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

Yi-Xiang J Wang

Yi-Xiang J Wang, Department of Imaging and Interventional Radiology, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong, China

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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

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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 The other four agents have been stopped for further development or withdrawn from the market.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

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.

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TO THE EDITOR

I read with interest the recent systemic review on superparamagnetic iron oxide (SPIO) for magnetic resonance imaging of focal hepatic lesions by Li *et al*[1]. 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[5,6], but did not receive regulatory approval. Combidex® and Sinerem® were primarily designed for lymph node imaging. Despite initial promising data[7], the pivotal study failed to demonstrate a consistent and statistically significant benefit for sensitivity and failed to confirm non-inferiority with regard to specificity[8]. Therefore their clinical development was stopped[4]. 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 Küpffer 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 current available in only limited countries[11].

SPIO for liver imaging was conceptualized when the speed of both single-slice CT scan and multiple-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].

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