A New Approach to Imaging Focal Liver Lesions in Patients With Reduced Kidney Function

Current magnetic resonance imaging (MRI) methods used to detect focal liver lesions can cause potentially fatal side effects in patients with poor kidney function. Alternative imaging techniques are being developed to address this clinical need

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The early detection and localisation of focal liver lesions is critical for optimal management of patients with liver cancer or a range of cancers that metastasise to the liver, including colorectal, breast, and gastric cancer. The gold-standard method for detecting focal liver lesions is contrast-enhanced MRI. However, in patients with poor kidney function, all gadolinium-based contrast agents (GBCAs) have regulatory black box warnings, as they put those patients at risk of the severe – and sometimes fatal – side effect, NSF.

As patients with poor kidney function may not be able to tolerate these contrast agents, the imaging methods currently used – unenhanced MRI or non-liver specific lower-risk GBCAs – significantly reduce the ability of clinicians to find and treat focal liver lesions, ultimately impacting the patient's chance of survival. This patient population, which is estimated to account for around 4% of all patients requiring a liver MRI, is in dire need of an alternative solution that provides similar imaging insights to those who undergo contrast drug-enhanced MRI.

The Risk of NSF

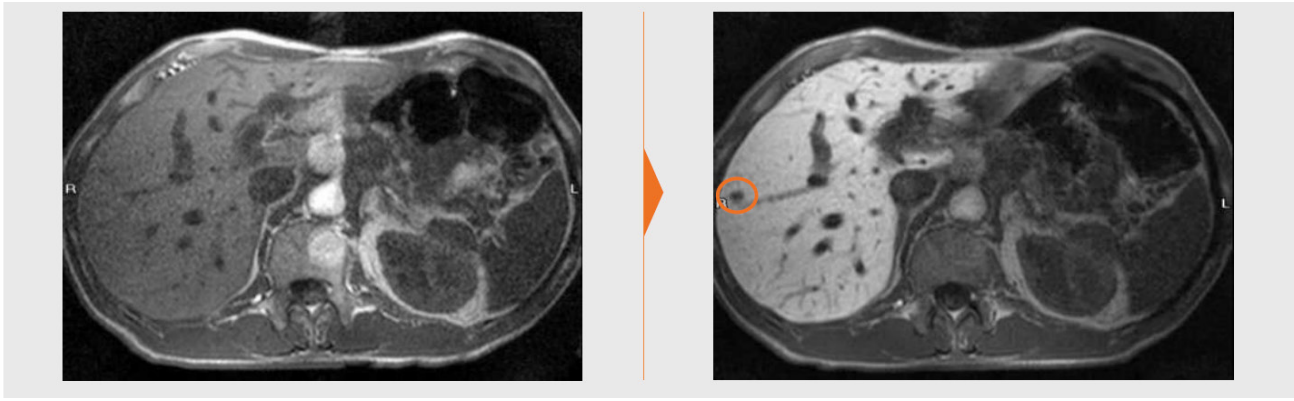
Although a rare condition, NSF is serious and potentially life-threatening. It causes sclerotic transformation and hardening of the skin, and can lead to joint contractures, and muscle and fascial fibrosis, which may lead to severe immobility. It can also affect the inner organs. NSF worsens over time and can cause death, which typically results from multi system failure. The FDA database has registered 3000+ cases of NSF since 2006 (of which 24% were fatal) and the severity of illness, time to disease manifestation, and GBCA dosing exposure vary individually (1, 2). It should be noted that not all global cases of NSF are reported to the FDA, however.

Regulatory agencies, including the FDA and EMA, have issued warnings about the use of GBCAs, and clinical guidelines restrict use in patients with severe kidney impairment. The American College of Radiology guidelines for GBCA administration advise against administration of group I and group III agents (see **Table 1**) in those on dialysis or with chronic kidney disease stage four or five to

Group	Classification
I	Gadodiamide, gadopentetate dimeglumine
II	Gadobenate dimeglumine, gadobutrol, gadoterate acid, gadoteridol
III	Gadoxetate

Table 1: American College of Radiology 2018 classification of gadolinium-based contrast agents into groups I, II, and III

Patient example from Phase III study



Unenhanced liver MRI
(without contrast agent)

Orviglance contrast enhanced liver MRI
Liver metastasis appears with Orviglance

Figure 1: MRI images showing ability of Orviglance to aid detection of liver metastasis compared with unenhanced MRI

avoid potential NSF development (2). It should also be noted that none of the group II GBCAs are FDA-approved for liver-specific imaging.

Researching Safe Alternative Contrast Agents

Orviglance (manganese chloride tetrahydrate, former working name Mangoral) is the first contrast agent in development for use in liver MRI in adults with severely impaired kidney function. It has been granted an Orphan Drug Designation by the FDA and is currently in Phase III development. Orviglance is an orally administrated contrast agent that has demonstrated high quality imaging compared to an unenhanced MRI (see **Figure 1**). It is based on the chemical element, manganese, which is a natural trace element in the body. It also contains an amino acid and a fat-soluble vitamin to increase the absorption of manganese from the small intestine into the portal liver vein. From here, the manganese is transported to the liver where it is taken up by normal liver cells, also known as the hepatocytes. The excretion is biliary and the systemic exposure minimal.

Promising Phase I and II Results

A total of six Phase I and II clinical studies with Orviglance have been completed in 127 healthy volunteers or patients with liver metastases (plus an additional 51 individuals in a compassionate use setting).
The safety assessments from these studies indicate that Orviglance is safe and well-tolerated. Observed adverse events (diarrhoea and nausea were most frequently reported) were mostly mild and transient in nature. The efficacy analyses show that diagnostic quality scores improved after use of Orviglance and provide support that it is an effective liver-specific non-gadolinium MRI contrast agent.
To further validate the results of the individual clinical studies and provide guidance for the design of the Phase III programme, Ascelia Pharma performed a consolidated re-evaluation of all the available imaging data, performed by an independent blinded reader. The results have been presented at global radiology conferences, including the Radiological Society of North America (RSNA), European Congress of Radiology (ECR) and Society for Advanced Body Imaging (formerly SCBT-MR).

This blinded read study containing data from 178 individuals showed that compared to unenhanced MRI, 33% more lesions were detected after an Orviglance-enhanced MRI. Orviglance also improved MRI performance in terms of lesion visualisation, conspicuity (contrast vs background) (p-value <0.0001), and delineation (border sharpness) (p-value <0.0001). In addition, quantitative parameters like lesion-to-liver contrast ratio were significantly improved on Orviglance-enhanced MRIs compared to unenhanced MRIs.

A further blinded read study was performed in 2020, revisiting images collected in a clinical trial performed at Karolinska University Hospital in Stockholm, Sweden, comparing Orviglance-enhanced MRI to an MRI enhanced with a gadolinium contrast agent (gadobenate dimeglumine) and an unenhanced MRI. The results were presented at RSNA 2021 (3).

The endpoints and evaluation criteria in the re-read study were: number and size of lesions detected, lesion border delineation, lesion contrast, and quantitative assessments. Three independent and experienced radiologists evaluated the images.

The results revealed that:

- A higher number of lesions was detected by Orviglance-enhanced MRI compared to unenhanced MRI for all readers
- A higher number of lesions was detected by Orviglance-enhanced

MRI compared to gadobenate dimeglumine MRI for all readers
- Two of the readers showed higher scores for lesion delineation for Orviglance-enhanced MRI compared to gadobenate dimeglumine MRI
- Signal-to-noise ratio and lesion-to-liver contrast was similar for Orviglance-enhanced MRI and gadobenate dimeglumine MRI

Ongoing Phase III Study: SPARKLE

SPARKLE is a global multicentre study of Orviglance in up to 200 patients with severe renal impairment and known or suspected focal liver lesions. Its aim is to investigate the efficacy and safety of Orviglance in the target population. Primary efficacy, in terms of lesion visualisation compared to unenhanced MRI, will be evaluated by three independent blinded readers. Following the completion of the SPARKLE study, Ascelia Pharma plans to submit a New Drug Application to the FDA with a subsequent launch expected in H2 2023.

Two supporting studies aim to provide further data about the use of Orviglance in clinical practice: one study includes patients with various degrees of hepatic impairment (impaired liver function) and the other is to determine the effect of food intake on Orviglance uptake, for which patient recruitment has been completed.

Summary

An effective alternative to GBCAs for use in liver MR imaging in adults with severely impaired kidney function represents an urgent unmet clinical need. In Phase I and II studies, Orviglance has shown that it is an effective liver-specific non-gadolinium liver MRI contrast agent. Results from the SPARKLE Phase III study are highly anticipated by the radiology community and patient groups. Orviglance might hold the key to ensuring cancer treatment and survival rates are improved for those suffering from severe kidney disease.

Orviglance is an investigational medicinal product and is not yet approved for use by regulatory authorities in any jurisdiction.

References

1. *Visit: fis.fda.gov/sense*
2. *Do C et al, Gadolinium-based contrast agent use, their safety, and practice evolution, Kidney 360; 1(6), 2020*
3. *K Shamsi et al, Orally administered Mangoral (Manganese Chloride Tetrahydrate) and intravenously administered Gadobenate Dimeglumine for MRI Of Colorectal Liver Metastases – an intraindividual comparison. Presented at RSNA 2021*

Carl Bjartmar has been Chief Medical Officer at **Ascelia Pharma** since 2018 and has a long and solid track record in late-stage orphan drug development. He has previously served in senior roles at large international pharma companies such as Lundbeck, Sanofi, and Genzyme, where he gained extensive experience in clinical development – in particular the development of novel therapies for rare diseases. Before joining Ascelia, Carl was most recently Chief Medical Officer for the Swedish biotech company Wilson Therapeutics.