Detection of chemotherapy-induced cardiotoxicity with antimyosin pretargeted imaging

H. William Strauss, MD,[a] and Giuliano Mariani, MD[b]

[a] Molecular Imaging and Therapy Section, Memorial Sloan Kettering Cancer Center, New York, NY

[b] Regional Center of Nuclear Medicine, University of Pisa, Pisa, Italy

Received Jan 5, 2018; accepted Jan 5, 2018
doi:10.1007/s12350-018-1192-0

See related article, pp. 1327–1344

Antimyosin antibody was created in response to a challenge Edgar Haber, MD, Chief of Cardiology at the Massachusetts General Hospital, gave his post-doctoral student, Ban An Khaw, PhD to develop a technique to specifically identify acute myocardial necrosis. Since Dr. Khaw had completed his training in immunology, his thoughts led him to consider creating an antibody that would recognize one of the least soluble proteins in the body, the heavy chain of cardiac myosin. Drs. Khaw and Haber reasoned that areas of severely damaged myocardium lose cell membrane integrity, allowing macromolecules such as enzymes and troponin to leak out, and allow macromolecules, such as antibodies recognizing insoluble cardiac myosin, to leak in and bind to the residual myosin protein at the site of damage. After numerous challenges were overcome, Khaw, Haber, and their colleagues Beller and Smith published a seminal article in The Journal of Clinical Investigation titled: 'Localization of cardiac myosin-specific antibody in myocardial infarction'[1] describing localization of intact radiolabeled polyclonal antimyosin antibody and localization of a radiolabeled $(Fab')_2$ antimyosin antibody fragment in experimental canine infarction. Although the concept worked, the intact antibody (molecular weight ~ 150 kDa) had a long residence time in the circulation, requiring a delay between antibody injection and imaging. To increase the rate of blood clearance, the antimyosin antibody was partially digested to produce the $(Fab')_2$ fragment (molecular weight ~ 110 kDa). Even the lower molecular weight $(Fab')_2$ required waiting up to 48 hours for sufficient blood clearance to record diagnostic images in experimental animals. To further decrease the interval between injection and imaging, Dr. Khaw purified the Fab (molecular weight ~ 50 kDa).[2] Although the Fab had the advantage of faster blood clearance, it had the disadvantage of decreased affinity for the heavy chain of cardiac myosin, since the Fab has only a single antigen recognition arm, while the larger $(Fab')_2$ had two. In spite of this limitation, the Fab worked well in experimental studies, and was selected for testing in human subjects. In parallel with the evolution from intact antibody to Fab fragment, Dr. Khaw changed radiolabels from ^{131}I for the intact antibody to ^{111}In-DTPA for the $(Fab')_2$, and subsequently to ^{99m}Tc-DTPA coupled to human antimyosin Fab for studies in patients with acute infarction.[3] Further fragmentation of antimyosin, to single chain sFv (molecular weight ~ 28 kDa, radiolabeled with ^{99m}Tc) was tested in mice and in a canine model of infarction.[4] The single chain fragment had similar immunoreactivity to the Fab. The half-time of sFv blood clearance was reduced from 2.8 hours for the Fab to 0.54 hours for the sFv, while achieving similar uptake in the experimental infarct. Infarcts were clearly visible 1 hour after sFv injection, while 3 hours was required for imaging with the Fab.

In addition to detecting acute myocardial infarction, antimyosin has been used to detect myocyte necrosis due to myocarditis[5-8] drug-induced cardiotoxicity[9,10] and heart transplant rejection.[11-14]

In spite of the published sensitivity of antimyosin imaging for the detection of myocyte necrosis, there

Reprint requests: H. William Strauss, MD, Molecular Imaging and Therapy Section, Memorial Sloan Kettering Cancer Center, New York, NY; *harry.strauss@gmail.com*

J Nucl Cardiol 2019;26:1345–7.
1071-3581/$34.00

remain a number of challenges to the use of this agent, including localization of antibody fragments in the liver, interfering with detection of small regions of myocardial uptake, and high uptake in the kidneys, a factor limiting the administered dose. In this issue of the Journal Panwar and colleagues apply both a 'pretargeting' approach to antimyosin imaging[15] to reduce the time required for clearance of the radiotracer from the blood and a charge modification approach to reduce non-specific tracer uptake in normal tissue.

Altai et al defined pretargeting[16] as follows:

> The core premise of pretargeting lies in administering the targeting vector and radioisotope separately and having the 2 components combine within the body. In this manner, pretargeting strategies decrease the circulation time of the radioactivity, reduce the uptake of the radionuclide in healthy non-target tissues, and facilitate the use of short-lived radionuclides that would otherwise be incompatible with antibody-based vectors.

Pretargeting was described by Claude Meares, David Goodwin and colleagues[17] in 1985. The technique has been primarily used in oncology, but about a decade ago bispecific pretargeted antibody imaging was applied to detect vascular disease.[18,19] Panwar et al applied the pretargeting concept using an Fab′ recognizing DTPA and an Fab recognizing myosin as the bispecific antibody for pretargeting. Eighteen hours after bispecific antibody administration ^{99m}Tc-DTPA[1] was administered. Images were recorded at 15 minutes, 3 and 24 hours after tracer administration. The investigators clearly demonstrate marked myocardial antimyosin uptake in animals treated with doxorubicin. The investigators also describe a less cardiotoxic form of doxorubicin, DTPA, and doxorubicin-conjugated polyglutamic acid (D-Dox-PGA). There was a marked decrease in myocardial uptake of the bispecific anti-myosin-anti-DTPA in the mice treated with the modified doxorubicin, D-Dox-PGA, compared to the animals treated with unmodified doxorubicin (Figures 7A and B in the Panwar manuscript).

We congratulate the investigators on their impressive results confirming the quality of pretargeted antimyosin antibody images. The demonstration of decreased cardiotoxicity with a modified doxorubicin, however may be of equal or even greater importance to patients with cancer. Additional studies appear warranted to document maintained tumoricidal activity of the modified doxorubicin in tumor bearing animals, as well as decreased cardiotoxicity in patients.

Although other imaging techniques, such as MIBG[20,21] and ^{99m}Tc-annexin V,[22] have been advocated to detect chemotherapy cardiotoxicity, clinical experience with these techniques is limited.

The major clinical approach to detect cardiotoxicity that has stood the test of time continues to be serial measurements of left ventricular ejection fraction.[23] The criteria for a significant reduction in LVEF described by Alexander et al[24] in his seminal publication remain valid.

Disclosure

The authors declare that there is no conflict of interest to disclose.

References

1. Khaw BA, Beller GA, Haber E, Smith TW. Localization of cardiac myosin-specific antibody in myocardial infarction. J Clin Investig 1976;58:439-46.
2. Khaw BA, Fallon JT, Strauss H, Haber E. Myocardial infarct imaging of antibodies to canine cardiac myosin with indium-111-diethylenetriamine pentaacetic acid. Science 1980;209:295-7.
3. Khaw BA, Gold HK, Yasuda T, Leinbach RC, Kanke M, Fallon JT, Barlai-Kovach M, Strauss HW, Haber E. Scintigraphic quantification of myocardial necrosis in patients after intravenous injection of myosin-specific antibody. Circulation 1986;74:501-8.
4. Nedelman MA, Shealy DJ, Boulin R, Brunt E, Seasholtz JI, Allen IE, McCartney JE, Warren FD, Oppermann H, Pang RH, Berger HJ, Weisman HF. Rapid infarct imaging with a technetium-99m labeled antimyosin recombinant single-chain Fv: Evaluation in a canine model of acute myocardial infarction. J Nucl Med 1993;34:234-41.
5. Yasuda T, Palacios IF, Dec GW, Fallon JT, Gold K, Leinbach RC, Strauss HW, Khaw BA, Haber E. Indium-111 monoclonal antimyosin antibody imaging in the diagnosis of acute myocarditis. Circulation 1987;76:306-11.
6. Dec GW, Palacios I, Yasuda T, Fallon JT, Khaw BA, Strauss HW, Haber E. Antimyosin antibody cardiac imaging: Its role in the diagnosis of myocarditis. J Am Coll Cardiol 1990;16:97-104.
7. Narula J, Southern JF, Dec GW, Palacios IF, Newell JB, Fallon JT, Strauss HW, Khaw BA, Yasuda T. Antimyosin uptake and myofibrillarlysis in dilated cardiomyopathy. J Nucl Cardiol 1995;2:470-7.
8. Jain D, Zaret BL. Antimyosin cardiac imaging in acute myocarditis. J Am Coll Cardiol 1990;16:105-7.
9. Carrió I, Estorch M, Berná L, López-Pousa J, Tabernero J, Torres G. Indium-111-antimyosin and iodine-123-MIBG studies in early assessment of doxorubicin cardiotoxicity. J Nucl Med 1995;36:2044-9.
10. Narula J, Strauss HW, Khaw BA. Antimyosin positivity in doxorubicin cardiotoxicity: Earlier than the conventional evidence. J Nucl Med 1993;34:1507-9.
11. Carrió I, Berná L, Ballester M, Estorch M, Obrador D, Cladellas M, Abadal L, Ginjaume M. Indium-111 antimyosin scintigraphy to assess myocardial damage in patients with suspected myocarditis and cardiac rejection. J Nucl Med 1988;29:1893-900.

[1] Tc-99m-DTPA was conjugated to succinylated polylysine. The polylysine altered the charge of the molecule to reduce non-specific binding.

12. Frist W, Yasuda T, Segall G, Khaw BA, Strauss HW, Gold H, Stinson E, Oyer P, Baldwin J, Billingham M, McDougall IR, Haber E. Noninvasive detection of human cardiac transplant rejection with indium 111 antimyosin (Fab) imaging. Circulation 1987;76:V81-5.
13. Carrio I. Indium-111 antimyosin antibodies for detection of rejection and drug induced cardiomyopathies. J Nucl Biol Med 1992;36:56-61.
14. Ballester M, Bordes R, Tazelaar HD, Carrió I, Marrugat J, Narula J, Billingham ME. Evaluation of biopsy classification for rejection: Relation to detection of myocardial damage by monoclonal anti-myosin antibody imaging. J Am Coll Cardiol 1998;31:1357-61.
15. Panwar R, Bhattarai P, Patil V, Gada K, Weisenberger A, Khaw BA. Imaging doxorubicin and polymer–drug conjugates of doxorubicin-induced cardiotoxicity with bispecific anti-myosin–anti-DTPA-antibody and Tc-99m-labeled polymers. J Nucl Cardiol. https://doi.org/10.1007/s12350-018-1190-2.
16. Altai M, Membreno R, Cook B, Tolmachev V, Zeglis BM. Pre-targeted imaging and therapy. J Nucl Med 2017;58:1553-9.
17. Reardan DT, Meares CF, Goodwin DA, McTigue M, David GS, Stone MR, Leung JP, Bartholomew RM, Frincke JM. Antibodies against metal chelates. Nature 1985;316:265-8.
18. Anderson CJ, Bulte JW, Chen K, Chen X, Khaw BA, Shokeen M, Wooley KL, VanBrocklin HF. Design of targeted cardiovascular imaging probes. J Nucl Med 2010;51:3S-17S.
19. Khaw BA, Tekabe Y, Johnson LL. Imaging experimental atherosclerotic lesions in ApoE knockout mice: Enhanced targeting with Z2D3-anti-DTPA bispecific antibody and ^{99m}Tc-labeled negatively charged polymers. J Nucl Med 2006;47:868-76.
20. Wakasugi S, Fischman AJ, Babich JW, Aretz HT, Callahan RJ, Nakaki M, Wilkinson R, Strauss HW. *Meta*iodobenzylguanidine: Evaluation of its potential as a tracer for monitoring doxorubicin cardiomyopathy. J Nucl Med 1993;34:1283-6.
21. Bulten BF, Verberne HJ, Bellersen L, Oyen WJ, Sabaté-Llobera A, Mavinkurve-Groothuis AM, Kapusta L, van Laarhoven HW, de Geus-Oei LF. Relationship of promising methods in the detection of anthracycline-induced cardiotoxicity in breast cancer patients. Cancer Chemother Pharmacol 2015;76:957-67.
22. Bennink RJ, van den Hoff MJ, van Hemert FJ, de Bruin KM, Spijkerboer AL, Vanderheyden JL, Steinmetz N, van Eck-Smit BL. Annexin V imaging of acute doxorubicin cardiotoxicity (apoptosis) in rats. J Nucl Med 2004;45:842-8.
23. Schwartz RG, Jain D, Storozynsky E. Traditional and novel methods to assess and prevent chemotherapy-related cardiac dysfunction noninvasively. J Nucl Cardiol 2013;20:443-64.
24. Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L, Duffy T, Schwartz P, Gottschalk A, Zaret BL. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979;300:278-83.