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## **New OFSEP recommendations for MRI assessment of multiple sclerosis patients: special consideration for gadolinium deposition and frequent acquisitions**

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Gadolinium, Multiple Sclerosis, Magnetic Resonance Imaging, Cohort Studies, OFSEP

## **Abstract**

### **Purpose:**

New multiple sclerosis (MS) disease-modifying therapies (DMTs), which exert beneficial effects through prevention of relapse, limitation of disability progression, and improvement of patients' quality of life, have recently emerged. Nonetheless, these DMTs are not without associated complications (severe adverse events like progressive multifocal leukoencephalopathy). Patient follow-up requires regular clinical evaluations and close monitoring with magnetic resonance imaging (MRI). Detection of new T2 lesions and potential brain atrophy measurements contribute to the evaluation of treatment effectiveness. Current MRI protocols for MS recommend the acquisition of an annual gadolinium (Gd) enhanced MRI, resulting in administration of high volume of contrast agents over time and Gd accumulation in the brain.

### **Methods**

A consensus report was established by neuroradiologists and neurologists from the French Observatory of MS, which aimed at reducing the number of Gd injections required during MS patient follow-up.

### **Recommendations**

The French Observatory of MS recommends the use of macrocyclic Gd enhancement at time of diagnosis, when a new DMT is introduced, at 6-month re-baseline, and when previous scans are unavailable for comparison. Gd administration can be performed as an option in case of relapse or suspicion of intercurrent disease such as progressive multifocal leukoencephalopathy. Other follow-up MRIs do not require contrast enhancement, provided current and previous MRI acquisitions follow the same standardized protocol including 3D FLAIR sequences.

## Introduction:

The “Observatoire Français de la Sclérose en Plaques” (OFSEP) is a nationwide French MS registry aiming to foster research on collected standardized clinical, biological and magnetic resonance imaging (MRI) data in routine follow-ups of persons with multiple sclerosis (MS). At a national level, the OFSEP cohort counts more than 68.000 patients. Currently, more than 100 imaging centers are contributing to the standardized MRI acquisitions [<http://www.ofsep.org/>][1]. In 2014, the imaging working-group established a consensus-based cerebral and spinal cord MRI protocol, compatible with 1.5T or 3T MR systems and with clinical time constraints [2]. In line with the MAGNIMS 2016 guidelines for MS patients under therapy [3–5], this protocol suggested the acquirement of both pre- and post-gadolinium (Gd) enhancement 2D- or 3D- T1 weighted images once a year. The Swedish work group published in 2017 a practical guideline to help clinicians regarding the use of MRI in MS[6] completing the publication from the consortium of MS centers paper published in 2016[7] (and updated online since then). Those new guidelines are an update primarily focusing on the use of Gd in a clinical practice.

Gd is a metallic element of the lanthanide group. Free  $Gd^{3+}$  has a strong affinity to calcium channels, and therefore is an intoxicating inhibitor of these channels and other enzymes [8]. Since the 2000s, the toxicity of Gd-based contrast agents (GBCA) has been described mainly in patients with renal failure who developed systemic nephrogenic fibrosis (NSF). More recently, concerns rise on gadolinium accumulation in the brain of patients[9,10]. These findings were attributed to the chelating structure of the administered GBCA: linear agents were found to accumulate more than macrocyclic agent in the dentate nucleus (DN) and the globus pallidus (GP) of subjects even after one dose [11,12]. GBCA accumulation has also been evidenced in the bones [13] and the brain of subjects with normal renal and hepatic functions and with an intact blood-brain barrier [14–16]. In a recent study, Vergauwen et al. reported accumulation of Gd in patients followed for hereditary tumor syndromes injected at least 5-fold [17]. This type of linear relationship between injection number and signal increase has also been observed for metastases follow-up and for MS [18]. Safety implications of Gd retention and its possible association with clinical manifestations are still unknown and under investigations [19]. Nonetheless, recent warnings were issued by the US Food and Drug Administration and the European Medicines Agency (EMA) who urged clinicians to use these agents sparingly and restricted severely the use of linear GBCA. In line with the EMA’s recommendations, the OFSEP imaging group has also recommended the use of macrocyclic GBCA for medical monitoring since March 2017.

Prevalence of MS has increased substantially in many regions since 1990 [20]. MS itself is rarely fatal and the life expectancy was found to be shorter by seven years in average with a rise in survival and in quality of life observed with the new therapeutic options available nowadays [21]. Early medical care has been related to a better quality of life [22] and new concept such as the no evidence of disease activity (NEDA) emerged to treat the patient as early as possible [23]. These therapies have recently emerged to prevent relapses, progression of disability and improve the patients' quality of life. In addition to regular clinical evaluations, infra-clinical detection of new lesions and brain atrophy measurements, contribute to the evaluation of treatment effectiveness. Furthermore, some DMTs are not without associated complications (severe adverse events i.e. progressive multifocal leukoencephalopathy). Patients' stratification decreases these risks but require a close MRI monitoring of patients. Current MRI protocols for MS recommend the acquisition of an annual gadolinium (Gd) enhanced MRI, resulting in a significant administration of contrast agents over time and risk of Gd accumulation in the brain. In this context of iterative MRIs, the actual screening protocol should be more cautious to avoid the accumulation of Gd in the brain even with macrocyclic GBCAs.

This OFSEP consensus report between neuroradiologists and neurologists, aims to reduce the number of Gd injections required, without affecting the accuracy of patient management. The OFSEP MRI protocol has been updated accordingly with regards to the new insights on Gd deposition in the brain and more frequent MRIs during the follow-up of treated patients.

## **OFSEP' Imaging Group 2020 recommendations for MS MRI follow-up**

### **General recommendations for the use of gadolinium**

In MS, GBCA is currently used: at the time of diagnosis to look for the McDonald criteria after a clinically isolated syndrome suggestive of MS [24], during follow-up, while on- or off- therapy, and when intercurrent diseases and side effects such as progressive multifocal leukoencephalopathy (PML) are suspected. Gd-enhancement in MS lesions indicate disruption of the blood-brain barrier which is a surrogate for recent and active inflammation. Not all new lesions on FLAIR are enhanced. However, time-series comparison of standardized sequences has shown that lesions would have been Gd-positive if imaged at lesions' onset [25]. Indeed, the three weeks duration of Gd-enhancement in individual lesions [26], associated with the annual MRI scan of MS patients, are not sufficient to consider Gd-enhancing lesions as a good marker to evaluate disease activity, since they only represent episodic occurrences of lesions (in the last month). Activity between two scans is therefore best evaluated by new T2- / FLAIR-lesions [4]. To predict long-term disability outcomes in treated-patients, Rio et al. [27] and Sormani et al. [28], proposed to score patients according to the relapse occurrence and with two or more new or enlarging T2 lesions.

Considering the previous arguments, the OFSEP imaging group recommends the use of GBCA in the following situations (Figure 1):

- 1- To establish a medical diagnosis on the first MRI or in absence of a previous MRI.
- 2- In the case of patients who are due to start a new DMT, to establish a new baseline and allow a further evaluation of the treatment effectiveness.
- 3- Additional Gd-enhanced scans can be performed six months (time to adjust in regard of the marketing authorization applications of the drug) after the introduction of the new drug to get a more accurate baseline scan and avoid biases linked to the delay of action [4,29].
- 4- In case of a relapse, an optional Gd-enhanced MRI can be proposed to evaluate the severity of the attack and the current inflammatory state.

GBCAs use is not required for the following scans in the absence of relapses and if all acquired follow-up scans are standardized for reliable comparison; isometric 3D FLAIR is the most relevant sequence.

The radiologist can decide to carry out complementary post-enhanced 3D T1, when faced with atypical imaging patterns during the follow-up or a doubt about a PML complication. In the case of GBCA administration, the spine can be scanned subsequently to the brain, to obtain a full picture of the lesion load.

## **Technical specification of the sequences**

### **Industrials**

To ensure an accurate reproducibility “in-space” and “in-time”, the following MRI protocol must be acquired the same way across the patchwork of systems available with the same quality from center to center over time. To overcome this complex issue, the main MRI manufacturers (namely in alphabetically order Canon, GE, Philips and Siemens) in collaboration with the OFSEP’s radiologists, have agreed to establish and install exam cards on demand or during upgrades and add them by default on new machines. These exam cards can also be downloaded from the OFSEP website (<http://www.ofsep.org/fr/espace-pros/l-imagerie/protocoles-d-acquisitions>).

### **Geometry**

3D sequences must have a minimal resolution of  $1\text{mm}^3$ , which most of 1.5T and 3T MRI scanners can acquire. Moreover, the 3D acquisitions can be reformatted to achieve 3-mm axial sections and sent to the PACS for rapid clinical readout. 2D sequences must have an in-plane millimetric resolution with a 3mm slice thickness (possibility of 4mm slice thickness for the T2\* sequence and  $\leq 3\text{ mm}$  for the 2D Diffusion Weighted Images). DTI should have more than 15 directions with an isotropic resolution of  $2\text{mm}^3$ . The inter-slice gap must always be 0.

### **Acquisition time**

The goal of this protocol is to provide high quality data useful in a clinical setting (university hospital, general hospital and private centers) and also for research (epidemiologic, data science, feature engineering...). To fit on a clinical slot, the implemented protocol must have a total acquisition time of 20 min for the full protocol, 15 min for routine protocol, and 10 min for the PML screening. This time does not consider the off-time to set up the patient nor the optional sequences. Parallel imaging is recommended (if available) but is highly depending on the head coil elements and acceleration method available on system; the trade-off remains to have enough signal-to-noise ratio to ensure good diagnosis. Other methods for accelerating MRI acquisition (compressed sensing) as well as techniques for simultaneous multi-slice acquisition for DTI, 3D FLAIR and 3D T1 are possible when available[30].



## **Guidelines for general management of imaging in MS patient**

### **General considerations**

Acquisitions must be performed on at least a 1.5T field strength with a clinical workflow set-up. The in-site referent radiologist is responsible to guarantee enough signal-to-noise ratio to exclude false-positive lesions. In each MRI center, either public or private, the list of referents must include:

- 1- A referent neuroradiologist for the clinical questions and for insuring the quality of the acquired data;
- 2- An MRI technician, responsible for the acquisition;
- 3- An informatic support responsible for data transfer throughout the PACS system;

All 3D sequences must be acquired with an isotropic resolution, ideally millimetric or sub-millimetric with no-gap and can be retro-reconstructed in different planes at the convenience of the physicians. Reconstruction of the MRI in the subcallosal plane (lower edge of the rostrum and lower edge of the splenium of the corpus callosum) has been retained over other planes, such as AC-PC plane, for its better reproducibility over time and over centers for MS studies [31]. When needed, the systemic infusion of macrocyclic GBCA (linear contrast agents are proscribed), at the standard dose of 0.1 mmol per kilogram of body weight, with a minimum delay time of 5 min (ideally during the acquisition of the FLAIR) [4]. Some sequences are also listed as optional due to the clinical constrain to limit the acquisition time. The MRI scan date must be as close as possible to the neurologist's visit date (ideally one month prior to the medical appointment). Written informed consent must be obtained from all patients to collect and use their data. Radiologists are of course welcome to add any sequences to the protocol which can be performed additionally to the OFSEP's protocol.

The two objectives of MRI scans in treated MS patients are:

- 1- To have a complete protocol at baseline and at re-baseline to evaluate the effectiveness of DMTs
- 2- To have an optimized and simplified follow-up MRI protocol without Gd-enhancement that could efficiently identify new lesions and assess the treatment efficiency.

Imaging processing tools has been developed to help radiologists detecting and identifying new and inflammatory lesions from subtracting consecutive scans [32] to artificial intelligence technic. Preliminary machine learning studies have shown the benefits of using texture analysis for the

assessment of acute inflammation on unenhanced T2 images with comparable results to Gd-enhanced MRIs [33]. The collection of both standardized clinical and imaging data provides priceless input for artificial intelligence (AI) algorithms. Indeed, the fields of application of AI for MS are rapidly growing to help clinicians in their clinical workflow by segmenting lesions or detect active lesions (MICCAI and ISBI challenges [34,35]) or by automatically segmenting the spinal cord and intramedullary MS lesions [36].

In the revised 2017 McDonald criteria [24], MRI is used to demonstrate the dissemination in space (DIS) by one or more hyperintense T2 lesion onto periventricular, cortical or juxtacortical areas, infratentorial brain regions and onto the spinal cord even for clinically isolated syndrome (CIS) patients. To fulfill the dissemination in time (DIT) condition, multiple scans must be performed and compared to identify new lesions on T2-FLAIR or on Gd-enhanced T1 images (if only one-time point is available). Gd injection is therefore relevant at this step as mentioned above.

### **Brain MRI: Baseline**

The protocol for an initial diagnosis must be the same as the treatment follow-up described below, completed with GBCA administration between the diffusion and the 3D-FLAIR, and a 3D Gd-enhanced T1 acquisition after the FLAIR. A 2D GRE T2\* or a susceptibility weighted image (SWI) to detect microbleeds (for the differential diagnosis) and central vein sign [37] can be performed additionally, at the end of the acquisition. SWI sequence remains optional for the follow-up visits since it is only mandatory for diagnosis.

#### *Key points:*

- GBCA injection (0.1 mmol/kg; only macrocyclic agents: gadoteridol, gadobutrol, gadoteric acid in agreement with the EMA' recommendations).
- 3D Gd-enhanced T1 images: evaluate active inflammatory lesions. If prior MRI scans are not available and a Gd-enhanced lesion appeared, DIT can be demonstrated. 3D T1 sequence can be acquired either with SE (the most sensitive being 3D SE with variable refocusing flip angle) or GE.

### **Brain MRI: re-baseline at 6 months post-treatment**

Six months post-treatment administration (time to adjust in regard of the marketing authorization applications of the drug), a screening MRI is recommended [4,29] with the following protocol: 3D unenhanced-T1, diffusion sequence with apparent diffusion coefficient (ADC), GBCA injection,

3D FLAIR, and 3D Gd enhanced-T1. Due to the DMT's delayed action, Gd enhancement is required for the detection of new lesions that could impact the alteration of the therapy plan. Previous MRIs must be accessible through the PACS for a real-time comparison with the actual scan in order to evaluate the disease burden before treatment. The thereafter yearly follow-up MRI will be acquired with the bellow recommendations until the therapy becomes less effective and new lesions appear.

### **Brain MRI: follow-up protocol**

Figure 2 illustrates the new follow-up MRI protocol for treated MS patient. In the new recommendations, dual PD-T2 becomes optional and GBCA use is limited. One major criticism of the first OFSEP protocol was its long scanning time, keeping in mind that sequences were primarily used in the clinical workflow and secondarily for research purposes. Optimized 3D FLAIR can significantly improve infratentorial lesion detection in MS compared to dual 2D PD/T2 [38] making the PD-T2 sequence optional. 3D FLAIR is a sequence widely available on most recent machine and the additional time that this sequence implies is offset by the clinical benefit granted in term of over-time and site-to-site comparison.

- 3D unenhanced T1; this sequence allows the segmentation of the brain for the measurement of brain atrophy, the study of “black holes” over time, and the identification of active lesions by direct subtraction with the 3D Gd-enhanced T1. Because 3D SE sequences are not available on all MR systems and not yet validated for brain atrophy, 3D GE remains suitable.
- Diffusion sequences with ADC map; 2D Diffusion Weighted Images with a b-value of 1000 s/mm<sup>2</sup> (slice thickness ≤ 3 mm) or Diffusion Tensor Images (number of directions ≥15) is useful for early detection of PML and offers information on lesions distribution over time[39]. ADC map is robust across acquisition equipment and suitable to use for multi-centers clinical use[40]. Multiband acquisitions can be performed for the DTI acquisition.
- 3D T2-FLAIR; this sequence is essential to assess DIS and DIT criteria. The T2 contrast alongside water suppression facilitates the detection of hyperintense periventricular lesions. The improved lesions detection with a good quality 3D FLAIR in the posterior fossa, turn the 2D PD/T2 sequence optional [38]. If 3D FLAIR is not available, both 2D FLAIR and 2D PD/T2 must be acquired. 3D DIR remains optional with a pre-enhancement acquisition [41,42]. Acquisition of 3D FLAIR and 3D DIR can be preferentially performed in sagittal plan to explore the first segments of the cervical cord. In addition, lesions detection in the optic nerves is possible, if fat saturation is activated[43].

Specific cases: patients at high risk of PML literature shows that patients under long-term monoclonal therapies such as natalizumab (more than two years) with an increased risk ( $\geq 1.5$ ) of reactivation of latent John Cunningham polyomavirus (JCV) are more likely to develop a PML [44,45]. Therefore, a close clinical and MRI monitoring is recommended. Two cases must be considered: 1- presence (JCV+) and 2- absence (JCV-) of serum antibodies against JCV. The imaging protocol and frequency of this class of patients have to be correlated with the stratification strategy that clinically assess MS patients under immunotherapy [46,47].

### **Anti-JCV antibody negative**

This class of patient has a low risk to develop a PML (1 in 10000 for natalizumab [46]) and is considered similar to the general follow-up treated patients: baseline, re-baseline and every year until a new exacerbation occurs.

### **Anti-JCV antibody positive with index $\geq 1.5$**

Patients with an index  $\geq 1.5$  present a risk to develop PML and must be imaged after 18 months of immunotherapy every 3-4 months with a quick but essential protocol (DWI+ADC, 3D FLAIR). 3D DIR can be performed optionally to detect cortical lesions [48,49]. This protocol performed under 10 min, alongside the quantification of the serology of JCV antibodies, allow an early detection of PML which offers the possibility to stop therapy accordingly, improving the overall survival of the patient and limit permanent brain damage [46].

### **Anti-JCV antibody positive with index $\leq 1.5$**

Patients with an index  $\leq 1.5$  have a higher risk to develop PML. They have to be scanned with a frequency of 3 months with a short OFSEP's protocol alongside with the quantification of the anti-JCV antibody index (Figure 2). In case of suspicious PML, 3D DIR and SWI can be performed, if available.

### **Spine MRI**

Recommendations for spinal cord assessment are unchanged. At baseline, neurologists are "free to acquire brain and spinal cord to have only one injection of Gadolinium". During the follow-up, it is not recommended to have an entire spinal cord examination every year but imaging the entire spine is recommended every three years at least.

The entire spine must be imaged in two or three acquisitions for each sequence with a slice thickness  $\leq 3$  mm.

- Sagittal SE T2 weighed images
- In case of lesion,
  - o Sagittal T1 weighted images post Gd-enhancement ...
  - o Axial GE T2 on the most prominent lesion
- Optional Short Tau-Inversion Recovery (STIR) or T1-weighted Phase-Sensitive Inversion Recovery (PSIR) more sensitive to lesions' detection [29,50] but artifacts are frequently observed. This sequence cannot replace the Sagittal T2-weighted image due to variability across the MRI scanner.

## **Conclusion**

Ever since Gd was found to deposit in the brain of patients with normal kidney function, GBCA use in clinical routine has been questioned. Based on the results of several studies and reports, it seemed crucial to review the MRI acquisition protocol for the follow-up of treated MS patients, both in terms of acquisition sequence and tracking frequency. The role of Gd is discussed as well as ways to assess new lesions over time to better adapt treatments. We propose new MRI recommendations that are more feasible and reliable in routine practice. A common effort from neuroradiologists and neurologists remains essential to harmonize these recommendations nationwide.

To homogenize clinical practices and develop more efficient automatic detection and volumetric analysis tools, MRI acquisition protocols must be standardized. Recently, FDA approved tools using AI have been used routinely. However, in order to compare the epidemiological results of these tools at a national and/or international level, MRI sequences must be acquired with as little variability as possible.

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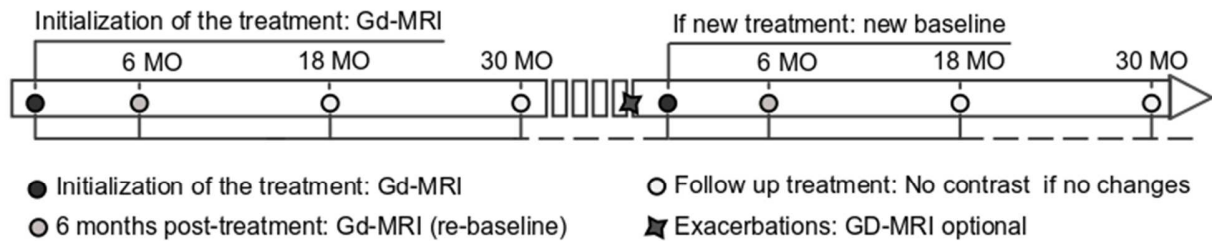
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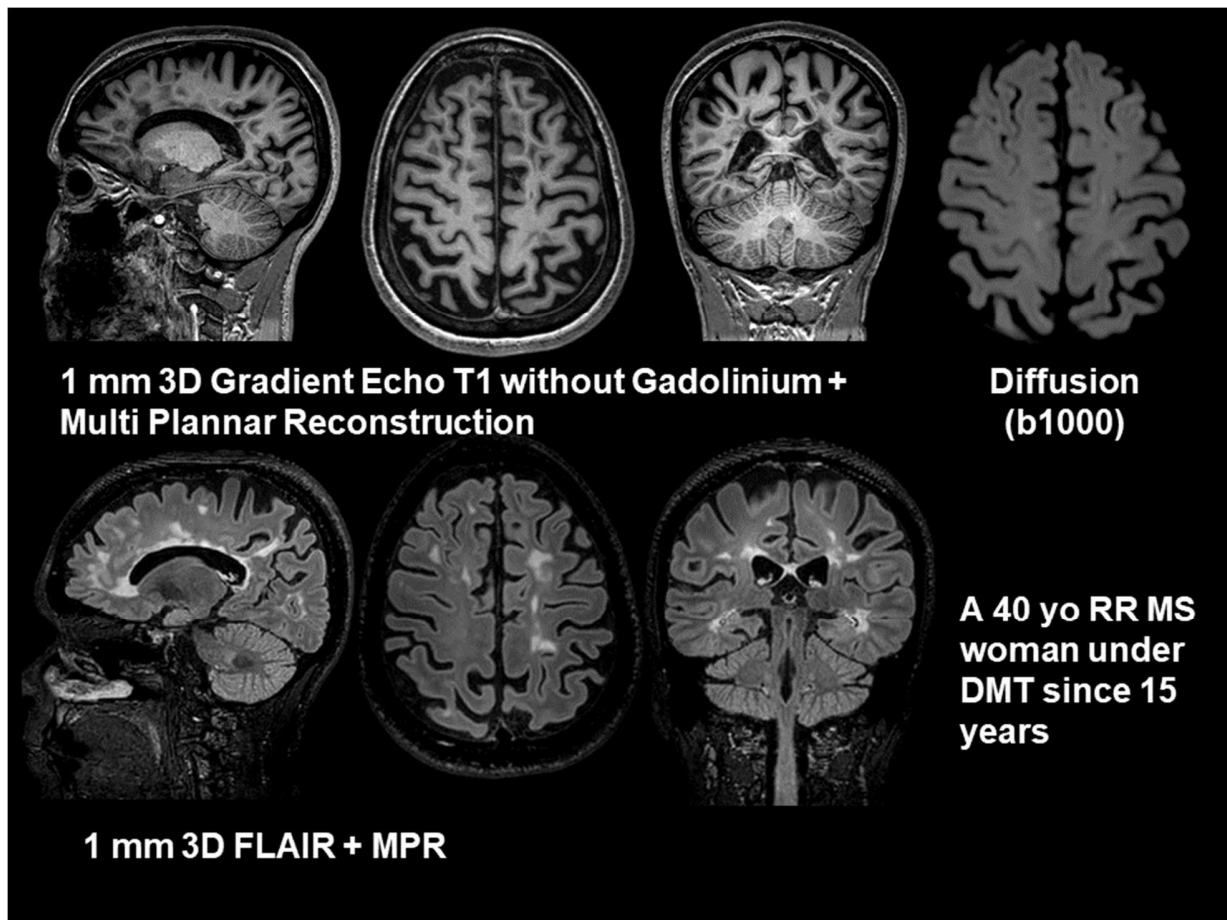
## Figures



In accordance with the suggestions made by the European Medicines Agency and the French National Agency for Drug Safety, the OFSEP recommends the use of macrocyclic agent at the dose of 0.1 mmol per kilogram of body weight.

**Figure 1: Milestones when Gadolinium is required**

The OFSEP' imaging group recommend the GBCA use for diagnosis at baseline or for any introduction to a new treatment. There is no need for iterative GBCA injection during the follow-up of clinically stable patients if 3D FLAIR acquired in two time-points are of good quality. In the case of exacerbations or at 6 months post-therapy, a Gd-MRI can be performed.



**Figure 2: Summary of the new follow-up MRI protocol for treated MS patient.**

If the patient is clinically stable and without any changes on therapy, the recommended protocol is limited to 3D unenhanced T1, 3D FLAIR, and diffusion sequences. All 3D sequences can be reconstructed in different orientations and at different levels (Multi Planar Reconstructions).

# 2018 OFSEP's Protocol



## Brain MRI

## Spine MRI

### Recommended sequences

#### Standard OFSEP's protocol

3D unenhanced T1  
Axial DWI b=1 000 + ADC  
*Gd Injection (0.1 mmol/kg) \**  
3D FLAIR  
3D Gd-enhanced T1

#### Standard OFSEP's protocol

Sagittal T2  
Sagittal Gd-enhanced T1 \*  
(1<sup>st</sup> diagnosis)

#### Short OFSEP protocol (PML scrutiny)

Axial DWI b=1 000 + ADC  
3D FLAIR

### Optional Sequences

Axial 2D TSE DP/T2 ou 3D T2  
DTI  $\geq$  15 directions with FA  
2D T2 EG (1st diagnosis)  
SWI  
3D DIR

Axial T2 GE of the most prominent lesion  
Axial Gd-enhanced T1 \*  
Sagittal STIR

### Moments to inject gadolinium

- At initial diagnosis
- If previous MRI is not available
- Introduction of new DMT
- 6 months after new DMT
- [Optional] In case of exacerbations
- [Optional] In case of suspicion of PML
- [Optional] Intercurrent diseases

**Figure 3. The OFSEP MRI protocol**

Flyer summarizing the moment to use Gd-based contrast agents and sequences for brain and spine scans under the OFSEP's recommendation.