without increased immunogenicity and with the anticipation of reproducible imaging efficacy.

One limitation of our study is that most patients underwent surgical resection, chemotherapy, and external radiation after their first imaging study, so that no reference study was available to better evaluate repeated imaging studies for changes, as would be possible with serial imaging. However, a recent prospective study conducted at 1 institution by Lechner et al. (P Lechner, P Lind, DM Goldenberg, unpublished data, 1999) followed up 40 patients with resected rectal cancer using arcitumomab imaging studies every 6 mo for the first 2 y and annually thereafter up to 5 y after primary surgery (7 studies total) or until recurrence. No elevated HAMA titers developed to preclude follow-up examinations, and only minor and transient side effects

(headache, nausea, and pruritus) occurred with repeated use. Most significant is the improved diagnostic performance reported by these investigators, in that serial arcitumomab imaging revealed recurrence with >95% accuracy. Their results independently support the ability of the imaging agent to detect sites of colorectal disease after multiple administrations. More important, the results indicate that arcitumomab imaging studies may be interpreted even more accurately in the setting of serial studies for postsurgical follow-up surveillance, when prior imaging studies are available for comparison, than in the setting of single studies for presurgical evaluation, which had formed the basis for the initial product approval (*1–3*).

CONCLUSION

Experience from 44 patients indicates that at least 2 injections of arcitumomab can be given safely to patients with colorectal cancer, without increased immunogenicity and with imaging efficacy equivalent to the first administration.

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