Eovist Injection and Resovist Injection: Two New Liver-Specific Contrast Agents for MRI

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In this short review, we describe two new liver-specific contrast agents for MRI that are in clinical development. The main differences among the liver-specific contrast agents available at present are also discussed briefly.

ABSTRACT: Eovist Injection (gadolinium-EOB-DTPA) is selectively taken up by hepatocytes, which will increase the signal intensity of normal liver parenchyma on T1-weighted images. This results in improved lesion-to-liver contrast because malignant tumors either do not contain hepatocytes or their functioning is hampered. Following intravenous (IV) bolus injection, Eovist Injection is excreted by both the renal and biliary routes. Clinical trials have evaluated the safety and efficacy of Eovist Injection up to a dose of 100 µmol/kg body weight. Resovist Injection (SHU-555A) contains iron-oxide nanoparticles coated with carboxydextran and is administered as an intravenous bolus injection at a fixed-volume dose, dependent on body weight. The uptake of Resovist Injection in the reticuloendothelial (RES) cells results in a decrease of the signal intensity of normal liver parenchyma on both T2- and T1-weighted images. Due to the altered phagocytic distribution and activity, the signal intensity in most metastatic tumors is not affected, resulting in improved lesion-to-liver contrast. Both Resovist Injection and Eovist Injection have exhibited acceptable safety profiles in clinical trials, and have the potential to provide additional information regarding lesion detection, classification, and characterization. [ONCOLOGY 14(Suppl 3): 37-40, 2000]

Despite being a vital organ, the liver has received little attention from a diagnostic radiology point of view, until recently. However, new developments in computed tomography (CT) and magnetic resonance imaging (MRI) have provided additional information regarding lesion detection, classification (benign vs malignant), and characterization (eg, metastasis, hemangioma). Simultaneously, there have been many recent developments in treatment procedures for primary and secondary hepatic tumors. Computed tomography and MRI are both imaging techniques that are used to acquire cross-sectional images of the liver. In several recent clinical studies, contrast-enhanced MRI has been shown to have a higher sensitivity for detecting lesions compared to CT.[1-5]

Liver-Specific Contrast Agents

When developing new liver-specific contrast agents for MRI, the main objectives are to improve lesion detection, classification, and characterization. The goals are to detect as many lesions as possible as early as possible and to increase the sensitivity of the MRI scan for detecting smaller lesions. Finally, if possible, the clinician would want to accurately classify and characterize all detected lesions. This may improve a patient's outcome because appropriate therapy could be initiated at an early stage. In this short review, we describe two new liver-specific contrast agents for MRI that are in clinical development. The main differences among the liver-specific contrast agents available at present are also discussed briefly.

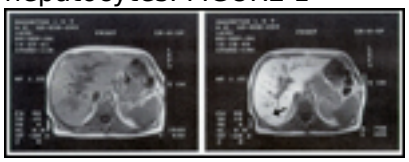
Agents That Target the Hepatocytes

Currently, there are two main strategies that are being followed for the development of liver-specific MR contrast media. One is to develop compounds that target hepatocytes. This type of contrast agent, known as a hepatocellular contrast agent, is taken up by normal hepatocytes, thus increasing the signal intensity of normal liver on T1-weighted images. These agents lead to an improvement in lesion-to-liver contrast because tumors either do not contain hepatocytes or the functioning of intratumoral hepatocytes is hampered. Examples of these types of contrast agents are Teslascan

Injection (mangafodipir trisodium, Nycomed, Inc), MultiHance (gadolinium-BOPTA, Bracco Diagnostics, Inc), and Eovist Injection (gadolinium-EOB-DTPA, Schering AG).
Teslascan Injection is already on the market in the United States. It is administered as a slow injection and therefore does not provide information about lesion classification/characterization based on tumor vascularity, nor does it assist in defining the tumor-vascular relationship.[6,7] MultiHance is currently marketed for liver MRI in Europe only. Due to its low uptake in the liver (about 5% in humans[8]), its behavior is very similar to that of the other extracellular contrast agents currently available. Also, accumulation-phase (steady-state) imaging can only be performed at about 40 to 120 minutes post injection (European Package Insert for MultiHance).

Eovist Injection

Eovist Injection or gadolinium EOB-DTPA is a water-soluble ethoxybenzyl derivative of gadolinium DTPA. The presence of the ethoxybenzyl group causes this compound to be selectively taken up by the hepatocytes. This uptake leads to enhancement of liver parenchyma on T1-weighted images. The osmolality and viscosity of Eovist Injection is 0.89 [mol/kg HO] and 1.22 [mPas @ 37°C], respectively. Due to approximately 11% protein binding, Eovist Injection also has high relaxitivity. The T1 relaxivities at 1.5 Tesla and 23°C for Eovist Injection and Magnevist Injection in plasma are 12.2 and 6.3 L/(mmol x s), respectively.
The plasma half-life of Eovist Injection is 1.14 to 1.65 hours at the doses tested in a phase I study (10 to 100 µmol/kg body weight). Eovist Injection has dual excretory pathways. After IV administration, the contrast media is not only distributed into the extracellular fluid, from which it is eliminated in urine, but also enters the hepatocytes, from where it is secreted into the bile, and eliminated in the feces. Again, from a phase I study, almost equal renal and hepatic excretion was seen for Eovist Injection at all doses tested. The median lethal dose in mice and rats following a single intravenous injection of Eovist is three to four orders of magnitude (10^3–10^4) higher than the anticipated clinical dose.
Clinical trials have shown that Eovist Injection can be administered as a bolus injection without significant safety concerns and without clinically relevant effects on vital signs.[9,10] Also, laboratory data revealed no relevant changes in blood or urinary parameters after administration of Eovist Injection.
• **MR Imaging With Eovist Injection**—Similar to contrast-enhanced CT, contrast-enhanced MRI of the liver using Eovist Injection exhibits a biphasic enhancement pattern (arterial and portal-venous phases). The dynamic phase MR data acquisition can be initiated immediately following an IV bolus administration of Eovist Injection. In addition, a later enhancement, which reaches a maximum about 20 minutes postinjection and lasts for about 2 hours, is due to uptake of the contrast agent into the hepatocytes. FIGURE 1



Eovist Injection-Enhanced MRI

MR imaging with Eovist Injection may also add another dimension to hepatocyte-phase imaging, which could provide additional information about lesion characterization based on the presence or absence of functional hepatocytes within the tumor. With the newer and faster MRI sequences (T1 Gradient-echo), the whole liver can be imaged in a single breath-hold during the arterial, portal-venous, and equilibrium phases. Figure 1 shows the effect of Eovist Injection during the dynamic phase (perfusion) and steady-state phase (hepatocyte accumulation phase) in a normal subject.

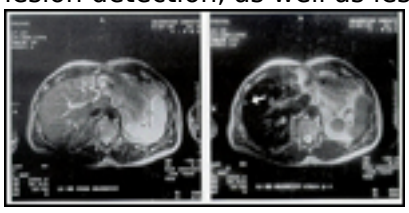
Agents That Target the Activity of the Reticuloendothelial Cells

The second approach to liver-targeted MRI is to use the reticuloendothelial (RES) cell activity of the liver. This method utilizes iron-oxide particles, which, when injected intravenously, are taken up by RES cells and cause a reduction in signal intensity of the liver parenchyma, mainly on T2-weighted images. These types of compounds are therefore known as T2 contrast agents.
Since hepatic tumors either do not contain RES cells or their activity is reduced, the contrast between liver and lesion is improved. An example of such a compound is Feridex I.V. (ferumoxides

injectable solution, Berlex Laboratories, Inc, licensed from Advanced Magnetics, Inc). This contrast agent is currently marketed in the United States, Europe (Endorem, Guerbet Laboratories SA), and Asia (Feridex I.V.). After dilution with 5% dextrose, Feridex I.V. is administered as a slow infusion over a period of 30 minutes.[11-13] During the initial phase III clinical trials, about 3.6% of all subjects experienced some type of lower back or leg pain during the infusion. The occurrence of these events was higher in cirrhotic patients. However, in most patients, these adverse reactions subsided following a short interruption in the infusion.
A clinical study has recently been concluded in which undiluted Feridex I.V. was administered as a 2-minute direct injection. Combidex (Ferumoxtran-10, Advanced Magentics, Inc), a contrast agent containing smaller iron particles, with potential for hepatic imaging, has recently been submitted for approval in the United States.

Resovist Injection

Resovist Injection contains ferucarbotran, a colloidal solution of iron-oxide nanoparticles coated with carboxydextran. The hydrodynamic diameter is about 60 nm with an iron core of 4 nm. Resovist Injection is a ready-to-use aqueous solution for intravenous injection. The R1 and R2 relaxivities at 0.47 T and 40°C in plasma are 19.4 + 0.3 and 185.8 + 9.3 L/(mmol x sec), respectively. The osmolality of the aqueous solution is 333 mOsmol/kg, which is similar to blood plasma (285 mOsmol/kg), and the viscosity is 1.03 mPa x sec.
These physiochemical properties allow Resovist Injection to be administered as a bolus injection at a fixed-volume dose depending on body weight. Patients weighing 35 to 60 kg receive 0.9 mL and patients weighing more than 60 kg receive 1.4 mL. At these doses, the peak blood level is in the range of 100 µmol Fe/L. This represents only a small fraction (less than 2%) of the estimated physiologic body pool of iron (3 to 5 g) in humans.[14,15]
• **MR Imaging With Resovist Injection**—The bolus administration of Resovist Injection, as compared to contrast agents that require slow injections or infusions, allows the clinician to obtain the following from a single injection:
• Dynamic imaging immediately after bolus injection. This is important for information regarding lesion classification and characterization.
• Pre- and post-contrast MRI sequences in one session (within 20 minutes).
Following a bolus injection of Resovist, dynamic imaging can be performed using either T1 or T2*-weighted sequences. Resovist Injection is taken up by RES cells of the liver and spleen. Most tumors, such as metastatic lesions and hepatocellular carcinomas, either do not contain RES cells or have impaired RES cell activity. The signal intensity of the tumors is not affected, resulting in an improvement in lesion-to-liver contrast. Additionally, published reports indicate that, because of the high T1 relaxivity of Resovist Injection, MR imaging of the liver vasculature can be performed to establish tumor-vessel relationships.[16-18] Accumulation-phase imaging can be performed 10 minutes post-injection utilizing T2-weighted sequences. Accumulation-phase imaging improves lesion detection, as well as lesion visualization, delineation, and conspicuity. FIGURE 2



Resovist Injection-Enhanced MRI

The accumulation of Resovist Injection, or the lack thereof, is expected to provide additional information regarding lesion classification and characterization. Certain benign tumors, such as focal nodular hyperplasia, contain functioning RES cells. Consequently, an MRI examination with Resovist Injection may be helpful in differentiating these tumors from various malignant lesions. Hemangioma also shows enhancement during the accumulation phase. This is due to slow blood flow in the vascular lakes of hemangioma. This feature is helpful in differentiating metastasis from hemangioma (Figure 2).
Resovist Injection has demonstrated a satisfactory safety profile in clinical trials. No dose dependency of adverse events within the tested dose range was noted. However, there was a transient decrease in Factor II, while the PTT continued within the normal range. A bolus injection of Resovist Injection has not shown clinically relevant effects on the cardiovascular system, as

indicated by recordings of vital signs, ECG, and cardiac rhythm.[19] Very few incidents of back or leg pain were reported after administration of Resovist Injection and in no cases was interruption of injection required.

Conclusions

Eovist Injection and Resovist Injection are new contrast agents that are being developed for liver MRI. Both agents have the potential to provide additional information regarding lesion detection, classification, and characterization. The combination of this information from dynamic imaging and accumulation phase imaging can be acquired with Resovist Injection or Eovist Injection. This is not possible with currently available gadolinium-based contrast agents (no accumulation phase) or with liver-specific contrast agents (no dynamic imaging). Magnetic resonance imaging of the liver utilizing these two contrast media has the potential to replace computed tomography as well as more invasive procedures, such as CT arterial portography (CTAP).

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