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REVIEW

Treatment Effects on Chronic Active Lesions in Multiple Sclerosis: Current Evidence and Future Perspectives

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ABSTRACT

***Introduction*:** Multiple sclerosis (MS) is characterized by chronic, compartmentalized inflammation persisting behind a relatively intact blood-brain barrier. This process can be assessed in vivo using neuroimaging biomarkers of chronic active lesions (CALs): paramagnetic rim lesions (PRLs), slowly expanding lesions (SELs), and lesions showing increased uptake of 18-kDa translocator protein (TSPO) positron emission tomography (PET) tracers. Given their association with more severe structural damage, clinical disability, and disease progression, CALs represent a biologically relevant target to assess whether disease-modifying therapies (DMTs) can modulate smoldering MS pathology.

***Methods*:** This narrative review summarizes current evidence on the effects of DMTs on CAL-associated imaging biomarkers and discusses implications for future clinical trial design targeting smoldering MS biology.

***Results*:** Despite their strong biological and clinical relevance, current evidence suggests that available DMTs have a limited and inconsistent effect on CAL occurrence and evolution over short- to medium-term follow-up. However, treatment effects may be more apparent at the microstructural level, potentially attenuating intralesional progressive microstructural damage accumulation. Interpretation of existing data is challenged by heterogeneous MS cohorts, variability in imaging methodologies, short follow-up durations, and the only partial biological overlap among PRLs, SELs, and TSPO-PET lesions, which capture distinct dimensions of chronic inflammatory activity.

***Conclusions*:** Future studies should include prospective, multimodal longitudinal designs with standardized imaging protocols and CAL-specific endpoints to better define treatment effects on compartmentalized inflammation.

Keywords: Multiple sclerosis; Chronic active lesions; Disease-modifying therapy

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Key Summary Points

Chronic active lesions (CALs) are associated with more severe structural damage and clinical disability, reflecting key mechanisms of smoldering multiple sclerosis (MS) biology

CALs are only partially modifiable with current disease-modifying therapies (DMTs); effects on paramagnetic rim lesions (PRLs) or slowly expanding lesions (SELs) are limited, though high efficacy (HE)-DMTs may attenuate intralesional damage accumulation

Interpretation of treatment effects is limited by heterogeneous methods, short follow-up, observational data, and partial overlap across PRL, SEL, and 18-kDa translocator protein (TSPO) positron emission tomography (PET) markers

Prospective multimodal longitudinal studies with CAL-specific endpoints are needed to assess therapies targeting compartmentalized inflammation

Preventing CAL formation may be more informative than treating established lesions; CAL markers (e.g., PRLs) may also facilitate patient stratification in trials and support risk stratification and therapeutic decisions in clinical practice

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neuro-axonal loss [1]. In addition to acute inflammatory activity associated with blood-brain barrier (BBB) disruption, neuropathological and neuroimaging studies indicate that chronic, compartmentalized inflammation behind a relatively intact BBB is a major driver in ongoing tissue injury and disability accumulation [1–3].

Chronic active lesions (CALs), also referred to as mixed active-inactive or smoldering lesions, represent a key pathological substrate of compartmentalized inflammation [2]. They are characterized by an inactive, demyelinated core surrounded by a rim of activated microglia/macrophages, often containing iron. This feature is consistent with persistent innate immune activation at the lesion edge in the context of a relatively intact BBB. This rim-associated activity is linked to continued myelin breakdown, axonal injury, and gradual lesion expansion over time [2].

Recent advances in magnetic resonance imaging (MRI) and positron emission tomography (PET) allow in vivo detection of CALs. Imaging correlates of CALs include: (1) paramagnetic rim lesions (PRLs) on susceptibility-based MRI, (2) slowly expanding lesions (SELs) identified by longitudinal deformation-based analyses of conventional T1- and T2-weighted images, and (3) lesions showing increased uptake of 18-kDa translocator protein (TSPO) PET tracers, reflecting activated microglia/macrophages [2]. Across the MS spectrum, these biomarkers are common and are associated with worse clinical disability, cognitive impairment, and more severe accumulation of structural brain damage [2, 4]. CAL-related metrics therefore offer an opportunity to capture treatment effects beyond suppression of acute inflammatory activity and to interrogate therapies aimed at "smoldering" MS biology.

In this narrative review, we summarize the pathophysiology, neuroimaging identification, and clinical relevance of CALs, with a particular focus on the effects of disease-modifying therapies (DMTs) on these lesions. Details of the literature search strategy and study selection criteria are summarized in Table 1.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PATHOPHYSIOLOGY OF CALS

MS lesions can be pathologically classified as active, chronic inactive, remyelinated, or

Table 1 Literature search strategy and study selection criteria used for this narrative review

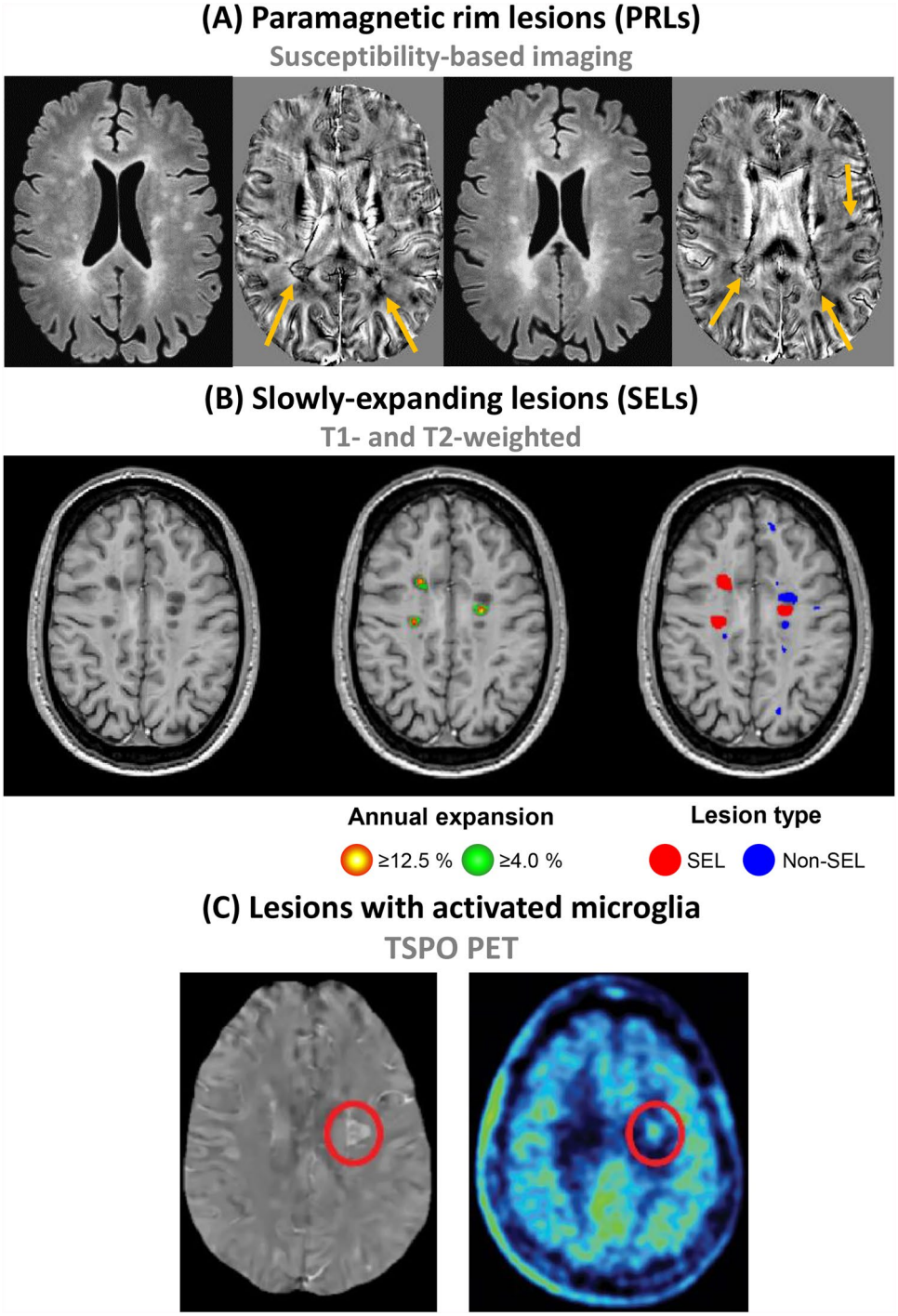
Sources	**PubMed (https://www.ncbi.nlm.nih.gov/pubmed)**
Period of time covered	From database inception to January 2026
Search terms	References for this review were identified through searches of PubMed using combinations of the following keywords: "chronic active lesions," "disease-modifying therapies," "iron rim lesions," "magnetic resonance imaging," "microglia," "microglial activation," "multiple sclerosis," "paramagnetic rim lesions," "PET," "radioligand," "quantitative susceptibility mapping," "slowly expanding lesions," "smoldering lesions," "susceptibility-weighted imaging," "treatment," and "TSPO PET"
Selection criteria and review preparation	1. Only papers published in English 2. The final reference list was generated with the consensus of all co-authors of this review on the basis of originality and relevance to the broad scope of this review, with a focus on the most recent articles published in the last 5 years

CALs [5]. In acute active lesions, demyelination is accompanied by widespread infiltration of blood-derived macrophages and activated microglia throughout the lesion core in the setting of BBB breakdown. With time, peripheral immune cell infiltration subsides, and the BBB reseals. Lesions may then evolve into a chronic inactive state or, alternatively, into CALs, in which activated microglia and macrophages persist at the lesion edge, while the lesion core becomes hypocellular and metabolically inactive.

A defining pathological feature of CALs is the presence of a rim of iron-laden microglia and macrophages at the lesion border [2, 6–8]. Iron accumulation is thought to derive from phagocytosed myelin debris and degenerating oligodendrocytes, leading to sustained oxidative stress, mitochondrial dysfunction, and pro-inflammatory signaling [2]. This iron-enriched microglial rim is closely associated with ongoing demyelination, axonal transection, and failure of effective remyelination, thereby contributing to the slow yet persistent expansion of these lesions [2].

NEUROIMAGING IDENTIFICATION OF CALS AND THEIR CLINICAL RELEVANCE

The in vivo identification of CALs has been enabled by advances in neuroimaging techniques that capture different aspects of chronic lesion activity. Although no single imaging marker fully recapitulates the pathological definition of CALs, several MRI- and PET-based metrics are considered imaging surrogates of these lesions and provide complementary pieces of information on their spatial distribution, temporal evolution, and biological activity (Fig. 1) [2].



Paramagnetic Rim Lesions

PRLs are detected on susceptibility-based MRI sequences, including susceptibility-weighted imaging (SWI), R2* relaxometry, phase imaging, echo-planar imaging (EPI)-based susceptibility acquisitions, and quantitative susceptibility mapping (QSM) [2, 4]. PRLs are defined by a persistent paramagnetic rim at the lesion edge. This appears hypointense on T2*-weighted magnitude images,

◂**Fig. 1** Representative examples of chronic active lesion visualization using different neuroimaging modalities. (**A**) On 3D axial FLAIR images, multiple hyperintense white matter lesions are visible. Some lesions (orange arrows) exhibit a hypointense rim on phase images derived from multi-echo gradient-echo T2*-weighted sequences, consistent with PRLs. (**B**) SELs are identified on longitudinal MRI by detecting gradual, concentric lesion expansion over time. This is achieved using deformation-based analyses, including voxel-wise assessment of the Jacobian of the non-linear deformation field derived from co-registered T1- and T2-weighted images acquired at multiple time points. Lesions are classified as SELs when they show sustained expansion, defined by a cluster with an annual volume increase ≥ 12.5% surrounded by voxels with an annual increase ≥ 4%. (**C**) Multimodal imaging of a chronic active lesion. QSM shows a peripheral paramagnetic rim (red circle), while PET using the ^{11}C-PK11195 tracer shows increased uptake in the same region, reflecting activated microglia/macrophages. From Kaunzner UW, Kang Y, Zhang S, Morris E, Yao Y, Pandya S, et al. Quantitative susceptibility mapping identifies inflammation in a subset of chronic multiple sclerosis lesions. Brain. 2019;142(1):133–45, with permission from Oxford University Press. *3D* three-dimensional, *FLAIR* fluid-attenuated inversion recovery, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PRL* paramagnetic rim lesion, *QSM* quantitative susceptibility mapping, *SEL* slowly expanding lesion, *TSPO* 18-kDa translocator protein

SWI, and filtered phase images and hyperintense on QSM and R2* maps, reflecting iron accumulation within activated microglia and macrophages [2].

MRI-histopathology correlation studies have demonstrated a close correspondence between PRLs and iron-laden microglial rims at the border of CALs [2, 6, 7, 9]. These findings support PRLs as a relatively specific imaging marker of chronic active pathology. From a biological perspective, PRLs are associated with more severe tissue damage than rim-negative lesions. PRLs exhibit more severe intra- and perilesional microstructural damage than rim-negative lesions, as shown by quantitative MRI metrics, including prolonged T1 relaxation times and more substantial diffusivity abnormalities consistent with demyelination, axonal loss, and gliosis. However, not all PRLs correspond to persistent T1-hypointense ("black hole") lesions [3, 6, 8].

Cross-sectional prevalence has been quantified in a systematic review and meta-analysis including 58 studies and 4532 patients with MS [4]. At the lesion level, the pooled PRL prevalence was 0.12 (95% confidence interval [CI] 0.09; 0.16) [4]. At the patient level, the prevalence of having at least one PRL was 0.52 (95% CI 0.47; 0.58) [4]. Notably, PRL prevalence did not significantly differ by clinical phenotype, age, or disease duration, indicating that PRLs represent a common pathological feature across the MS spectrum. Clinically, PRLs are associated with more severe physical disability, cognitive impairment, and brain atrophy [2, 9–11].

Longitudinal studies show that PRLs typically emerge early during lesion formation and may persist for several years [6, 7, 12, 13]. In newly forming lesions, a phase rim frequently appears in association with a centripetal pattern of gadolinium (Gd)-enhancement. This pattern reflects BBB opening at the lesion edge, and the rim may persist after resolution of BBB leakage [12]. Approximately half of newly enhancing centripetal lesions (12 of 22; 55%) develop a persistent rim, whereas the rim disappears within the first few months in the remaining lesions (10 of 22; 45%) [12]. Persistent-rim lesions exhibit reduced lesion shrinkage and progressive T1-hypointensity between months 3 and 12, consistent with impaired tissue repair and sustained lesion-edge inflammatory activity [12]. A QSM study has further shown that PRLs are characterized by early and sustained iron-related susceptibility changes [13]. About half of newly enhancing lesions develop a susceptibility rim. In most cases, this rim is already detectable at lesion onset and persists on follow-up imaging in nearly 90% of rim-positive lesions [13]. PRLs tend to expand over the first 3–4 years [6], with QSM remaining high up to 4 years [13]. They then generally stabilize, whereas rim-negative lesions usually stabilize or regress [7]. Over longer follow-up (up to 7 years) [7, 10], a subset of PRLs may lose their paramagnetic rim, a phenomenon thought to reflect partial resolution or exhaustion of chronic inflammatory activity.

Importantly, longitudinal data indicate that PRLs are dynamic lesions over mid-term follow-up [7, 10, 14]. Across two prospective cohorts followed for approximately 5 and 8 years, PRLs

were present at baseline in about 49–50% of patients [10, 14]. At the patient level, 15–18% of individuals developed at least one new PRL over follow-up [10, 14]. At the lesion level, approximately 34–36% of baseline PRLs lost their paramagnetic rim, typically after several years of persistence. This finding corresponded to an annualized PRL disappearance rate of approximately 4.40% of lesions and to a mean annualized disappearance of approximately 0.19 PRLs per subject [10, 14].

The appearance of new PRLs over time was independently associated with a higher risk of disability progression and progression independent of relapse activity, whereas PRL disappearance is associated with more favourable clinical trajectories [10], supporting their role as long-term biomarkers of chronic lesion activity, disease evolution, and, possibly, treatment response.

Recently, consensus recommendations have been proposed to standardize PRL visualization and classification across scanners and field strengths. These recommendations emphasize exclusion of acute inflammatory activity and minimum morphological and technical criteria to improve reproducibility [2]. To ensure chronicity and avoid misclassification of acute inflammatory lesions, current consensus recommendations emphasize exclusion of Gd-enhancement. When longitudinal imaging is unavailable, they also require confirmation that the lesion core was present on a T2-weighted scan obtained at least 3 months, and ideally 6 months, earlier. Otherwise, lesions should be classified as 'possible PRLs' pending confirmation on follow-up imaging [2].

Slowly Expanding Lesions

SELs are defined as pre-existing T2-hyperintense white matter (WM) lesions that exhibit linear, slow, concentric, and sustained radial expansion over time, reflecting chronic lesion activity rather than acute inflammation [2, 15]. SELs are identified using deformation-based morphometric approaches applied to serial MRI scans. These methods are typically based on non-linear registration of longitudinal T1- and T2-weighted images and voxel-wise analysis of local expansion (e.g., Jacobian-based metrics). To ensure that expansion reflects gradual and persistent lesion growth rather than transient inflammatory fluctuations, SEL identification generally requires at least three time points acquired over approximately 1–2 years or longer when available. It also requires exclusion of lesions showing Gd enhancement at baseline or during follow-up [2, 15]. A practical advantage is that SEL detection relies on conventional T1- and T2-weighted sequences routinely acquired in clinical practice and in trials. Accordingly, SELs can be evaluated retrospectively, and they are therefore feasible in settings where susceptibility-based sequences are unavailable [2, 15].

SELs are common across the MS spectrum, with a substantial proportion of patients exhibiting at least one SEL [2, 15, 16]. Higher SEL number and volume are associated with worse clinical disability and more severe structural damage, including a greater proportion of persistent T1 hypointense lesion tissue and more severe brain atrophy [2]. In addition to sustained expansion over years, SELs are characterized by progressive intralesional tissue injury. This includes declining T1 signal intensity and magnetization transfer ratio (MTR) and increased diffusivity abnormalities compared with non-SEL lesion tissue [2, 15, 17–20]. SEL number, volume, and associated microstructural changes predict subsequent disability worsening and longer-term disease progression [2].

TSPO-Positive Lesions on PET

PET using radioligands targeting the 18-kDa TSPO provides an in vivo molecular measure of innate immune activation, primarily reflecting activated microglia and macrophages within focal lesions, at lesion borders, and in perilesional and normal-appearing white matter (NAWM) [2, 21–28].

Lesions showing increased TSPO uptake at their rim are considered PET correlates of CALs, reflecting sustained microglial activation [2, 21–28]. Compared with MRI-based markers, TSPO-PET captures a broader spatial and biological spectrum of chronic inflammatory activity,

including focal, perilesional, and diffuse innate immune activation. At the patient level, higher TSPO-PET signal has been associated with greater clinical disability, cognitive impairment, and faster disease progression, as well as with more pronounced neurodegeneration [2, 21–28]. Longitudinal TSPO-PET studies further suggest that persistent or increasing tracer uptake within lesions and surrounding tissue reflects ongoing tissue injury and is associated with unfavorable clinical outcomes [2, 21–28].

EVIDENCE FOR TREATMENT EFFECTS ON CALS

Paramagnetic Rim Lesions

Studies Including Mixed/Heterogeneous DMTs

Early evidence from cross-sectional studies suggests that PRL prevalence alone may be relatively insensitive to ongoing DMT exposure (Table 2). In a cohort of 192 patients with MS evaluated using 7- and 3-T susceptibility-based MRI, 108 patients (56.2%) harbored at least one PRL [9]. No significant differences were observed between untreated individuals and those receiving interferon beta, glatiramer acetate, fingolimod, natalizumab, or ocrelizumab [9]. However, owing to its cross-sectional design and heterogeneous treatment exposure, this study did not directly assess the effects of specific DMTs on PRL formation, persistence, or resolution.

Similarly, a cross-sectional study of 84 patients with MS treated for at least 2 years with teriflunomide, fingolimod, natalizumab, or ocrelizumab identified PRLs in 32.1% of patients using 3-T susceptibility-based MRI, with no significant differences in PRL prevalence across treatment groups [29].

Longitudinal data provide a more nuanced perspective. In a retrospective study of 27 patients with MS treated with heterogeneous DMTs (dimethyl fumarate, fingolimod, ocrelizumab) or left untreated, baseline PRL counts did not differ across groups [30]. However, over 2 years, a progressive reduction in the T1-/T2-weighted ratio was observed within PRLs [30]. This quantitative MRI marker is sensitive to myelin and neurite content, as well as to tissue integrity. The decline was significantly greater in untreated patients [30]. These findings suggest that DMTs may partially attenuate microstructural damage within PRLs but that this effect may be detectable only with longer follow-up and sensitive quantitative metrics [30].

Moderate-Efficacy DMTs

Evidence on the effects of moderate-efficacy (ME) DMTs on PRLs is limited and derives from a small number of observational studies [31, 32].

In a longitudinal QSM study of 34 patients with clinically isolated syndrome (CIS) or relapsing-remitting (RR) MS harboring at least one PRL at baseline, patients treated with dimethyl fumarate ($n = 18$) showed a significantly greater annual reduction in magnetic susceptibility within PRLs compared with those treated with glatiramer acetate ($n = 16$) [32]. This difference was observed over a median follow-up of approximately 3–5 years and corresponded to an approximately 2.3-fold greater reduction [32]. However, PRL number and volume did not decrease in either group, indicating no evidence of PRL resolution or prevention of new rim formation despite microstructural changes.

In a subcohort of 76 patients with RRMS from a larger cohort of 100 patients treated with teriflunomide, PRLs were highly prevalent at baseline, with 81.6% of patients harboring at least one PRL and a median of four PRLs per patient [31]. Longitudinal susceptibility-weighted imaging over a mean follow-up of approximately 17–24 months demonstrated that both PRL number and volume remained stable or increased during treatment, suggesting that teriflunomide did not limit PRL accumulation or expansion [31].

High-Efficacy DMTs

In a longitudinal study of 152 patients with MS followed with standardized 3-T susceptibility-based MRI for a mean of 8.2 years, 50% of patients harbored at least one PRL at baseline [14]. During follow-up, incident PRLs developed in 18.4% of patients, while 36.1% of

Table 2 Study characteristics and main findings of studies evaluating the effects of DMTs on neuroimaging biomarkers of CALs in MS

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
PRLs						
Mixed therapies						
Interferon beta, glatiramer acetate, fingolimod, natalizumab, or ocrelizumab	192 patients with RR/PMS (149 treated: $n = 149$, untreated: $n = 43$)	Cross-sectional	7 T: pre-Gd 2D high-resolution gradient DE T2*/phase imaging; 3 T: pre-Gd whole-brain 3D segmented echo-planar T2*/phase imaging	PRL count	PRLs present irrespective of treatment	[9]
Teriflunomide, fingolimod, natalizumab, ocrelizumab	84 patients with MS (teriflunomide: $n = 16$, fingolimod: $n = 17$, natalizumab: $n = 13$, ocrelizumab: $n = 38$)	Cross-sectional	3 T: 3D gradient-echo SWI-EPI	PRL count	No differences between DMTs regarding PRL prevalence	[29]
Dimethyl fumarate, fingolimod, ocrelizumab	27 patients with RRMS/PMS (dimethyl fumarate: $n = 6$, fingolimod: $n = 6$, ocrelizumab: $n = 7$ or untreated: $n = 8$)	Longitudinal (baseline MRI within 6 months of treatment start and 2 annual FU MRI)	3 T: SWI	PRL T1/T2 ratio	No difference in PRL T1/T2 ratio between treated and untreated patients at baseline and year 1 Lower PRL T1/T2 ratio in untreated vs treated at year 2	[30]
ME-DMTs						

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Teriflunomide	76 patients with RRMS	Longitudinal (baseline and FU MRI in 34 patients. median time to FU 17.2 [2.9–48.8] months)	3 T: SWI	PRL count and volume	PRL number ($p = 0.007$) and volume ($p < 0.001$) increased from baseline to FU MRI	[31]
Glatiramer acetate, dimethyl fumarate	34 patients with CIS/RRMS (glatiramer acetate: $n = 16$, dimethyl fumarate: $n = 18$)	Longitudinal (baseline MRI and at least 2 FU MRI, mean total time observed 5.01 for glatiramer acetate and 2.99 for dimethyl fumarate)	3 T: axial 3D multi-echo GRE sequence for QSM	PRLs susceptibility	Dimethyl fumarate patients showed a 2.77-unit reduction in PRL susceptibility per year, above that observed in the glatiramer acetate group (95% CI − 5.87; − 0.01)	[32]
HE-DMTs						
ME-DMTs: fingolimod, glatiramer acetate, interferon beta-1a, immunoglobulin, mycophenolate; HE-DMTs: azathioprine, methotrexate, ocrelizumab	152 patients with MS (HE-DMTs: $n = 25$, ME-DMTs: $n = 108$, untreated: $n = 19$)	Longitudinal (baseline and 5–10 years FU MRI)	3 T: 3D T2*-weighted GRE for QSM	PRL count	DMT use associated with lower odds of new PRLs (for HE-DMT: OR = 0.088, $p = 0.024$; for ME-DMT: OR = 0.269, $p = 0.049$) but not disappearance	[14]
Cladribine	52 patients with RRMS	Longitudinal (baseline and 12- and 24-month MRI after treatment)	3 T: 3D SWAN susceptibility-based imaging (magnitude and phase) with Gd	PRL count	Reduction in PRL count in cladribine-treated patients (IRR = 0.68, 95% CI 0.49; − 0.95, $p = 0.02$)	[33]

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Ocrelizumab, rituximab	72 patients with RRMS/PMS (anti-CD20 mAbs: $n = 46$ [ocrelizumab: n = 45, rituximab: $n = 1$], untreated: $n = 26$)	Longitudinal (baseline and FU 3 T MRI after 2 years)	3 T: 3D multi-echo GRE sequence for QSM	PRL count, volume, magnetic susceptibility and T1 times	No significant treatment effects on count, volume ($p = 0.68$), QSM (estimate + 0.005 ppm) and T1 times ($p = 0.39$)	[34]
Ocrelizumab, teriflunomide,	62 patients with MS (teriflunomide: $n = 31$, crelizumab: $n = 31$)	Longitudinal (baseline and FU 3 T MRI, median FU 3.1 years in the ocrelizumab group and 1.9 years in the teriflunomide group)	3 T: 3D segmented EPI	PRL count	No PRL count difference between treatment groups ($p = 0.96$)	[35]
Anti-CD20 mAbs, interferon beta-1a, fingolimod	54 patients with POMS (anti-CD20 mAbs: $n = 16$, other DMTs: $n = 6$), untreated: $n = 32$)	Longitudinal (baseline MRI and in 45 patients FU MRI, median 17 months)	3 T: susceptibility-based imaging (SWI or equivalent)	PRL count	Lower number of PRLs was associated with anti-CD20 treatment (IRR = 0.640, 95% CI 0.447; 0.917, $p = 0.015$)	[36]
Ocrelizumab	29 patients with RRMS/PMS	Longitudinal (MRI before and after treatment initiation)	3 T: 3D multi-echo GRE for QSM	PRL susceptibility	After ocrelizumab initiation, PRLs showed decreased QSM with accelerated decline after 4 months of treatment	[37]
Novel therapies						
Tolebrutinib	32 patients with RRMS	Longitudinal (baseline and 16 weeks FU MRI)	3 T: multi-echo spoiled GRE	PRL count	PRL number stable across all tolebrutinib dose groups and placebo	[40]

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Evobrutinib, teriflunomide	479 patients with RMS (evobrutinib: $n = 242$; teriflunomide: $n = 237$)	Longitudinal	3 T: multi-echo spoiled GRE or SWAN sequence	PRL count	Over FU, similar adjusted annualized rate of new PRLs between treatment arms (0.274 [95% CI 0.204; 0.367] with evobrutinib vs 0.261 [0.195; 0.351] with teriflunomide) No significant difference in PRL accrual ($p = 0.59$)	[41]
SELs						
HE-DMTs						
Ocrelizumab	555 patients with PPMS from the ORATORIO trial (ocrelizumab: $n = 384$, untreated: $n = 171$)	Longitudinal (baseline and 24w, 48w and 120w FU MRI)	1.5 T or 3 T: T1- and T2-weighted images	SEL count and T1 intensity	The prevalence of patients harboring at least one SEL was not significantly affected by treatment Ocrelizumab-treated patients showed a significantly attenuated reduction in T1 intensity within SELs compared with placebo (− 0.20 vs − 0.24, $p = 0.005$) and a lower proportion of lesions classified as SELs	[19]

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Fingolimod, natalizumab	52 patients with RRMS (fingolimod: $n = 24$, natalizumab: $n = 28$)	Longitudinal (baseline and 6, 12 and 24 months FU MRI)	3 T: T1- and T2-weighted images	SEL count, volume, T1 intensity and MTR values	Greater increase in SEL volume at 24 months in the fingolimod group ($p = 0.002$) MTR values in SELs remained stable in both groups. T1 intensity decreased over time in both groups, reaching statistical significance only in the fingolimod group (but no significant between-group differences)	[20]
Natalizumab	600 patients with SPMS from the ASCEND phase III trial (natalzumab: $n = 308$ natalizumab, untreated: $n = 292$)	Longitudinal (baseline and week 108 FU MRI)	1.5 T or 3 T: T1- and T2-weighted images	SEL count and volume	Reduced SEL count ($p < 0.0001$), volume ($p < 0.0001$) and T1 LV accumulation ($p < 0.0001$) in the natalizumab group compared to placebo	[43]
Fingolimod	324 patients with PPMS from the INFORMS trial (170 with ≥ 1 new lesions at year 1)	Longitudinal (baseline and yearly up to 3 years FU MRI)	1.5 T or 3 T: T1-weighted images	SEL count and volume	New lesions occurred more often in the placebo group Lower SEL count ($p = 0.019$) and volume ($p = 0.015$) were found among fingolimod-treated patients	[44]

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Novel therapies						
Tolebrutinib	111 patients with RRMS	Longitudinal (SEL volume at 12 weeks was assessed in a subset of 111 participants)	1.5 T or 3 T: T1- and T2-weighted images	SEL volume	Median SEL volume was lowest in the highest-dose group (60 mg) compared with lower doses, suggesting a dose-dependent trend toward reduced SEL burden over the short observation period	[40]
Evobrutinib, teriflunomide	Patients with RMS from evolutionRMS1 and evolutionRMS2. Evobrutinib: $n = 347$ and 352, teriflunomide: $n = 362$ nd 362 across, respectively	Longitudinal (baseline and up to 96 weeks FU MRI)	1.5 T or 3 T: T1- and T2-weighted images	SEL count and volume	Over FU, evobrutinib-treated patients exhibited lower SEL volume and a smaller proportion of T2-hyperintense lesion volume classified as SELs compared with teriflunomide	[41]
Evobrutinib, dimethyl fumarate	261 patients with RRMS/PMS (evobrutinib 75 mg bid: $n = 53$, evobrutinib 75 mg qd: $n = 51$, evobrutinib 25 mg qd: $n = 50$, dimethyl fumarate: $n = 54$, placebo: $n = 53$)	Longitudinal (baseline and weeks 12, 16, 20, 24, 48 and end of treatment FU MRI)	1.5 T or 3 T: T1- and T2-weighted images	SEL count and volume	Significant decrease in SEL volume with evobrutinib 75 mg bid vs placebo/evobrutinib 25 mg qd ($p = 0.047$) and vs dimethyl fumarate ($p = 0.011$)	[45]

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Ibudilast	195 patients with PMS from the SPRINT-MS trial (ibudilast: $n = 97$ and placebo: $n = 98$)	Longitudinal (baseline and weeks 24, 48, 72, and 96 FU MRI)	3 T: T1- and T2-weighted images	SEL count, volume and MTR values	Ibudilast was found to reduce SEL volume (23%, $p = 0.003$) and MTR change (0.22%/year, $p = 0.04$)	[46]
TSPO-positive lesions on PET						
ME-DMTs						
Teriflunomide	12 patients with RRMS and 12 HC	Longitudinal (baseline and 8 and 24 weeks FU [^{11}C]-PK11195 PET)	3 T MRI: 3D multi-echo GRE for QSM PET: ^{11}C-PK11195 TSPO-PET	DVR	Baseline higher proportion of TSPO-positive voxels compared to HC No significant differences in NAWM or thalamic DVR After 1 year no significant longitudinal changes	[22]
HE-DMTs						
Natalizumab	18 patients with MS (natalizumab: $n = 9$, untreated: $n = 9$)	Longitudinal (baseline and 1 year FU [^{11}C]-PK11195 PET)	3 T MRI: 3D multi-echo GRE for QSM PET: ^{11}C-PK11195 TSPO-PET	DVR	5 treated patients had a reduced number of BPRLs at FU 4 untreated patients had an increase in the number of BPRLs at FU	[24]
Natalizumab	18 patients with MS	Longitudinal (baseline and 6 months FU [^{11}C]-PK11195 PET)	PET: ^{11}C-PK11195 TSPO-PET	VT	Uptake reduction in Gd + lesions and a more modest decrease in Gd-lesions at FU No significant changes in NAWM and GM	[47]

Table 2 continued

DMTs	Population	Study design	Imaging protocol	CAL outcomes	Main findings	References
Natalizumab	21 patients with MS (natalizumab: $n = 10$, untreated: $n = 11$)	Longitudinal (baseline and 1 year FU [^{11}C]-PK11195 PET)	PET: ^{11}C-PK11195 TSPO-PET	DVR	A significant decrease in TSPO binding in NAWM and perilesional WM over FU in treated patients GM uptake remained stable irrespective of group	[48]
Fingolimod	10 patients with RRMS and 8 HC	Longitudinal (baseline and 6 months FU [^{11}C]-PK11195 PET)	PET: ^{11}C-PK11195 TSPO-PET	DVR	After treatment, a significant reduction in TSPO binding was observed within T2-hyperintense WM lesions (− 12.31%, $p = 0.040$) Uptake in NAWM and GM remained unchanged	[49]

1.5 T 1.5 T, *2D* two-dimensional, *3D* three-dimensional, *3 T* 3 T, *BPRL* broad paramagnetic rim lesions, *CAL* chronic active lesion, *CI* confidence interval, *CIS* clinically isolated syndrome, *DE* dual echo, *DMT* disease-modifying therapy, *DVR* distribution volume ratio, *EPI* echo planar imaging, *FDR* false discovery rate, *FU* follow-up, *Gd* gadolinium, *GM* gray matter, *HC* healthy control, *HE-DMT* high-efficacy disease-modifying therapy, *IRR* incidence rate ratio, *LV* lesion volume, *ME-DMT* moderate-efficacy disease-modifying therapy, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MTR* magnetization transfer ratio, *NAWM* normal-appearing white matter, *OR* odds ratio, *P* progressive, *PET* positron emission tomography, *PMS* progressive multiple sclerosis, *POMS* pediatric-onset multiple sclerosis, *PP* primary progressive, *PPMS* primary progressive multiple sclerosis, *PRL* paramagnetic rim lesion, *QSM* quantitative susceptibility mapping, *RR* relapsing-remitting, *RRMS* relapsing-remitting multiple sclerosis, *SEL* slowly expanding lesion, *SPMS* secondary progressive multiple sclerosis, *SUVR* standardized uptake value ratio, *SWAN* susceptibility-weighted angiography *SWI* susceptibility-weighted imaging, *T2** T2 star, *TSPO* translocator protein, *VT* volume of distribution, *WM* white matter

baseline PRLs disappeared [14]. Importantly, baseline treatment with high-efficacy (HE)-DMTs (including natalizumab, fingolimod, and anti-CD20 therapies) was independently associated with a reduced risk of new PRL formation, whereas no association was observed with PRL disappearance, suggesting a preventive rather than reparative effect.

DMT-specific evidence includes a retrospective single-center cohort of 52 people with RRMS treated with oral cladribine and followed for 24 months [33]. PRLs were present in 61.5% of patients at baseline, and cladribine treatment was associated with a significant reduction in PRL count (incidence rate ratio = 0.68, 95% CI 0.49; 0.95; $p = 0.02$), independent of prior treatment exposure and on-study inflammatory activity [33].

Given their mechanism of action, anti-CD20 therapies have received particular attention. A multicenter study included 72 patients with MS (46 treated with anti-CD20 antibodies [45 ocrelizumab and 1 rituximab] and 26 untreated) followed for approximately 22–24 months with harmonized high-resolution 3-T susceptibility imaging [34]. Among 202 PRLs identified at baseline, no PRL disappeared in anti-CD20-treated lesions. Mixed-effects models showed no significant treatment-related effects on PRL volume, magnetic susceptibility, or quantitative T1 values. Notably, the only PRL disappearance occurred in an untreated patient, and progression independent of relapse activity was more frequent in patients harboring four or more PRLs despite anti-CD20 treatment [34], supporting the persistence of biologically active CALs under B-cell depletion.

Consistent findings emerged from real-world data including 495 patients with MS treated with ocrelizumab and 128 treated with teriflunomide, with median follow-up durations of 3.1 and 1.9 years, respectively [35]. In the subset of patients with susceptibility imaging available (62 patients with MS, 31 treated with ocrelizumab, 31 with teriflunomide), no significant differences in longitudinal PRL burden were observed between treatment groups, suggesting no clear advantage of anti-CD20 therapy in modifying PRL accumulation.

In contrast, a study in patients with pediatric-onset MS suggests a potential benefit of early anti-CD20 therapy. In a multicenter cohort of 59 pediatric patients with MS, anti-CD20 treatment was independently associated with a lower number of PRLs compared with other DMTs or no treatment (incidence rate ratio [IRR] = 0.64, 95% CI 0.45; 0.92) [36]. However, interpretation requires caution. Given the short disease duration at imaging and the limited longitudinal follow-up, some rim-positive lesions may represent subacute or transitional lesions rather than fully established CALs. This limits inference regarding modulation of long-standing PRLs.

Additional longitudinal evidence from a single-arm study of 29 patients with MS treated with ocrelizumab and followed for a median of 4.1 years using advanced susceptibility source-separation techniques showed a greater post-treatment reduction in iron-related susceptibility within PRLs compared with non-PRLs [37]. Changes emerged a few months after treatment initiation, but no PRL disappearance was observed, and myelin-related susceptibility changes were modest, indicating partial modulation of intralesional iron-related pathology without resolution of chronic active rims.

Novel Therapies: BTK Inhibitors

Bruton's tyrosine kinase (BTK) is expressed in B lymphocytes and myeloid-lineage cells, including macrophages and microglia, and regulates key pro-inflammatory signaling pathways [38, 39]. Several BTK inhibitors (BTKi) are small molecules capable of penetrating the BBB, providing a strong mechanistic rationale for targeting CNS-compartmentalized inflammation and microglial activation within CALs.

Evidence on BTKi effects on PRLs is currently limited and largely exploratory. In a phase 2b randomized placebo-controlled trial of the brain-penetrant BTKi tolebrutinib (NCT03889639), susceptibility-based imaging was available in 32 patients with relapsing MS followed for 16 weeks [40]. At baseline, 16 participants (50%) harbored at least one PRL. Over the short follow-up period, PRL number remained stable across all tolebrutinib dose groups and placebo, with changes observed in only two individuals (one

without follow-up susceptibility-based imaging and one with a small lesion not detected on the final scan) [40].

PRLs were also evaluated as exploratory imaging outcomes in the two phase 3 trials comparing the BTK inhibitor evobrutinib with teriflunomide in relapsing MS (evolutionRMS1 [NCT04338022] and evolutionRMS2 [NCT04338061]) [41]. In a large MRI subcohort with susceptibility-based imaging available (242 patients in the evobrutinib group and 237 in the teriflunomide group), the adjusted annualized rate of new PRLs was similar between treatment arms (0.274 [95% CI 0.204; 0.367] with evobrutinib vs 0.261 [0.195; 0.351] with teriflunomide) over follow-up, with no significant difference in PRL accrual (lesion rate ratio = 1.05, 95% CI 0.70; 1.57; $p = 0.59$) [41].

Beyond effects on PRL evolution, emerging evidence suggests that PRLs may act as predictive biomarkers of treatment response to BTKi. Post hoc analyses of three phase 3 trials of tolebrutinib, GEMINI 1 (NCT04410978) and 2 (NCT04410991) (relapsing MS; tolebrutinib vs teriflunomide) and HERCULES (NCT04411641) (secondary progressive [SP] MS); tolebrutinib vs placebo), evaluated baseline PRL burden as a prognostic and predictive biomarker for disability accumulation and treatment response [42]. Overall, 653 participants (61%) had PRLs. In GEMINI, the proportion of participants with 0, 1–3, or ≥ 4 PRLs at baseline was 38%, 35%, and 27%, respectively, with similar proportions in HERCULES. Across all trials, higher baseline PRL burden was associated with a greater risk of disability accumulation [42]. Notably, the relative treatment effect of tolebrutinib increased with higher PRL burden: in GEMINI trials, relative risk reductions for 6-month confirmed disability progression were − 18%, − 46%, and − 49% in participants with 0, 1–3, and ≥ 4 PRLs, respectively, while in the HERCULES trial, corresponding effects were + 17%, − 15%, and − 54% [42]. These findings suggest that BTKi may preferentially benefit patients with a higher burden of chronic active pathology, consistent with its CNS-bioactive mechanism of action, although these results remain post hoc and require confirmation in prospective analyses.

Slowly Expanding Lesions

High-Efficacy DMTs

A longitudinal observational study evaluated patients with RRMS initiating fingolimod ($n = 24$) or natalizumab ($n = 28$) and followed for 24 months [20] (Table 2). SELs were detected in 18 fingolimod-treated patients (75%) and 13 natalizumab-treated patients (46%). Fingolimod-treated patients exhibited a higher number and volume of SELs, as well as greater longitudinal T1 signal decline within SELs, compared with natalizumab-treated patients, suggesting less pronounced chronic tissue damage under natalizumab [20].

In SPMS, a post hoc analysis of the ASCEND trial (NCT01416181) included patients treated with natalizumab or placebo and followed for 108 weeks [43]. SELs were identified in a similar number of natalizumab-treated ($n = 82$) and placebo-treated patients ($n = 91$). However, compared with placebo, natalizumab was associated with a significantly lower rate of SEL-related T1 hypointensity accumulation and a reduced likelihood of longitudinal SEL tissue damage progression, despite no effect on SEL number or baseline SEL presence [43].

In primary progressive MS (PPMS), a post hoc analysis of the ORATORIO trial (NCT01194570) evaluated SELs in 732 patients randomized to ocrelizumab or placebo and followed for at least 120 weeks [19]. SEL candidates accounted for 5.1% and 7.1% of pre-existing T2-hyperintense WM lesion volume in ocrelizumab- and placebo-treated patients, respectively, while high-confidence SELs represented 2.5% and 3.4% [19]. Although SELs constituted a relatively small fraction of total T2-hyperintense WM lesion volume, they accounted for a disproportionately large share of T1-hypointense lesion volume accumulation over follow-up [19]. Thus, a relatively limited subset of lesions contributed substantially to the accrual of destructive tissue damage over time. Compared with placebo, ocrelizumab significantly reduced T1-hypointense volume accumulation within SELs, without affecting the proportion of lesions classified as SELs, indicating attenuation of chronic tissue

damage within established SELs rather than prevention of SEL formation.

A complementary preventive effect was suggested by a post hoc analysis of the INFORMS trial (NCT00731692) in PPMS, which included 324 patients randomized to fingolimod or placebo and followed for up to 3 years [44]. This analysis focused on the fate of newly formed T2-hyperintense WM lesions and their conversion into definite or possible SELs. Fingolimod significantly reduced both the number and volume of new T2-hyperintense WM lesions evolving into SELs compared with placebo, indicating an effect on early lesion trajectories rather than modulation of pre-existing SELs [44].

Novel Therapies: BTK Inhibitors

SELs have also been evaluated as exploratory outcomes in clinical trials of BTKis, often within MRI subcohorts distinct from those used for PRL analyses.

In the phase 2b trial of the brain-penetrant BTKi tolebrutinib (NCT03889639), 130 patients with relapsing MS were followed for 16 weeks [40]. SEL volume at 12 weeks was assessed in a subset of 111 participants. Median SEL volume was lowest in the highest-dose group (60 mg) compared with lower doses, suggesting a dose-dependent trend toward reduced SEL burden over the short observation period [40].

More extensive evidence derives from the phase 3 evolutionRMS1 (NCT04338022) and evolutionRMS2 (NCT04338061) trials comparing evobrutinib with teriflunomide in relapsing MS [41]. SEL analyses were performed in predefined MRI subcohorts with longitudinal imaging available, including 347 and 352 evobrutinib-treated patients and 362 teriflunomide-treated patients across evolutionRMS1 and evolutionRMS2, respectively [41]. Over up to 96 weeks of follow-up, evobrutinib-treated patients exhibited lower SEL volume and a smaller proportion of T2 lesion volume classified as SELs compared with teriflunomide [41]. This contrasted with the absence of treatment-related differences observed for PRL accrual.

Consistent findings were reported in a post hoc analysis of the 48-week phase 2 trial of evobrutinib in relapsing MS (NCT02975349) [45]. Across 223 patients receiving different evobrutinib doses, placebo switched to evobrutinib, or open-label dimethyl fumarate, evobrutinib was associated with a dose-dependent reduction in SEL volume, with the greatest effect observed at 75 mg twice daily [45]. Similar dose-dependent effects were observed when SEL volume was expressed as a proportion of baseline T2-hyperintense WM lesion volume, whereas no significant effect was detected with dimethyl fumarate [45].

Other Therapies

In the phase II SPRINT-MS trial (NCT01982942), 195 patients with progressive MS were randomized to ibudilast or placebo and followed with longitudinal MRI for 96 weeks [46]. Median SEL volume over the study period was lower in the ibudilast group, and after adjustment for baseline T2 lesion volume, ibudilast was associated with a 23% reduction in SEL volume [46]. In addition, ibudilast attenuated SEL-related tissue damage, as reflected by a smaller decline in MTR within SELs over time, supporting a modulatory effect on chronic lesion-associated microstructural injury [46].

TSPO-Positive Lesions on PET

Moderate-Efficacy DMTs

Evidence on the effects of ME-DMTs on TSPO-defined inflammation is limited (Table 2). In an open-label, non-interventional longitudinal study, 12 patients with RRMS treated with teriflunomide for at least 6 months underwent [^{11}C]-PK11195 TSPO-PET and QSM at baseline and at 1-year follow-up [22]. Compared with healthy controls, patients exhibited a higher proportion of PET-defined "active voxels," indicating increased innate immune activation. Over follow-up, no significant changes were observed in global TSPO uptake, the proportion of active voxels, lesion load, brain volume, or iron-rim lesion number, suggesting limited effects of teriflunomide on TSPO-PET–defined chronic inflammatory activity [22].

High-Efficacy DMTs

More consistent evidence is available for HE-DMTs—particularly natalizumab—from three longitudinal [^{11}C]PK11195 TSPO-PET studies [24, 47, 48].

In a first longitudinal study, 18 patients with MS initiating natalizumab underwent TSPO-PET at baseline and after 6 months of treatment; a subset was additionally scanned at 3 months [47]. Natalizumab was associated with a significant reduction in TSPO signal within focal lesions, including both Gd-enhancing and non-enhancing lesions [47]. In 13 Gd-enhancing lesions from 5 patients, TSPO uptake decreased markedly from baseline to 6 months, with an early reduction already detectable at 3 months [47]. A smaller but significant reduction was also observed in non-enhancing lesions, whereas no significant longitudinal changes were detected in NAWM or cortical gray matter [47].

A subsequent work extended these observations to perilesional WM and NAWM [48]. In a longitudinal cohort including 10 patients treated with natalizumab and 11 untreated patients scanned with [^{11}C]-PK11195 PET at baseline and after 1 year, natalizumab treatment was associated with a reduction in TSPO uptake in NAWM and in the perilesional rim (3–6 mm) surrounding chronic T2-hyperintense WM lesions [48]. By contrast, untreated patients showed a significant increase in perilesional TSPO signal over the same period. This finding suggests progressive compartmentalized inflammation in the absence of treatment.

Additional evidence comes from a multimodal study integrating histopathology, TSPO-PET, and MRI [24]. In this work, broad rim lesions (BRLs) were defined histopathologically as a subset of CALs characterized by extensive myeloid activation at the lesion edge. An in vivo counterpart was also proposed, termed radiological broad rim lesions (rBRLs) and identified by increased TSPO uptake in a broad perilesional rim extending beyond the narrow susceptibility-defined rim typical of conventional PRLs [24]. In the longitudinal TSPO-PET component, nine patients treated with natalizumab were followed for 1 year and compared with nine untreated patients [24]. Over follow-up, five of nine natalizumab-treated patients showed a reduction in rBRL number, whereas four of nine untreated patients exhibited an increase, supporting a treatment-related modulation of extensive rim-associated innate immune activation [24].

Evidence for other HE-DMTs derives from a prospective longitudinal study evaluating fingolimod using [^{11}C]-PK11195 TSPO-PET [49]. Ten patients with RRMS initiating fingolimod underwent PET at baseline and after 24 weeks of treatment, with seven patients additionally scanned at 8 weeks. Over 24 weeks, fingolimod treatment was associated with a significant reduction in TSPO uptake within T2-hyperintense WM lesion areas (mean decrease 12.31%, $p = 0.040$), whereas no significant longitudinal changes were observed in NAWM or cortical gray matter, indicating a preferential effect on focal lesion-associated microglial activation [49].

Expert Opinion: Treatment Effects on CALs, Current Evidence and Future Perspectives

Emerging evidence supports CALs as a core substrate of compartmentalized inflammation in MS and highlights the complementary value of advanced neuroimaging markers—PRLs, SELs, and TSPO-PET-positive lesions—in capturing distinct dimensions of this pathology. Across imaging modalities, CALs consistently associate with more severe tissue destruction, physical and cognitive deficits, and disability progression. Importantly, these markers provide insights beyond conventional measures of acute inflammatory activity and offer a window into disease mechanisms central to smoldering MS biology, positioning CALs as attractive therapeutic targets and informative trial outcomes.

Despite this strong biological and clinical rationale, current evidence indicates that CALs are only partially modifiable by existing DMTs. Across studies, most DMTs show limited or inconsistent effects on established PRL or SEL burden. Even therapies with a compelling mechanistic rationale to influence chronic inflammation, such as anti-CD20 agents and, more recently, CNS-penetrant BTKi, have not shown robust or consistent reductions in PRL number

or rim disappearance, and their effects on SEL-related metrics remain modest. These findings underscore that compartmentalized inflammation represents a disease component that is, at least in part, resistant to current immunomodulatory/immunosuppressive strategies. However, this may potentially also reflect the slow dynamics of CAL formation and evolution, which typically unfold over several years and may exceed the duration of most clinical trials and imaging follow-up.

Nevertheless, a more nuanced interpretation emerges when lesion-intrinsic tissue damage is considered rather than lesion burden alone. DMTs, particularly HE-DMTs, may attenuate intralesional microstructural damage over time, even in the absence of clear reductions in PRL or SEL number or volume. Slower accumulation of T1 hypointensity, reduced iron-related susceptibility changes, and relative preservation of MTR or diffusivity metrics within SELs support the hypothesis that treatments can mitigate ongoing demyelination and axonal injury inside CALs. This may occur without necessarily inducing visible rim resolution or preventing slow lesion expansion. Clinically, this distinction may be highly relevant as therapies may exert meaningful neuroprotective effects within CALs even when macroscopic imaging markers appear stable.

Interpretation of treatment effects is further complicated by the fact that PRLs, SELs, and TSPO-PET-positive lesions are not interchangeable markers and only partially overlap [44, 50]. Although all are considered imaging correlates of CALs, they capture distinct biological and methodological dimensions of chronic lesion activity. PRLs are identified cross-sectionally using susceptibility-based MRI and primarily reflect iron-laden microglia/macrophages accumulating at the lesion edge. SELs are defined longitudinally using deformation-based analyses of serial MRI scans and capture sustained concentric expansion and progressive tissue injury over time, based on deformation-based analyses of serial MRI scans. These two MRI-derived markers therefore emphasize different aspects of chronic lesion evolution: PRLs highlight the inflammatory rim component, whereas SELs reflect the dynamic lesion expansion and progression of tissue damage within pre-existing lesions. Accordingly, PRLs and SELs, enlarging or non-enlarging and with or without a paramagnetic rim, likely represent different biological substrates or stages along a continuum of chronic compartmentalized pathology. Consistent with this interpretation, SELs are generally more prevalent than PRLs, whereas lesions fulfilling criteria for both entities appear to represent the most destructive CAL subtype, helping to explain discrepancies across studies, particularly regarding treatment effects. TSPO-PET provides a molecular readout of innate immune activation and often detects a broader burden of inflammatory activity, including perilesional and diffuse activation that does not meet PRL or SEL criteria. Compared with MRI-based markers, TSPO-PET may capture a broader spectrum of inflammatory activity, including lesions that do not display a paramagnetic rim or measurable expansion, reflecting activated microglia and macrophages within lesions, at lesion borders, and in surrounding WM.

Several methodological and conceptual limitations also constrain the current evidence base. Imaging acquisition, post-processing pipelines, and lesion definitions remain heterogeneous across studies, despite recent consensus efforts [2]. Differences in MRI field strength, susceptibility-sensitive sequences, spatial resolution, rim definitions, and analytical approaches can substantially influence the detection and characterization of chronic active lesions. For example, PRLs have been identified using a variety of susceptibility-based MRI techniques, including T2-weighted imaging, SWI, and QSM. These sequences have been acquired across a wide range of field strengths, from 1.5 to 7 T, and with variable spatial resolution and acquisition dimensionality (two-dimensional vs three-dimensional). These technical differences can significantly affect rim visibility and detection sensitivity, contributing to the substantial heterogeneity reported across studies [2, 4]. In addition, only some studies have adopted recently proposed consensus recommendations for PRL definition and assessment [2], further limiting comparability across cohorts and imaging platforms. Methodological variability also affects the identification of SELs. These lesions are typically

defined using longitudinal deformation-based analyses of serial MRI scans. Such approaches often require multiple time points to confirm sustained lesion expansion and to distinguish chronic expansion from transient inflammatory changes or lesion confluence. Differences in longitudinal methods and analytical thresholds therefore limit comparability and meta-analytic synthesis.

Many studies are cross-sectional or have relatively short follow-up durations, which is suboptimal for capturing the slow evolution of CALs. Treatment studies are often observational, include heterogeneous patient populations, and frequently assess CAL-related outcomes as exploratory rather than primary endpoints.

Additional sources of heterogeneity arise from differences in TSPO-PET methodology, including the use of distinct radioligands, quantification strategies, and reference regions. These factors may influence estimates of microglial activation and limit comparisons across studies. Moreover, TSPO-PET often detects a broader spatial spectrum of innate immune activation—including perilesional and diffuse inflammatory activity, which may not correspond directly to PRLs or SELs identified on MRI.

Moreover, the biological specificity of current imaging markers is incomplete, particularly early in the disease course, when not all rim-positive or expanding lesions necessarily represent fully established CALs. Beyond imaging methodology, interpretation of treatment effects may also be influenced by additional confounding factors, including small sample sizes, heterogeneous patient populations spanning different disease stages, variability in treatment exposure duration, and the potential impact of prior or concomitant therapies.

Timing is also likely a critical factor in interpreting treatment effects on CALs. The fate of a lesion to become chronically active appears to be largely determined within the first months after lesion formation [7, 12]. At the same time, the subsequent evolution of CALs is typically slow and may unfold over several years. This temporal mismatch means that many imaging studies—often characterized by relatively short follow-up durations—may not adequately capture meaningful treatment-related changes in established PRLs, SELs, or TSPO-PET-positive lesions. Accordingly, evaluating the dynamics of these markers many years after lesion onset may underestimate potential pharmacological effects. Future efforts should prioritize determining whether treatments can prevent newly formed lesions from evolving into CALs. Although this approach is challenging in the context of high-efficacy DMTs, where the incidence of new T2-hyperintense WM lesions is low, focusing on baseline Gd-enhancing lesions may represent a feasible strategy. In these lesions, timing can be inferred more reliably, allowing investigation of the early determinants of CAL development and the potential for treatments to modify this trajectory.

In parallel, CAL-related imaging markers, particularly PRL burden, may be leveraged for patient stratification in both clinical trials and clinical practice. In trials, PRL burden may help identify patient subgroups with a higher load of chronic active pathology. These patients may be more likely to benefit from therapies targeting compartmentalized CNS inflammation. This could also improve the interpretability of treatment effects and potentially reduce required sample sizes. In the clinical setting, PRL assessment may support risk stratification and therapeutic decision-making by identifying individuals with a greater propensity for disability accumulation and a differential response to treatments with CNS-compartmentalized mechanisms of action.

Looking forward, priorities include prospective, adequately powered longitudinal studies integrating at least PRLs and SELs within the same individuals to clarify temporal relationships and biological hierarchies among these markers. CAL-specific endpoints should be incorporated into clinical trials, particularly those targeting smoldering MS biology, as they may provide sensitive intermediate outcomes not captured by conventional MRI or relapse-based measures [51]. Finally, the development of novel therapies targeting CNS-compartmentalized inflammation, especially brain-penetrant agents acting on microglia and resident immune cells, should be paired with rigorous evaluation using harmonized, multimodal CAL-focused imaging biomarkers. This approach will

be essential to determine whether CALs can be effectively targeted to alter the long-term course of MS.

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Declarations

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