Cerebral neoplastic enhancing lesions: Multicenter, randomized, crossover intraindividual comparison between gadobutrol (1.0 M) and gadoterate meglumine (0.5 M) at 0.1 mmol Gd/kg body weight in a clinical setting

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A B S T R A C T

Objective: Two macrocyclic extracellular contrast agents, one-molar neutral gadobutrol and ionic gadoterate meglumine, were compared to determine the overall preference for one or the other in a clinical setting.

Materials and methods: Multicenter, randomized, single-blind, intra-individually controlled, comparison study with a corresponding blinded read. Efficacy analysis was based on 136 patients who underwent identical MRI examinations: group A first received 1.0 M gadobutrol followed by 0.5 M gadoterate meglumine 48 h to 7 days later; group B had a reversed administration order. Three independent blinded readers assessed off-site their overall diagnostic preference (primary efficacy parameter) based on a matched pairs approach.

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1. Introduction

The role of contrast in diagnosis and follow up of cerebral tumors is well established. Due to its high tissue contrast and its non-invasiveness, magnetic resonance imaging (MRI) is accepted as the most sensitive method for diagnostic work-up of brain tumors. To enhance the tumor contrast and to differentiate the different aspects of the lesion the use of MR contrast media based on gadolinium (Gd) is therefore standard [1,2].

As a consequence several clinical studies to search for the most effective use of contrast, dose, and delayed imaging have been published [3,4]. Moreover, more recently, due to the availability of different Gd agents, several studies have been performed to see if differences in diagnostic imaging were achieved by different agents, related to their different physicochemical characteristics. Among the different characteristics of Gd agents relaxivity has been advocated to be advantageous to receive higher enhancement [5–8].

In the recent decade, gadobutrol, a nonionic macrocyclic Gd³⁺ chelate, became available for intravenous use. It is formulated for commercial use at a concentration of 1.0 M, whereas other extracellular Gd-based contrast agents (GBCA) used for this indication are formulated in a concentration of 0.5 M Gd/L. Notable compared to other Gd agents it has a quite high relaxivity. Recent small series of patients reported superiority of gadobutrol in the detection of cerebral metastases [6,7]. Furthermore, gadobutrol is a macrocyclic agent as is gadoterate meglumine. Due to their high kinetic stabilities both contrast agents are favored over linear Gd chelates to minimize the risk for nephrogenic systemic fibrosis (NSF) [9,10].

Our aim was to compare two macrocyclic compounds with different physicochemical properties, above all relaxivity and concentration. Both were used at an equimolar dose of Gd/kg body weight to see whether there was a different impact on diagnostic imaging of cerebral tumors.

2. Materials and methods

2.1. Research design and study population

The study was designed as a multicentric randomized intradividual crossover comparison of gadobutrol with gadoterate meglumine. Between March 2008 and May 2009 a total of 166 patients were recruited in 12 Italian centers in compliance with “International Conference on Harmonization Good Clinical Practice” guidelines following approval by applicable ethics committees/institutional review boards. Prior to the start of the study informed consent was obtained from each patient.

Patients with known cerebral intra axial or extra axial neoplastic lesions (primary or secondary enhancing lesions) who were scheduled for contrast-enhanced MRI were included. Exclusion criteria were mainly intended to guarantee the patients’ safety and encompassed (i) the standard MRI exclusion criteria (contrast agent hypersensitivity, implanted metallic devices), (ii) patients presenting with renal insufficiency, and (iii) clinically unstable patients.

Demographic data, details to the diagnosis as well as medical/surgical history details were recorded. All patients underwent two identical MRI examinations separated by at least 48 h to prevent any effect of carryover but not more than 7 days to minimize the chance of lesion evolution/progression of disease in between the two examinations. Eligible patients were randomized prospectively into group A or group B, which differed by the order of contrast agent administration. The 80 patients randomized to group A first received a single dose of gadobutrol (1.0 M). In their second MRI examination they received gadoterate (0.5 M). In the remaining 80 patients the treatment order was reversed. With regard to image evaluation the study was double-blinded. For safety purposes, each patient stayed in the hospital for at least 2–4 h after the MRI examination was completed. After 20–28 h the patients were contacted for another follow-up.

2.2. Contrast agents

Two extravascular GBCA with high complex stability due to their macrocyclic structure were compared [9]. Their kinetic dissociation half-life is $T1/2 = 24$ h (pH 1), which can be extrapolated to a $T1/2$ of over 1000 years at pH 7.4 [11]. Gadobutrol 1.0 M (Gadovist®, Bayer Schering Pharma AG, Berlin, Germany) is a hydrophilic, neutral (nonionic) contrast agent with a $T1$-relaxivity of 5.2 L mmol⁻¹ s⁻¹ and a $T2$-relaxivity of 6.1 L mmol⁻¹ s⁻¹. Gadoterate meglumine (Dotarem®, Guerbet, France) is a hydrophilic, ionic contrast agent with a $T1$-relaxivity of 3.6 L mmol⁻¹ s⁻¹ and a $T2$-relaxivity of 4.3 L mmol⁻¹ s⁻¹ (measured in plasma, at 1.5 T and 37 °C) [12]. Both contrast agents were administered in equimolar doses of 0.1 mmol/kg body weight.

2.3. Magnetic resonance imaging

The MRI examination was performed using a standard head coil for brain imaging on scanners from Siemens, Philips and General Electrics, respectively. The same field strength of 1.0 T (in 21% of all patients) or 1.5 T (in 79% of all patients) was used for both MRI examinations. For pre contrast MRI T1-weighted and T2-weighted spin-echo/turbo spin echo and fluid-attenuation inversion recovery scans covered the whole brain. In case of the second contrast administration, which was to be performed at the earliest 24 h after the first MRI examination, the pre-contrast MRIs ensured that there was no remaining contrast of the previous contrast-enhanced MRI. Then the appropriate dose of gadobutrol or gadoterate was administered intravenously as a bolus by hand or by automatic injector via a peripheral vein (preferably the antecubital vein) at a flow rate of 1.0–2.0 mL/s. Immediately after start of contrast injection a T1-weighted spin-echo/turbo spin echo sequence (image pixel size $≤ 0.37$ mm², TR/TE $< 600$ ms/$< 15$ ms, number of excitations 1–2, slice thickness 3–4 mm, interslice gap $≤ 30$%, and flip angle 90°) had

Results: Superiority of gadobutrol over gadoterate meglumine was demonstrated for the qualitative assessment of overall preference across all readers by a statistically significant difference between both contrast agents for this primary endpoint. Preferences in lesion enhancement (secondary endpoint) were also found significantly in favor of gadobutrol. For preference in lesion delineation from surrounding tissue/edema and for internal structure only a trend towards a higher proportion for gadobutrol was found (except for internal structure reported by one reader, which showed a result of statistical significance). Lesion contrast and relative lesion enhancement (quantitative parameters) were statistically significantly higher for gadobutrol compared to gadoterate meglumine.

Conclusion: Contrast-enhanced MRI of neoplastic brain lesions at a dose of 0.1 mmol Gd/kg body weight, assessed in a standardized off-site blinded reading, results in a significantly higher qualitative and quantitative preference for gadobutrol compared to gadoterate meglumine.

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2.4. Qualitative assessment by blinded reading and on-site investigators

Image evaluation was done in a prospectively planned, randomized off-site blinded reading. Assessments were given by three independent radiologists (two neuroradiologists and one general radiologist to reflect the actual conditions under daily routine) who had not been involved in the clinical part of the study. The images did neither contain any information regarding clinical site, manufacturer of the scanner, dose and type of contrast agent used, nor patient data. For each patient, all images from the first and the second examinations were displayed simultaneously. In a qualitative matched-pairs assessment of all post-contrast T1-weighted images of an individual patient, each blinded reader had to express his overall preference for one or the other examination or neither of them as primary endpoint, using the three-point scale with 1 (gadobutrol better than gadoterate meglumine), 0 (no preference for a contrast agent), and −1 (gadobutrol worse than gadoterate meglumine). Secondary efficacy parameters included the preference for an examination concerning the intensity of lesion enhancement, lesion delineation from its surrounding tissue, and information on the internal lesion structure, as assessed qualitatively by all three individual blinded readers comparably to the primary endpoint. Qualitative on-site assessments by the clinical investigators were performed in the same way and were also evaluated as secondary efficacy parameters.

2.5. Quantitative assessment by blinded reading

For the quantitative assessment, one off-site blinded signal intensity reader evaluated the images also in a matched pairs approach as another secondary efficacy parameter. Following both examinations, signal intensities (SI) of pre contrast and post contrast T1-weighted MRI scans were measured in the same region of interest. To ensure this, the region of interest defined in the first examination was copied onto the imaging data of all other sessions. Slight adaptations were allowed if needed, e.g. to correct for differing orientations of the slices. The region of interest was defined as a homogeneously enhancing area in the central part of the enhancement to avoid partial volume effects. As reference region a normal white matter on the contralateral site was defined. Noise was assessed from a region outside the brain in phase-encoding direction. Based on the SI values from these regions, lesion-to-brain ratio (= S\text{lesion}/S\text{brain}) and contrast-to-noise ratio [= (S\text{lesion} − S\text{brain})/S\text{noise}] were calculated for pre contrast and post contrast images. As contrast measurements were acquired with the same receiver gain settings, the percentage of lesion enhancement was calculated as follows: 100 × (S\text{post} − S\text{pre})/S\text{pre}.

2.6. Statistical analysis

Statistical calculations were done with software SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA). The primary efficacy variable (qualitative overall preference to one or the other contrast agent or neither of them) was tested for each reader’s assessment by Wilcoxon signed rank tests and across blinded readers using logistic regression analysis based on generalized estimation equations with a two-sided level of significance of 5%. The multiple measurements by the readers were taken into account using compound symmetry as working correlation matrix. All secondary endpoints with regard to preference for one or the other contrast agent were done by reader using Wilcoxon signed rank tests. The evaluations were performed by the blinded readers only, if at least one enhancing lesion was present. The clinical investigator assessed the images regarding preference, when at least one lesion was seen.

Interreader agreement was evaluated by Cohen’s kappa coefficient [13]. Evaluation of quantitative SI measurements was done by presenting mean values and standard deviation for lesion-to-brain ratio, contrast-to-noise ratio and relative lesion enhancement. Differences in technical parameters between the two contrast agents were tested by paired t-tests.

3. Results

3.1. Patients

The efficacy analysis was based on a total of 136 patients. Initially, 166 patients were enrolled into the study. Before receiving any contrast media three patients withdrew their informed consent, one patient did not meet the inclusion/exclusion criteria, one patient was not collaborative, and one patient had an adverse event after pre contrast imaging. Of the remaining 160 patients, 80 (39 male, 41 female) were randomized into group A and first received a single dose of gadobutrol (1.0 M). In their second MRI examination they were to receive gadoterate meglumine (0.5 M). In the other 80 patients (42 male, 38 female) randomized to group B the treatment order was reversed. Nine patients dropped out after their first MRI, five patients in group A and four patients in group B: three patients withdrew their informed consent; two patients underwent surgery before the second MRI examination could take place; two patients had major protocol deviations, as the first MRI had shown only ischemic lesions without enhancement; in one patient instead of the second MRI a computed tomography had been performed; one patient was lost during follow up.

151 patients completed the study by having both MRI examinations. Of those, 15 patients could not be considered due to major protocol deviations such as different sequence parameters between the two examinations, differing duration between contrast administration and start of T1-weighted sequence, interval between both MRI examinations was less than the minimum 48 h, assignment to the order of contrast agent administration was not according to the randomization list, missing post contrast T1-weighted coronal data set, or second MRI was performed without contrast enhancement T1 sequences.

Both treatment groups were comparable as regards their demographic data (mean age 59.8 years in group A, 60.2 years in group B, 60.0 years for all 160 patients in the FAS). Lesion types encompassed supratentorial and infratentorial lesions; in detail diagnoses were meningiomas (33%), glial tumors of high grade (28%), metastases (21%), pituitary adenoma (8%) and unknown/other (10%, in detail the latter encompassed Schwannoma (4), neurinoma (2), extra-axial tumor (1), cystic lesion (1), atypical meningioma (1), oligodendrogioma (1), neuraoma acoustic (1), radionecrosis (1), emiangioblastoma (1), relapse ganglioma (1), ependymoma (1),...
unknown (1)) with a roughly comparable distribution in group A and group B.

### 3.2. Qualitative image assessment by three blinded readers and on-site investigators

Across readers and when excluding assessments "no preference" in the ITT population, "gadobutrol better than gadoterase meglumine" was reported in a proportion of 66% (131 assessments of a total of 199 assessments, in which preference for one of the two contrast agents was stated, 95% confidence interval 57% to 74%, $p = 0.0007$), i.e. in significantly more than 50% of cases. Thus, superiority of gadobutrol over gadoterase meglumine is concluded as a statistically significant difference between both contrast agents was demonstrated.

In Table 1 the individual readers' assessments are displayed. For reader 1, reader 2 and the investigator's assessment, gadobutrol was found to be superior to gadoterase meglumine ($p < 0.05$).

Interreader agreement was judged as a fair agreement (0.26–0.33) based on the weighted Kappa in pair-wise comparisons between the individual [13].

The preferences in lesion enhancement were found significantly in favor of gadobutrol for all three readers' and the investigator's assessment ($p < 0.05$), whereas for preference in lesion delineation from surrounding tissue and edema and internal structure only non-significant trends towards a higher proportion for gadobutrol was found except for internal structure reported by reader 1. In case of reader 1, gadobutrol was found statistically significantly superior to gadoterase meglumine ($p = 0.0466$) (Table 2).

Table 3 shows exemplary images of brain tumors of two patients are shown following gadobutrol and gadoterase meglumine administration, respectively (Figs. 1 and 2). Both figures show examples of improved image quality of gadobutrol in comparison to gadoterase meglumine in the visual assessment of the intensity of lesion enhancement, the delineation of the contrast enhancing tumor parts and the internal lesion structure identification.

### 3.3. Quantitative image assessment

Lesion contrast as well as relative lesion enhancement were statistically significantly higher for gadobutrol compared to gadoterase meglumine (Table 3).

The mean of the contrast to noise ratio was higher following gadobutrol administration than following gadoterase meglumine administration. As the standard deviation was very large, this difference in the mean values was not judged to be of statistical significance (Table 3).

#### Table 1
Overall preference of gadobutrol versus gadoterase meglumine MR examination following post contrast evaluation.

<table>
<thead>
<tr>
<th>Observer</th>
<th>N</th>
<th>Preference for gadobutrol, N (%)</th>
<th>No preference, N (%)</th>
<th>Preference for gadoterae meglumine, N (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>124</td>
<td>67 (54)</td>
<td>24 (19)</td>
<td>31 (27)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Reader 2</td>
<td>120</td>
<td>22 (18)</td>
<td>91 (76)</td>
<td>7 (6)</td>
<td>0.0034</td>
</tr>
<tr>
<td>Reader 3</td>
<td>130</td>
<td>42 (32)</td>
<td>60 (46)</td>
<td>28 (22)</td>
<td>0.0945</td>
</tr>
<tr>
<td>Clinical investigator</td>
<td>136</td>
<td>58 (43)</td>
<td>42 (31)</td>
<td>36 (26)</td>
<td>0.0224</td>
</tr>
</tbody>
</table>

* The clinical investigators performed their qualitative assessments on all examinations. The blinded readers evaluated the preference only in cases, where at least one enhancing lesion was detected by the reader.

* $p$-Value of the two-sided Wilcoxon signed rank test.

#### Table 2
Overall preference of gadobutrol versus gadoterase meglumine MR examination by qualitative assessment parameter.

<table>
<thead>
<tr>
<th>Observer</th>
<th>N</th>
<th>Preference for gadobutrol, N (%)</th>
<th>No preference, N (%)</th>
<th>Preference for gadoterae meglumine, N (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Intensity of lesion enhancement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>124</td>
<td>68 (55)</td>
<td>24 (19)</td>
<td>32 (26)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Reader 2</td>
<td>120</td>
<td>21 (18)</td>
<td>92 (77)</td>
<td>7 (6)</td>
<td>0.0057</td>
</tr>
<tr>
<td>Reader 3</td>
<td>130</td>
<td>49 (38)</td>
<td>51 (39)</td>
<td>30 (23)</td>
<td>0.0316</td>
</tr>
<tr>
<td>Investigator</td>
<td>136</td>
<td>55 (40)</td>
<td>51 (38)</td>
<td>30 (22)</td>
<td>0.0060</td>
</tr>
<tr>
<td>B. Lesion delineation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>124</td>
<td>26 (21)</td>
<td>81 (65)</td>
<td>17 (14)</td>
<td>0.1727</td>
</tr>
<tr>
<td>Reader 2</td>
<td>120</td>
<td>6 (5)</td>
<td>109 (91)</td>
<td>5 (4)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Reader 3</td>
<td>130</td>
<td>19 (15)</td>
<td>99 (76)</td>
<td>12 (9)</td>
<td>0.2140</td>
</tr>
<tr>
<td>Investigator</td>
<td>136</td>
<td>24 (18)</td>
<td>92 (68)</td>
<td>20 (15)</td>
<td>0.5526</td>
</tr>
<tr>
<td>C. Internal structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>124</td>
<td>32 (26)</td>
<td>74 (60)</td>
<td>18 (15)</td>
<td>0.0466</td>
</tr>
<tr>
<td>Reader 2</td>
<td>120</td>
<td>7 (6)</td>
<td>110 (92)</td>
<td>3 (3)</td>
<td>0.3438</td>
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<tr>
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<td>24 (18)</td>
<td>89 (69)</td>
<td>17 (13)</td>
<td>0.2797</td>
</tr>
<tr>
<td>Investigator</td>
<td>136</td>
<td>38 (28)</td>
<td>74 (54)</td>
<td>24 (18)</td>
<td>0.0752</td>
</tr>
</tbody>
</table>

* The blinded readers gave a qualitative assessment, if enhancing lesions were present and combined images were evaluable, whereas the pre-requisite of the presence of an enhancing lesion was not given for the clinical investigators.

* $p$-Value of the two-sided Wilcoxon signed rank test.

#### Table 3
Signal intensity measurements.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion-to-brain ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>124</td>
<td>1.596</td>
<td>0.360</td>
<td></td>
</tr>
<tr>
<td>Gadoterae meglumine</td>
<td>122</td>
<td>1.541</td>
<td>0.372</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>122</td>
<td>0.059</td>
<td>0.176</td>
<td>0.0003</td>
</tr>
<tr>
<td>Contrast-to-noise ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>124</td>
<td>129.337</td>
<td>335.065</td>
<td></td>
</tr>
<tr>
<td>Gadoterae meglumine</td>
<td>122</td>
<td>98.281</td>
<td>146.182</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>122</td>
<td>32.693</td>
<td>304.003</td>
<td>0.2372</td>
</tr>
<tr>
<td>% Enhancement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>122</td>
<td>97.062</td>
<td>55.644</td>
<td></td>
</tr>
<tr>
<td>Gadoterae meglumine</td>
<td>122</td>
<td>89.164</td>
<td>53.427</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>122</td>
<td>8.938</td>
<td>26.044</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

* Measurements were obtained in a off-site read by one blinded reader.

* $p$-Value of the two-sided paired t-test on difference.
3.4. Adverse events

For the 160 patients who received at least one dose of contrast agent, within the 28-h follow-up period 10 adverse events in eight patients were recorded. All 10 events (6 following gadobutrol, 4 following gadoterate meglumine) were unrelated to the administration of the contrast agents. They were of mild intensity and resolved within 2 days at most. No unexpected adverse events were reported.

4. Discussion

Results of previous studies contributed to our knowledge that the differences in physicochemical properties of the Gd chelates might result in differences in imaging properties [5,6,14]. Although not completely explained yet, relaxivity plays a role, but it is not the only characteristic of a contrast agent that may influence the imaging quality. Gadobutrol, formulated at 1 M, contributes to the higher shortening of T1 relaxation time by an increased Gd concentration per unit volume and a high T1 relaxivity [6,12]. In this study, an advantage of gadobutrol compared to gadoterate meglumine was proven in the confirmatory analysis, in which “overall preference” after a blinded reading that met all the standards for regulatory clinical trials had been the pre-determined primary efficacy parameter. The three blinded readers had neither knowledge of any patient details nor of MRI procedures, but they had access to all MR images, which were offered to them simultaneously in a randomized order. To judge the robustness of the result, the inter-reader agreement was calculated. In the pairwise comparisons, in addition to agreement by chance alone, agreement was judged to be fair using Cohen’s kappa coefficient [13]. Overall preference for
Gadobutrol was also given by clinical investigators, which were blinded to details of the contrast agent administered. The on-site analyses of the qualitative assessment of lesion enhancement and information on the internal lesion structure also showed the preference for gadobutrol over gadoterate meglumine.

Even if it is difficult to describe the potential clinical impact of our result, as it is for the results of previous comparative studies [5,7], it can be assumed that the diagnostic process is facilitated when preference is accorded for one examination over another due to the presence of a specific contrast agent. Lesions that enhance better are easier to be identified, delineated and characterized. Furthermore, better enhancement is expected to facilitate the depiction even of small lesions in the usual clinical setting. With the results of our study, we cannot prove this question unequivocally, as there were no differences in the number of lesions detected in either treatment group. This might be due to the artificial situation of a blinded read like the one used, in which the radiologists were forced to look for lesions more thoroughly and, consequently, had more chances to see one.

Based on the physicochemical properties it was expected that gadobutrol may offer advantages compared to gadoterate meglumine [12]. In animal experiments it could be shown that differences between contrast agents translate into enhancement benefits for gadobutrol [15,16]. Superiority with regard to image quality of gadobutrol was also indicated by the results of clinical trials performed with smaller number of patients [6,7].

With the present study designed as a crossover intrindividual comparison using standardized data acquisition and an
independent off-site blinded reading evaluation previous assumptions concerning the better image quality with gadobutrol are confirmed in a large number of patients. Patients received the contrast agents sequentially in a randomized order. The treatment order had no effect, as a complete washout was guaranteed before the following MRI examination, which was confirmed by the unenhanced T1 in the second imaging session. To avoid any changes due to tumor growth in between the two examinations, both MRI recordings had to be performed within 7 days at most. Such a setting matches with previous investigations [5] and was carefully designed to evaluate whether there are subtle differences between both GBCA.

Not only the qualitative assessments, but also the quantitative assessments were in favor of gadobutrol with a significantly stronger enhancement resulting in a better lesion contrast. Thus, the differences in the physicochemical properties of gadobutrol and gadoterate meglumine [6,12,17] appear to have resulted in different enhancement characteristics.

As a limitation of this study may be seen that 2D imaging was used for practical reasons as a 3D approach was not feasible in all study centers. A drawback of this kind of acquisition is the difficulty in reaching perfect alignment of the images or to assess the lesions volumetrically. Moreover, as this was a multicenter study with different MR equipments in different centers it was not possible to adopt automated correction for alignment which nowadays is provided by most manufacturers on recent MR softwares. However, this potential bias is common in previous comparative studies, too, and did not influence the qualitative image assessment.

In our study, MRI was performed using field strengths of 1.0 and 1.5 T, respectively. Superiority of gadobutrol enhancement at higher field strengths has already been shown in animal experiments [15,16,18]. Our results indicate that there might be an advantage of gadobutrol over gadoterate meglumine in clinical investigations at field strengths >1.5 T, as, based on the physicochemical data [12], the higher relaxivity of gadobutrol compared to gadoterate meglumine is also given at 3.0 T.

With only 10 adverse events, which were not drug related, the excellent safety profile known for both contrast agents [19,20] was confirmed in our study. It should be noted that the present study with its limited duration of follow-up was not designed to study any long-term effects of contrast agents containing Gd.

5. Conclusions

In this study, for the visualization of enhancing brain lesions gadobutrol was statistically superior compared to gadoterate meglumine when using equal Gd doses. Following standardized data acquisition under routine conditions in twelve different study centers the overall preference for gadobutrol was higher compared to gadoterate meglumine as shown in an off-site blinded reading. This was also supported by the assessments of the (blinded) on-site investigators.

Both contrast agents were very well tolerated. No drug related AEs occurred within the 28 h follow-up period.

Conflict of interest

Simona Gatti is an employee of Bayer Schering Pharma. At the time this manuscript was prepared, also Matthias Voth was an employee of Bayer Schering Pharma. The other authors were clinical investigators of the clinical trial which was funded by Bayer Schering Pharma.

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