Comparison of Two Superparamagnetic Viral-Sized Iron Oxide Particles Feridex and Combidex in Imaging Intracranial Tumors

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Purpose
Iron particles being studied in MR imaging may act as a model for in vivo viral vector delivery in brain tumor patients. Our animal results (1, 2) suggest that this is feasible to initiate study in clinical patients. The study is designed to optimize the MR imaging parameters and scan timing for the two agents and to assess the degree and type of iron uptake in brain tumors after intravenous infusion of these iron particles. Comparison of the uptake of the two agents to gadolinium uptake was also made.

Materials & Methods
Eight patients with primary and metastatic brain tumors were randomized to either agent, Feridex or Combidex in this IRB approved protocol. All patients had MR imaging with gadolinium at least 24 hours before iron infusion. Feridex was administered i.v. in three patients at the recommended clinical dose and MR imaging was obtained 30 minutes and 4 hours after Feridex infusion. Combidex (Advanced Magnetics) was administered i.v. under an FDA approved IND in five patients at a dose of 2.6 mg Fe/kg, diluted in 50 ml normal saline, infused at 4 cc/min. Because of the increased intravascular half life, an MR image was obtained 6 hours and 24 hours after Combidex infusion. MR scans included T1, FSE T2 and proton density (PD), gradient echo T2 (GET2) and in three patients echoplanar gradient echo T2 (EPIT2). Four of the eight patients underwent biopsy within 24 hours after the second MR image. Histologic and ultrastructural evaluation of specimens are being carried out to assess the exact localization of iron, whether they can cross both the anatomical (tight junction) and the physiologic (basal lamina) barrier.

Results
Despite at least some degree of gadolinium enhancement in all tumors no sign of iron uptake, i.e. T1 or T2 signal changes were seen after Feridex i.v. with the maximum clinical approved dose at either examination time. Four of the five patients with Combidex i.v. showed T1 and T2 shortening consistent with iron uptake. The signal changes were stronger and extended into a larger area in the 24 hours post-Combidex MR study. Three of these four patients had signal changes in the approximate region where gadolinium enhancement was seen. One patient showed only partial iron uptake compared to the Gadolinium enhancing regions.

Conclusion
Gadolinium enhancement, indicating blood-brain barrier breakdown may or may not mean that viruses given for gene therapy can penetrate into the tumor. The lack of uptake of Feridex might be a consequence of its variable and larger particle size, its short plasma half life (30 min) and its rapid opsonization. Variable uptake of longer plasma half life (24–30 hours) Combidex in
gadolinium enhancing regions might be a consequence of the larger and more viral size of this iron particle compared to the size of gadolinium. The increase in signal changes in the 24 hour post-Combidex study better delineates uptake and decreases the blood-pool effect. As expected, the most striking signal changes could be observed on the T1, GET2 and EPIT2 images, suggesting that these sequences might be the best to evaluate iron uptake. Exact localization of Combidex particles is currently being assessed at the light and EM level.

**References**