Multiple sclerosis

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Multiple sclerosis remains one of the most common causes of neurological disability in the young adult population (aged 18–40 years). Novel pathophysiological findings underline the importance of the interaction between genetics and environment. Improvements in diagnostic criteria, harmonised guidelines for MRI, and globalised treatment recommendations have led to more accurate diagnosis and an earlier start of effective immunomodulatory treatment than previously. Understanding and capturing the long prodromal multiple sclerosis period would further improve diagnostic abilities and thus treatment initiation, eventually improving long-term disease outcomes. The large portfolio of currently available medications paved the way for personalised therapeutic strategies that will balance safety and effectiveness. Incorporation of cognitive interventions, lifestyle recommendations, and management of non-neurological comorbidities could further improve quality of life and outcomes. Future challenges include the development of medications that successfully target the neurodegenerative aspect of the disease and creation of sensitive imaging and fluid biomarkers that can effectively predict and monitor disease changes.

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Introduction

Multiple sclerosis, a neuroinflammatory disease of the CNS that causes demyelination and neuronal injury, is one of the most common causes of non-traumatic disability among young adults (aged 18–40 years).[1] The chronic accumulation of physical and cognitive disability among people with multiple sclerosis has substantial effects on social, economic, and individual wellbeing. The annual economic burden of multiple sclerosis in the USA was estimated at US$85·4 billion.[2] Similar findings were reported for the EU, where annual mean costs ranged from €22 800 (for mild disease) to €57 500 (for severe disease) in purchasing power parity, with direct medical costs accounting for up to 68% of these total costs.[3]

This Seminar reviews the latest findings that have improved our understanding of the epidemiological, pathophysiological, diagnostic, and management aspects of multiple sclerosis. Within the past 5 years, new crucial aspects were revealed, pertaining to a newly defined multiple sclerosis prodromal stage; disease causes and pathophysiology; development and application of new imaging and fluid biomarkers for earlier diagnosis and more accurate prognostic and monitoring metrics for multiple sclerosis progression; and approval of new disease-modifying therapies (DMTs).

Epidemiology

Based on the latest Multiple Sclerosis Atlas, a joint project between the Multiple Sclerosis International Federation and WHO, 2·8 million people have multiple sclerosis worldwide. A global increase of half a million new cases of multiple sclerosis since 2013 is attributed to greater life expectancy and global population growth; better data collection; and improved worldwide multiple sclerosis diagnosis. The prevalence of multiple sclerosis varies among different geographical regions, with the highest rates reported in the WHO European region and region of the Americas (111–300 cases per 100 000) and lowest in the WHO African region and Western Pacific region (5 per 100 000). Multiple sclerosis prevalence substantially differs by sex, with an overall ratio of 3:1 for females to males.[4] Although the global average age at multiple sclerosis diagnosis was estimated at age 32 years, some studies suggest a shift towards older age at disease onset and increasingly greater incidence of multiple sclerosis after age 50 years.[5] The overall improvement in multiple sclerosis prognosis also results in increased prevalence of an ageing multiple sclerosis population.[6] Therefore, routine clinical management should incorporate the effect of age-related comorbidities, safety concerns, effectiveness of treatment, drug interactions, and differential diagnosis of cognitive decline.[7]

Multiple sclerosis prodrome and radiologically isolated syndrome

Over the past 5 years, increasing interest in defining the multiple sclerosis prodrome has resulted in improved understanding of early signs and symptoms that can indicate multiple sclerosis onset.[8] Retrospective data from health administrative and clinical databases from four Canadian provinces identified that people with multiple sclerosis had increasingly greater rates of hospital admissions, physician claims, and prescriptions preceding the multiple sclerosis diagnosis than people without multiple sclerosis.[9] Similar UK-based data showed that people with multiple sclerosis have greater health-care use 10 years before their official diagnosis

Search strategy and selection criteria

The references and information included in this Seminar were found through MEDLINE and PubMed searches for "multiple sclerosis" from database inception up to March 1, 2023. We selected studies published in English and German that provided the most relevant advances, were published in high-impact, peer-reviewed journals, and with results based on satisfactory numbers of study participants (≥10 people). We largely selected publications in the past 5 years but did not exclude commonly referenced and highly regarded older publications.

than matched controls without the disease, with most visits attributed to non-specific symptoms related to the gastrointestinal and urinary system, anxiety, depression, fatigue, insomnia, and pain.[10] These trends were equally present in young (aged <40 years) and older people (aged ≥40 years) with multiple sclerosis.[10] Furthermore, direct biological changes, such as an increase in serum neurofilament light (NF-L) concentrations in the prodromal multiple sclerosis period, can be measured as early as 6 years before disease onset.[11] Of note, the prodromal stage of multiple sclerosis has only been investigated in retrospective, population-based studies. Development of prospective, individual-level studies are highly warranted.

In comparison to the multiple sclerosis prodrome, the presence of characteristic multiple sclerosis lesions on MRI in individuals imaged for unrelated indications has been formalised as radiologically isolated syndrome.[12,13] Meta-analyses identified that approximately 0·06% of healthy individuals will present with definite demyelination.[14] The prevalence of radiologically isolated syndrome increases among asymptomatic family members of people with multiple sclerosis, with up to 8% meeting the primary neuroimaging outcome, dissemination in space, of the McDonald diagnostic criteria.[15,16] People with radiologically isolated syndrome might have increased prevalence of headaches, greater cognitive impairment, or slower manual dexterity (or a combination of these) than controls.[17,18] Over 5 years, 20–50% of people with radiologically isolated syndrome will have a clinical demyelinating event and be subsequently diagnosed with multiple sclerosis, whereas a small number will exhibit a purely progressive phenotype.[19,20] Enhancing lesions, spinal cord lesions, and being younger than 37 years are related to fast conversion to multiple sclerosis.[21] The role of treatment in preventing transition to multiple sclerosis is currently unclear and trials are ongoing (NCT03122652 and NCT02739542). Treatment with dimethyl fumarate in radiologically isolated syndrome resulted in a statistically and clinically significant reduction in the risk of first clinical demyelinating event by 82% compared with placebo.[22]

	Number of clinical attacks	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
Scenario 1	≥2 clinical attacks	≥2	None
Scenario 2	≥2 clinical attacks	1 (clear-cut historical evidence of clinical attack with corresponding lesion in a distinct anatomical location)	None
Scenario 3	≥2 clinical attacks	1	DIS
Scenario 4	1 clinical attack	≥2	DIT
Scenario 5	1 clinical attack	1	DIS and DIT

DIS=dissemination in space. DIT=dissemination in time.

Table 1: **The 2017 McDonald criteria for diagnosis of multiple sclerosis**

Diagnosis

Compared with previous versions, the 2017 McDonald diagnostic criteria provide improved accuracy in the diagnosis of multiple sclerosis on the basis of clinical, imaging, and fluid indicators.[23] Neurological and radiological expertise are necessary to exclude alternative diagnoses and determine key diagnostic aspects supporting dissemination in space and time of the underlying pathology (table 1).[23] Dissemination in space describes the development of lesions in four distinct anatomical locations within the CNS (the periventricular brain region, cortical or juxtacortical brain region, infratentorial brain region, or spinal cord) and therefore indicating a multifocal CNS process. Dissemination in space can be shown by one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in at least two of the four areas of the CNS. Although the criteria suggest presence of one or more periventricular lesions to be sufficient for diagnosis, this recommendation should be carefully applied in individuals who are older than 50 years or have a history of vascular risks. Dissemination in time describes the development or appearance of new CNS lesions over time. Dissemination in time can be shown by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI.

New additions to the 2017 criteria are the inclusion of both symptomatic and asymptomatic brain and spinal cord MRI lesions to demonstrate dissemination in space and time and use of cerebrospinal fluid-specific oligoclonal bands as a substitute for a second clinical event or MRI activity.[24] The inclusion of optic nerve lesions detected through MRI, visual evoked potentials, or optical coherence tomography without previous history of optic neuritis does not provide additional value for demonstration of dissemination in space and time. However, data published in 2021 suggested that optic nerve lesions detected with visual evoked potentials could improve the sensitivity and accuracy of the current criteria, particularly when used in people with multiple sclerosis presenting with acute optic neuritis.[25] MRI standardisation regarding acquisition and analysis of the orbits could allow inclusion of the optic nerves as the fifth anatomical region in future revisions of the criteria; such revisions could also discuss the potential addition of multiple sclerosis-specific MRI features (eg, central vein sign, paramagnetic rim lesions, slowly expanding lesions, or fluid biomarkers (eg, NF-L).

In 2021, a consensus report by three major multiple sclerosis organisations (Magnetic Resonance Imaging in Multiple Sclerosis, Consortium of Multiple Sclerosis Centers, and North American Imaging in Multiple Sclerosis Cooperative) provided updated recommendations on how and when to use MRI for multiple sclerosis

diagnosis, prognosis, and treatment monitoring.[26] Despite concerns regarding CNS accumulation of gadolinium-based contrast agents, contrast administration remains crucial in determining dissemination in time and differential diagnosis. The consensus report highly recommends use of gadolinium-based contrast agents and detection of contrast-enhancing lesions during the diagnostic process due to their ability to predict future disease activity, prognosis, and potentially future disability progression. Moreover, use of gadolinium-based contrast agents is recommended as a monitoring tool to capture disease activity before initiating or changing DMT.[26] However, gadolinium-based contrast agents are not recommended for routine MRI monitoring, particularly in people who are relapse-free as subclinical disease activity can be assessed through detection of new T2 lesions. Although the ability to detect cortical lesions remains disputed in the literature, the 2017 McDonald revision allows cortical lesions to be considered when determining dissemination in space. Since the spinal cord is one of the four anatomical regions that can fulfil criteria for dissemination in space in the McDonald criteria and is crucial in the differential diagnosis, the standardised MRI protocol recommends use of at least two sagittal spinal cord sequences.

Differential diagnosis

The neuroinflammatory and neurodegenerative nature of early multiple sclerosis should be differentiated from other neuroinflammatory disorders via careful review and collective interpretation of the clinical or neurological features, MRI results, and blood (serum or plasma) or cerebrospinal fluid findings (table 2). Inappropriate use of the McDonald diagnostic criteria, absence of typical multiple sclerosis demyelinating clinical events, and over-reliance on MRI abnormalities could all result in multiple sclerosis misdiagnosis.[27] Recommendations geared towards prevention of multiple sclerosis misdiagnosis in atypical and challenging presentations have been proposed.[27,28]

Clinical phenotypes

The phenotype classification of relapsing–remitting, secondary progressive, or primary progressive disease should be provisionally asserted at the time of multiple sclerosis diagnosis.[29] Information should be obtained at each assessment about the occurrence of relapses or new lesions on MRI (active disease) versus stability or progression of neurological status.[29] Traditionally, up to 85% of people with multiple sclerosis initially present with a single, usually monofocal, demyelinating attack and might not fully satisfy the criteria for diagnosis at the time of first symptom onset, classified as clinically isolated syndrome.[30] Although the majority of these people will transition into multiple sclerosis, a small portion will not have a second demyelinating attack and remain clinically stable. Risk factors contributing to greater odds of transition to multiple sclerosis include the number of T2 lesions (0 for low risk, 1–9 for medium risk, or ≥10 lesions for high risk), lesion location (eg, infratentorial), and presence of cerebrospinal fluid oligoclonal bands.[31,32] The greater sensitivity of the 2017 McDonald criteria allows earlier multiple sclerosis diagnoses than the 2010 McDonald version[33] and eventual earlier initiation of appropriate DMTs.[34]

Most people with multiple sclerosis present with a relapsing–remitting multiple sclerosis phenotype, characterised by alternating periods of acute neurological dysfunction (ie, relapses) separated by relative clinical stability (ie, remissions). Relapses are defined as events of new neurological symptoms, such as motor weakness, sensory deficits, loss of balance, vision loss, or double vision that last at least 24 h and cannot be attributed to confounding factors such as ongoing infections or metabolic imbalance. Disease activity varies among people with multiple sclerosis and is commonly measured by the frequency of clinical relapses or MRI presence of contrast-enhancing lesions or new (or newly enlarging) T2 lesions. Natural history studies suggest that inflammatory activity would typically occur at an average of one relapse per year with a clear age-dependent decrease.[35] The relapse rate in paediatric-onset multiple sclerosis is also substantially higher than in adult-onset multiple sclerosis and compared with later stages of the disease.[36] If diagnosed at later stages and left untreated, the majority of people with multiple sclerosis will have chronic accrual of disability and up to half would transition to secondary progressive multiple sclerosis 15 years after diagnosis.[37] Although relapses might be associated with some residual relapse-associated worsening, the long-term worsening is mainly driven by insidious disease-activity-free progression (ie, progression independent of relapse activity).[38] Disability progression is commonly coupled with an increased rate of brain atrophy that occurs even in the early stage of relapsing–remitting multiple sclerosis.[38] Long-term disability progression is not predicted by the relapse frequency[39] nor by presence of so-called no evidence of disease activity (defined as a combination of no relapses, MRI activity, or 2-year progression).[40] Presence of oligoclonal bands, more T2 lesions, and older age are all associated with greater risk of disability progression independent of relapse activity, steeper Expanded Disability Status Scale (EDSS) increase, and reaching major disability outcomes, such as EDSS of 6·0 (need of unilateral walking support).[41] Moreover, higher spinal cord lesion burden, atrophy, and cortical volume loss are also associated with disease worsening and faster progression to major disability milestones.[42] However, over the past 30 years, a substantially smaller proportion of people with relapsing–remitting multiple sclerosis (15–20%) transitioned to the progressive disease stage than previously (approximately 50%).[38] This change in the natural history of the disease has been attributed to

	Clinical features	MRI features	Cerebrospinal fluid and blood biomarkers
Neuromyelitis optica spectrum disorder	Presentation after age 10 years; 4:1 female:male ratio; recurrent episodes of myelitis, optic neuritis, possible nausea, and vomiting; poor recovery after an optic neuritis episode	Bilateral optic neuritis lesions involving the chiasm and optic tracts; common LETM (≥3 segments) with patchy enhancement, can extend in the brainstem; focal lesions in the area postrema, midbrain, and diencephalon	Anti-AQP-4 presence; rare oligoclonal bands presence; common pleocytosis
Myelin oligodendrocyte glycoprotein spectrum disorder	Presentation before age 10 years, but also in older population; presentation often similar to acute disseminated encephalomyelitis in children; 1:1 female:male ratio; 50% of individuals have relapses and 50% have monophasic disease; common papillitis; good recovery after an optic neuritis episode	Common LETM; optic neuritis can be unilateral or bilateral; large cerebellar lesions extending through the cerebellar peduncles	Anti-MOG presence; rare oligoclonal bands presence; common pleocytosis
Acute disseminated encephalomyelitis	Monophasic; presentation usually before age 10 years; multifocal symptoms and encephalopathy	Bilateral and asymmetrical small punctate to tumefactive lesions present in the supratentorial, cerebellar, and spinal cord regions	Common pleocytosis
Susac's syndrome	More common in females; encephalopathy; visual and hearing loss; memory loss and behavioural disturbances	Multiple small callosal and splenial lesions; infratentorial lesions in the brainstem and middle cerebellar peduncles; leptomeningeal enhancement	Oligoclonal bands absence
Neurosarcoidosis	Higher prevalence in Black and female populations than non-Black and male populations; cranial neuropathies, acute or chronic meningitis, encephalopathy, and seizures	Persistent and simultaneous enhancement of all lesions; meningeal involvement and cranial nerve changes; intramedullary contrast-enhancing spinal lesions and associated intradural lesions	Increased ACE in the cerebrospinal fluid; increased blood and cerebrospinal fluid levels of soluble IL-2 receptor; rare oligoclonal bands presence
Primary angiitis of the CNS or secondary CNS vasculitis	1:2 female:male ratio; commonly in people with a median age of 50 years; encephalopathy; headaches, cognitive symptoms, alteration in consciousness	Infarctions in multiple vascular areas (lacunae); microbleeds; periventricular, confluent, non-specific T2 lesions sparing U-fibres; meningeal enhancement	Rare oligoclonal bands presence
Neuro-Behçet's disease	Meningoencephalitis; myelopathy; recurrent parenchymal disease; non-parenchymal disease (secondary to vascular changes)	Enhancing brainstem, basal ganglia, and subcortical white matter lesions; spinal cord involvement; cerebral vein thrombosis; systemic features include oral and urogenital ulcerations, cutaneous lesions (pathergy test), ocular disease, gastrointestinal involvement, and renal disease	Common pleocytosis; HLA-B5/51; pathergy test
Neuroborreliosis (Lyme disease)	Endemic to North America and Europe; influenza-like symptoms and erythema migrans; late stage cardiac (eg, myocarditis and arrythmia), neurological (eg, neuropathy, encephalitis, and meningitis) and rheumatological (eg, arthritis) symptoms	Periventricular or subcortical T2 hyperintensities; meningeal enhancement; enhancement of the cranial nerves (most commonly facial nerve)	Borrelia burgdorferi-specific antibody index; leukocytosis
Neurosyphilis	Acute bacterial-like meningitis or meningomyelitis; ischaemic stroke; symptoms related to posterior uveitis or otitis; tabes dorsalis, dementia, and Argyll Robertson pupil	T1-hypointense and T2-hyperintense syphilitic gummas with dural tail sign; meningeal enhancement; enhancement of the cranial nerves; involvement of the dorsal column of the spinal cord	Reactive to VDRL and FTA-ABS tests; moderately elevated protein levels; lymphocytosis
CADASIL or CARASIL	Presentation at age 30–50 years (earlier in CARASIL than CADASIL; mean age of 32 years *vs* 45 years); multiple transient ischaemic attacks and strokes in different vascular territories; migraines, psychiatric symptoms, and dementia	Confluent white matter lesions; cerebral microbleeds	Autosomal dominant (CADASIL) or recessive (CARASIL); presence of mutations in the *NOTCH3* gene on chromosome 13 (CADASIL) and the *HTRA1* gene on chromosome 10 (CARASIL); oligoclonal bands absence
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	Subacute presentation; multiocular brainstem symptoms, cranial nerve and cerebellum involvement; spinal cord symptoms	Pontine lesions with punctate, linear, or patchy enhancement; presence of lesions in 2 of 3 regions: pons, brachium pontis, and cerebellum; rare basal ganglia and spinal cord involvement	Rare transient oligoclonal bands presence
Hereditary spastic paraparesis	Progressive and symmetric lower limb limitations and gait disturbance; hyper-reflexia and spasticity; mild sensory abnormalities in lower extremities	T2 hyperintensities within the posterior limb of the internal capsule and frontal horns of the ventricles; iron deposition in globus pallidus; atrophy of the corpus callosum, cerebellum, and spinal cord	Autosomal dominant (up to 80%) variants of *SPAST*, *ALT1*, or *KIF1A* and *REEP1*; autosomal recessive variants of *CYP7B1*, *SPG7*, and *SPG11*; X-linked variants
Adult-onset genetic leukodystrophies*	Variable degree of cognitive impairment; spasticity and ataxia; inheritance patterns within families	Symmetrical white matter involvement of T2 hyperintensities with specific pattern of distribution (parieto-occipital, frontal, periventricular, subcortical pattern, brainstem, and cerebellar patterns); distinctive features (cysts, cavitations, calcifications, enhancement, and spinal cord involvement)	Single gene sequences; exome sequencing; metabolic testing

CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CARASIL=cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. FTA-ABS=fluorescent treponemal antibody test absorption. LETM=longitudinal extensive transverse myelitis. VDRL=Venereal Disease Research Laboratory. *Adult-onset genetic leukodystrophies can be included in specific differential diagnosis and should consider any of the following rare adult-onset entities: X-linked adrenoleukodystrophy, adult Krabbe disease, metachromatic leukodystrophy, L-2-hydroxyglutaric aciduria, adult Alexander disease, cerebrotendinous xanthamatosis, and Nasu-Hakola disease.

***Table 2*: Differential diagnosis of multiple sclerosis mimics**

earlier diagnosis and initiation of DMTs and general improvements in the management of other age-related comorbidities.[38]

The secondary progressive multiple sclerosis phenotype is typically characterised by periods of disability worsening that occur without any clinical or radiological evidence of new acute inflammation, although superimposed clinical relapses and new focal MRI activity can still occur (active secondary progressive multiple sclerosis). The transition to the progressive phenotype is assigned retrospectively, typically years after the onset of the chronic worsening. Multiple factors contribute to the delayed reclassification, including fluctuating symptoms, age-related functional decline, and few effective treatments for this stage of the disease.[43] Attempts at operationalising the secondary progressive multiple sclerosis diagnosis could result in earlier detection of the transition to progressive multiple sclerosis.[44] For example, a registry-based study suggested that combining an EDSS score of 4·0, pyramidal score of 2·0, and 3-month confirmed disability progression in the absence of relapse has up to 78% accuracy in identifying people with multiple sclerosis who will have a progressively worsening disability trajectory in the following 5 years.[44] In terms of MRI predictors, the presence of gadolinium-enhancing lesions, spinal cord lesions, and cortical lesions at the time of diagnosis are all associated with greater likelihood of and faster transition to secondary progressive multiple sclerosis.[45,46] Development of algorithms that could standardise the definitions for active and non-active secondary progressive multiple sclerosis would allow more homogeneous trial recruitment for secondary progressive multiple sclerosis and improve the interpretation of results from drug trials.[47]

At diagnosis, a small portion of people with multiple sclerosis (10–15%) are classified with the primary progressive multiple sclerosis phenotype, with slow disability progression apparent from the start of the disease. It is currently unknown whether this particular phenotype is distinct from secondary progressive multiple sclerosis or if people with primary progressive multiple sclerosis have a long prodromal and undiagnosed stage characterised by neurodegenerative and chronic inflammatory changes. Some people with primary progressive multiple sclerosis can have classic superimposed relapses.

An emerging view suggests that the multiple sclerosis phenotypes of early relapsing and secondary progressive disease are part of a single continuum, with overlapping pathophysiological mechanisms and no clear-cut boundaries.[48,49] The concept of a variable neurological reserve (ie, neural mechanisms of compensation after cerebral injury) and its loss with ageing represents one potential explanation as to why people with multiple sclerosis would present with different phenotypical presentations and different times of transition to the progressive stage of the disease.[47,50]

Cognitive impairment

Cognitive impairment is common among people with multiple sclerosis and predicts compromised quality of life and day-to-day function.[51] Deficits occur early in the disease course,[52] even in clinically isolated syndrome and radiologically isolated syndrome.[53,54] The prevalence of cognitive impairment is roughly 30–40% in relapsing–remitting disease, but up to 70% of people with progressive multiple sclerosis are affected.[55] Most often, information processing speed, working memory, and episodic memory are compromised;[51] higher executive function, verbal fluency, and visual–spatial processing are less frequently affected. As cognitive complaints are intertwined with depression and anxiety, formal performance-based (so-called objective) testing is the mainstay for valid measurement.[56] Cognitive impairment in people with multiple sclerosis has a negative effect on personal relationships and self-esteem and can lead to social isolation;[57,58] it is especially relevant for employment status[59,60] and fitness to drive.[61]

Specific tools are available to assess cognitive impairment in a standardised manner as part of the routine neurological visit.[62,63] The Brief International Cognitive Assessment for Multiple Sclerosis is a 15 min battery of tests, including of visual memory, visuospatial memory, and information processing speed.[63] The oral response Symbol Digit Modalities Test included in the battery of tests requires 5 min of clinician time and is the most reliable and sensitive cognitive test available for multiple sclerosis care.[64] People with multiple sclerosis with a large cognitive reserve are able to process information in a more efficient manner and can sustain more damage to the brain before the damage begins to affect their daily functioning. Vocational monitoring can facilitate early implementation of preventive measures, such as work accommodations, disclosures, and timely retraining for more suitable job responsibilities.

The routine use of the Symbol Digit Modalities Test provides the means to study changes in cognition that occur with acute disease activity (ie, relapse). Decline on this test indicates a clinically meaningful worsening of cognitive function or specifically slowed cognitive processing.[60,65–67] The test is recommended as the minimum bedside cognitive screening assessment tool in people with multiple sclerosis every 2–3 years.[68] Use of the Symbol Digit Modalities Test in clinical settings and applying the findings to the EDSS has been shown to improve the accuracy of the EDSS score when monitoring disability or changes during relapses.[69]

Most phase 3 trials on DMTs in people with multiple sclerosis evaluate relapses and progression of physical disability as the primary outcomes, although cognitive testing is often included as a secondary or exploratory outcome. A systematic review published in 2020 examined the effects of DMTs on processing speed, concluding a small beneficial effect.[70] However, the Canadian 2020 Treatment Optimization in Multiple Sclerosis

recommendations state that there is insufficient evidence to support switching DMTs to improve cognition.[56]

Causes

Similar to other inflammatory diseases, a definite cause of multiple sclerosis is uncertain but epidemiological and association studies indicate that an interplay between environmental and lifestyle factors (eg, smoking, body mass, nutrition, sunlight, and vitamin D) and susceptibility genes influence pathological processes that could be triggered by viral infections, such as Epstein-Barr virus.[71,72]

Genetic factors

The interplay of complex genetic factors influence multiple sclerosis susceptibility.[73] The risk of multiple sclerosis within families increases with the percentage of genetic sharing, resulting in an age-adjusted risk in monozygotic twins of 20–30%. The heritability of multiple sclerosis involves polymorphisms in many genes and each of these variants contributes only a small part to the overall disease risk. Genome-wide association studies have identified more than 200 genetic risk variants associated with multiple sclerosis susceptibility,[74] most of which involve pathways of peripheral immune cells and resident microglia, with the strongest association with polymorphisms in *HLA* genes, in particular *HLA-DRB1*15:01*. Furthermore, the genomic map provides compelling evidence that multiple sclerosis is primarily a neuroinflammatory disease and not primarily a neurodegenerative disorder that is complicated by superimposed inflammatory events. Risk genes for multiple sclerosis do not overlap with those for multiple sclerosis progression or those of other neurodegenerative diseases.[75] Until now, most research effort has been put into disentangling genes associated with multiple sclerosis susceptibility; further efforts are being undertaken by the International Multiple Sclerosis Genetics Consortium to elucidate how heritable contributions affect individual phenotypes and prognosis. For example, a recent genome-wide association study showed that presence of rs10191329 in the DYSF-ZNF638 locus confers faster disease progression (shortening of the time to walking aid by 3·7 years) and is associated with greater cortical pathology.[76]

Environmental factors

A prospective, case-controlled analysis of active-duty US military personnel provided the strongest evidence to date for a potential causal link between Epstein-Barr virus infection and onset of multiple sclerosis.[72] Blood samples acquired at the start of military service and biennial follow-ups showed that all but one of the 35 cases of multiple sclerosis (97%) that were negative for Epstein-Barr virus at baseline seroconverted before the multiple sclerosis diagnosis. Epstein-Barr virus seroconversion resulted in a 32·4 times increased hazard ratio for multiple sclerosis diagnosis.[72] Mechanistically, another study showed that the Epstein-Barr virus transcription factor EBNA-1 has high-affinity molecular mimicry with the hepatic and glial cell adhesion molecule (glialCAM).[71] Post-hoc analyses of multiple cohorts of multiple sclerosis samples substantiated plasma reactivity against the particular epitopes of EBNA-1, glialCAM, and phosphorylated glialCAM.[72] However, it remains unknown whether the Epstein-Barr virus infection represents only a trigger of the disease or plays an important role in the ongoing multiple sclerosis pathogenesis.

Other important environmental and lifestyle risk factors linked with increased risk for multiple sclerosis include low ultraviolet radiation exposure, passive and active tobacco exposure, obesity in early adolescence, vitamin D insufficiency, and diet-related changes within the gut microbiome. Mendelian randomisation studies suggest that genetic traits related to high BMI are associated with higher multiple sclerosis risk than people with typical BMI, a finding that remains statistically significant after adjusting for vitamin D.[77] Some lifestyle risk factors, such as smoking, have also been related to faster disease progression and decreased DMT effectiveness.[78,79]

Pathophysiology

The adaptive immune system, consisting of T and B lymphocytes, is a key driver in the hypothesised multiple sclerosis pathogenesis, especially for the development of focal lesions and clinical relapses (figure 1). Different organs, such as the gut and possibly the lung, sense environmental signals and shape immune responses within lymphoid tissues. Distinct microbiota alterations were specifically linked to the development and progression of multiple sclerosis.[80–82] Moreover, growing evidence shows that immune cells survey CNS homoeostasis and regulate tissue responses from surrounding meningeal lymphatics and from a distinct immune cell reservoir of the skull bone marrow.[83,84]

The relapsing phenotype

Circumscribed inflammatory foci, the so-called multiple sclerosis lesions or plaques, develop around a central vein, disseminated throughout the CNS, in both the white matter and cortical and deep grey matter. Focal lesions are considered the manifestation of acute inflammatory damage in the CNS, with variable loss of myelin, oligodendrocytes, and axons. Active and chronic active plaques contain densely populated phagocytic cells, pronounced at the edge of the demyelination.[85] By contrast, chronic inactive plaques are sharply circumscribed hypocellular lesions without relevant active myelin degradation. Chronic inactive plaques contain fewer myelin-forming oligodendrocytes than active or chronic active plaques but are characterised by a marked gliosis reaction (ie, sclerosing), which gives the disease its name. Although new myelin sheaths can form

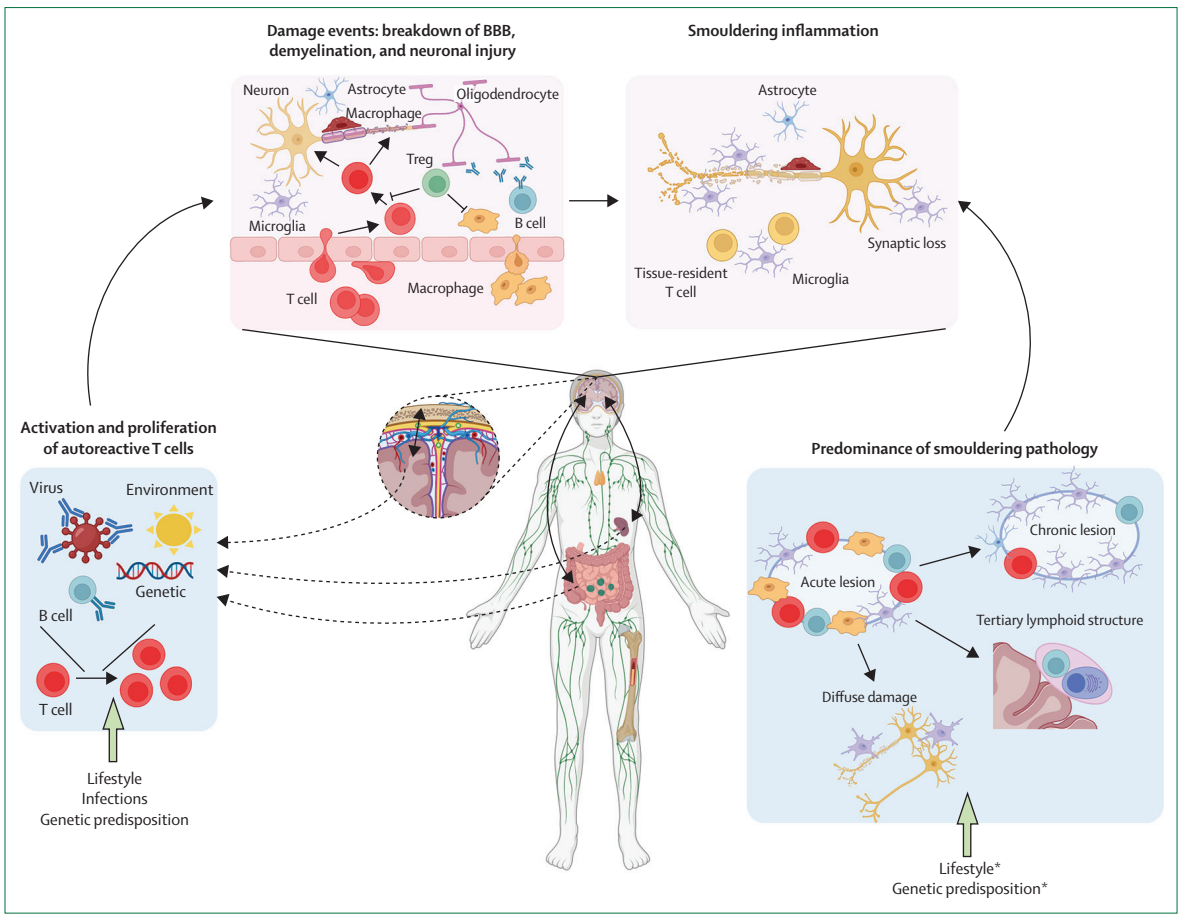

Figure 1: **Multiple sclerosis pathology**
Multiple sclerosis is a complex disease in which innate and adaptive immune cells reach the CNS via different routes, including the gut and meninges, and play a role in acute focal and chronic smouldering pathology that is present in both the relapsing and progressive course of the disease. Lifestyle factors, such as nutrition, environmental factors, infections, and genetics, influence both initiation and progression of the disease. BBB=blood–brain barrier. *The exact mechanisms by which lifestyle and genetic predispositions influence the acute and smoldering pathology still remain unknown. Figure created with BioRender.com.

in lesions that are called shadow plaques, the functional capacity of remyelinated axons might remain incomplete.[86] Pathological processes in multiple sclerosis affect the entire CNS tissue, with the macroscopically visible foci being merely the most apparent histopathological feature. Myelin injury or loss in multiple sclerosis has been mainly linked to atypical macrophage or antibody and complement activation, as well as direct injury of oligodendrocytes through immune-mediated apoptosis.[87] Moreover, axonal damage is detectable at early disease stages and is not limited to focal lesions. Even in white matter that appears normal morphologically and by MRI, numerous axons are damaged in many people with multiple sclerosis.[88] Furthermore, diffuse changes within the cortical neurons are present, with both local oxidative injury and distant retrograde degeneration contributing to the injury.[89,90]

During a multiple sclerosis relapse, pathological activation of autoreactive lymphocytes directed against endogenous CNS components leads to clonal expansion of these cells. Activated immune cells can cross the CNS blood–brain barrier and migrate into the parenchyma. Locally within the CNS, T cells are reactivated by renewed antigen presentation and initiate an inflammatory cascade, recruiting further immune cells. This chain reaction leads to focal oedema, destruction of myelin and oligodendrocytes, and damage to neuronal and axonal structures. Clinically, the occurrence of demyelinating lesions within an eloquent CNS area could lead to development of new focal neurological symptoms. So far, both the nature of the (initial) autoantigen and how autoreactive T cells are activated are unclear.

T lymphocytes play a central role in multiple sclerosis pathology: inflammatory lesions contain considerable numbers of both $CD4^+$ and $CD8^+$ T cells;[91] the largest group of genes from genome-wide susceptibility screens is involved either in T-cell pathways themselves or in antigen presentation to T cells;[74] in experimental autoimmune encephalomyelitis models, adoptive transfer of both Th1-polarised and Th17-polarised CNS

autoantigen-specific cells can transfer disease to recipient animals;[92,93] and several immunomodulatory treatments interfere with T-cell activation, proliferation, or migration. T-cell pathology in multiple sclerosis can best be described as a shift of the immune network towards an autoimmune state[94] with peripheral imbalance of proinflammatory Th1 and Th17 cells and functionally impaired regulatory T cells and $CD8^+$ T-cell response. Within the CNS, T cells can either initiate an inflammatory cascade, attracting further leukocytes, or directly interact with resident cells, resulting in direct T-cell mediated damage of oligodendrocytes and neurons.

B cells also play a key role in multiple sclerosis pathology, as shown, for example, by the hallmark presence of intrathecal IgG synthesis (ie, oligoclonal bands), the clinical response of people with multiple sclerosis to B-cell-targeting therapies, the presence of tertiary lymphoid structures containing B cells and T cells and a reservoir of B cells in the skull bone marrow[95] linking meningeal inflammation to cortical damage,[96] the ability of B cells to act as potent antigen-presenting cells towards T cells,[97] and the proinflammatory role of B-cell-derived cytokine production on immune networks.[98] Although the tertiary lymphoid structures can be seen within acute and early multiple sclerosis,[99] their greater prevalence is commonly associated with progressive multiple sclerosis phenotypes and linked to higher tissue injury than in people without such lymphoid structures.[100]

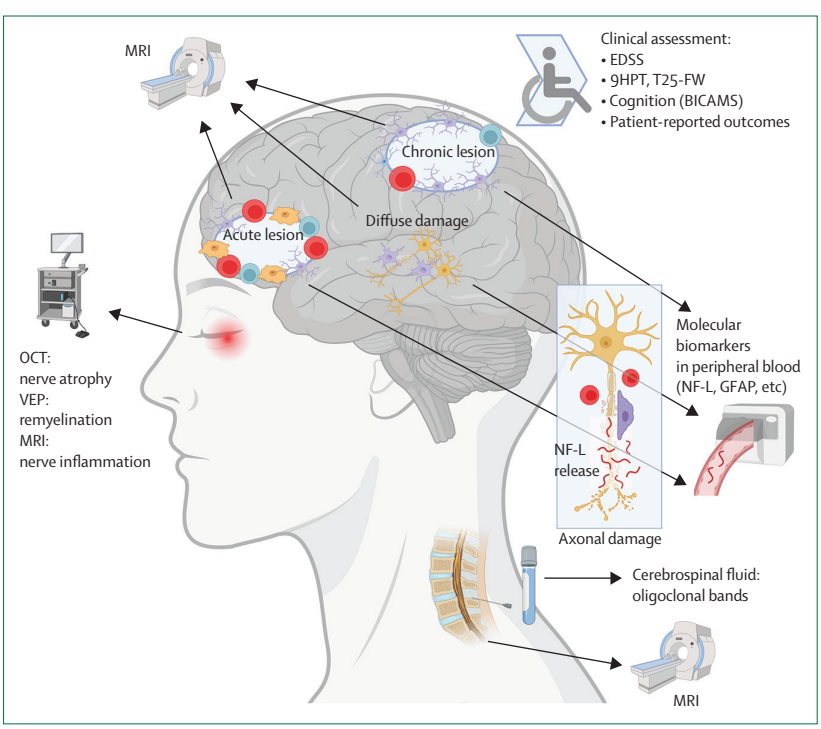

Figure 2: **Biomarkers in multiple sclerosis**
Pathological processes in multiple sclerosis can be assessed and quantified by different paraclinical biomarkers, including brain and spinal cord MRI, OCT, analysis of cerebrospinal fluid, and peripheral blood (via single molecule array). BICAMS=Brief International Cognitive Assessment for Multiple Sclerosis. EDSS=Expanded Disability Status Scale. OCT=optical coherence tomography. T25-FW=timed 25-foot walk. VEP=visual evoked potentials. 9HPT=nine-hole peg test. Figure created with BioRender.com.

From relapsing to smouldering inflammation

Apart from focal relapses, the second pillar of the hypothesised multiple sclerosis pathogenesis is the development of a chronically sustained CNS pathology, leading to compartmentalised CNS inflammation, neuronal network dysfunction, insufficient repair mechanisms, and chronic neurodegeneration (figure 1). Smouldering inflammation is an umbrella term summarising the non-relapsing biological and clinical aspects of multiple sclerosis. This progressive component determines the long-term outcome of people with multiple sclerosis and is insufficiently targeted by currently approved therapies.

Microglia residing in the CNS are highly plastic surveillants of brain parenchyma integrity, rapidly reacting to potential threats by encapsulation of dangerous foci[101] or by clearing toxic factors. However, microglia might have a pathological role in multiple sclerosis via increased phagocytosis and demyelination;[102] initiating neuronal inflammation and injury; overactive synaptic pruning, potentially associated with cognitive dysfunction;[103] and driving smouldering inflammation in the edge of chronically active multiple sclerosis lesions. In the context of CNS autoimmunity, myeloid cells constitute an ontogenically heterogeneous, plastic population that includes microglia, infiltrating bone marrow-derived cells (eg, macrophages), and different populations of border-associated macrophages. Knowledge of the differential contribution of these myeloid cells in CNS pathology is rapidly evolving.[104] Infiltrating immune cells are further able to recruit astrocytes, which can be shifted into a disease-promoting state via GM-CSF pathways[105] and might be involved in maintaining chronic CNS inflammation.[106,107]

Overall, CNS inflammation driven by innate immune cells, astrocytes, and compartmentalised, tissue-resident T cells and B cells[108] creates a tissue microenvironment inhibiting remyelination and promoting neuronal damage.[109] Additional pathways involved in acute inflammation, as well as chronic neuronal and axonal injury, include oxidative stress, glutamate excitotoxicity, high intracellular calcium concentrations, ion channel disturbances, and mitochondrial dysfunction. As these pathways are closely linked and act synergistically, neuroprotective strategies targeting multiple pathways simultaneously might be necessary.

Diagnostic and prognostic biomarkers

MRI

Imaging measures remain a key clinical tool for the diagnosis and monitoring of people with multiple sclerosis

and are an essential component of the continuously updated multiple sclerosis diagnostic criteria (table 1; figure 2). However, improper application of MRI diagnostic criteria could contribute to misdiagnosis.[110] In the past decade, advancement in MRI technology has allowed typical characteristics of multiple sclerosis lesions to be better defined. In particular, use of double inversion recovery and phase-sensitive inversion recovery helped increase recognition of cortical lesions, which have been added to the multiple sclerosis diagnostic criteria.[26]

Most brain-based MRI measures currently used in clinical settings show unreliable performance in predicting long-term disease progression and conversion to progressive multiple sclerosis.[111] More sophisticated imaging techniques discussed hereafter could facilitate the identification of imaging biomarkers that would better predict disease progression, at a tissue-specific level in the brains and spinal cords of people with multiple sclerosis.

Lesion-based biomarkers of disease progression

MRI measures, which typically capture lesion burden in the white matter, are used in routine clinical practice for diagnosis and monitoring of people with multiple sclerosis (figure 3 and panel). Apart from clinical measures of T2 and T1 lesion volume and accrual of new, or newly enlarging, T2 lesions, the remaining MRI-based measures mentioned hereafter are mainly ascertained within research protocols and remain experimental in nature.

Cortical lesions have a substantial impact on disease progression and correlate with cortical and global brain atrophy, clinical disability, and cognitive dysfunction.[112,113] Nevertheless, intracortical and subpial lesions are poorly detectable with widely used 1·5 T or 3 T MRI scanners, mostly due to their small size and low MRI contrast within the grey matter. The introduction of 7T MRI was instrumental in overcoming this issue, as it increases the specificity and sensitivity in detecting cortical pathology.[114]

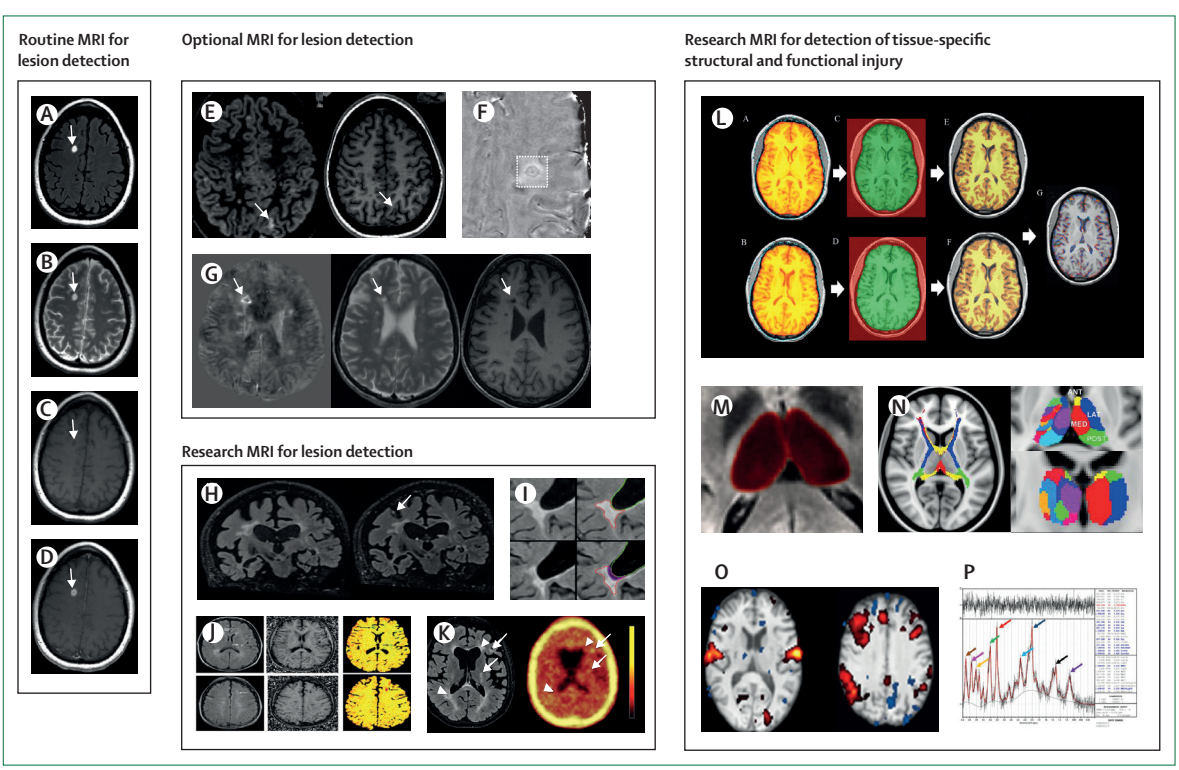

Figure 3: **Use of MRI in diagnosis and prognosis of multiple sclerosis**
Routine MRI for lesion detection shows a white matter lesion (indicated with an arrow) on a FLAIR (A), T2-weighted imaging (B), T1-weighted imaging without contrast (ie, black hole; C), and T1-weighted imaging with contrast (ie, enhancing lesion; D). Optional MRI for lesion detection shows a cortical lesion (arrow) on double inversion recovery (left) and on the inversion recovery 3D T1-weighted imaging (right; E), central vein sign on phase imaging (F), and paramagnetic rim lesion (arrow) on quantitative susceptibility mapping (left) and their corresponding correlates on T2-weighted imaging (middle) and T1-weighted imaging (right; G). Research MRI for lesion detection shows leptomeningeal enhancement (arrow) on 3D FLAIR after 10 min delay of gadolinium injection, pre-contrast (left) and post-contrast (right; H), atrophied lesion volume showing shrinkage (magenta area) of the lesional tissue in the cerebrospinal fluid over 5 years (I), use of magnetisation transfer imaging to detect remyelinating lesions (green spots) and demyelinating lesions (red spots; J), and PET with TSPO [^{18}F]-peripheral-type benzodiazepine receptor 06 for detection of microglia activation (arrows) on the right and corresponding FLAIR image on the left (K). Research MRI for detection of tissue-specific structural and functional injury shows segmentation of 3D T1- weighted imaging to obtain measure of whole brain atrophy (L), segmentation of thalamus with artificial intelligence on FLAIR image (M), use of diffusion-tensor tractography to segment thalamus into its subnuclei (N), functional MRI to detect known sensory-motor, frontoparietal, and default mode networks (O), and magnetic resonance spectroscopy output with point resolved spectroscopy sequence on a 3-T scanner to detect relevant metabolic peaks (P). FLAIR= fluid-attenuated inverse recovery. 3D=three dimensional.

***Panel*: Consensus on the use of MRI for multiple sclerosis diagnosis, prognosis, and treatment monitoring**

MRI protocol for multiple sclerosis diagnosis

- Three recommended brain sequences, with an emphasis on sagittal three-dimensional (3D) fluid-attenuated inverse recovery (FLAIR) as a core sequence that should be acquired in tandem with an axial T2-weighted imaging (turbo or fast spin echo) sequence and an axial T1-weighted sequence acquired after contrast administration
- Three recommended spinal cord sequences; at least two of sagittal T2-weighted sequences (turbo or fast spin echo), proton density-weighted sequences (turbo or fast spin echo), or short T1 inversion-recovery sequences and Sagittal T1-weighted sequences (turbo or fast spin echo) after contrast
- Optional MRI for lesion detection:
  - Detection of cortical lesions (double inversion recovery or phase-sensitive inversion recovery)
  - Susceptibility-based imaging for assessment of central vein sign and chronically active lesions (ie, paramagnetic rim lesions)
  - Diffusion-weighted imaging
  - Axial and coronal fat-suppressed T2-weighted imaging of the optic nerve
  - High-resolution T1-weighted sequences for quantitative assessment of brain volume

MRI protocol for assessment of disease activity and monitoring effectiveness of disease-modifying therapy

- Two core axial and one sagittal FLAIR (ideally 3D FLAIR) and T2-weighed sequences (fast or turbo spin echo), with all remaining sequences being optional or not required

MRI protocol for safety monitoring during disease-modifying therapy use

- Core FLAIR and T2-weighted sequences and diffusion-weighted imaging
- All remaining sequences are listed as optional or not required

The assessment of cortical lesions on double inversion recovery and phase-sensitive inversion recovery images generated by artificial intelligence and obtained in clinical routine practice[115] and the use of prospective time-efficient (5–7 min) synthetic MRI sequences[116] could maximise the ability to synthesise new contrasts from acquired data.

The assessment of chronic active lesions by MRI has also garnered attention and might represent the imaging correlate of smouldering inflammation.[106,117] Chronic active lesions can be detected as slowly expanding lesions by conventional T2-weighted and T1-weighted image sequences with serial MRI,[118] or as paramagnetic rim lesions with gradient-echo-based or T2* echo-planar imaging sequences. The paramagnetic rim lesions are usually detected on susceptibility-based MRI sequences, such as phase-imaging, susceptibility-weighted imaging, and quantitative susceptibility mapping, which are highly sensitive to accumulation of iron. Slowly expanding lesions reflect an ongoing chronic inflammation and are strongly associated with disability progression and conversion to progressive multiple sclerosis.[106,119] A correlative histopathological study showed that chronic active lesion edges have a significantly greater number of iron-loaded, activated immune cells with specific "microglia inflamed in MS [multiple sclerosis]" clusters than normal white matter, which could represent substrate for the MRI contrast and act as a driver of the paramagnetic rims seen on susceptibility-based MRI sequences.[106]

Leptomeningeal inflammation is typically characterised by presence of B-cell infiltrates in the meninges or as tertiary lymphoid-like structures.[120] Leptomeningeal contrast enhancement probably reflects the presence of focal leptomeningeal inflammation, based on available histological data,[121] and is associated with cortical atrophy and worse clinical outcomes.[122,123] Atrophied lesion volume is a promising imaging marker, which represents white matter lesion volume subsumed into the cerebrospinal fluid over time. This new lesion-based neurodegenerative MRI biomarker showed stronger association with clinical disability than new or enlarging lesions and brain atrophy and had a greater ability to predict conversion to progressive multiple sclerosis than T2 lesions and brain atrophy.[124]

MRI for detection of tissue-specific structural and functional injury

Non-conventional MRI methods used for detection of tissue-specific structural and functional injury have the ability to uncover widespread tissue damage in people with multiple sclerosis, which can be present throughout the normal-appearing white matter and grey matter (figure 3). Lesion-induced and neurodegenerative processes in multiple sclerosis that are measured as whole brain, cortical, and thalamic atrophy are closely associated with physical disability and cognitive impairment.[125] Although development of new advanced MRI post-processing techniques and use of artificial intelligence[126] are rapidly enabling automatic quantification of brain atrophy in clinical routine practice, numerous technical limitations and natural physiological fluctuations in brain volume currently restrict reliable assessment of brain atrophy rates on an individual level.

Additional non-conventional MRI techniques (eg, magnetisation transfer imaging, myelin water fraction, diffusion-tensor imaging, magnetic resonance spectroscopy, quantitative susceptibility mapping, functional MRI, and arterial spin labelling) are used to detect and predict structural and functional correlates of tissue-specific injury in multiple sclerosis.[111] Myelin-based imaging and synthetic T1 or T2 relaxometry are increasingly being adopted as exploratory outcomes, but the routine clinical use of these sequences is scarce.[127]

Although most of the newly developed sequences focus on visualising the pathological mechanisms affecting the brain, the presence and extent of spinal cord damage is of particular relevance in multiple sclerosis. Both spinal cord lesions and atrophy are shown to be highly predictive of subsequent disease progression.[128]

PET

PET imaging continues to gain traction in the field of multiple sclerosis, especially with the development of radiotracers capable of visualising pathological processes, including myelination status, infiltrating leukocytes, and microglia activation.[86,129] Furthermore, microglia activation can be detected using tracers that bind to translocator protein (TSPO). Increased TSPO binding in cortical and subcortical grey matter, normal-appearing white matter, and lesional and perilesional white matter has been reported in various studies and has been linked with progressive multiple sclerosis, worsening brain atrophy, and longer disease duration.[129] However, the routine clinical use of PET imaging in multiple sclerosis is hampered by multiple logistical and safety concerns.

Optical coherence tomography and evoked potentials

The thickness of several retinal layers, such as the retinal nerve fibre layer and ganglion cell and inner plexiform layers, measured by optical coherence tomography, have been correlated with brain atrophy and disease progression.[130,131] Outcomes based on optical coherence tomography and visual evoked potentials are increasingly used as exploratory endpoints in remyelinating and progressive multiple sclerosis studies. For example, a double-blind, randomised, placebo-controlled study of clemastine fumarate (ReBUILD trial)[132] showed a statistically significant reduction in visual evoked potentials latency as a measure of repair and remyelination.

Fluid-based biomarkers

In addition to imaging techniques, current research efforts are geared towards developing and validating multiple cerebrospinal fluid and blood-based biomarkers for routine diagnostics and prognostics.[133] The most promising is NF-L, a neuroaxonal cytoskeletal protein and indicator of neuronal injury.[134] Although early studies measured NF-L concentrations in the cerebrospinal fluid, the invasiveness of repeated acquisition restricted its use.[134] Development of highly sensitive fourth-generation neurofilament assays has allowed reliable quantification of picomolar NF-L concentrations in the blood.[134] In people with multiple sclerosis, serum NF-L concentrations increase with clinical and radiological activity, are predictive of future neurodegenerative changes and disability worsening, and can be responsive to treatment effects.[135,136] Therefore, group-based comparisons of serum NF-L levels are now incorporated in most clinical trials as an exploratory outcome.[137] The use of serum NF-L at the individual level is infrequent due to high interindividual variability and low specificity.[138] Development of adjusted percentile-based cutoffs and Z scores are proposed for the routine clinical monitoring of people with multiple sclerosis and their treatment response.[139] Biomarkers such as GFAP, CHI3L1 (a measure of astrocytic response), and molecular markers based on the Epstein-Barr virus could have additional value in predicting disease progression.[140,141]

Overall, new developments in imaging and fluid biomarkers have not yet arrived in clinical practice and therefore present a tremendous mission for the community of multiple sclerosis researchers.

Treatment

A vast body of evidence provides general consensus recommending initiation of a DMT in people with confirmed relapsing multiple sclerosis and people with clinically isolated syndrome at high risk of developing multiple sclerosis. Most DMTs have primarily anti-inflammatory effects, showing a decrease in clinical relapse rate, MRI-based activity, and short-term disability worsening when administered during the relapsing phase of the disease (clinically isolated syndrome, relapsing–remitting multiple sclerosis, and active secondary progressive multiple sclerosis). Only one drug, ocrelizumab, is approved for primary progressive multiple sclerosis with a demonstrated decrease in disability progression.[142] The complete list of currently approved DMTs, their mechanism of action, relative effectiveness, and main safety characteristics are shown in table 3. Although few DMTs are approved for treatment of paediatric-onset multiple sclerosis (eg, fingolimod and teriflunomide), observational studies suggest most DMTs approved for adults have equivalent effectiveness and tolerability in children.[143–145] Apart from a few active comparator trials, direct comparison of different DMTs is limited to data derived from independent real-world observational studies, registries, and meta-analyses.[146,147]

Multiple recommendations and practice guidelines regarding the use of DMTs in people with multiple sclerosis have been developed by major neurological associations, including the American Academy of Neurology,[148] the European Committee for Treatment and Research in Multiple Sclerosis and European Medicines Agency,[149] and the UK-based National Institute for Health and Care Excellence.[150] The recommendations are commonly derived through deductive inferences, generally accepted principles of care, systematic literature reviews, and strong evidence from other similar conditions. However, the applicability of each treatment recommendation will depend on drug availability and the insurance policies and health-care systems in different countries. Therefore, it is important to develop and implement local expert recommendations for use of DMT and management of adverse events in clinical practice.

Clinical trials and multiple long-term observational studies showed that DMT initiation at the time of the first demyelinating clinical event suggestive of multiple

	Medication name, route, and schedule of administration	Year of regulatory approval	Mechanism of action	Relative reduction in relapses or disease progression	Main adverse events
Injection-based medications (based on year of approval)					
Interferon beta-1b	Betaferon and Extavia (0·25 mg subcutaneous injection every other day)	1993 (Betaferon) and 2009 (Extavia)	Interferon beta reduces antigen presentation and T-cell proliferation; it alters cytokine and MMP expression and restores suppressor function	ARR: 31% *vs* placebo, CDW: no effect	Injection-site reactions, influenza-like symptoms, depression, increased liver enzymes, and rare liver toxicity; low efficacy due to binding and neutralising antibodies
Interferon beta-1a	Avonex (30 mg intramuscular injection once a week) and Rebif (44 mg subcutaneous injection 3 times a week)	1997 (Avonex) and 1998 (Rebif)	Interferon beta reduces antigen presentation and T-cell proliferation; it alters cytokine and MMP expression and restores suppressor function.	Avonex—ARR: 32% *vs* placebo, CDW: 37% *vs* placebo; Rebif—ARR: 33% *vs* placebo, CDW: 38% *vs* placebo	Injection-site reactions, influenza-like symptoms, depression, increased liver enzymes, and rare liver toxicity; low efficacy due to binding and neutralising antibodies
Peg-interferon beta-1a	Plegridy (subcutaneous or intramuscular 125 µg injection once every two weeks)	2014 (subcutaneous) and 2021 (intramuscular)	Peg-interferon beta-1a is distinguished from other formulations by the addition of a PEG chain to the Interferon beta-1a molecule	ARR: 36% *vs* placebo, CDW: 38% *vs* placebo	Injection-site reactions, influenza-like symptoms, depression, increased liver enzymes, and rare liver toxicity; low efficacy due to binding and neutralising antibodies
Glatiramer acetate	Copaxone and generic equivalent medications (subcutaneous injection every day for 20 mg preparation and 3 times a week for 40 mg preparation)	1996 (Copaxone 20 mg) and 2014 (Copaxone 40 mg)	Glatiramer acetate shifts the immune response from a proinflammatory state, with Th1 T cells, to regulatory, non-inflammatory Th2 T cells; switches from proinflammatory cytokine release of IL-2 and IL-12 to anti-inflammatory cytokines such as IL-1, IL-4, and IL-10	ARR: 29% *vs* placebo, CDW: not investigated	Injection-site reactions and immediate post-injection general reaction, rare fat atrophy or necrosis, and elevated liver enzymes
Ofatumamab	Kesimpta (subcutaneous 20 mg injection once a month)	2020	Fully human anti-CD20 antibody that binds the receptor located on the pre-B and mature B lymphocytes, resulting in antibody-dependent cellular cytolysis and complement-mediated lysis	ARR: 50% *vs* teriflunomide, CDW: 46% *vs* teriflunomide	Injection-site reactions, lymphopenia, and increased risk of infections (upper respiratory tract, urinary tract, and herpes infection)
Oral medications (based on year of approval)					
Fingolimod	Gilenya (oral 0·5 mg capsule once daily)	2010	Activates lymphocyte S1P receptor via high-affinity receptor binding and induces S1P down-regulation that prevents lymphocyte egress from lymphoid tissues	ARR: 54% *vs* placebo, CDW: 30% *vs* placebo	Lymphopenia, increased risk of infections, bradyarrhythmia and heart block, macular oedema, and liver dysfunction
Teriflunomide	Aubagio (oral 14 mg tablet once daily)	2012	Selectively and reversibly inhibits dihydro-orotate dehydrogenase, a key mitochondrial enzyme in the de novo pyrimidine synthesis pathway, leading to a reduction in proliferation of activated T and B lymphocytes	ARR: 35% *vs* placebo, CDW: 26% *vs* placebo	Hair loss, nausea, skin rash, peripheral neuropathy, elevated liver enzymes, and teratogenic effects
Dimethyl fumarate	Tecfidera (oral 240 mg capsule twice daily)	2013	Affects both Nrf-2-dependent and independent pathways, resulting in an anti-inflammatory immune response	ARR: 53% or 44% *vs* placebo, CDW: 38% or 21% *vs* placebo*	Gastrointestinal adverse effects, flushing, lymphopenia and increased risk of infections, elevated liver enzymes, and rare PML
Cladribine	4 doses of 4–10 (bodyweight-dependent) tablets of 10 mg Mavenclad, administered in week 1, week 3, week 46, and week 48	2019	Increases the expression of DCK, leading to lymphocyte apoptosis; it disrupts intracellular processes, inhibiting DNA synthesis and repair, ribonucleotide enzymes, and alternating endonuclease activity	ARR: 58% *vs* placebo, CDW: 33% *vs* placebo	Increased risk of infection due to lymphopenia and leukopenia, teratogenic effects, and potential risk for malignancies
Siponimod†	Mayzent (oral 1 or 2 mg [based on *CYP2C9* genotype] tablet once daily)	2019	Highly selective $S1PR_1$ and $S1PR_5$ modulator, with both receptors (mainly $S1PR_1$) pivotal in pathways regulating lymphocyte egress from lymph nodes; $S1PR_1$ present on astrocytes might play a role in myelination and CNS repair	In secondary progressive multiple sclerosis: ARR: 55% *vs* placebo, CDW: 26 *vs* placebo	Lymphopenia and increased risk of infections, macular oedema, hypertension, cardiac conduction abnormalities, and risk of PML
Diroximel fumarate	Vumerity (oral 462 mg capsules twice daily)	2019	Anti-inflammatory immune response through targeting of the Nrf-2-dependent and independent pathways; better tolerated and less gastrointestinal adverse events than dimethyl fumarate	ARR: 79·5% *vs* baseline relapse rate, CDW: not available	Flushing, lymphopenia and increased risk of infections, elevated liver enzymes, rare PML, and lower rate of gastrointestinal adverse events than dimethyl fumarate

(Table 3 continues on next page)

	Medication name, route, and schedule of administration	Year of regulatory approval	Mechanism of action	Relative reduction in relapses or disease progression	Main adverse events
(Continued from previous page)					
Monomethyl fumarate	Bafiertam (oral 95 mg capsules twice daily)	2020	Affects both Nrf-2-dependent and independent pathways, resulting in an anti-inflammatory immune response; metabolised version of dimethyl fumarate and active metabolite	Approval based on bioequivalence with dimethyl fumarate data	Gastrointestinal adverse events, flushing, lymphopenia and increased risk of infections, and elevated liver enzymes
Ozanimod	Zeposia (oral 0·92 mg tablet once daily)	2020	Highly selective $S1PR_1$ and $S1PR_5$ modulator, with both receptors (mainly $S1PR_1$) pivotal in pathways regulating lymphocyte egress from lymph nodes; $S1PR_1$ present on astrocytes may play a role in myelination and CNS repair	ARR: 38% *vs* interferon beta-1a intramuscularly, CDW: 5% *vs* interferon beta-1a (ns)	Lymphopenia and increased risk of infections, macular oedema, hypertension, cardiac conduction abnormalities, and risk of PML
Ponesimod	Ponvory (oral 20 mg tablet once daily)	2021	Selectively binds only $S1PR_1$ present on lymphocytes resulting with $S1PR_1$ internalisation and degradation; sequestration of lymphocytes in lymph nodes that prevents egress of lymphocytes into the circulation and CNS	ARR: 30·5% *vs* teriflunomide, CDW: 17% *vs* teriflunomide (ns)	Lymphopenia and increased risk of infections, macular oedema, hypertension, cardiac conduction abnormalities, and risk of PML
Intravenous medications (based on year of approval)					
Mitoxantrone‡	Novantrone (intravenous 12 mg/m² infusion once every three months)	2000	Suppression of T cells, B cells, and macrophages proliferation; impairs antigen presentation and decreases the secretion of proinflammatory cytokines; enhances T-cell suppressor function and inhibits macrophage-mediated myelin degradation	ARR: 66% *vs* placebo; significant decrease in EDSS increase *vs* placebo	Neutropenia and leukopenia with increased risk of infections, hair loss, nausea, cardiotoxicity, risk of leukaemia, and infertility
Natalizumab	Tysabri (intravenous 300 mg infusion once a month)	2004	Anti-ITGA4 antibody that blocks binding of leukocytes on endothelial side of the blood–brain barrier, which prevents trans-endothelial migration into the CNS	ARR: 67% *vs* placebo; CDW: 42% *vs* placebo	Highest PML risk among DMTs, elevated liver enzymes, and secondary antibody-mediated autoimmunity
Alemtuzumab	Lemtrada (5 per day 12 mg intravenous infusions in year 1 and 3 per day 12 mg intravenous infusions in year 2; if needed, additional courses of 3 per day 12mg intravenous infusions after >1 year from the second dose)	2007	An anti-CD52 humanised monoclonal antibody resulting in depletion of CD52-bearing B and T cells; repletion of the lymphocytes results in restoration of tolerogenic immune networks	ARR: 49% *vs* interferon beta-1a; CDW: 42% *vs* interferon beta-1a	Cardiovascular diseases (ie, aortic dissection, myocardial infarction, and pulmonary haemorrhage), secondary autoimmunity (ie, autoimmune thyroid disease, immune thrombocytopenic purpura, and anti-GBM disease), and increased risk of infections
Ocrelizumab	Ocrevus (intravenous 600 mg infusion once every 6 months)	2017	An anti-CD20 antibody that depletes circulating immature and mature B cells; spares CD20-negative plasma cells; complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity	ARR: 46% *vs* interferon beta-1a; CDW: 40% *vs* interferon beta-1a	Lymphopenia and decrease in IgG and IgM concentrations leading to increased infection risk (upper respiratory tract, urinary tract, and herpes infections)
Ublituximab	Briumvi (intravenous 450mg infusion once every 6 months)	2022	An anti-CD20 antibody that depletes circulating immature and mature B cells; spares CD20-negative plasma cells; complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (25–30 times greater potential of other anti-CD20 antibodies)	ARR: 59% (ULTIMATE I) and 49% (ULTIMATE II) *vs* teriflunomide; CDW: 16% *vs* teriflunomide (ns)	Lymphopenia and decrease in IgG and IgM concentrations leading to increased infection risk (upper respiratory tract, urinary tract, and herpes infections)

Notably, the DMT daclizumab (Zinbyta) was withdrawn in 2018 due to safety concerns. Other off-label medications, such as rituximab, intravenous immunoglobulins, azathioprine, mycophenolic acid, and cyclophosphamide have been sparsely used. The ARR and CDW data were based on the published pivotal clinical trials and the European Medicines Agency data on DMT efficacy of DMTs. Anti-GBM=anti-glomerular basal membrane. ARR=annualised relapse rate. CDW=confirmed disability worsening. DMT=disease-modifying therapy. EDSS=expanded disability status scale.MMP=matrix metalloproteinase. ns=not significant. PEG=polyethylene glycol. PML=progressive multifocal leukoencephalopathy. *For both ARR and CDW, the first % is from the DEFINE trial and the second % is from the CONFIRM trial. †Approved on the basis of the EXPAND trial data that tested the safety and efficacy of siponimod in secondary progressive multiple sclerosis. ‡Mitoxantrone was tested in the MIMS trial regarding the safety and efficacy in progressive multiple sclerosis.

Table 3: **DMTs for multiple sclerosis**

sclerosis prolongs the time to the next relapse and decreases the 2-year conversion to relapsing–remitting multiple sclerosis by 40–45% compared with placebo.[149,151] The benefit of early DMT start in clinically isolated syndrome is further shown through long-term trial extensions in which patients who switched from placebo to active treatment remained more disabled at 5-year, 8-year, and 11-year follow-ups than patients who were on

active treatment from the start.[152,153] Guidelines generally recommend starting DMTs in all patients with clinically isolated syndrome (regardless of whether they satisfy the dissemination in space and time criteria); high-effectiveness therapy could be considered in patients with clinically isolated syndrome and presumed unfavourable prognosis (high MRI lesion burden, infratentorial pathology, or partial relapse recovery).[149,148] The entire spectrum of DMTs can be considered for treatment of people with relapsing–remitting multiple sclerosis, clinically isolated syndrome, and active secondary progressive multiple sclerosis; strong evidence suggests that use of DMTs reduces inflammatory activity and delays long-term disability progression. Medication should be chosen on a patient-by-patient basis, considering disease activity or severity, patient characteristics and comorbidities, and acceptable drug safety profile. Incorporating patient preferences regarding the mode of administration, education about the safety profile, and establishing realistic expectations leads to better DMT adherence. The DMT benefit in people with primary progressive and secondary progressive multiple sclerosis might be greater in younger patients than older patients and could reduce progression in some disability metrics, such as hand dexterity.[154]

Due to the paucity of clinical trial data, the decision to use high-effectiveness (eg, anti-CD20 monoclonal antibodies) versus lower-effectiveness (eg, interferon-beta products of glatiramer acetate) drugs as the initial DMT is challenging and should incorporate multiple risk–benefit considerations.[155] The escalation strategy uses first-line and moderate-effectiveness medications that provide disease control in the majority of people with multiple sclerosis. Breakthrough activity would necessitate escalating treatment with more potent medication. Although this strategy better manages the rare risk of adverse events that accompany high-potency DMTs, the threshold for escalation is not standardised and is highly variable among countries and providers.[156] Contrarily, an immediate use of high-effectiveness DMTs (anti-CD20 antibodies, natalizumab, alemtuzumab, and cladribine) shortly after the diagnosis, known as induction strategy, relies on achieving early and effective disease control and can be followed by de-escalation and maintenance with less potent immunomodulating drugs.[155] Post-hoc analyses of multiple relapsing–remitting multiple sclerosis trials and real-world data suggest greater benefit of high-effectiveness therapy in younger people with multiple sclerosis (age <40 years) than older people.[157–159] Currently, several ongoing trials are investigating the comparative efficacy of these two treatment strategies (NCT03535298 and NCT03500328). Another induction-based strategy is the use of near-complete immunoablation followed by autologous haematopoietic stem-cell transplantation that can halt any inflammatory activity without continuous use of a DMT.[160] Due to the greater safety risks associated with this intervention than other DMTs, it is typically reserved only for aggressive multiple sclerosis phenotypes with inflammatory activity that is not responsive to any other DMT. A study comparing the efficacy of autologous haematopoietic stem-cell transplantation versus high-potency DMTs is currently ongoing (NCT04047628).

Regardless of the initial approach, emergence of new inflammatory activity, adverse events, or poor adherence prompts providers to consider switching DMTs.[148,161,162] Treatment response should be assessed 3–6 months after DMT initiation, via new clinical relapses, disability progression, or MRI activity (presence of ≥2–3 new, or newly enlarging, T2 lesions) and followed by annual MRI examinations.[163] Such signs, indicating poor treatment effectiveness, justify switching from moderate-effectiveness to high-effectiveness DMT (a so-called vertical switch). Concerns regarding serious adverse events (eg, progressive multifocal leukoencephalopathy and malignancies), low drug tolerability, and injection fatigue could necessitate a switch to a DMT with similar effectiveness (a so-called horizontal switch). When switching DMTs, aspects such as wash-out period (regression of lymphopenia), carry-over progressive multifocal leukoencephalopathy risk, and rebound activity should be carefully considered.[164]

The use of immunosuppressive drugs in older people with multiple sclerosis, often with additional comorbidities, could increase the risk of serious adverse events. The little DMT efficacy in people with multiple sclerosis older than 50 years in randomised clinical trials[165] raised questions regarding the risk–benefit ratio in this population. Most observational studies suggest that DMT discontinuation is non-inferior to continuing therapy in preventing new relapses after the age of 50 years.[166] A 2-year prospective trial (NCT04754542) that investigated the discontinuation versus continuation of DMTs in people with multiple sclerosis after age 55 years with inactive disease did not show inferiority between the two groups. Since relapses and inflammatory activity are typically low in the older population, future discontinuation studies should investigate whether DMT discontinuation has any effect on long-term outcomes. A recent observational study indicates that people who were previously stable and ageing (aged ≥55 years) with multiple sclerosis who discontinue their DMT have new disability worsening.[167] Common factors associated with disease activation after DMT discontinuation include younger age, relapsing–remitting multiple sclerosis, MRI activity at the time of discontinuation, and shorter duration of previous clinical stability.[7,168]

The increased risk of adverse events and infections due to irreversible and long-term immunosuppression induced by the depletion of B cells has influenced the development of a new class of DMT, named Bruton's tyrosine kinas inhibitors (IBtk).[169,170] IBtk-based DMTs are small molecule medications that target and inhibit expression of the main signalling enzyme within the B-cell receptor,[170] achieving short-term and reversible B-cell silencing that has a

functionally similar immunosuppressive outcome to B-cell-depleting therapy.[169] IBtk has superior pharmacovigilance characteristics and greater CNS penetration than its antibody-based counterparts.[171] In phase 2 trials, evobrutinib, tolebrutinib, and fenebrutinib achieved statistically significant MRI activity reduction compared with placebo.[172,173]

In addition to the long-term preventive immunomodulatory therapies, the treatment of acute relapses commonly includes short-term corticosteroids (3–5 days of 1 g methylprednisolone by infusion or 5 days of 500 mg or 1250 mg oral prednisone) with no inferiority between options.[174,175] If resistant to corticosteroids, use of plasma exchange or immunoadsorption are also recommended.[148,176] Appropriate relapse treatment could promote accelerated and greater recovery that might influence the long-term disability outcomes.[177]

During the COVID-19 pandemic, people with multiple sclerosis on highly immunosuppressive therapies were particularly vulnerable to COVID-19 and at greater risk of unfavourable outcomes. Multiple nationwide studies showed that people with multiple sclerosis treated with anti-CD20 medications have two-times greater risk of severe COVID-19 outcomes (odds ratio 2·05; 95% CI 1·39–3·02).[178,179] Anti-CD20 and sphingosine-1-phosphate modulators also lower the benefit from SARS-CoV-2 vaccination and reduce seroconversion.[180] People with multiple sclerosis treated with these DMTs can still benefit from a mixed T-cell and B-cell vaccine response, additional booster doses, and passive COVID-19 prophylaxis (tixagevimab and cilgavimab).[181,182]

Comprehensive care and symptom management

The comprehensive care of people with multiple sclerosis should incorporate strategies for improving symptom management and general quality of life. A multidisciplinary team that consists of the neurology provider, radiologists, urologists, physiotherapists, pharmacists, nutritionists, psychologists, social workers, and primary care providers is crucial in achieving better outcomes. People with multiple sclerosis can benefit from strategic use of symptomatic therapy for spasticity, fatigue, paraesthesia, bladder and bowel dysfunction, sexual dysfunction, walking impairment, and mood control. However, a trial published in 2021 questioned the sustained benefit of some off-label fatigue-based interventions, with no superiority over placebo.[183] Multiple sclerosis outcomes can also be improved by better management of multiple comorbid diseases, such as hypertension, hyperlipidaemia, diabetes, and obesity—comorbidities linked to increased disease activity.[184,185] Therefore, proper nutrition, weight control, and management of lifestyle-based factors are increasingly emphasised as important modifiers that could not only lead to improved patient-reported outcomes but could also influence the disease process itself.[186] An increasing number of ongoing trials aim to investigate the effectiveness of controlled exercise regimens, specific diets, and aggressive management of comorbid diseases in people with multiple sclerosis.[187–189] Lastly, future efforts should aim at improving access to health care for underserved people with multiple sclerosis.[190]

Unmet needs and future directions

The therapeutic development in multiple sclerosis over the past years is a remarkable example of progress in medicine. The major challenge remains understanding and targeting the continuous neurodegeneration in people with multiple sclerosis. Fostering research efforts within this area with a faster clinical translation of novel interventions for CNS neuroprotection and repair will be integral to achieving this goal.

Currently approved DMTs are less effective in older people with multiple sclerosis, yet ageing also correlates with an increased risk of progressive disease. To this end, understanding immunosenescence and how it intertwines with CNS ageing could prompt therapy development. Several novel therapeutic trials are planned or currently under way, investigating strategies fostering neuroprotection or remyelination (or both). These include distinct mechanisms of action linked to remyelination, such as clemastine (NCT02521311) alone or in combination with metformin—which presumably is capable of inducing endogenous neural progenitor cells (NCT05131828 and NCT04121468), and neuroprotective strategies, such as lipoic acid through antioxidative activity (NCT03161028). Randomised trials completed in the past few years for progressive multiple sclerosis that showed neuroprotective favourable MRI outcomes (ie, ibudilast[191]) and clinical benefit on halting progression and improving neurological deficits (ie, masitinib[192]) await further substantiation. In general, although not yet achieved in classic neurodegenerative diseases, repair could ultimately be possible in chronic neuroinflammation.

Furthermore, novel therapeutic concepts based on long-standing research ideas are reflected in trials, such as the allogeneic Epstein-Barr virus T-cell approach that stems from a potential role of this viral infection in multiple sclerosis disease progression (NCT03283826) and preventive vaccine strategies (NCT05164094 and NCT04645147). Emerging evidence for the role of the gut microbiome resulted in a double-blinded, placebo-controlled study of allogeneic versus autologous faecal microbial transplantation (NCT04150549).

Lastly, greater use of protocols to detect cortical lesions and further validation of characteristic multiple sclerosis imaging biomarkers, such as central vein sign and paramagnetic rim lesions, could improve the specificity of the upcoming multiple sclerosis diagnostic criteria. An increase in the number of periventricular lesions needed for multiple sclerosis diagnosis in people older than 45 years with clinically isolated syndrome could aid the differential diagnosis from the prevalent small-vessel disease-derived MRI changes.

The continuous advances in basic immunology, neuroscience, and imaging or omics techniques combined with computational efforts that are driving the rapid ongoing scientific progress will eventually become amenable for use in clinical practice.

Contributors

All authors contributed to the conceptualisation, visualisation, writing, and editing of this manuscript and all authors agreed to the publication of this paper.

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