REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, Volume 58, no. 3, pages: 245–255
DOI: 10.5603/pjnns.98592

ISSN: 0028-3843, e-ISSN: 1897-4260

# Clinical and therapeutic challenges of smouldering multiple sclerosis

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**This article has been co-published in the Polski Przegląd Neurologiczny, 2024, doi: 10.5603/ppn.100783.**

## ABSTRACT

**Introduction.** Assessment of the clinical course, neuroimaging and histopathological changes suggests that multiple sclerosis (MS) should not be defined merely as a focal inflammatory disease of the central nervous system (CNS) because the essence of the disease is due to a diffuse, 'smouldering', pathophysiological process.

**State of the art.** Progression independent of relapse activity (PIRA) is the clinical indicator of smouldering MS. Multiple pathomechanical factors determining smouldering MS have been identified, i.e. continuous activation of microglia, which is the source of smouldering inflammation and the failure of remyelination in MS.

**Clinical implications.** Our paper presents new neuroimaging markers, including paramagnetic rim lesions (PRLs) and slowly expanding lesions (SELs), potential methods for clinical evaluation and promising therapeutic options, i.e. Bruton's tyrosine kinase inhibitors that prevent PIRA in smouldering MS. With the duration of MS, the efficacy of the current immunomodulatory treatment is reduced, and its effect is insufficient to control smouldering MS.

**Future directions.** Innovative insights into the pathophysiology and clinical course warrant the need for a holistic approach to MS. The efforts of clinicians should be aimed at indicating subtle neurological deficits in physical performance and cognitive functioning to characterise the disease progression in its early stages. Undoubtedly, a new era for MS is coming in which new resonance markers will be used together with clinical methods to assess smouldering MS, and the treatment will include combination therapy with consideration of drugs that reduce relapse rates and therapy aimed at inhibiting disease progression.

**Keywords:** smouldering multiple sclerosis, microglia, Bruton's tyrosine kinase inhibitors

(*Neurol Neurochir Pol 2024; 58 (3): 245–255*)

## Introduction

According to the commonly accepted definition, multiple sclerosis (MS) is a chronic autoimmune and inflammatory disease of the central nervous system (CNS), leading to demyelination, axonal damage and neurodegeneration [1, 2]. The clinical, histopathological and neuroimaging data, however, indicates that MS is not a focal inflammation of the CNS. The nature of the condition is due to a diffuse 'smouldering' pathophysiological process that occurs with concomitant

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Submitted: 18.12.2023 Accepted: 22.03.2024 Early publication date: 06.06.2024

inflammation that is a response of the immune system to other primary causes of the disease [3].

This innovative approach has allowed the introduction of the term *smouldering MS*, which is characterised as chronic neuroinflammation in the white matter, the subpial region and the cortex associated with cortical neurodegeneration and the loss of brain volume, which results in disability progression [3–5]. The natural history of the disease often indicates clinical deterioration in MS patients, who present with disability progression with the simultaneous absence of inflammatory activity, understood as the absence of relapses and the absence of new or expanding demyelinating lesions on T2-weighted images or contrast-enhancing lesions on T1-weighted images on magnetic resonance imaging (MRI). This process is referred to as progression independent of relapse activity (PIRA), which is a clinical indicator of smouldering MS that needs to be distinguished from relapse-associated worsening (RAW) [6]. In addition, Kappos et al. have confirmed that PIRA and RAW are non-mutually exclusive processes leading to confirmed disability accumulation (CDA) in relapsing and progressive phenotypes of MS [6]. Progressive and irreversible disability caused by axonal and neuronal loss is found in the early stages of the disease [7, 8], which further suggests a continuum of relapsing and progressive phenotypes of MS.

Histopathologically, smouldering MS is characterised by chronic active plaques with an inactive centre and an active rim with microglia, macrophages and oligodendrocytes. In post mortem studies, chronic active plaques are predominant around 47 years of age and occur almost exclusively in progressive forms, thus confirming the dynamic nature of pathological processes in MS [9].

The aims of this study were to present MS in the context of smouldering disease, to discuss its biological and immunological causes, and to identify the determinants and potential radiological biomarkers of smouldering MS and their use in daily clinical practice, both in terms of disease progression and new therapeutic options.

## State of the art

### Immune system and smouldering MS

Many studies have confirmed the important role of activated innate and adaptive immune cells in the pathogenesis of MS [10, 11]. The population of autoreactive B and T lymphocytes represents identifiable factors leading to peripheral pathological processes in the immune system in MS patients. Due to their activity, acute peripheral inflammation is observed. This manifests as focal inflammatory lesions in the CNS and relapses [12]. In turn, pro-inflammatory microglia, macrophages and resident B cells are responsible for chronic CNS neuroinflammation, which develops in the early period of the disease and leads to CDA [10]. The autoimmune pathological process of MS is the result of the two associated inflammatory pathways, i.e. acute peripheral neuroinflammation and chronic neuroinflammation.

However, according to the 'smouldering MS' concept, focal inflammatory lesions of the CNS are only secondary to the loss of axons and neurons. Their destruction results in the release of myelin antigens, which initiate pathological processes in the immune system [3, 13].

### Determinants of smouldering MS

Disruption of axonal continuity with subsequent conduction block and the loss of synapses leads to acute focal inflammatory lesions. These processes develop over several days or weeks, and their clinical manifestation is RAW [3, 14]. Late pathological processes that occur over weeks and months play an essential role in the pathomechanism of smouldering MS. These include demyelination and energy deficits that contribute to delayed neurodegeneration associated with relapses. Permanently demyelinated nerve fibres are metabolically overburdened, thus becoming more susceptible to physiological stress. They have increased energy demand for axonal conduction, leading to axonal degeneration [14, 15]. The remyelination process in MS is incomplete and becomes ineffective with age, thus being the basis of smouldering MS [16]. In addition, during active demyelination, iron is released from damaged oligodendrocytes and myelin, and initiates the formation of pro-inflammatory cytokines, reactive oxygen species, and chronic oxidative stress, which plays a crucial role in the pathophysiology of MS [17–19], especially in progressive phenotypes [20]. Mitochondrial defect, inducing virtual hypoxia, occurs due to oxidative stress [21].

After the period of delayed neurodegeneration associated with relapses, long-term post-inflammatory neurodegenerative processes develop in the course of MS. They include activation of microglia and the innate immune system, viral infections, lifestyle and energy deficits. Premature age-related neurodegenerative processes that result in late disability play an essential role [3].

### Role of microglia in smouldering MS

Under homeostatic conditions, microglia are the main source of immune cells in the CNS [22, 23]. Microglial cells were first characterised by Pio del Rio Hortega in 1920 who described microglia as a structure derived from primitive macrophages during haematopoiesis in the yolk sac [24]. The uniqueness of microglial cells within the CNS parenchyma is related to their high capacity for self-renewal and proliferation [25]. These processes are independent of blood myeloid precursors, and distinguish microglia from bone marrow-derived macrophages that reside in perivascular spaces, meninges, or choroid plexus (CP) [26]. However, microglial cells are related to macrophages and can acquire a pro-inflammatory M1 or anti-inflammatory M2 phenotype in response to various stimuli as in the case of macrophages [27, 28]. Both M1 and M2 represent a spectrum of activation patterns and

form a continuum that allows mutual switching depending on the cause [23, 29, 30]. As a result, microglial cells activate a neurotoxic pathway which leads to progressive neurodegeneration, or they can show neuroprotective activity [31]. Under physiological conditions, microglial cells determine synaptic integrity, neurogenesis, preservation of neuronal connectivity, normal functioning of oligodendrocytes, normal myelination and remyelination. Microglial cells also affect vasculogenesis and blood-brain barrier (BBB) permeability [22, 23, 32]. The pathogenic activity of microglial cells leads to the activation of pro-inflammatory factors, increased phagocytosis and demyelination, inhibition of remyelination and synaptic and neuronal pathology resulting in cognitive impairment (CI) [33–35].

Over the past two decades, research has focused on the role of microglial cells in the pathophysiology of different CNS diseases [32]. Microglial cell activation and recruited macrophages are found in MS in acute and chronic active and inactive lesions. Pathological microglial cells become a source of free radicals and pro-inflammatory cytokines. These cells also accumulate iron released from damaged oligodendrocytes and myelin. As a result, axonal damage occurs, which contributes to neurodegeneration in smouldering MS [35, 36]. Continuous activation of microglia is a source of smouldering inflammation and failure of remyelination in MS, although this effect depends on the stage of lesions [37].

## Neuroimaging markers of smouldering MS

For many years, it was believed that the clinical progression of MS was associated with the occurrence of new demyelinating lesions on subsequent MRI scans. However, there is now awareness of the possibility of increased disability with the absence of new lesions on T2-weighted images when the simultaneous presence of chronic inflammation, focal inflammatory lesions and cerebral atrophy in MS is considered. The identification of more advanced MRI parameters to detect chronic active and inactive lesions is highly warranted [38]. Their division is set out in Table 1.

## Paramagnetic rim lesions (PRLs)

Smouldering lesions on MRI represented by paramagnetic rim lesions (PRLs) are characterised by the presence of hypointense linear or dot-like areas on T2* susceptibility-weighted imaging (SWI) in white matter lesions that involve 75% of the lesion rim. The rim must cover at least three consecutive slices and reflects ongoing inflammation at the plaque border represented by iron-laden microglia, macrophages and oligodendrocytes [4, 9, 39]. PRLs are mostly detected in the supratentorial and cortical areas and in the cerebellum. However, on rare occasions they occur in the cerebral cortex and are usually not found in the spinal cord. To date, no specific MRI recommendations have been developed but PRLs have been detected on high-field MRI (7T, 3T) using 3DT2*SWI sequences, echo-planar imaging (3DT2*EPI), and quantitative susceptibility mapping (QSM-SWI) [38, 40, 41].

Considering MRI findings (3–7T) and post mortem studies, PRLs are present in 10–59% of patients, even in very early stages of MS [41–44]. In 47% of patients who presented with the symptoms of clinically isolated syndrome (CIS), at least one PRL was observed, whose presence was associated with a 100% risk of conversion to MS [45]. In their study involving 192 participants, Absinta et al. identified at least one PRL in 56% of patients with MS regardless of any disease-modifying therapy (DMT). Additionally, at least four PRLs occurred 1.6-fold more frequently in progressive phenotypes [41]. The detection of PRLs was associated with a more aggressive clinical course of MS, motor and cognitive disability at a younger age, a higher risk of PIRA, disease progression, and conversion to secondary progressive MS (SPMS).

## Slowly expanding lesions (SELs)

Slowly expanding lesions (SELs) represent smouldering lesions on MRI that show constant and concentric expansion on T2-weighted images with the signal decrease on T1-weighted images in follow-up studies [4]. They are not contrast enhanced, and can be visualised with typical T1-weighted and T2-weighted MRI sequences. The constant decrease in T1 signal intensity of SELs reflects tissue damage and the morphology of smouldering plaques. The core of such lesions is typically characterised by an accumulation of axonal damage [4, 46] with a rim of activated microglia at the edges of SELs, thus contributing to remyelination failure [41]. Therefore, the presence of SELs on MRI is associated

**Table 1.** MRI parameters and their application

| MRI parameters | Basic | Advanced | Chronic active lesions |
|---|---|---|---|
| 1 | new or enlarging lesions on T2-weighted and T1-weighted images | DTI | PRLs |
| 2 | brain and spinal atrophy | T1/T2 relaxometry | SELs |
| 3 | - | MTR | CPV |
| 4 | - | - | leptomeningeal inflammation |
| Application | unrelated to MS relapse (assessment two months before or after relapse) | assessment of micro-damage (NAWM and NAGM), mainly for scientific purposes | potential biomarkers of smouldering MS |

MRI — magnetic resonance imaging; DTI — diffusion tensor imaging; MTR — magnetisation transfer; NAWM — normal-appearing white matter; NAGM — normal-appearing grey matter; PRLs — paramagnetic rim lesions; SELs — slowly expanding lesions; CPV — choroid plexus volume

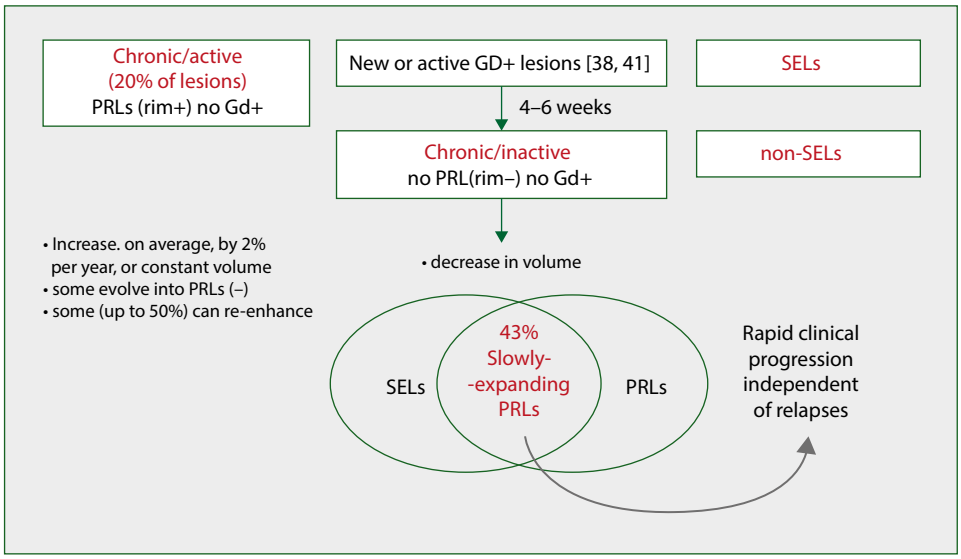


**Figure 1.** Evolution of active and inactive lesions on MRI

with irreversible neuronal destruction [47] and such lesions are more common in primary progressive MS (PPMS) [47]. As in the case of PRLs, the presence of at least four SELs is associated with a higher risk of cognitive impairment (CI), faster Expanded Disability Status Scale (EDSS) progression, disease progression, and conversion to SPMS. These lesions are more common in the elderly and in patients with a longer duration of MS [4, 48–50]. The evolution of active and inactive lesions on MRI is set out in Figure 1.

## Positron emission tomography (PET)

Pathological changes involving the inflammatory activity of microglia can even occur in normal-appearing white matter (NAWM). Visualisation of NAWM is not possible with conventional MRI. These lesions reflect microstructural damage, including the loss of myelin sheaths and axons and disruption of the BBB [51], and their presence is associated with disability progression and CI [51, 52]. Advanced imaging techniques, such as PET, allow the assessment of translocator protein (TSPO) expression that is related to immune cell density in MS, and is used to determine the activity of macrophages and microglial cells in NAWM [3, 53]. It has been confirmed that in SPMS patients, increased TSPO expression is associated with CDA, the rate of brain atrophy [54] and the time interval [55, 56], something not observed in RRMS.

## Optical coherence tomography (OCT)

Based on the assumption that the retina is an extension of the CNS, it is possible to use ophthalmic imaging techniques to potentially assess axonal and neuronal degeneration in MS patients [57]. Optical coherence tomography (OCT), which was first introduced in 1991, is a non-invasive method that provides cross-sectional images of the retina by evaluating the ganglion cell layer (GCL) and the retinal nerve fibre layer (RNFL) formed by ganglion cell axons [58]. An episode of optic neuritis occurs in c.30–70% of MS patients. However, even 94–99% of patients have demonstrated demyelinating plaques within their optic nerves at post mortem [59]. Acute inflammation in the optic nerve region, axonal transection, loss of trophic factors, mitochondrial abnormalities, and chronic demyelination are the most likely causes of retrograde degeneration of nerve fibres forming optic nerves that originate from the RNFL and the GCL [60]. Histopathological and *in vivo* OCT studies have confirmed that retrograde degeneration is the main cause of the thinning of the RNFL and GCL-inner plexiform layer complex (GC-IPL) in MS patients [60–62], which is inversely related to disease duration [62, 63]. Studies have reported a correlation between the progression of GC-IPL thinning and the presence of new lesions on T2-weighted images [62] and active lesions on MRI [58]. Additionally, studies have found an association between the thinning of the RNFL and the GC-IPL and long-term disability progression [57, 59]. The risk of MS progression has been shown to be three times higher when RNFL thickness < 88 $\mu$m [58].

Reduced RNFL is also correlated with the occurrence of CI as assessed by the symbol digit modality test (SDMT) [58]. Introduced in 2014, OCT-angiography (OCT-A) allows imaging of retinal and choroidal microvasculature. It shows higher sensitivity compared to OCT in the early stages of the disease, and in detecting progression in advanced MS. A reduced vessel density (VD) in the macular and peripapillary areas is also confirmed in the course of the disease [64, 65]. A higher level of disability, as measured by the EDSS, has been shown to be associated with lower VD [64].

**Table 2.** Biological profile and use of BTKi in MS therapy

| | Tolebrutinib | Fenebrutinib | Evobrutinib | Orelabrutinib | Remibrutinib |
|---|---|---|---|---|---|
| Half-life period (hours) | 2 [96] | 4.2–9.9 [97] | 2 [98] | 1.5–4 [99] | 1–2 [100] |
| Penetration into CNS | Yes [96] | No data | Yes | Yes | No data |
| Oral dosage/day (mg) | 60 with food [74] | 2 × 200 [1] | 2 × 45 with food [1] | low, medium and high doses [1] | 2 × 100 [1] |
| Clinical trials [1] | **tolebrutinib *vs.* placebo**<br>125 RMS patients; Phase IIb, RDB NCT03996291<br>**GEMINI1/2**<br>(tolebrutinib *vs.* teriflunomide)<br>est. 900 RMS patients; Phase III, RDB NCT04410978/ NCT04410991<br>**HERCULES**<br>(tolebrutinib *vs.* placebo)<br>est. 1,290 SPMS patients; Phase III, RDB NCT04411641<br>**PERSEUS**<br>(tolebrutinib *vs.* placebo)<br>est. 990 PPMS patients;<br>Phase III, RDB<br>NCT04458051 | **FENopta**<br>(fenebrutinib *vs.* placebo)<br>est. 102 RMS patients; Phase II, RDB NCT05119569<br>**FENhance**<br>(fenebrutinib *vs.* teriflunomide *vs.* placebo)<br>est. 736 RMS patients; Phase III, RDB NCT04586023/NCT04586010<br>**FENtrepid**<br>(fenebrutinib *vs.* ocrelizumab *vs.* placebo)<br>est. 946 PPMS patients; Phase III, RDB, NCT04544449 | **evobrutinib *vs.* dimethyl fumarate *vs.* placebo**<br>267 RMS patients; Phase II, RDB NCT02975349<br>**Evolution RMS 1/2**<br>(evobrutinib *vs.* teriflunomide)<br>est. 898 RMS patients; Phase III, RDB NCT04338022/NCT04338061 | **orelabrutinib *vs.* placebo**<br>est. 160 RMS patients; Phase II, RDB NCT04711148 | **remibrutinib *vs.* teriflunomide**<br>est. 800 RMS patients; Phase III, RDB NCT05147220/NCT05156281 |
| End-points in clinical trials[1] | AE, ARR, (clinical and radiological) progression | AE, ARR, (clinical and radiological) progression | AE, EDSS progression, radiological progression, safety | AE, ARR, demyelinating lesions on MRI | ARR, (clinical and radiological) progression |

BTKi — Bruton's tyrosine kinase inhibitors; MS — multiple sclerosis; CNS — central nervous system; est. — estimated; RMS — relapsing multiple sclerosis; RDB — randomised double-blind clinical trial; SPMS — secondary progressive multiple sclerosis; PPMS — primary progressive multiple sclerosis; AE — adverse events; ARR — annualised relapse rate; EDSS — Expanded Disability Status Scale; MRI — magnetic resonance imaging. Sourse: clinicaltrials.gov

## Clinical and therapeutic implications

### Bruton's tyrosine kinase (BTK) and BTK inhibitors (BTKi)

The dichotomy of MS pathophysiology is based on the assumption that relapses develop as a consequence of *de novo* CNS infiltration of immune cells, while MS progression is driven by a CNS-trapped inflammatory circuit between CNS-established haematopoietic cells and CNS-resident cells, including microglia, astrocytes and oligodendrocytes [66]. The mechanism of action of disease-modifying therapies (DMTs) involves inhibition of the infiltration of autoreactive T and B lymphocytes in the peripheral immune system and reduction of relapses with some effect on disability progression. BTK inhibitors (BTKi) are a promising therapeutic option to prevent PIRA in smouldering MS [67].

BTK is a cytoplasmic non-receptor tyrosine kinase that is expressed in haematopoietic cells, mainly in B cells and myeloid cells (i.e. dendritic cells, mast cells, neutrophils, macrophages) and in haematopoietic stem cells, platelets and erythrocytes except for T cells and NK cells. In the CNS, BTK is expressed in microglia and (to a lesser extent) in astrocytes. BTK function is crucial for the maturation and function of B cells and for intracellular signalling of B cells and myeloid cells, including microglial cells [66, 68]. Therefore, BTK inhibition results in peripheral modulation of B cells, their maturation, proliferation, production of autoantibodies and cytokines, as well as decreased macrophage activity and decreased microglial activity in the CNS [69].

BTKi represent a currently investigated strategy for the treatment of MS, not only reducing pathogenic cell migration into the CNS and secondary activation, but also potentially normalising the microglial phenotype, inhibiting demyelination and axonal damage with subsequent remyelination [70]. BTKi belong to a group of small molecules that are used in the treatment of oncological and haematological diseases. Depending on their mode of action and binding to BTK, BTKi can be divided into covalent irreversible BTKi (evobrutinib, tolebrutinib, remibrutinib, orelabrutinib) and non-covalent reversible BTKi (fenebrutinib and BIIB091) [71]. The efficacy and safety of BTKi for the treatment of relapses and progressive MS phenotypes are being evaluated in clinical trials: Phase III (evobrutinib, tolebrutinib and fenebrutinib), Phase II (orelabrutinib) and Phase I (BIIB091) [66, 71]. Due to the selectivity of BTKi, their toxicity is reduced and adverse events (AEs) are limited. Unlike other DMTs that cause lymphocyte depletion, the use of BTKi is rarely associated with infections secondary to lymphopenia [71]. Fenebrutinib and orelabrutinib are the most selective agents [72]. However, the safety data from Phase II clinical trials has indicated that headache, upper respiratory tract infections, a mild increase in liver enzymes and elevated lipase levels are the most common AEs related to evobrutinib and tolebrutinib [73, 74]. *In vitro* studies have found that fenebrutinib causes greater suppression of B cells and myeloid cells compared to evobrutinib and tolebrutinib. In turn, tolebrutinib has demonstrated greater CNS penetration compared to evobrutinib and fenebrutinib, which potentially is responsible for greater inhibition of microglial activity and a better therapeutic effect for progressive MS phenotypes [71].

A Phase IIb clinical trial whose aim was to determine the relationship between the dose of tolebrutinib and the reduction in demyelinating lesions on MRI in patients with relapsing MS phenotypes, found that tolebrutinib (60 mg/d) reduced new active lesions by 85%, and new or enlarging lesions on T2-weighted images by 89%, in patients treated with tolebrutinib compared to a placebo. The analysis confirmed that tolebrutinib reduced the volume of SELs, which reflects the presence of activated microglia, neuronal destruction and CDA [74]. Preclinical and animal findings showed that tolebrutinib had a direct effect on microglial cells, altering their expression to a more homeostatic phenotype [75]. Furthermore, analysis of cerebrospinal fluid (CSF) proteomic data showed that proteins associated with active MS, such as CD79B and CD27, were modulated in tolebrutinib-treated patients to the levels found in healthy volunteers [76]. Therapy with ocrelizumab and natalizumab in PPMS [4] and SPMS [77] patients, respectively, was associated with a reduction in the number of SELs. However, the effects of natalizumab and fingolimod on SEL occurrence seemed modest yet comparable in RRMS [78].

In turn, in their analysis of the effect of DMT on inhibiting the progression of pathological changes on MRI, Eisele et al. estimated that the T1/T2 ratio of iron rim lesions (IRLs), which reflects demyelination, axonal damage and neuronal loss, was significantly lower at 2-year follow-up in patients on fingolimod, dimethyl fumarate and ocrelizumab compared to patients without DMTs. Their findings suggest that DMTs have a limited beneficial delayed effect on smouldering MS lesions [79].

A comparison of BTKi with respect to their biological profile and their use in MS therapy is set out in Table 2.

Since the primary endpoints relating to a decrease in the annual relapse rate (ARR) were not achieved, the EVOLUTION RMS 1 and 2 Phase III trial (evobrutinib *vs.* teriflunomide) was unexpectedly finished early in December 2023. The safety and tolerability profile of evobrutinib was in line with that obtained in the Phase III trial.

## Clinical assessment and smouldering MS

Routine neurological assessment and evaluation of patients according to the EDSS are not sufficiently sensitive methods to detect lesions in terms of gait performance, upper limb function, or CI [80, 81]. In addition, considering ongoing relapses and their persistent symptoms, the identification of smouldering MS and CDA can be challenging in daily clinical practice. Cadavid et al. suggested the use of 'EDSS-Plus', which additionally includes a 9-Hole Peg Test (9HPT) and a timed 25-foot walk (T25FW), which clearly distinguished SPMS progressors from non-progressors [82]. The Overall Disability Response Score (ODRS) can be used instead. This also includes the Paced Auditory Serial Addition Test (PASAT-3) [83, 84].

The use of the above tests resulted in defining PIRA in a large percentage of patients treated with ocrelizumab and interferon beta-1a (87% and 78%, respectively) [6].

Despite many controversies, the technology associated with using mobile devices is becoming more commonly used in MS. The introduction of mobile devices, biosensors, telemedicine applications and platforms may provide new data on the natural clinical course of the disease, CDA and smouldering MS [85–87].

Assessment of CI is an important aspect in the identification of smouldering MS. CI occurs in Clinically Isolated Syndrome (CIS) and Radiologically Isolated Syndrome (RIS) and evolves throughout the course of the disease [88]. Studies have confirmed the relationships between the onset of CI and cortical thinning, atrophy of the corpus callosum and thalami, and the lesion volume of white matter. In the early stages of MS, the development of CI is most likely caused by lesions localised in the white matter, while concomitant thalamic atrophy exacerbates CI. The finding of relatively mild CI at the onset of the disease is associated with significant destruction of the brain tissue [89], and the diagnosis of CI shows only a poor association with MRI activity of the disease as measured by new or enlarging lesions on T2-weighted sequences [89, 90].

Visualisation of at least one PRL on MRI with concurrent CI increases the risk of RIS conversion to MS [41, 43]. Irrespective of inflammatory changes, axonal degeneration and neuronal network damage associated with CI have been seen on functional MRI [91]. Undoubtedly, the implementation of systematic assessment of CI in routine clinical practice allows for faster diagnosis and better monitoring of smouldering MS.

## Future directions

Previous observations on the natural course of MS indicated that focal inflammatory activity in the form of relapses and/or the presence of contrast-enhanced lesions or new or enlarging lesions on T2-weighted images has no prognostic value in terms of long-term disability in patients who are not treated with immunomodulatory therapies and in those on DMT [92].

Therefore, focal inflammation is only a response to the primary cause of MS, and the use of DMT does not affect the drivers of MS. The above discrepancy between focal inflammatory activity and disability progression is referred to as the clinico-radiological paradox [3]. This poses a therapeutic challenge, and hence the need to analyse pathophysiological processes in MS with simultaneous abandonment of the NEDA criteria (no evidence of disease activity) and indicating a continuum of the relapsing and progressive phases in smouldering MS.

The use of DMT in MS patients over the past three decades has allowed effective follow-up of relapse activity and MRI activity [93]. However, the inhibition of disability progression with available therapies is still insufficient.

The following should become the primary management template for preventing disease progression: effective reduction of chronic inflammation in the CNS; prevention of further axonal loss; remyelination with subsequent restoration of neural tissue; neuroprotective action; and elimination of any factors determining smouldering MS.

Some questions arise as to (1) why lesion formation occurs only in some patients, and (2) whether microglial checkpoint dysregulation [94], or increased sensitivity of CNS tissues to MS-related inflammation, is responsible for the increased predisposition to the formation of chronic active lesions. As a result, the above processes may be responsible for abnormal and incomplete remyelination. Older age at the formation of chronic active lesions is prognostically unfavourable, which is related to other important observations indicating that inflammation in MS does not decrease with age, but rather becomes compartmentalised in the CNS.

Undoubtedly, clinicians should focus on increasing awareness of patients related to the limitation of modifiable factors that potentially drive smouldering MS, such as poor diet, lack of physical activity, comorbid infections and diseases, tobacco smoking or diurnal rhythm disturbances, which further identifies MS as a multidisciplinary disease.

In addition to innovative approaches to the pathological processes in the immune system, new radiological markers are milestones in identifying smouldering MS. Detection of at least four PRLs or SELs is associated with a higher risk of disability progression, a faster increase in the EDSS, and an increase in the risk of CI. Therefore, in the future it seems possible to use them as markers for predicting the course of MS and markers for potential monitoring and assessment of the efficacy of DMT [4, 41].

Due to the fact that PRLs represent active lesions on MRI, the term 'disseminated in time' (DIT) can be regarded as the simultaneous presence of gadolinium-enhancing and non-enhancing PRLs, which could be included in the McDonald criteria in the future [45]. There has also been a suggestion according to which the term 'disseminated in space' (DIS) could be applied when the presence of ≥1 T2-hyperintense PRL characteristic of MS is reported [40]. These intriguing concepts require intensive efforts aimed at establishing international recommendations for the definition and reporting of PRLs, standardisation of SWI images, and evaluation of the possibility of PRL imaging using different magnetic field inductions (including 1.5 T) with simultaneous specialised training for neurologists and neuroradiologists in the above domain [40].

Clinicians should focus on indicating subtle neurological deficits in terms of physical performance and cognitive functioning to characterise the disease progression, which is difficult to determine clearly during a standard neurological examination. The inclusion of daily routine physical, cognitive, occupational and social activities into daily clinical practice will probably facilitate an effective indication of the effects

of smouldering MS. Determination of gait and upper limb performance using 9HPT and T25FW, which are used in clinical trials, can provide a tool for improving identification of progressive disability accumulation. A complete neurological evaluation should include the assessment of CI, which affects 34–65% of patients and can develop even in the initial stage of MS. In the case of mild phenotypes of MS in patients with EDSS < 3 over a 15-year period, progressive CI is found despite motor function sparing [95].

Bearing the above in mind, routine cognitive assessment is highly warranted, using, for instance, the Symbol Digit Modalities Test (SDMT) [95]. The high sensitivity of SDMT allows the detection of CI, which is often the only indicator of disease progression and smouldering MS. In addition, the use of currently available telemedicine devices should be considered. Such devices include biosensors, applications and other activity-tracking techniques.

Over the next few years, the primary goal should include management aimed at increasing the awareness of disease progression, which begins at the time of MS diagnosis, and how an apparently mild course of MS can be associated with progressive neurodegeneration.

The clinical and diagnostic identification of smouldering MS should have therapeutic implications that prove effective in inhibiting disease progression. BTK, which is involved in the activation of B cells and microglia, may be the final target of therapy. The analyses have clearly demonstrated that BTKi, as relatively small molecules, can penetrate the BBB, inhibit immune cells in the CNS, and suppress chronic inflammation and associated chronic progression. It seems important to distinguish the molecules with the best clinical effects in MS and with a favourable profile of AEs.

There is no doubt that the effectiveness of the DMTs is lower the longer the duration of MS, and their effect is insufficient to control smouldering MS. As a result, attempts are being made to define the most important therapeutic challenge of the future with the need to plan treatment that effectively inhibits disease progression from MS diagnosis and in a long-term perspective. Smouldering MS suggests a different pathophysiological and clinical approach, which results in the beginning of a new era of DMT, in which MS treatment will be based on combination therapy, including drugs that reduce relapse activity and therapy that inhibits disease progression. Therefore, dual-mechanism drugs are an alternative.

The above assumptions imply global modifications and changes in clinical and therapeutic approaches in the medical community and in MS patients.

## Conclusions

An innovative approach to the pathophysiology and course of MS has contributed to the formulation of the concept of 'smouldering MS'. According to this concept, the autoimmune pathological process of the disease is the result of co-existing acute peripheral inflammation and chronic neuroinflammation in the CNS. The clinical indicator of 'smouldering MS' is PIRA, which co-exists with RAW, jointly leading to progressive disability. The progression of MS begins at the time of diagnosis. Therefore, it is crucial to determine diagnostic biomarkers that could identify the subtle neurological deficits of patients in terms of physical performance and cognitive function. New radiological markers (i.e. PRLs or SELs) are of revolutionary importance in the diagnosis of smouldering MS. The efficacy of current immunomodulatory MS therapies is limited. In future, combination therapy should be considered to reduce the relapse activity and the progression of disability from the onset of the disease.

## Article information

**Acknowledgements:** *The authors would like to thank Assistant Professor Arkadiusz Badziński, PhD, for his assistance in the translation of the manuscript.*
**Authors' contributions:** *Study concept and design: NN and MAS; data collection: all authors; draft manuscript preparation: NN. All authors reviewed the results and approved the final version of the manuscript.*
**Funding:** *None.*
**Conflict of interest:** *None.*
**Supplementary material:** *None.*

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