

Assessment of Disease Activity in Multiple Sclerosis Phenotypes with Combined Gadolinium- and Superparamagnetic Iron Oxide–enhanced MR Imaging¹

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Purpose:

To compare magnetic resonance (MR) imaging features of multiple sclerosis (MS) lesions after the administration of a gadolinium-based contrast agent and ultrasmall superparamagnetic iron oxide (USPIO) particles among the clinical phenotypes of MS and over time.

Materials and Methods:

This study was approved by the local ethics committee, and written informed consent was obtained from all patients. Twenty-four patients with MS (10 with relapsing and 14 with progressive forms) underwent clinical and gadolinium- and USPIO-enhanced MR examinations at baseline and 6-month follow-up. The number of lesions that enhanced with gadolinium alone, USPIO alone, or both was compared with the Pearson χ^2 or Fisher exact test, and lesion sizes were compared with the Wilcoxon Mann-Whitney *U* test. At 6-month follow-up, the lesion signal intensity on precontrast T1-weighted images and the enhancement after repeat injection of the contrast agent were compared with the baseline postcontrast imaging features by using the McNemar test.

Results:

Fifty-six lesions were considered active owing to contrast enhancement at baseline; 37 lesions (66%) in 10 patients enhanced with gadolinium. The use of USPIO helped detect 19 additional lesions (34%), and two additional patients were classified as having active disease. Thus, the use of both agents enabled detection of 51% (19 of 37 lesions) more lesions than with gadolinium alone. Enhanced lesions were more frequently observed in the relapsing compared with the progressive forms of MS ($P < .0001$). USPIO enhancement, in the form of ringlike patterns, could also be observed on T1-weighted images in patients with progressive MS, enabling the detection of five lesions in addition to the five detected with gadolinium in this phenotype. Lesions that enhanced with both contrast agents at baseline were larger (mean size, 6.5 mm \pm 3.8; $P = .001$) and were more likely to persistently enhance at 6-month follow-up (seven of 27 lesions, $P < .0001$) compared with those that enhanced only with gadolinium (mean size, 4.9 mm \pm 2.2; one of nine lesions) or USPIO (mean size, 3.5 mm \pm 1.5; 0 of 17 lesions).

Conclusion:

The combination of gadolinium and USPIO in patients with MS can help identify additional active lesions compared with the current standard, the gadolinium-only approach, even in progressive forms of MS. Lesions that enhance with both agents may exhibit a more aggressive evolution than those that enhance with only one contrast agent.

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A pivotal role of magnetic resonance (MR) imaging in multiple sclerosis (MS) is to assess radiologic disease activity (1), which is used for diagnosis (2), to guide therapeutic strategies (3,4), and as a surrogate marker to evaluate treatment efficacy in clinical trials (5).

Currently, enhancement with a gadolinium-based contrast agent is the primary sign of disease activity in a given lesion. Such enhancement indicates the accumulation of the contrast agent in the interstitial space owing to increased blood-brain barrier (BBB) permeability; consequently, it can only be considered to be a nonspecific and indirect marker of inflammatory cell infiltration and is known to lack sensitivity (1). Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles may be used to track iron-laden macrophages in the central nervous system (6–8). Previous studies have validated the feasibility of using USPIO in patients with MS (9,10), showing that macrophage infiltration obtained with USPIO was distinct and probably complementary to the increased BBB permeability seen with gadolinium. A new generation of USPIO (11) will soon be available for

human application, and clear direction for USPIO use is still to be defined.

Although previous studies focused on patients with active relapsing-remitting (RR) MS (9,10), the use of USPIO in the progressive forms of MS has yet to be investigated. Pathologic studies have described a less prominent role for inflammation in primary progressive (PP) forms compared with RR forms (12). Nevertheless, some subtle BBB abnormalities (13) and some inflammatory cells (activated microglia) (14) have been described in lesions from progressive MS. Furthermore, the relevance of USPIO enhancement in terms of ongoing tissue damage remains to be elucidated. Vellinga et al (10) suggested that some patterns of USPIO enhancement could reflect a beneficial aspect of inflammation, possibly associated with repair mechanisms. However, many proinflammatory phagocytic cells, which could be tagged with USPIO, are known to attack the myelin and to remove the myelin debris, leading to tissue destruction (15).

The aim of this longitudinal MR imaging study was to compare MR imaging features of MS lesions after the administration of a gadolinium-based contrast agent and USPIO particles among the clinical phenotypes of MS and over time.

longitudinal, phase IIb study between 2004 and 2007 after screening with specialized medical evaluations performed at the MS departments of four different university hospitals (located in Basel, Switzerland; Bordeaux, France; Lille, France; and Milan, Italy). Before initiating the study, we obtained approval from the local ethics committee and written informed consent from all patients.

To compare the MR phenotypes with the clinical phenotypes (relapsing vs progressive MS), we included patients with RR MS and those with a progressive form of the disease (secondary progressive [SP] MS and PP MS).

Patients were included if they were at least 18 years old; if their Expanded Disability Status Scale (EDSS) (16) score was 3 or less (patients with RR MS) or at least 3.5 and 6.5 or less (patients with SP MS and PP MS) before prestudy relapse; and, in patients undergoing ongoing disease-modifying treatment, if maintenance of the same treatment regimen was planned during the next 6 months. Patients with RR and SP MS were included if they developed relapse in the previous 24 hours (minimum) to 21 days (maximum) that

Advances in Knowledge

- The use of both ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles and a gadolinium-based contrast agent enabled a 51% increase in the detection of active multiple sclerosis (MS) lesions (56 enhanced lesions) compared with the use of gadolinium alone (37 enhanced lesions).
- USPIO offers the potential to demonstrate some inflammatory activity in progressive MS.
- Compared with lesions that enhanced only with gadolinium or USPIO, those that enhanced with both agents were larger and showed enhancement on follow-up images after 6 months (seven of 27 lesions, 26%).

Materials and Methods

Patients and Study Design

Although Guerbet Laboratories (Aulnay, France) provided the contrast agents, the authors had direct control of the data and information that was submitted for publication. Twenty-four patients with clinically definite MS (2) were included in a prospective,

Implication for Patient Care

- MS disease activity and lesion heterogeneity can be better evaluated in individual patients by using a combination of USPIO and gadolinium compared with the use of gadolinium alone.

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Abbreviations:

BBB = blood-brain barrier
EDSS = Expanded Disability Status Scale
MS = multiple sclerosis
PP = primary progressive
RR = relapsing-remitting
SP = secondary progressive
USPIO = ultrasmall superparamagnetic iron oxide

Author contributions:

Guarantor of integrity of entire study, V.D.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, T.T., S.R., M.R., K.G.P.; clinical studies, T.T., S.R., M.K., B.B., J.P.P., E.W.R.; statistical analysis, S.R., K.G.P.; and manuscript editing, T.T., S.R., M.F., M.K., M.R., D.H.M., K.G.P., E.W.R.

Potential conflicts of interest are listed at the end of this article.

was untreated with steroids until 24 hours after USPIO administration; patients with PP MS were included while they had no relapse.

Patients were excluded from the study if they had been treated with steroids during the previous 2 months, had contraindications to MR imaging, had known allergy to dextrans or drugs containing iron salts, were pregnant or breast feeding, or received iron oxide nanoparticles within 7 days before USPIO-enhanced imaging.

To investigate the evolution of each initial postcontrast MR imaging feature, patients underwent repeat evaluation at 6 months (17). Evaluations at baseline and 6-month follow-up included the collection of EDSS scores and documentation of the date of the patient's last relapse and treatment status. In addition, patients underwent two MR examinations, both at baseline and at 6-month follow-up (one at day 0 for gadolinium evaluation and one at day 1 for USPIO evaluation). A standardized protocol was followed in all contributing centers by using 1.5-T units (Siemens, Malvern, Pa; Philips, Best, the Netherlands). The first MR examination included axial T1-weighted spin-echo images (repetition time msec/echo time msec = 484/12), T2-weighted turbo spin-echo images (4531/99), T2*-weighted gradient-echo images (977/24, 15° flip angle), and T1-weighted images obtained 5 minutes after intravenous administration of 0.1 mmol/kg gadolinium chelate (Dotarem; Guerbet, Aulnay, France). For all sequences, the section thickness was 5 mm with a 0.5-mm gap, the field of view was 23 cm², and the matrix size was 512². Immediately after the first MR examination, USPIO (ferumoxtran-10 [Sinerem, Guerbet; also known as Combidex, AMAG Pharmaceuticals, Cambridge, Mass]) was injected over approximately 30 minutes (2.6 mg of iron per kilogram body weight diluted in 100 mL of saline) and MR imaging was performed 24–48 hours later in accordance with recommendations (18). USPIO-enhanced MR imaging included axial T1-weighted, T2-weighted, and T2*-weighted sequences, which were performed with the same parameters

and section orientation as the gadolinium evaluation. For both baseline and 6-month follow-up, 30 images were obtained 24 hours after USPIO administration and 14 were obtained 24–48 hours after USPIO administration; there were no significant differences in terms of USPIO enhancement with the imaging delay ($P = .99$).

Image Analysis

All images were anonymized and evaluated in reading sessions in which the evaluators were blinded to the demographic and clinical data.

To assess the presence of enhanced lesions, two readers (S.R., a neurologist with 5 years of experience, and T.T., a neuroradiologist with 7 years of experience) independently evaluated the images obtained at baseline and 6-month follow-up. In case of disagreement, images were discussed with a neuroradiologist (M.K., with 10 years of experience) to reach a consensus. USPIO-enhanced lesions were classified as hyperintense on T1-weighted images and/or hypointense on T2- and T2*-weighted images compared with the surrounding brain. Gadolinium-enhanced lesions were classified as hyperintense to surrounding brain on T1-weighted images. Lesions were classified as enhancing with gadolinium alone, USPIO alone, or both. The post-USPIO pattern was further defined on T1-weighted images, as described by Vellinga et al (10), as ringlike enhancement, focal enhancement, or “return to isointensity” of lesions that were hypointense on unenhanced T1-weighted images. Unenhanced images were always used for comparison, and USPIO- and gadolinium-enhanced lesions were judged together as they would theoretically be in clinical situations.

The maximum diameter of each enhanced lesion was also assessed on T1-weighted images (S.R. and T.T.), considering only the larger diameter in lesions that enhanced with both agents, and the mean values between the two observers were reported. In addition, one observer (S.R.) counted the plaques on T2-weighted images and classified them as iso- or hypointense to

surrounding brain on T1-weighted images, as previously described (19).

Evaluation at 6-month Follow-up

The “radiologic scarring” that occurs at 6 months was investigated in comparison with the postcontrast MR features at baseline. It was first determined whether lesions that enhanced at baseline were still enhanced after 6 months at a similar location, which would suggest persisting inflammatory activity. It was also determined whether lesions that enhanced at baseline became a “black hole” (ie, deeply hypointense compared to the surrounding brain) on the T1-weighted image at 6 months—a finding indicative of tissue damage (19).

The radiologic and clinical activity at 6 months was investigated in comparison with the postcontrast MR imaging features at baseline. Radiologic activity was defined as new lesion(s) and/or enhanced lesion(s) on T2-weighted images at 6-month follow-up. Clinical activity was defined as a new relapse that occurred between baseline and 6 months and/or a 1-point increase in the EDSS score (or a 0.5-point increase if the EDSS score was at least 5.5 or 1.5-point increase if the EDSS score was 0). A relapse was defined as patient-reported symptoms or objectively observed signs that are typical of an acute inflammatory demyelinating event in the central nervous system, current or historical, with duration of at least 24 hours after a period of stability or improvement that had lasted at least 4 weeks, in the absence of fever or infection (20).

Safety

Patients were monitored clinically after each USPIO injection, and adverse events and treatments performed in cases of postinjection reaction were noted.

Statistical Analysis

Interobserver agreement for the detection of the enhanced lesions was calculated with the Cohen κ coefficient, and the reproducibility for the maximum diameter measurements of enhanced

lesions was determined with the intraclass correlation coefficient.

Demographic and clinical characteristics of patients with the different clinical phenotypes were compared by using the Fisher exact test for categorical data and the Wilcoxon Mann-Whitney *U* test for quantitative data.

The sensitivity of USPIO and gadolinium in the detection of active lesions in MS, including the comparison of MR imaging phenotypes with clinical phenotypes, was investigated by using baseline data. The number of each postcontrast MR feature (enhancement with gadolinium alone, USPIO alone, or both) in the entire cohort was investigated and compared between patients with RR MS (relapsing group) and those with SP or PP MS (progressive group), who are in the progressive phase of the disease and might be regarded as essentially similar (21). The Pearson χ^2 or Fischer exact test was used when appropriate.

Because more active and aggressive lesions are expected to have larger spatial extension, we also compared the size of the lesions for each postcontrast MR feature by using the Wilcoxon Mann-Whitney *U* test. Then, the number of lesions that became hypointense on the T1-weighted image or that continued to enhance at 6-month follow-up, as determined by comparison with the initial postcontrast MR imaging features at baseline, were compared with the McNemar test for paired data. Descriptive clinical and radiologic activities at 6-month follow-up, according to the baseline postcontrast MR imaging features, were also presented.

Statistical analyses were performed by using software (SPSS statistics 18, SPSS, Chicago, Ill; MedCalc Package, version 9.2.1.0, MedCalc Software, Mariakerke, Belgium).

Results

Twenty-four patients were enrolled and evaluated at baseline, and data from 6-month follow-up were available for 20 patients (83%). Three patients did not undergo follow-up because they experienced USPIO-related side effects at

baseline, and one patient was lost to follow-up. Two additional follow-up images at 6 months were not considered in the analysis because of insufficient image quality due to motion artifacts. Consequently, the final analysis included 24 patients with clinical and radiologic data at baseline and 20 patients with clinical and 18 with radiologic data at 6-month follow-up. Characteristics of the population are summarized in Table E1 (online). Patients with PP and SP MS were pooled and categorized as the progressive group (there was no significant difference with regard to the demographic characteristics of these patients). The relapsing group—patients with RR MS—was younger ($P = .006$), exhibited shorter disease duration ($P = .006$), had a higher proportion of woman ($P = .01$), and had a lower baseline EDSS score ($P < .0001$).

Sensitivity of USPIO and Gadolinium for the Detection of Active Lesions and Comparison of MR Phenotypes with Clinical Phenotypes

With regard to reproducibility, the interobserver agreement was 87% ($\kappa = 0.68$) for the detection of gadolinium enhancement, 81% ($\kappa = 0.56$) for the detection of USPIO enhancement on T1-weighted images, and 85% ($\kappa = 0.66$) for the detection of USPIO enhancement on T2- or T2*-weighted images. Only enhanced lesions that reached consensus were analyzed below.

In the 24 patients evaluated at baseline, 1287 lesions were counted at T2-weighted imaging. Fifty-six lesions demonstrated enhancement with gadolinium and/or USPIO. Among these 56 lesions, 37 lesions (66%) in 10 patients enhanced with gadolinium (nine with gadolinium alone and 28 with USPIO and gadolinium). The use of USPIO enabled the identification of 19 additional lesions (34% of all enhanced lesions identified or 51% more lesions than with gadolinium alone), which led to two additional patients being classified as having radiologic active disease (Fig 1). All lesions that enhanced with USPIO ($n = 47$, 28 with both USPIO and gadolinium and 19 with USPIO alone) exhibited high signal intensity

on T1-weighted images. Twenty-five of the 47 lesions (53%) had low signal intensity on T2-weighted images and even lower signal intensity on T2*-weighted images at the same location.

On the basis of the clinical phenotypes (Table 1), a significantly greater number of enhanced lesions was found in the relapsing group (46 of 429 lesions, 10.7%) than in the progressive group (10 of 858 lesions, 1.2%) ($P < .0001$). Results were similar for both USPIO and gadolinium (Table 1, $P < .0001$). USPIO helped identify five additional lesions in the progressive group and 14 additional lesions in the relapsing group. This represented 50% and 30% of all enhanced lesions, respectively, for these groups; the difference was not significant ($P = .28$). Qualitatively, lesions with USPIO enhancement in the progressive group had a ringlike pattern without signal loss on T2-weighted images (Fig 2), whereas those observed in the relapsing group had focal enhancement in 82% of cases (32 of 39 lesions) and could be seen as an area of low signal intensity on T2-weighted images in 64% of cases (25 of 39 lesions). Of the 56 enhanced lesions, 43 (77%) were in 13 patients who were not undergoing a disease-modifying treatment and 13 (23%) were in 11 patients undergoing a disease-modifying treatment.

Characteristics and Progression of Each Postcontrast MR Imaging Feature

The reliability of measurements of the enhanced lesions was good, with an intraclass correlation coefficient of 0.98. Lesions that enhanced with both USPIO and gadolinium were significantly larger (mean diameter \pm standard deviation, 6.5 mm \pm 3.8) than those that enhanced only with USPIO or gadolinium (mean diameter, 3.5 mm \pm 1.5 and 4.9 mm \pm 2.2, respectively; $P = .001$).

Of the 56 lesions that enhanced at baseline, 53 could be analyzed at 6 months. Seven of the 27 lesions (26%) that enhanced with both USPIO and gadolinium at baseline showed enhancement with both agents at 6-month follow-up, whereas only one of the 26 lesions (3.8%) that enhanced

Table 1

Postcontrast MR Imaging Features at Baseline according to Clinical Phenotypes

Clinical Phenotype	No. of Lesions	Unenhanced Lesions	Enhanced Lesions					Total
			Enhanced with Gd Alone	Enhanced with USPIO Alone	Enhanced with Both USPIO and Gd	All Gd-enhanced Lesions	All USPIO-enhanced Lesions	
Relapsing group (RR MS)	429	383 (3)	7 (2)	14 (2)	25 (7)	32 (7)	39 (7)	46 (7)
Progressive group (SP MS and PP MS)	858	848 (9)	2 (1)	5 (4)	3 (3)	5 (3)	8 (5)	10 (5)
<i>P</i> value*	...	<.001	.008	.0003	<.0001	<.0001	<.0001	<.0001

Note.—Except where indicated, data are numbers of lesions, with numbers of patients with at least one lesion in parentheses. There were 10 patients in the relapsing group and 14 in the progressive group. Gd = gadolinium.

* *P* value for comparison of the number of lesions between the relapsing group and the progressive group.

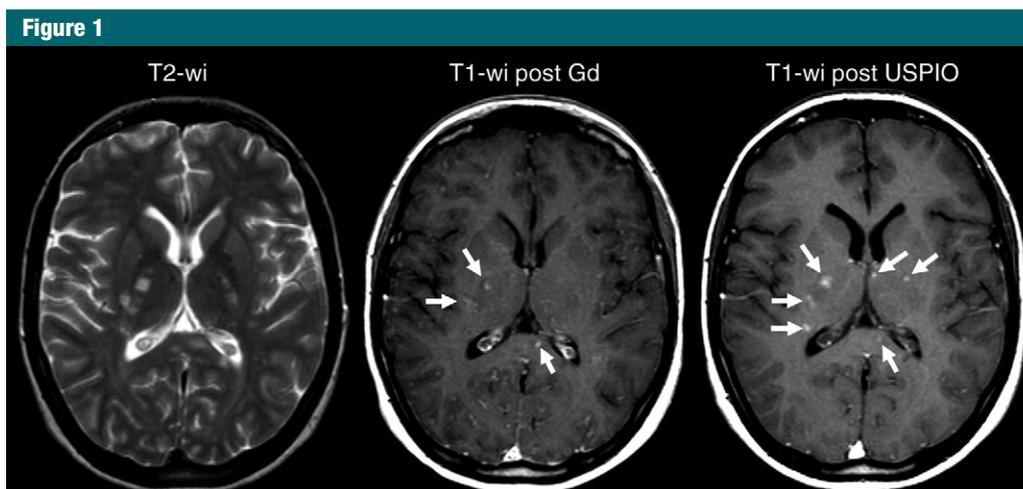


Figure 1: Mismatch between gadolinium- and USPIO-enhanced images obtained at baseline in 23-year-old woman with RR MS without disease-modifying treatment. Left, axial unenhanced T2-weighted image (4531/99) shows multiple hyperintense lesions. Middle, axial gadolinium-enhanced T1-weighted image (484/12) shows three enhanced lesions (arrows). Right, axial T1-weighted image (484/12) obtained 24–48 hours after injection of USPIO shows the same three lesions along with three additional active lesions that enhanced only with USPIO (arrows).

with only gadolinium or USPIO were enhanced at 6-month follow-up ($P < .0001$; Table 2, Fig 3). One lesion with persistent enhancement was large (diameter, 16 mm), whereas the others measured 4–5 mm (mean diameter, 4.6 mm). Furthermore, among the 45 lesions without persistent enhancement, 14 of the 20 lesions (70%) that enhanced with both USPIO and gadolinium at baseline were “black holes” on T1-weighted images at 6 months, compared with 13 of 25 lesions (52%) that enhanced only with gadolinium or USPIO ($P = .16$).

A description of the radiologic and clinical activity at 6-month follow-up according to the baseline postcontrast MR imaging features is shown in Table E2 (online).

Safety

An adverse event that was considered to be possibly or probably related to USPIO administration was seen in nine of 24 patients (38%) at baseline and four of 20 patients (20%) at 6-month follow-up. The most frequent adverse events were pain in the extremities, headache, dyspnea, rash, and

urticaria; all of these symptoms disappeared without sequelae. At baseline, four patients received treatment for the adverse event, including oral antihistamines in two patients, an analgesic (acetaminophen) in one patient, and intravenous steroids for an adverse reaction of moderate intensity with erythema and skin rash in another. At 6-month follow-up, two patients had the same type of adverse events as those seen at baseline, and two patients had a de novo reaction. No relationship between the occurrence of such events and the patient’s

age, sex, disease course, or concomitant medications was found.

Discussion

This longitudinal MR imaging study confirms and extends the findings of previous reports (9,10) showing improved sensitivity for the detection of active MS lesions when using the information conveyed by USPIO and gadolinium compared with gadolinium alone; the use of USPIO enabled the detection of 51% more lesions than would have been detected if gadolinium was used alone, with additional lesions detected in both relapsing and progressive forms of the disease. In addition, our data suggest that lesions enhanced by both USPIO and gadolinium could represent a more severe subgroup because they were larger and more often found to be active or associated with tissue destruction at 6-month follow-up.

To our knowledge, this is the first report of USPIO-enhanced lesions in progressive forms of MS; previous investigations have focused on relapsing forms of the disease (9,10). Our results suggest that this contrast agent could be helpful in assessing residual inflammatory activity associated with chronic MS by means of a simple visual analysis of lesions on USPIO-enhanced T1-weighted images (T2, which is classically modified when a high amount of iron has accumulated [22], was mostly unchanged). Such sensitivity to weak inflammation is consistent with the findings of Vellinga et al (23), who reported a moderate USPIO signal modification in the normal-appearing white matter. Although inflammatory activity is higher in patients with relapsing disease (12), in those with progressive forms histopathologic studies have found numerous macrophages and activated microglia in certain lesions, classifying these as “chronic actives” (12). USPIO signal alterations may, therefore, represent residual phagocytic cell recruitment or microglia turnover of peripheral mononuclear cells that had taken up USPIO while in the circulating blood. Alternatively, USPIO could potentially pass freely through

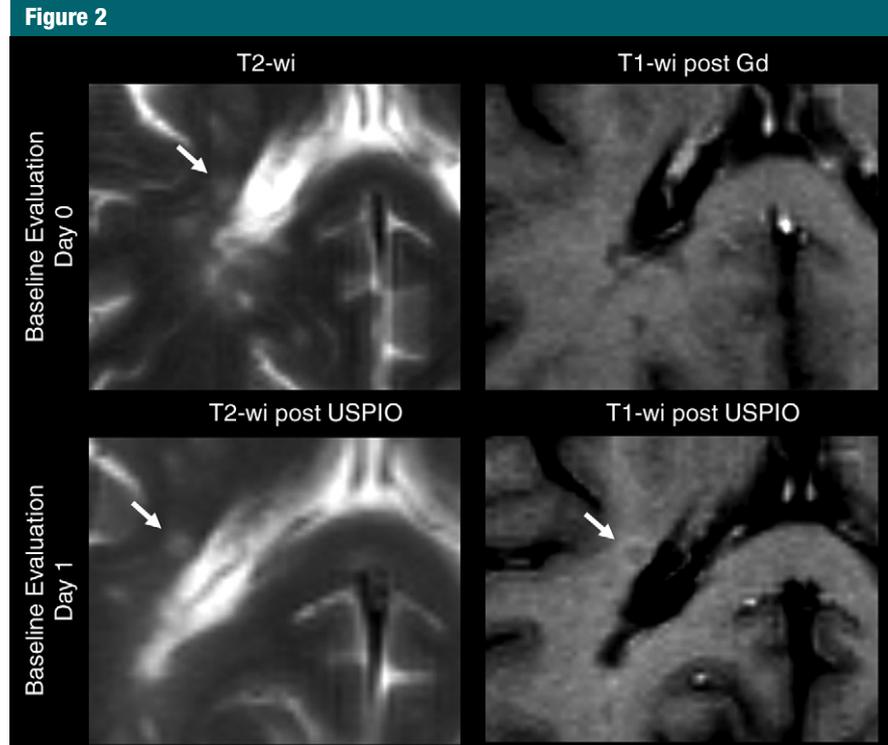


Figure 2: Enhancement of PP MS lesions. Images obtained at baseline in 49-year-old woman with PP MS without disease-modifying treatment. Right periventricular lesion seen on axial T2-weighted image (T2-wi, 4531/99) did not enhance on T1-weighted image (T1-wi, 484/12) obtained a few minutes after gadolinium (Gd) injection, whereas images obtained 24–48 hours after USPIO injection show mild ringlike enhancement at T1-weighted imaging without any signal loss at T2-weighted imaging (arrows).

a low-grade damaged BBB during the 24–48 hours of circulation and then be retained by microglia phagocytosis, as persistent but weak BBB leakage was reported in progressive forms (13). Such chronic inflammation, reported to develop with a mainly intact BBB (14), could also help explain why visual analysis of gadolinium-enhanced images has little sensitivity in detecting such moderate inflammation despite the improvements reported when using triple doses of gadolinium (24) or with quantitative analysis, such as T1 maps after gadolinium administration (25).

To date, neuroinflammation, as depicted with gadolinium, is not associated with neurodegeneration and is poorly predictive of later disability or activity (26,27). Lesions that enhance with both contrast agents may represent a subgroup in which more severe

BBB damage and cellular infiltration have occurred because these were larger, more prone to be enhanced at follow-up, and more frequently associated with ongoing destruction. This finding can be related to the pathogenic roles of proinflammatory macrophages that directly attack myelin and collaborate with the other components of the immune system (15). The persisting enhanced lesions may be reactivated lesions or long-lasting inflammatory foci, with persisting macrophage infiltration following long-lasting myelin degradation after the severe tissue disruption that occurs during the acute stage. There was also a trend for lesions that enhanced with both USPIO and gadolinium at baseline to evolve toward hypointense lesions on T1-weighted images at 6-month follow-up, but this did not reach statistical significance. To further investigate whether these lesions

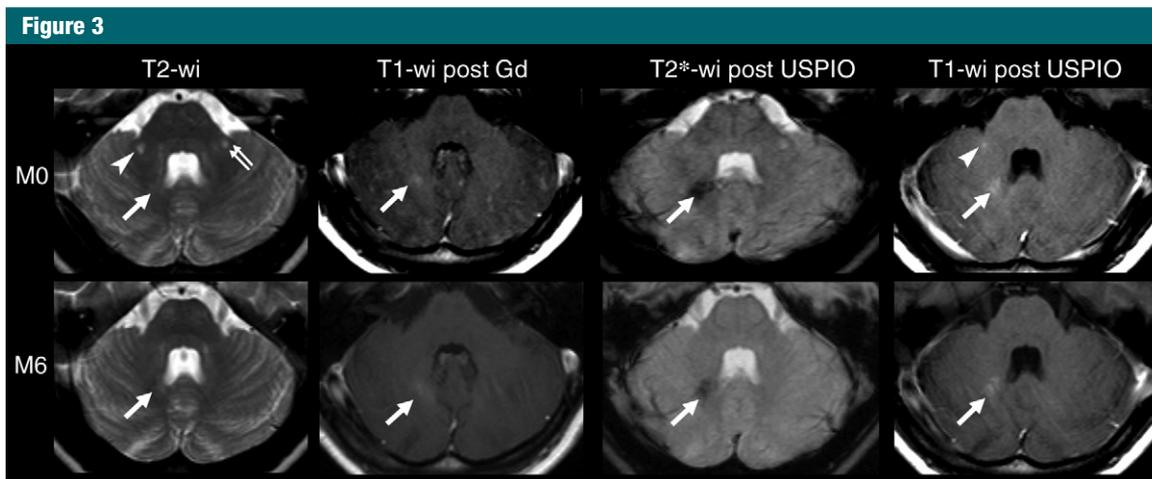


Figure 3: Lesions with persistent USPIO and gadolinium enhancement. Images obtained at baseline (M0) and 6-month follow-up (M6) in 23-year-old woman with RR MS without disease-modifying treatment. Baseline MR images were obtained 8 days after clinical relapse; the patient did not experience additional relapses between baseline and 6-month follow-up. Axial T2-weighted images (T2-wi, 4531/99) were unenhanced, and T1-weighted images (T1-wi, 484/12) were obtained a few minutes after gadolinium injection and 24–48 hours after injection of USPIO. Axial T2*-weighted images (T2*-wi, 977/24, 15° flip angle) were obtained 24–48 hours after USPIO injection. A right cerebellar active lesion that enhanced with both gadolinium and USPIO at baseline was still enhanced at same location with both contrast agents at 6-month follow-up (single arrows). At baseline, one lesion seen in right middle cerebellar peduncle on T2-weighted image showed enhancement on USPIO-enhanced T1-weighted image (arrowheads). In addition, one lesion was seen in left middle cerebellar peduncle without any enhancement (double arrows). These findings were not present on follow-up images.

Table 2

Comparison of MR Imaging Findings at Baseline and 6-month Follow-up

Findings at Baseline	Findings at 6-month Follow-up		
	Hypointensity on T1-weighted Images*	Isointensity on T1-weighted Images	Persistent Enhancement
Enhanced with USPIO alone	9	8	0
Enhanced with gadolinium alone	4	4	1
Enhanced with both USPIO and gadolinium	14	6	7
Total	27	18	8

Note.—Data are numbers of lesions. Fifty-three lesions were evaluated at 6-month follow-up.

* Hypointensity on T1-weighted images obtained at 6-month follow-up (black hole) was used as a marker of tissue destruction (19). Because this finding can be related to edema in the case of active lesions, persistent enhanced lesions were not classified according to their pattern on T1-weighted images.

are chronic persistent black holes (19), a follow-up period of longer than 6 months (and at least 1 year) should be considered in a future study. However, Vellinga et al (10), who investigated USPIO (SHU555C; Schering, Berlin, Germany) in 14 patients with RR MS, suggested that USPIO enhancement was associated with beneficial aspects of inflammation (eg, repair mechanisms).

Patient characteristics may have contributed to this difference, but it is interesting to note that the physicochemical properties of SHU555C differ from those of ferumoxtran-10, which was used in the present study, and may target different macrophage populations (proinflammatory [M1] or immunomodulatory [M2]) (28). This assumption requires further research to be

validated. The results presented herein are consistent with those found in animal experiments using ferumoxtran-10 in which intraindividual differences at the beginning of inflammation were associated with the severity of acute and chronic tissue damage, including axonal loss (28,29).

This study has limitations, most of which are related to the small number of patients. Nevertheless, it represents the largest study of USPIO administration in patients with MS to date. In addition, the short follow-up duration does not allow firm conclusions to be made regarding the predictive value of clinical progression. With respect to the highly dynamic and evolving BBB environment, certain differences between the gadolinium and USPIO may also be related to the interval between the two examinations, which cannot be compressed. Finally, although the favorable outcome of all adverse events supports the notion that USPIO is safe (30), the number of minor adverse events was higher than expected. In this context, a new generation of USPIO (P904; Guerbet, Aulnay, France [11]) is now in

preparation for phase I trials, and the slight coating modifications are thought to increase tolerance while maintaining the same properties.

In future studies, more advanced sequences, such as three-dimensional T1-weighted gradient-echo or three-dimensional susceptibility-weighted sequences, may increase the sensitivity of USPIO. Alternative gadolinium agents, which are characterized by a high R1 and a reversible binding ability to albumin (31), are commercially available but their utility as compared with the results presented herein has yet to be investigated. The new generation of USPIO agents could prove interesting for investigating the importance of “rings” on phase images obtained at 7.0 T, which are suspected to represent iron-rich macrophages (32). More generally, USPIO could become a useful surrogate marker of disease activity after validation (5).

In conclusion, this study underpins the potential advantages of using both a gadolinium-based contrast agent and USPIO in patients with MS to increase the sensitivity of MR imaging in the detection of disease activity, even in progressive forms, and suggests that lesions that enhance with both contrast agents represent a subgroup with more severe features.

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