Efficacy of Dotarem -enhanced MRA in the diagnosis of peripheral artery disease compared to Gadovist enhanced MRA

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Purpose

To compare the diagnostic performance of 0.1mmol/kg of Dotarem® enhanced-MRA and Gadovist® enhanced-MRA at 3T
Methods and Materials

Study Design

This was a prospective, phase IV, double-blind, randomized, multinational study (DALIA). Institutional review board and regulatory approval were granted from each out of the 15 European centers (Austria, France, Germany, Italy, Spain) involved in this trial.

The study was registered at http://www.clinicaltrials.gov/ (registration no. NCT 01026389).

Patients

Peripheral CE-MRA was performed in 189 consecutive patients scheduled for peripheral DSA. This included 149 men and 40 women aged 24-91 years (mean age 66.4±10.7 years). Indication for DSA was the clinical diagnosis of peripheral arterial occlusive disease (PAOD) in the clinical stages II to IV according to the classification by Fontaine. After obtaining written informed consent, patients underwent peripheral CE-MRA at 3T after randomisation either during administration of Gd-DOTA (group A) or gadobutrol (group B). MR angiographies were performed within 1-30 days before the planned intra-arterial (ia) DSA.

Inclusion criteria were age above 18 years and no history of allergic reaction to MR contrast media. Patients with contraindications for magnetic resonance imaging (MRI) such as pacemaker, implanted metallic devices, aneurysm clip, severe claustrophobia, and metallic joint replacement were excluded. Additionally, patients with known severe adverse drug reaction or contraindication to one of the investigational products as well as patients after stent graft or stent placement into the abdominal aorta or the iliac arteries were excluded.

Furthermore, patients who had a major cardiovascular event within 30 days prior to the screening were not enrolled.

Contrast Agents

The contrast injection protocol involved the administration of 0.1 mmol/kg Gd-DOTA (Dotarem®, Guerbet, Roissy, France) at a flow rate of 1.0ml/s followed by 25-30 ml of saline in 92 patients. In the remaining 92 patients 0.1 mmol/kg gadobutrol (Gadovist®, Bayer HealthCare, Leverkusen, Germany) at a flow rate of 0.5ml/s was applied followed by 25-30 ml of saline.

Digital Subtraction Angiography
All DSA were performed within a range of 1-30 days after MR examination. The average time interval was 7.8±9.0 days.

Intra-arterial DSA have been performed within 1 - 30 days after the study MRA (at least 24 hours after contrast injection during MR angiography). All DSA examinations were performed as part of the normal medical treatment. In cases where an endovascular treatment was performed for the PAOD, diagnostic angiograms were obtained prior to the intervention to allow for comparison to contrast-enhanced MR angiography.

**Study Evaluation Criteria**

For analysis purposes, the arterial vascular system was divided into 21 segments per patient: aorta; common iliac; external iliac/common femoral; superficial femoral; deep femoral; popliteal; anterior tibial; posterior tibial; peroneal; dorsal pedal; media pedal. For every vascular segment, the absence or presence of arterial stenosis was assessed.

The primary efficacy endpoint was the degree of agreement (within patient accuracy) in stenosis assessment as rendered by both MR angiographic protocols compared to the reference standard (ia-DSA). This agreement was assessed in a blinded fashion on-site at patient level.

For every vascular segment, the absence or presence of arterial stenosis was assessed. In case of the presence of stenosis, the severity was calculated according to the following calculation:

Percental stenosis [%] = 100 x (1-[narrowest diameter / normal diameter]).

According to above mentioned calculation, each lesion was graded as follows: 0 = no significant stenosis (0-50%); 1 = moderate stenosis (51-69%); 2 = severe stenosis (70-99%); 3 = occlusion (100%). For further analysis, groups 0 and 1 were summarized as "non-significant" stenosis.

In addition, sensitivity and specificity values as well as positive and negative predictive values (PPV and NPV) in stenosis assessment were calculated.

Furthermore, the image quality in every segment was rated using a 5-point scale (5: providing the expected information, 4: providing sufficient information, 3: not providing all the expected information, 2: not providing enough information, 1: not applicable). Additionally, the visualization of the collateral circulation was classified using the same 5-point scale as described above. The venous overlap interfering with arterial visualization was graded using a 4-grade scale (4: not seen, 3: partially seen, 2: seen, 1: non-assessable). Finally, the diagnostic confidence was rated using a 5-point scale (5: excellent, 4: high, 3: moderate, 2: poor, 1: not assessable).
Safety Assessment

Vital signs (blood pressure, heart rate) were monitored just before each MRA procedure, 15 and 30 minutes after. Injection-site tolerance was also assessed by asking the patients 30 minutes after the procedure using a questionnaire.

Additionally, all patients were monitored for adverse events (AEs) during the study participation.

Statistical Analysis

For the primary endpoint, statistical testing was based on the comparison of the lower limit of the 95% confidence interval (CI) of the difference between groups to the non-inferiority margin for the PP population. The non-inferiority of Gd-DOTA-MRA compared to gadobutrol-MRI was established if this lower limit of CI was superior to the non-inferiority margin (-6.5%).

The secondary endpoints were explored by using a logistic regression model with adjustment on centres.
Results

Patients Eligible For Analysis

A total of 189 patients were enrolled in 15 centers in 5 European countries (Spain, France, Germany, Italy, Austria). Five patients were excluded from the safety analysis because they did not receive any injection; three out of them were excluded prior to randomization. Therefore, 184 patients were eligible for the safety analysis.

A total of 14 patients were excluded from the all-included (AI) population due to withdrawals from the study, leading to a number of 175 patients eligible for the intent-to-treat (ITT) population. Among the ITT population, 19 were excluded from the per-protocol (PP) population due to protocol deviation making 156 patients eligible for the PP analysis, 77 within the Gd-DOTA group and 79 within the gadobutrol group.

Primary Efficacy Endpoint

In the PP population (156 patients), at the patient level, the agreement between MRA and DSA was higher with Gd-DOTA (80.6±16.1%) compared to gadobutrol (77.1±19.6%). The mean difference in agreement (Gd-DOTA - gadobutrol) was 3.5% (95 %CI: [-2.2%; 9.1%]). As the lower limit of 95% CI (-2.2%) was superior to the non-inferiority margin (-6.5%), the non-inferiority of Gd-DOTA-MRA over gadobutrol-MRA was demonstrated.

Similar results were found in the ITT population (75.8%±18.9% vs 69.0%±24.2%, respectively, D=6.8%).

Secondary Efficacy Endpoints

Sensitivity, specificity and predictive values

In the PP population, the sensitivity in the detection of significant stenosis was 72.3% (191 out of 264 relevant stenosis correctly assessed) with a specificity of 92.6% (763 out of 824 non-relevant stenosis correctly diagnosed) with Gd-DOTA compared to a sensitivity of 70.6% (168 out of 238 relevant stenosis) and a specificity of 92.3% (756 out of 819 patent segments) with gadobutrol. There were no significant differences between group Gd-DOTA and gadobutrol (sensitivity: #=1.3%, p=0.79; specificity: #=0.1%, p=0.98).

The positive and negative predictive values for the detection of relevant stenosis were similar in both groups (PPV: 75.8% with Gd-DOTA vs 72.7% with gadobutrol; NPV: 91.3% vs 91.5%, respectively) in the PP population.
Similar results were found in the ITT population. The MRA sensitivity for detecting significant stenosis (>50%) was 73.7% with Dotarem® and 69.5% with Gadovist®; the specificity (92%), PPV (75.8% versus 72.5%), NPV (91%).

Diagnostic confidence

No difference between the two groups was found with regard to the diagnostic confidence, which was rated as "high" or "excellent" in 67/77 (87.0%) patients with Gd-DOTA compared to 68/79 (86.0%) patients with gadobutrol in PP population.

Diagnostic confidence (86.3% vs 86.2%) was also similar in both groups in the ITT population.

Quality assessment

Visualization of patients’ arteries

The expected/sufficient information was obtained for 1261 (80.9%) arteries with Gd-DOTA compared to 1279 (80.1%) arteries with gadobutrol in the PP population.

Similar results were found with regard to the assessment of collateral circulation at patient level. The expected/sufficient information was obtained in 65/77 (84.4%) patients diagnosed using Gd-DOTA-enhanced MRA compared to 66/79 (83.5%) using gadobutrol-enhanced MRA in the PP population.

Similar results were found in the ITT population.

Venous overlap

Venous overlap was "partially seen" or "not seen" in 67 (87.1%) patients with Gd-DOTA compared to 64 (81.0%) patients with gadobutrol in the PP population.

Similar results were found in the ITT population.

Clinical Safety

In two patients (2.2%) an adverse event occurred after Gd-DOTA injection. These events present by folliculitis (mild intensity and not related) and burning sensation (mild intensity and possibly related to contrast agent). In two patients (2.2%) an adverse event was observed after gadobutrol injection. This event was injection site extravasation (mild intensity and not related) in one patient and hot flush (mild
intensity and possibly related to contrast agent) in the other patient. No serious adverse events occurred after injection of any contrast agent.

Variations from baseline in vital signs were comparable between groups, and no clinically significant out of range variation was observed.
Conclusion

1) No significant difference in the agreement with DSA between the two MRA groups. Non-inferiority of Dotarem® compared to Gadovist® confirmed for peripheral MRA.

2) No significant differences in the sensitivity and specificity in the detection of relevant stenoses. Non-inferiority of Dotarem® compared to Gadovist® confirmed.

3) High values of sensitivity, specificity, NPV and PPV in the detection of relevant stenoses.

4) Clinical usefulness of peripheral MR angiography at 3 Tesla confirmed in a large patient population.
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