Current status of superparamagnetic iron oxide contrast agents for liver magnetic resonance imaging

Wang YXJ, Department of Imaging and Interventional Radiology, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong, China

Author contributions: Wang YXJ designed research, analyzed data, and wrote the paper.

Conflict-of-interest statement: The author declares no conflict-of-interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Yi-Xiang J Wang, PhD, MMed, Department of Imaging and Interventional Radiology, Faculty of Medicine, the Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China. yixiang_wang@cuhk.edu.hk
Telephone: +852-26322289

Received: May 28, 2015
Peer-review started: May 31, 2015
First decision: August 26, 2015
Revised: September 15, 2015
Accepted: November 9, 2015
Article in press: November 9, 2015
Published online: December 21, 2015

Abstract
Five types of superparamagnetic iron oxide (SPIO), i.e. Ferumoxides (Feridex® IV, Berlex Laboratories), Ferucarbotran (Resovist®, Bayer Healthcare), Ferumoxtran-10 (AMI-227 or Code-7227, Combidex®, AMAG Pharma; Sinerem®, Guerbet), NC100150 (Clariscan®, Nycomed), and (VSOP C184, Ferropharm) have been designed and clinically tested as magnetic resonance contrast agents. However, until now Resovist® is current available in only a few countries. The other four agents have been stopped for further development or withdrawn from the market. Another SPIO agent Ferumoxytol (Feraheme®) is approved for the treatment of iron deficiency in adult chronic kidney disease patients. Ferumoxytol is comprised of iron oxide particles surrounded by a carbohydrate coat, and it is being explored as a potential imaging approach for evaluating lymph nodes and certain liver tumors.

Key words: Superparamagnetic iron oxide; Liver; Hepatocellular carcinoma; Magnetic resonance imaging; Resovist; Gd-EOB-DTPA; Primovist; Eovist

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Superparamagnetic iron oxide nanoparticle for liver imaging was conceptualized when the speed of both single-slice computed tomography (CT) scan and multiple-slice magnetic resonance imaging (MRI) was slow. It was difficult to accurately observe the “wash-in” and “wash-out” of liver lesion blood flow dynamics. However, recently spiral CT and later multi-slice CT revolutionized liver imaging. MRI scan is also currently much faster due to the improved gradient technology and fast data acquisition sequences. These techniques increased the sensitivity and specificity of dynamic imaging using small molecular agents such as iodinated CT contrast agents and Gadolinium based MRI contrast agents. Gd-EOB-DTPA-enhanced liver MRI is currently emerging as the leading method for diagnosis and staging of hepatocellular carcinoma.
TO THE EDITOR

I read with interest the recent systematic review on superparamagnetic iron oxide (SPIO) for magnetic resonance imaging of focal hepatic lesions by Li et al. This paper further confirmed the value of SPIO in liver magnetic resonance imaging (MRI). I hope to make some additional comments. Five types of SPIO, i.e., Ferumoxides (Feridex®, IV, Berlex Laboratories), Ferucarbotran (Resovist®, Bayer Healthcare), Ferumoxtran-10 (AMI-227 or Code-7227, Combidex®, AMAG Pharma; Sinerem®, Guerbet), NC100150 (Clariscan®, Nycomed,) and (VSOP C184, Ferropharm) have been designed and clinically tested as MR contrast agent. They all have a core composed of SPIO crystals, but have different coating materials and different hydrodynamic size and therefore different in-vivo pharmacokinetic profiles[1-5]. Clariscan® and VSOP C184 were designed for MR angiography and blood pool imaging[6,7], but did not receive regulatory approval. Combidex® and Sinerem® were primarily designed for lymph node imaging. Despite initial promising data[8], the pivotal study failed to demonstrate a consistent and statistically significant benefit for sensitivity and failed to confirm non-inferiority with regard to specificity[9]. Therefore their clinical development was stopped[10]. Feridex® and Resovist® were primarily designed for liver imaging, and received regulatory approval in the United States and Europe respectively, as well as number of other countries such as Japan. Feridex® cannot be administered as an intravenous bolus as it may be associated with severe back pain, while Resovist® can be administered by fast bolus injection, and therefore imaging of the arterial phase is feasible. However, it has been shown that there is no significant difference in the number of Kupffer cells between well-differentiated hepatocellular carcinoma (HCC) and the surrounding healthy liver tissue[9]. Another study showed how Resovist®-enhanced MRI is less efficient than Gd-BOPTA-enhanced dynamic MRI in the detection and characterization of HCC[10]. This can be explained by SPIO’s inability to evaluate the pathological vascularity of liver nodules. Due to lack of clinical users, Feridex® has been withdrawn from the market, and Resovist® is currently available in only limited countries[11].

SPIO for liver imaging was conceptualized when the speed of both single-slice CT scan and multi-slice MRI was slow. It was difficult to accurately observe the “wash-in” and “wash-out” of liver lesion blood flow dynamics. However, recently spiral CT and later multi-slice CT revolutionized liver imaging. MRI scanning is also currently much faster due to the improved gradient technology and fast data acquisition sequences. These techniques increase the sensitivity and specificity of dynamic imaging using small molecular agents such as iodinated CT contrast agents and Gadolinium based MRI contrast agents.

Another SPIO agent Ferumoxytol (Feraheme®, AMAG Pharmaceuticals, United States; Rienso®, Europe) has been approved for the treatment of iron deficiency in adult chronic kidney disease patients. Ferumoxytol is comprised of iron oxide particles surrounded by a carbohydrate coat. The agent is taken up by macrophages and ultimately the reticuloendothelial system, opening the door for a potential imaging approaches to evaluate lymph nodes and certain liver tumors[12].

Several recent studies demonstrated that MRI using hepatocyte-specific contrast agent (Gd-EOB-DTPA, Primovist®, Europe; Eovist®, United States; Bayer HealthCare) can provide better diagnostic performance for the detection and characterization of HCCs in cirrhotic livers than dynamic CT or dynamic MRI using extracellular agents[13]. Gd-EOB-DTPA-enhanced liver MRI is currently emerging as the leading method for diagnosis and staging of HCC[13].

REFERENCES

1. Li YY, Chen ZG, Wang JC, Zhang ZM. Superparamagnetic iron oxide-enhanced magnetic resonance imaging for focal hepatic lesions: systematic review and meta-analysis. World J Gastroenterol 2015; 21: 4334-4344 [PMID: 25892885 DOI: 10.3748/wjg.v21.i14.4334]
2. Corot C, Robert P, Idée JM, Port M. Recent advances in iron oxide nanocrystal technology for medical imaging. Adv Drug Deliv Rev 2006; 58: 1471-1504 [PMID: 17116343 DOI: 10.1016/j.addr.2006.09.013]
3. Wang YX, Hussain SM, Krestin GP. Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. Eur Radiol 2001; 11: 2319-2331 [PMID: 11702180 DOI: 10.1007/s003300100908]
4. Wang YX. Superparamagnetic iron oxide based MRI contrast agents: Current status of clinical application. Quant Imaging Med Surg 2011; 1: 35-40 [PMID: 22566052]
5. Klein C, Nagel E, Schnackenburg B, Bornstedt A, Schalla S, Hofmann V, Lehning A, Fleck E. The intravascular contrast agent Clariscan (NC 100150 injection) for 3D MR coronary angiography in patients with coronary artery disease. MAGMA 2000; 11: 65-67 [PMID: 11186991 DOI: 10.1007/BF02678498]
6. Wagner M, Wagner S, Schnoor J, Schellenberger E, Kivelitz D, Krug L, Dewey M, Laule M, Hamm B, Taupitz M. Coronary MR angiography using citrate-coated very small superparamagnetic iron oxide particles as blood-pool contrast agent: initial experience in humans. J Magn Reson Imaging 2011; 34: 816-823 [PMID: 21769977 DOI: 10.1002/jmri.22683]
7. Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tahatabaei S, van de Kaa CH, de la Rosette J, Weissleder R. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003; 348: 2491-2499 [PMID: 12815134 DOI: 10.1056/NEJMoa022749]
8. European Medicines Agency. International Nonproprietary Name (INN): superparamagnetic iron oxide nanoparticles stabilised with dextran and sodium citrate. 2008. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500676463.pdf
9. Tanaka M, Nakashima O, Wada Y, Kage M, Kojiro M. Pathomorphological study of Kupffer cells in hepatocellular carcinoma and hyperplastic nodular lesions in the liver. Hepatology
Wang YXJ. Superparamagnetic iron oxide in liver imaging

1996; 24: 807-812 [PMID: 8855180 DOI: 10.1053/jhep.1996.v24.pmi008855180]

10 Kim YK, Kim CS, Kwak HS, Lee JM. Three-dimensional dynamic liver MR imaging using sensitivity encoding for detection of hepatocellular carcinomas: comparison with superparamagnetic iron oxide-enhanced mr imaging. J Magn Reson Imaging 2004; 20: 826-837 [PMID: 15503325 DOI: 10.1002/jmri.20188]

11 Maurea S, Mainenti PP, Tambasco A, Imbriaco M, Mollica C, Laccetti E, Camera L, Liuzzi R, Salvatore M. Diagnostic accuracy of MR imaging to identify and characterize focal liver lesions: comparison between gadolinium and superparamagnetic iron oxide contrast media. Quant Imaging Med Surg 2014; 4: 181-189 [PMID: 24914419]

12 Bashir MR, Bhatti L, Marin D, Nelson RC. Emerging applications for ferumoxytol as a contrast agent in MRI. J Magn Reson Imaging 2015; 41: 884-898 [PMID: 24974785 DOI: 10.1002/jmri.24691]

13 Lee JM, Park JW, Choi BI. 2014 KLCSG-NCC Korea Practice Guidelines for the management of hepatocellular carcinoma: HCC diagnostic algorithm. Dig Dis 2014; 32: 764-777 [PMID: 25376295 DOI: 10.1159/000368020]

P- Reviewer: Pierre P, Radmard AR
S- Editor: Gong ZM
L- Editor: A
E- Editor: Liu XM
