

National Consensus on Diagnosis and Treatment of Multiple Sclerosis

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Sofia, 15 March 2021

Initiative of Movement Disorders and Multiple Sclerosis Society:

Bulgarian Society of Neurology

National Consensus on Diagnosis and Treatment of Multiple Sclerosis

Today, March 15, 2021, we, the undersigned experts, have reached a consensus on the diagnosis and treatment of multiple sclerosis:

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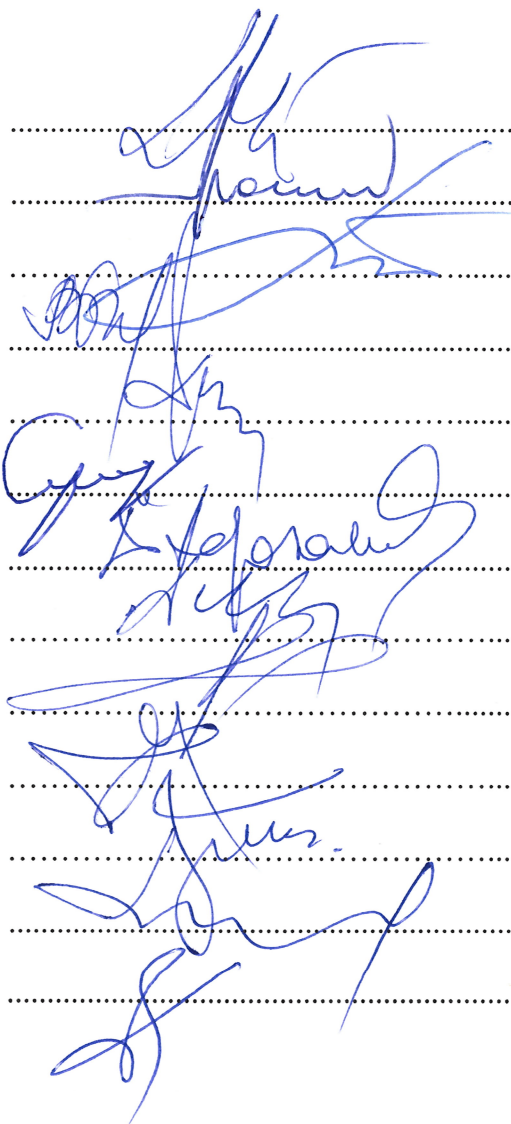
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The image shows a series of handwritten signatures in blue ink, each corresponding to one of the names listed on the left. The signatures are written over horizontal dotted lines. The signatures are stylized and vary in complexity, with some being more legible than others. The names listed are: Acad. Prof. Iv. Milanov, Acad. Prof. L. Traykov, Prof. Iv. Tournev, Prof. V. Bojinova, Prof. D. Maslarov, Prof. A. Kaprelyan, Prof. L. Haralanov, Prof. K. Genov, Prof. P. Atanasova, Assoc. Prof. S. Ivanova, Assoc. Prof. N. Topalov, Assoc. Prof. M. Danovska, and Assoc. Prof. D. Bogdanova.

Multiple sclerosis (MS) is an **autoimmune disease** with genetic predisposition, which in combination with environmental factors, triggers a cascade of immune responses and leads to disturbances of the blood-brain barrier. The result is an inflammatory demyelination of the white brain matter in the central nervous system (CNS), involving T- and B-lymphocytes, and macrophages. The transmission disturbances in CNS signals lead to clinical neurologic deficit.

The worldwide **incidence** and prevalence of MS varies with geographic and racial differences. The greatest incidence tends to be in Northern geographic regions and in subjects with Caucasian ancestry.

The prevalence of MS in Bulgaria is 44.5/100,000, and the incidence is 1.03/100,000 population, which means that nearly 3,600 people in Bulgaria suffer from MS and each year 80 new patients are diagnosed. The statistical data presented is from 1997 and differs from that in neighboring countries or high-risk Central European regions, where prevalence rate exceeds 100/100,000 population. The increase in prevalence and incidence is probably due to better and earlier detection and lower mortality. Assuming a two-fold increase in rates, the number of MS patients in Bulgaria is approximately **7,000** – with approximately **160** new diagnosed patients each year.

The disease affects primarily young people aged between 30-34 years. In 3-10% of MS cases, the onset occurs in childhood and adolescence. Women are affected approximately twice as often as men. MS is a chronic disease, with duration of 10 to 15 years (13 years on average) depending on the clinical course of the disease.

MS is classified into **3 clinical forms depending on the clinical course of the disease over time** (Appendix 1). The 2013 International MS Phenotype Group revisions further characterize the MS phenotypes, and differentiate between patients eligible for treatment with active inflammation (new relapses and/or new MRI activity) from those with declining and irreversible disability progression.

Relapsing-remitting MS (RRMS) is the most common course for the disease – in 85% of patients (**approximately 5,950 patients in Bulgaria**), and RRMS is characterized

by clearly defined attacks of neurologic dysfunction (relapses) followed by several weeks of slow recovery (partial or complete). Subsequent attacks (exacerbations) occur at irregular intervals of time. However, there is no apparent progression of the disease between relapses. This clinical pattern of the disease includes cases with relapses and cumulative damage due to incomplete recovery, although they are difficult to distinguish from secondary-progressive MS. For 62% of patients (**approximately 4,340 patients in Bulgaria**) the disability score according to Kurtzke Expanded Disability Status Scale (EDSS) is less than 5 points.

In *secondary-progressive MS* gradually accumulating irreversible disability with or without separate relapses, minor remissions and plateaus have been observed. 70% of patients with RRMS would transition into the secondary progressive form of MS (SPMS) within 6 to 10 years from the onset of the disease. Although the time for transition to secondary progressive MS might be longer, when the onset of the disease is in childhood or adolescence, significant disability may be accumulated, and the patient will be disabled about 10 years earlier compared to adult patients.

Primary progressive MS affects a relatively small number of patients (10%) (i.e. **about 700 patients in Bulgaria**). Approximately **16** are new diagnosed patients each year. It is characterized with a steady and slow decline in neurological symptoms and deficit from the beginning, without clearly defined relapses or remissions, although occasional plateaus and temporary minor improvement might be observed. Compared with the remitting-relapsing form PPMS is associated with early severe disability, a smaller number of lesions on MRI and prevalence of degeneration over inflammation. Immunogenic differences have been established, such as higher incidence of HLA-DR4 positive patients compared to RRMS patients.

Depending on the ***degree and rate of neurological decline***, MS is further subdivided into benign and malignant forms.

Diagnosis of *benign forms* is retrospective, when 15 years from disease onset the rate and severity of relapses and progressing neurological deficit are much milder compared to those in other patient groups. The benign form of the disease is characterized by mild disability and the patient remains relatively fully functional. However, disability associated with cognitive impairment, fatigue, depression, and pelvic floor disorders is often disregarded in such patients. A diagnosis of benign MS changes over time. Ten years after diagnosis 1/3 of patients have a benign MS phenotype, while their number decreases to only 1/5 after 20 years.

Malignant MS is observed in a small number of patients. The disease develops quickly with frequent relapses and continuous disability progression leading to quick severe neurological deficit (within months or several years).

The clinical course is characterized with occasional transient or progressive neurological decline (pyramidal symptoms, co-ordination and balance disturbances, sensory or pelvic floor disorders).

Disease onset is often manifested with vision disorders or eye movement abnormalities (in 49% of patients), followed by limb paresis or paresthesia (42%), coordination disturbances (23%), or pelvic floor disorders (10%). Symptoms may be isolated or may occur concomitantly (in 30-50% of

patients). Initial manifestations, such as vertigo, trigeminal neuralgia, paroxysmal symptoms, extrapyramidal motor dysfunction or dysarthria, are less common (5%).

Over the course of the disease, all patients develop vision disorders or eye movement abnormalities, paresis or paresthesia in the arms and legs (88%), coordination disturbances (82%), pelvic floor disorders (63%) or cognitive impairments (40%).

A relapse is diagnosed using certain criteria. Pseudo-relapse (periods of exacerbations), triggered by concomitant diseases, fever or infection should be excluded. The interval between relapses is defined as the time of onset of one relapse to the beginning of the next one.

Criteria for onset of a new relapse include:

- Appearance of a new neurological symptom
- Reappearance of an old neurological symptom
- Worsening of an existing symptom of > 0.5 point on the Kurtzke scale
- Duration > 24 hours
- Absence of fever or concomitant conditions
- A period of neurological stability or improvement for at least 30 days

The diagnosis is based on the 2017 revision of Thompson et al. to the McDonald Criteria (appendix 2). In the revisions well established criteria for dissemination of MRI lesions in both space and time approved by the European collaborative research network studying MRI in MS (MAGNIMS), are used (appendix 3). In the 2017 criteria, as well as the 2010 modifications, the number of lesions and investigated brain areas required to define dissemination in time and space are reduced to a minimum. Gadolinium enhancement of lesions is no longer required to define dissemination in space (DIS), since it is a marker of dissemination in time and not in space. The co-presence of asymptomatic gadolinium-enhanced and non-enhanced lesions at any time is a criterion to define DIT, without a need for MRI follow-up to demonstrate DIT. Obviously the two demyelinating lesions have not appeared during the same demyelinating event, and their concomitant presence is indicative of 2 or more events occurring at different time points. However, a sound differential diagnosis is required to prove that the contrast-enhanced lesion is not induced by competing conditions. A major challenge is to distinguish typical MS lesions from lesions found in other conditions.

In comparison to McDonald 2010 criteria, in 2017 revision, cortical lesions in addition to juxtacortical lesions can be used to fulfill MRI criteria for dissemination in space.

In patient with a typical clinically isolated syndrome, fulfilment of clinical or MRI criteria for dissemination in space, and no better explanation for the clinical presentation, demonstration of CSF oligoclonal bands (in the absence of atypical CSF findings) allows a diagnosis of multiple sclerosis to be made. This consensus recommendation allows the presence of CSF oligoclonal bands to substitute for the requirement of fulfilling dissemination in time in this situation.

2017 revision recommended including symptomatic and asymptomatic MRI lesions in the determination of dissemination in space and dissemination in time. (in comparison, in 2010 revision asymptomatic lesions have been excluded).

MRI lesions in the optic nerve in a patient presenting with optic neuritis could not be used currently in MS diagnosis (there is no confirmation from several studies in 2017 to increase the specificity of the diagnostic criteria if this anatomical compartment is included). MAGNIMS recommended not to include optic neuritis and 3 periventricular lesions as additional criteria in McDonald 2017 until additional longitudinal studies on large cohorts of MS patients with a precision MRI and serological protocols have been conducted. In McDonalds 2017 revision for some patients (e.g., individuals older than 50 years or those with vascular risk factors) it might be prudent for the clinician to seek a higher number of periventricular lesions, than to trust only lesion.

In 2017 revision by Thompson et al. to the McDonald criteria, the following considerations are included in order to avoid misdiagnosis of multiple sclerosis (MS):

The McDonald criteria were not developed to differentiate multiple sclerosis from other conditions but to identify multiple sclerosis or a high likelihood of the disease in patients with a typical clinically isolated syndrome once other diagnoses have been deemed unlikely, i.e. those criteria are not for differential diagnosis.

Integration of the history, examination, imaging, and laboratory evidence by a clinician with multiple sclerosis-related expertise remains fundamental in making a reliable diagnosis of multiple sclerosis or an alternative diagnosis.

In the absence of a clear typical clinically isolated syndrome, caution should be exercised in making the diagnosis of multiple sclerosis. The diagnosis should be confirmed by further clinical and radiological follow-up. In such cases, the expert neurologist should consider postponing initiation of long-term disease-modifying therapies, pending longer follow-up to accumulate additional evidence supporting the diagnosis.

Caution should be taken in accepting a historical event as an attack in the absence of contemporaneous or current objective evidence providing corroboration (clinical, neuroimaging, CSF).

The threshold for additional testing should be low, (including for spinal cord MRI or CSF examination) when clinical and brain MRI evidence supporting the diagnosis of multiple sclerosis are insufficient.

The diagnostic criteria for primary progressive multiple sclerosis in the 2017 revision remain almost the same. The diagnostic criteria for primary-progressive multiple sclerosis include presence of 1 year of disease progression (retrospectively or prospectively determined) and MRI criteria for DIS: presence of 2 out of 3 criteria – 1 T₂ lesion in at least 1 typical MS area (periventricular, cortical or juxtacortical, infratentorial); – 2 or more T₂ lesions in the spinal cord – positive CSF findings (oligoclonal bands and/or elevated IgG index). As in the main criteria cortical and juxtacortical lesions can be used in fulfilling MRI criteria for dissemination in space. Symptomatic and asymptomatic MRI lesions are allowed to be used in the determination of dissemination in space and dissemination in time.

The “multiple sclerosis”, “possible multiple sclerosis”, and “not multiple sclerosis” diagnostic categories are being used. Patients meeting all clinical criteria and no better explanation for the clinical presentation, will be diagnosed with multiple sclerosis. Failure to meet any of the MS diagnostic criteria, will result in a “possible MS” diagnosis. Where even part of the criteria is not met or another diagnosis arises during the evaluation that better explains the clinical presentation, the MS diagnosis will be ruled out.

The clinical diagnosis based on objective clinical evidence of two or more relapses can be most reliable, however brain MRI should be performed in all patients in whom the diagnosis of multiple sclerosis is being considered, unless MRI is not possible. In some cases, patient-reported historical events with symptoms and evolution characteristics for MS, but for which no objective neurological findings are documented, might be reasonable evidence of a prior demyelinating event. However, at least 1 relapse should be confirmed by objective neurological findings. Before a definitive diagnosis of MS can be made, at least 1 relapse should be corroborated by objective findings from neurological examination, visual evoked potential response (in patients reporting visual disturbance), or results from MRI exam consistent with demyelination in affected area of the CNS further to neurological symptoms, reported by the patient.

With the new criteria as well as with the previous one, in the majority of cases MS is diagnosed as early as the first clinical signs, and symptoms which in practice reduces the number of patients with clinically isolated syndrome.

Clinically isolated syndrome (CIS) is the first clinical event that is compatible with any possible future development of multiple sclerosis but it is isolated in time. CIS symptoms are more

pronounced when the three typical CNS regions are involved – the optic nerve, brainstem, and spinal cord. As in the past McDonald criteria, with the new one diagnostic criteria, MRI was formally included in the diagnostic process of patients presenting with CIS.

Radiologically isolated syndrome refers to the presence of MRI anomalies suggesting multiple sclerosis, but without clinical symptoms. The increasing usage of MRI in daily practice has led to incidental identification of nonspecific T₂ abnormalities, classified as “unidentified bright objects”. Some of these changes are highly suggestive of multiple sclerosis for their location (periventricular, corpus callosum) and morphology (ovoid, well defined, homogeneous). Patients with radiologically isolated syndrome are at high risk of deterioration of lesions on MRI within the following 3 years, and development of clinically isolated syndrome within 5 years. 80% of these patients progress to clinically definite multiple sclerosis. In 2017 revision of McDonald criteria there is a consensus in patients with radiologically isolated syndrome, to continue to require clinical manifestations to make the diagnosis of multiple sclerosis. However, the new criteria allow the use of historical radiological evidence for dissemination in space and dissemination in time in patients with radiologically isolated syndrome to support the diagnosis of multiple sclerosis, once a typical clinically isolated syndrome occurs.

In cases of complaints of limb weakness, loss of balance, visual disturbances due to retrobulbar neuritis, pelvic floor disorders or numbness in the limbs, in patients who are not diagnosed with multiple sclerosis or manifestation of new symptoms in already diagnosed patients, the general practitioner or the ophthalmologist or the neurologist should refer the patient without delay to neurologists, multiple sclerosis specialist at a University center for diagnosis and management of multiple sclerosis (UCDM-MS).

The neurologist should clarify the diagnosis using the 2017 revisions of McDonald diagnostic criteria by Thompson et al., administer relevant laboratory tests and consultations, and admit the patient to UCDM-MS. The neurologist should also define the course of multiple sclerosis, and the annual number and the severity of MS relapses.

Diagnostic methods aim at an early diagnosis and the use of modern treatment methods. Early diagnosis of MS can be often challenging because the first manifestations are typically non-specific, mild, and quickly resolving. Currently, there is no specific laboratory test. Many medical conditions are associated with multifocal brain lesions on MRI or relapsing-remitting clinical

symptoms in young age. 5% of these patients are misdiagnosed, meaning that 1 out of 20 patients does not actually has this disorder.

Laboratory diagnostic methods include:

1. Ophthalmologic examination: vision, fundus examination, perimetry. Temporal pallor of the optic disc is a typical symptom of preceding retrobulbar neuritis.

Optical coherence tomography (OCT) provides evidence for atrophy or swelling in specific retinal layers. In optic neuritis and ganglion cell damage, the axonal retrograde degeneration leads to thinning of the retinal nerve fiber layer. The examination of the optic nerve can be used for assessment of CNS neurodegeneration. Several studies have reported a correlation between retinal changes and MS activity.

2. Neurophysiological examinations: visual, brainstem auditory, motor action, and somatosensory evoked potentials. Evoked potentials tests are used in the search for “silent” CNS lesions. Evoked potentials which can reveal subclinical lesions in CNS regions, but without clinical symptoms of damage, are tested. The changes in evoked potentials are expressed in prolonged latency, changes in wave amplitude and configuration, as well as interhemispheric asymmetries. In MS patients evoked potential tests very often show prolonged latency of components due to demyelination, but the changes are not disease-specific. Except for visual evoked potentials, the other tests also show changes in conditions in which axonal degeneration occurs first and degradation of myelin is secondary.

The *visual evoked potentials* (VEP) test is of highest diagnostic value. It shows typical latency prolongation in the P100 wave with preserved wave configuration. In the presence of clinically established vision damages the test is not justified. When a patient has had a negative VEP test, and the next testing shows typical latency prolongation, this might be suggestive of a new lesion.

3. Neuroimaging investigations – magnetic resonance imaging (MRI) is a modality of choice. The techniques include axial and parasagittal T₁- and T₂-weighted imaging, serial imaging, gadolinium-DTPA enhanced imaging and FLAIR sequencing.

In *T₂-weighted imaging*, hyperintensities (bright spots) are observed in patients in both early (with prevailing inflammation) and late stages (prevailing tissue damage and gliosis) of MS.

The number of lesions on MRI at different time points is compared by “*disease burden*” measuring – the total area of T₂ lesions in mm².

In *T₁-weighted imaging*, hypointense lesions (also known as “black holes”) are detected, suggesting acute brain swelling or severe tissue damage. They correlate with the severity of clinical symptoms and are histopathologically consistent with a demyelination lesion with axonal damage

and reactive gliosis. Chronic T₁ hypointense lesions (black holes) are more specific for severe tissue damage compared to T₂-weighted imaging abnormalities.

FLAIR imaging (fluid-attenuated inversion recovery technique) enhances contrast ratio between cerebrospinal fluid and lesions. This method allows better distinction between ventricular fluid (dark) and periventricular T₂ lesions (bright) and increases contrast between lesions and CSF, especially contrast from cortical and juxtacortical lesions in the grey brain matter.

Gadolinium is a contrast agent, used to increase the sensitivity in T₁-weighted imaging. Contrast provides information of increases of blood-brain barrier (BBB) permeability due to inflammation. Contrast agents typically do not cross BBB unless its permeability is increased. The examination is useful for distinguishing new lesions from old ones. The enhancement from Gadolinium correlates with inflammation and is observed in all new plaques. It lasts for 2 to 6 weeks and is consistent with the duration of relapse. However, if corticosteroid therapy is initiated in a patient with MS relapse, a contrast study is invalid because therapy restores the blood-brain barrier.

MRI diagnosis requires objective evidence of lesions disseminated in space (brain) and time – at least “open ring” pattern of contrast material enhancement of some lesions, it is very specific MS sign. MS lesions are typically located in lower part of corpus callosum, bordered by the liquor (the so-called calloso-septal interface), the periventricular or supratentorial brainstem regions, the cerebellum, and in the neck area of the spinal cord. They are usually ovoid in shape with size > 6 mm in diameter. The lesions should be larger than 3 mm in cross-sectional diameter and at least one of them should be larger than 5 mm. It should be considered that MRI detected lesions are typical, but not specific for MS. Gadolinium enhancement of lesions and presence of lesions in corpus callosum are prominent features, since they are not typical for vascular damage. Shape and orientation of lesions in corpus callosum are also important because in MS, inflammation affects vessels running perpendicular to corpus callosum. Ovoid elongated lesions resembling the fingers of the hand – the so-called Dawson's fingers, are a classic sign of MS. The presence of T₂- hyperintense lesions in the spinal cord is specific for MS, because such lesions are not age-related. They should be at least 3 mm in diameter but should also extend over less than two spinal cord segments in length, and should not affect the entire transverse section of the spinal cord. The use of MRI findings alone as a stand-alone criterion for initiation, continuation, change or discontinuation of immune-modifying therapy in MS is not justified. There is moderate correlation among MS lesions on MRI, clinical findings, and clinical disability.

MRI lesions in children are more in number and larger in size, with more Gd-enhancing lesions and more frequent posterior fossa involvement.

Differential diagnosis of abnormal MRI findings in children should exclude other multifocal conditions manifested with hyperintense T₂-weighted lesions, but with different shape or location.

4. Cerebrospinal fluid analysis (general CFS parameters and electrophoresis) provides different type of information – i.e. about inflammation and immune disorders. It can be useful in patients with atypical clinical presentation or MRI lesions. The most specific finding is the presence of oligoclonal bands detected by agarose gel electrophoresis (AGE) or isoelectric-focusing. In patients with multiple sclerosis, the analysis shows two types of abnormalities in the cerebrospinal fluid, indicative of immune-mediated pathology:

1. Presence of oligoclonal bands of IgG, preferably detected by isoelectric-focusing. Found only in the CSF, but not in the serum (testing is mandatory) and present in 90% of MS patients. Once acquired, they persist throughout the whole life of MS patients.

2. Lymphocytic pleocytosis, which if present, should be higher than 50 WBC/mm³.

5. The testing for neutralizing antibodies (NAbs) to interferon- β therapy might help in guiding the choice and individualization of treatment strategies. NAbs appear 6 to 24 months after initiation of therapy. Persistent, high-titer neutralizing antibodies reduce the efficacy of IFN- β therapy. It is recommended that tests for the presence of NAbs should be performed 18 months after therapy initiation. In patients with persistent positive NAbs, switching to first or second-line therapies (depending on the disease activity) different from IFN- β therapies should be considered.

Not all diagnostic procedures are required but only those, which are sufficient to diagnose MS as per the revised diagnostic criteria. Depending on the facilities available, the procedures should be performed in the order indicated herein.

Differential diagnosis of multiple sclerosis requires exclusion of many conditions in which clinical presentation or laboratory test results are similar to those in MS. The diseases which should be considered in differential diagnosis of MS are:

1. Monophasic Demyelinating Disorders

Acute disseminated encephalomyelitis (ADEM) usually begins after a viral infection or vaccination. This monophasic inflammatory demyelinating condition is more common in children. It starts rapidly with acute onset of fever, general brain symptoms, multifocal neurological symptoms and epileptic seizures. MRI lesions can be identical to those in MS but more often are more extensive and poorly outlined. The level of albumin in CSF is elevated.

Transverse myelitis is an acute, monophasic disorder with symptoms of bilateral symmetrical damage below certain spinal cord level in contrast to the typical asymmetric involvement in multiple sclerosis. MRI of the brain is normal, while spinal cord MR imaging shows severe lesions.

Devic's syndrome (disease) (neuromyelitis optica) is characterized by a monophasic course and rare recurrent attacks, acute bilateral or unilateral optic neuritis, papillitis and subsequent development of myelitis and paraplegia. Most often occurs in children and young people at an average age of 25 years. MRI of the brain can show periventricular demyelinating lesions. Lesions extending over ≥ 3 vertebral segments in the central part of the spinal cord are detected. According to the Mayo clinic diagnostic criteria of 2006, the diagnosis neuromyelitis optica requires the presence of optic neuritis, acute myelitis and at least 2 of three additional criteria – adjacent spinal cord lesions on MRI extending over ≥ 3 vertebral segments, MRI negative/non-diagnostic for MS and NMO-IgG (AQP4) seropositivity.

Optic neuritis is a common initial manifestation of MS, so it should be distinguished from monosymptomatic MS. Patients with retrobulbar neuritis, who have MRI lesions, often develop MS within periods of varying length, while patients with normal MRI have better prognosis and may never develop MS. Optic neuritis is characterized by quick decrease in visual acuity in one or both eyes, retrobulbar pain, absence of visual brightness and color vision and frequent central scotoma. Vision improves for a period of several weeks to several months. The visual disturbances are due to primary optic nerve demyelination and should be distinguished from secondary demyelination in optic neuropathy which mimics retrobulbar neuritis. Secondary optic nerve demyelination most often may result from compression, ischemia or toxic damage. Local viral, bacterial or fungal infections can also lead to optic nerve inflammation. Cases of post-viral and post-vaccination optic neuritis have been reported, as well as optic neuritis associated with collagenosis. Leber hereditary optic atrophy should be excluded.

Balo's concentric sclerosis is a variant of multiple sclerosis characterized by atypical lesions composed of alternate bands of demyelinated and myelinated white matter. A mixture of concentric white matter lesions and lesions typical for MS is found on MRI.

Schilder's disease (diffuse cerebral sclerosis) is associated with bilateral hemispheric demyelination in childhood. The clinical manifestations are aphasia, dementia, seizures and elevated intracranial pressure. T₂-weighted MRI shows large confluent areas of demyelination in the white matter.

2. Autoimmune Diseases

Behçet's disease is a multi-system inflammatory disease with CNS involvement. Optic nerves and spinal cord (myelon) are often affected. Typical manifestations are ulcers affecting the mucosa of the mouth cavity and the perineum. CSF and MRI findings are very similar to those in MS, but lesions in the deep grey matter and leptomeningeal changes are detected on MRI.

Systemic lupus erythematosus is a multi-organ autoimmune disease with fluctuating course. In 30% of patients, hyperintense lesions larger than 6 mm are detected on MRI, and elevated IgG levels, and in some cases – oligoclonality in CSF. Differential diagnosis is even more challenging in clinical presentations with myelopathy and vision disturbances. The presence of antinuclear antibodies (ANAs) is disease-specific but can also be found in 25% of MS patients.

Sjogren's syndrome is an autoimmune disease characterized by progressive damage of both salivary and lacrimal glands, and CNS involvement with clinical manifestations similar to those in MS in 25% of patients. The disease course is mostly relapsing-remitting, with multiple periventricular lesions on MRI, myelopathy, and oligoclonal CSF bands. The differential diagnosis is guided by the presence of gland alterations, neuropathy, myositis and serological abnormalities.

Sarcoidosis is a multi-system granulomatous disorder affecting primarily the lymphoreticular system. 5% of patients experience symptoms of CNS origin. The disease course is relapsing-remitting and the first clinical manifestations can be neurological symptoms, such as cranial nerve lesions, visual disturbances and pyramidal symptoms. CSF analysis might show oligoclonality. MRI findings are consistent with MS, but detection of leptomeningeal enhancement is typical in gadolinium-based MRI.

3. Vascular Autoimmune Disorders

Antiphospholipid syndrome may manifest with progressive myelopathy, spinocerebellar injury or neuromyelitis optica syndrome. MRI findings show diffuse or confluent white matter lesions very similar to those in multiple sclerosis. Cerebrospinal fluid analysis shows normal cell counts and oligoclonal fractions in 15% of patients. The final diagnosis requires presence of IgG and IgM anticardiolipin antibodies and lupus anticoagulant testing.

Vasculitis can be characterized by multi-organ involvement or predominant involvement of the central nervous system. MRI shows infarction in cerebral grey matter. In vasculitis with primary CNS involvement, T₂ lesions in periventricular and deep white matter are detected, very similar to MS lesions. Differential diagnosis in acute stroke largely depends on the DWI sequence. The diagnosis requires ESR testing, an antinuclear antibodies test, magnetic resonance angiography and brain biopsy.

Sneddon's syndrome is usually seen in younger adults and is characterized by onset of livedo reticularis and recurrent stroke-like episodes. An MRI typically shows multiple small white and gray matter lesions caused by strokes. The diagnosis requires testing for antiphospholipid antibodies, angiography and skin biopsy.

Venous occlusive and cardioembolic disease is observed in young people without vascular risk factors but with a family history of venous thrombosis. The disease course is characterized by intermittent focal neurological symptoms. Lesions on MRI are stroke-like and do not resemble those in multiple sclerosis apart from small white matter lesions. Testing for the presence of hypercoagulability and Doppler ultrasonography, and echocardiography are required. Results from CSF analysis are within reference range.

4. Infectious Diseases

Progressive multifocal encephalopathy is caused by JC virus infection in the central nervous system normally seen in immunocompromised individuals. Its course is characterized by continuous progression of cognitive, language and vision impairments. A fluctuating disease course resembling multiple sclerosis is rarer. MRI imaging detects enlarging juxtacortical T₂ lesions in the white matter, which are usually more confluent than those in multiple sclerosis and non-contrast enhancing. Final diagnosis is based on brain biopsy.

Lime disease often manifests as neuroborreliosis with acute meningitis, cranial neuritis, myelopathy or encephalitis. MRI and spinal fluid changes are difficult to distinguish from those in MS. However, white matter T₂-lesions are not periventricular. Antibodies to *Borrelia burgdorferi* have been detected, but they are not absolutely disease-specific and can also be observed in other inflammatory diseases of the central nervous system, including MS.

Lues (syphilis) also affects CNS causing optic neuritis, vasculitis, myelopathy and chronic encephalopathy, which makes the differential diagnosis a challenge. MRI findings depend on the stage of the disease and include infarction, nonspecific white matter lesions, chancres and meningeal enhancement. Diagnosis is based on the results of a serologic and CSF VDRL tests and micro hemagglutination assay for *T. pallidum*.

HIV-1 leukoencephalopathy is caused by the HIV-1 virus. This virus usually induces typical HIV-related neurocognitive disorders and more rarely milder recurrent disorders manifesting optic neuritis, myelopathy and cognitive dysfunction, which resemble those in multiple sclerosis. CNS complications often occur in the later stages of HIV infection, but in 10% of patients these are the presenting features of AIDS. MR imaging shows T₂ lesions in the white matter which are confluent

and larger than those in multiple sclerosis. CSF analysis and evoked potentials testing show the same changes as in multiple sclerosis. Elevated levels of total protein and presence of abnormal cells in the CSF might be found but rarely in CSF with oligoclonal IgG bands. Diagnosis is based on positive HIV-1 serologic testing and low CD4 cell count.

5. Degenerative Diseases

Adrenoleukodystrophy (ALD) is a genetic disorder associated with accumulation of very long chain fatty acids (VLFA). The X-linked variant of ALD occurs in adolescents or adults and is characterized by progressive myelopathy and neuropathy, which in the absence of a family history, makes differential diagnosis a serious challenge. The course of the disease is relapsing-remitting or progressive, with manifestations of paraparesis, ataxia and cognitive disorders. Testing for VLFA in plasma may guide diagnosis, which is difficult because both CSF analysis and MR imaging show changes seen in MS.

Mitochondrial encephalopathy, with lactic acidosis and stroke-like episodes (MELAS) occurs in childhood. It is a hereditary disease characterized by external ophthalmoparesis, proximal muscle weakness and seizures. MRI findings include cortical and subcortical stroke-like lesions visible on T₂-weighted MRI and FLAIR imaging. The final diagnosis requires analysis of CSF levels of lactate and pyruvate.

Leber hereditary optic neuropathy (LHON) is mainly characterized by bilateral subacute optic atrophy. It affects primarily adult males and is accompanied by myelopathy, ataxia and sensory disturbances. T₂-weighted MR imaging detects white matter lesions identical to MS lesions. No CSF alterations are found. The diagnosis is confirmed after DNA testing.

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is associated with gene mutations in chromosome 19. The first symptoms occur between 30 and 50 years of age, with recurrent stroke-like episodes and subsequent development of dementia. MRI findings show multiple subcortical lesions. The diagnosis is built on the basis of CSF investigations within the normal range and genetic analysis.

Cerebellar atrophies (spinocerebellar ataxia, Friedreich's ataxia and olivopontocerebellar atrophy) are distinguished based on a family history, absence of remissions and normal CSF test results.

Vitamin B₁₂ (cobalamin) deficiency or dysmetabolism, a result of metabolic defects or acquired B₁₂ deficiency causes progressive myelopathy (especially with involvement of posterior and lateral columns of the spinal cord) and polyneuropathy. MRI shows transient T₂ hyperintensities in

the cerebral white matter and spinal cord. The lesions disappear after correction of B₁₂ deficiency. The diagnosis is based on low **vitamin B12 levels** in blood.

6. Spinal Cord Disorders

Arnold-Chiari malformation is associated with isolated spinal cord syndromes and involvement of the caudal cranial nerves and the cerebellum, ataxia and elevated intracranial pressure. MRI shows craniocervical junction abnormalities.

Myelopathy with progressive para- and quadriparesis in middle age should be distinguished from MS. Causes such as external or internal spinal cord compression, cervical spondylosis and vitamin B₁₂ deficiencies should be ruled out. MRI may prove the presence of spinal and cerebral lesions in MS.

Amyotrophic lateral sclerosis may cause diagnostic problems, because its early stages are characterized by absence of lower motor neuron signs and prominent upper motor neuron signs. MRI findings are normal. The diagnosis requires electromyographic evidence of multilevel injury of the anterior horn of spinal cord in at least 3 extremities.

The diseases to be considered in differential diagnosis can be divided into three main categories, depending on whether they have only clinical, clinical and MRI, or clinical, MRI and CFS features similar to those in MS.

Diseases which resemble MS in clinical presentation, but have different MRI findings:

1. Wegener's Granulomatosis
2. Isolated spinal cord syndromes
3. Compressive lesions
4. B₁₂ deficiency
5. Intracranial tumors
6. Arnold Chiari malformation

Diseases which resemble MS in clinical presentation and MRI criteria:

1. AIDS
2. Cerebellar degenerations
3. Mitochondrial encephalopathy
4. Cerebrovascular disorders
5. CADASIL

Diseases which resemble MS in clinical presentation, MRI and CSF criteria:

1. Vasculitis:
 - Sjogren's syndrome
 - Polyarthritis nodosa
 - Systemic lupus erythematosus
 - Behcet's disease
2. Lyme disease
3. Sarcoidosis
4. Adrenoleukodystrophy
5. HTLV-1
6. Leber hereditary optic atrophy
7. Acute disseminated encephalomyelitis

Treatment

The most important goal of treatment is to slow down disease progression and reduce long-term disability in MS patients. The choice of treatment differs depending on the disease course and whether the disease is in relapse phase or in remission. Treatment is generally divided into 3 main categories: management of relapses, disease-modifying therapy and symptomatic management.

Management of relapses aims at rapid recovery of neurological symptoms experienced during the relapse. Exacerbations in relapsing-remitting multiple sclerosis prompt urgent intervention by a neurologist.

- In patients already diagnosed, the neurologist should determine whether the patient's condition is a relapse by using relevant criteria.
- In case of a new relapse, its severity should be determined in order to decide whether steroid therapy is indicated, or not.
- Mild relapses do not require steroid treatment. The patient should be closely monitored, and if the relapse is caused by an infection, the infection should be treated and the patient should be given non-steroid anti-inflammatory drugs for 1 to 2 weeks.
- The presence of acute and pronounced visual, motor and cerebellar symptoms or gait disturbances is an indication for corticosteroid treatment. In such cases immediate steroid therapy (Appendix 4) and symptomatic management (Appendix 5) in hospital settings is

recommended depending on the relapse severity.

- Plasma exchange (plasmapheresis) is a second-line therapy for GCS-resistant relapses.

Glucocorticosteroids (GCS) are the most efficient therapy for relapse management. They are used as first-line therapy for management of relapses because of their anti-inflammatory and immunosuppressive effects and the ability to improve blood-brain barrier (BBB). Steroid treatment leads to reduction of activated T-lymphocytes with prevailing reduction of T-helper cells than T-suppressor cells. GCSs improve the tightness of the blood-brain barrier and affect the cascade of immune responses leading to demyelination. Glucocorticosteroids, given in therapeutic doses, do not influence the disease course even with low-dose, long-term treatment. They only accelerate the neurologic recovery after relapse.

The different types of glucocorticosteroids differ in the ratio between glucocorticoid and undesirable mineralocorticoid activity.

Methylprednisolone is a first-line drug for relapse management because of its long biologic half-life of 18-36 hours, very good anti-inflammatory effect, weak mineralocorticoid activity and very good ability to cross the blood-brain barrier. It is used in doses from 500 to 1,000 mg daily (depending on the relapse severity), given intravenously in serum glucose for 3 to 5 days, but in refractory symptoms treatment can be extended to 10 days. Low-dose treatment is not recommended for their undesirable effects – frequent recurrences. Initial treatment is followed by the so-called dose tapering – injections or oral administration of lower doses. Dosage is adjusted in 10 to 12 days in increments of 10-20 mg every 3 days, starting from 80 mg daily. Dose tapering prevents reopening of the blood-brain barrier.

If a new relapse occurs soon (within days to weeks) after the end of steroid treatment, a second, shorter (3 days) course of steroids is recommended.

In patients with symptoms persisting for 8 to 12 weeks, steroid treatment can also be used but with a lesser effect.

In children methylprednisolone is used at a dose of 20 to 30 mg/kg daily administered intravenously as a single dose of 0.2 to 0.5 g (maximum 1g) daily in saline for 2 hours. Steroid treatment continues 4 to 6 days. The treatment is discontinued after complete recovery and in case of partial recovery the dose should be gradually tapered off with oral prednisone given every 2 to 3 days.

The side effects of steroid treatment include gastrointestinal disorders, ulcers, hypertension, arrhythmia, diabetes mellitus, various infections, osteoporosis, acne, thrombosis, mania, depression, etc. To avoid gastrointestinal side effects, preventive therapy with H₂-receptor antagonists (Ranitidine

300 mg/day twice daily administration, etc.) is recommended. During treatment, blood pressure can be controlled by changing the dosage of antihypertensive therapy (in hypertensive patients) or with diuretics and β -blockers. Blood pressure returns to normal following cessation of a steroid cycle. The onset of signs of mania, depression or acute psychotic symptoms requires discontinuation of steroid treatment and timely initiation of appropriate treatment (anxiolytic agents, neuroleptics, tranquilizers and antidepressants).

Use of ACTH (synthetic analogues Cortrosin[®], Synacthen[®]) is not recommended because the mechanism of action is similar to that of glucocorticoids. The treatment effect of ACTH occurs more slowly (after 1 month) compared to that of methylprednisolone (after 1 week). Moreover, ACTH is associated with more adverse effects, including allergies, which persist even after drug withdrawal, because of its prolonged effect.

Plasmapheresis is a procedure in which the patient's plasma is separated and removed from the blood. The removed amount of plasma is replaced with plasma substitute in a 1:1 ratio. It can be used for managing of recent acute and severe relapses with incomplete recovery of neurological symptoms after steroid treatment. The treatment consists of 7 procedures every 1-2 days with replacement of 54 ml/kg plasma with a mixture of 5% albumin and saline in each single session.

Side effects are hypotension, septicemia, bronchopneumonia, coagulation disturbances, central line complications and hypocalcemia.

Treatment with disease-modifying drugs is used in periods outside relapses to reduce the clinical and subclinical activity of the disease contributing to long-term disability. The choice of therapy depends on the disease course and activity. Currently, most of the drugs from this class are used in a *relapsing-remitting course* of the disease. Only interferon β -1b and siponimod have proved effectiveness in patients with *secondary progressive* multiple sclerosis. In patients with primary progressive multiple sclerosis clinical efficacy has been proven only for ocrelizumab.

Treatment in patients with **relapsing-remitting course** of disease is initiated with **first-line drugs: Interferon beta-1a** (Avonex[®], Rebif[®] and Plegridy[®]) and **interferon β -1b** (Betaferon[®] and Extavia[®]), the synthetic copolymer glatiramer acetate, dimethyl fumarate and teriflunomide.

Interferon beta is 166-amino acid glycoprotein produced by fibroblasts and some other cells in response to viral infections. Natural human beta-interferon is produced from human fibroblasts, but large-scale production requires the use of recombinant DNA technologies.

Two recombinant molecules have been produced from human beta-interferon by genetic engineering. Interferon beta-1a is produced from Chinese hamster ovary cells and therefore is glycosylated like the natural protein. Interferon β -1b is produced from strain of *Escherichia coli* and

as such it differs from the natural sequence at position 17, which has been mutated, is one amino acid shorter than the natural protein, lacking the N-terminal methionine residue and also lacks the glycosylation at asparagine residue at position 80 that exists in the natural protein. These changes have been made in view of the stability of the molecule and do not affect its function. The two products have equal physical and chemical properties, and equal pharmacodynamic and pharmacokinetic characteristics.

In multiple sclerosis, beta-interferon inhibits the activation and proliferation of the autoreactive T-cells and their transmigration across the blood-brain barrier to the CNS, where they mediate myelin/oligodendrocyte damage. Interferon beta stimulates the production of anti-inflammatory cytokine interleukin 10 and inhibits the production of IFN-gamma, which enhances immune responses. Clinical improvement is observed after 2 to 12 months of treatment and the effect lasts for 6 months following discontinuation of IFNs.

Interferon **β -1b (Betaferon[®], Extavia[®])** is the first interferon approved for the treatment of multiple sclerosis in the USA (1993) and EU (1995). Administered subcutaneously every other day at a dose of 250 μ g, equal to 8 million IU.

Interferon β -1a is available in two forms.

The ***intramuscular*** injection (**Avonex[®]**) is administered once a week at a dose of 6 million IU (30 μ g).

The ***subcutaneous*** injection (**Rebif[®]**) is administered 3 times a week at a dose of 12 million IU (44 μ g).

Published clinical trials with each one of the three drugs have confirmed undoubtedly their clinical efficacy. Interferons reduce the rate and severity of relapses as corroborated by MRI findings. Their clinical efficacy in patients with relapsing-remitting MS was first confirmed with interferon β -1b in 1993. The medication reduces the annual relapse rate by 30%, with 31% of patients remaining relapse-free during the first 2 years of treatment; the time to first relapse is doubled, the severity of relapses and the number of moderate and severe type of relapses is reduced by 50%. Interferon also extends the time to disability progression and reduces the number of hospitalizations and number of patients in need of corticosteroid treatment. MRI findings show 75% annual reduction of new lesions. Other IFNs have shown consistent results.

Pegylated interferon β -1a for subcutaneous administration (Plegridy[®]) was approved in 2014 by FDA and EMA for the treatment of patients with multiple sclerosis. The recommended dose is 125 μ g s.c. every 2 weeks. The treatment starts with 63 μ g at dose 1, increasing to 94 μ g at dose 2, and the full dose of 125 micrograms is reached with the third administration. The prolonged

absorption of the drug results in longer half-life, higher stability and activity and extended dosing intervals. The reduction in clearance rate and immunogenicity does not interfere with the drug safety and tolerability.

Clinical trials have shown reduction of the annual relapse rate by 36%, and reduction of the risk of sustained disability progression by up to 38%. The number of new or newly enlarged T₂ lesions is reduced by up to 67%), the number of T₁ hypointense lesions by up to 53% and the number of Gd-enhancing lesions – by up to 86%.

The side effects of beta-interferon treatment include local skin reactions, flu-like symptoms and rarely fatigue, worsening of depression, asthenia, headache, hepatic transaminase increase, cytopenia and thyroid disorders. The adverse drug reactions associated with subcutaneous administration of pegylated interferon β -1a do not differ from those with the conventional dosage forms. Flu-like symptoms such as hyperpyrexia, chills and myalgia are mostly manifested in the first 24 hours after the first dose and resolve within 6-7 days. They are more manifested with interferon β -1b due to more frequent dosing. The use of nonsteroid anti-inflammatory drugs (ibuprofen, aspirin) at initiation of interferon therapy helps reduce flu-like effects. Local skin reactions at the site of injection can be reduced by training patients or nurses injecting the drug on proper injection techniques and use of rotation charts to alternate injection sites.

The biological activity of interferon β -1b is much more pronounced and stable compared with interferon β -1a intramuscular injection once a week. Interferon β -1b has the highest biological activity followed by interferon β -1a subcutaneous injection and β -1a intramuscular injection with the lowest biological activity due to its smaller weekly dosage. The biological activity of pegylated interferon β -1a is significantly higher and more stable over time compared with the conventional dosage form.

The clinical efficacy of the three β -interferon types is also different due to differences in dosing. Less frequent dosing is more convenient and associated with less side effects but the clinical efficacy is lower. The highest reductions in the annual relapse rate and number of severe relapses and hospitalizations and the longest time to first relapse have been observed in patients treated with interferon β -1b. The clinical efficacy of pegylated interferon β -1a is higher than that of interferon β -1a intramuscular injection and similar to that of interferon β -1b and interferon β -1a subcutaneous injection.

The four beta-interferon agents are not interchangeable and in patients with aggressive disease, the use of interferon β -1b or pegylated interferon β -1a is preferred.

Neutralizing antibodies (NAbs) will be developed in 10-35% of patients after 1-year treatment with beta-interferon which reduces clinical efficacy. NAbs are mostly seen with interferon

β -1b due to more frequent dosing. Immunogenicity is highest in Betaferon and Extavia (35%), lower in Rebif (15% to 23%), and weakest in Avonex[®] (2% to 5%). Only 1-3% of patients receiving pegylated interferon β -1a will develop persisting neutralizing antibodies. NAbs may disappear over time and then the clinical efficacy of the drug will be recovered.

When testing for neutralizing antibodies is impossible, the changes in therapy are based on clinical parameters. Availability of antibodies against one of the beta interferon types means that switching to another interferon is worthless because of cross-reaction among NAbs and IFN β -1a and IFN β -1b. However, such cross-reactivity is not seen with other drugs, which makes the switching to another therapy possible, in case of lack of clinical efficacy of IFN treatment.

Glatiramer acetate (copolymer-I) is administered subcutaneously, once daily at a dose of 20 mg/ml. It is a molecule composed of synthetic polypeptides of four amino acids: L-glutamine, L-lysine, L-alanine and L-tyrosine in a fixed ratio. Approved in 1996 in the USA for the treatment of patients with relapsing-remitting multiple sclerosis.

The mode of action of GA is associated with induction of specific suppressor cells of the T helper 2 (Th2) type which migrate to the brain and suppress the activation of myelin basic protein by the reactive T helper (Th1) type cells which produce pro-inflammatory cytokines and induces production of Th2 type cells that produce anti-inflammatory cytokines. Furthermore, the GA-acetate reactive T cells release brain-derived neurotrophic factor (BDNF), which accelerates the recovery of damaged axons and neurons and promotes remyelination. The main effect of the drug is suppression of inflammation and autoimmune responses in multiple sclerosis.

GA reduces the rate of clinical relapses and the number of new or newly enlarged lesions on MRI by 30%. There is no data about its efficacy in secondary progressive form of the disease.

The first **generic glatiramer acetate** 20 mg was approved by FDA in 2015.

Glatiramer acetate 40 mg/ml for subcutaneous use 3 times a week was approved by FDA in 2015 for the treatment of relapsing-remitting multiple sclerosis. It has the same clinical efficacy as the conventional dose of 20 mg/ml daily.

The side effects are mainly local: pain, erythema, pruritus, inflammation and hardening of the tissues, which resolve spontaneously. Rarely causes fatigue, depression, asthenia, headache, allergic and post-injection systemic reactions. GA does not cause flu-like symptoms.

GA induces development of *neutralizing antibodies* reaching peak titers 3 to 6 months after initiation of treatment, after which the levels decrease. The presence of NAbs does not reduce the therapeutic efficacy of glatiramer acetate.

Dimethyl fumarate (Tecfidera®) is a fumaric acid derivative with anti-inflammatory, cytoprotective and immunomodulating properties. The drug was approved in 2013 by FDA and EMA for the treatment of relapsing-remitting multiple sclerosis. For oral use in patients aged between 18 and 65 years. The starting dose is 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day.

Dimethyl fumarate activates the transcriptional pathway of the nuclear factor (Nrf2), which leads to activation of the synthesis of anti-inflammatory interleukins, reduction of proinflammatory cytokines, stimulation of the expression of antioxidant and detoxification enzymes and reduction of leukocyte adhesion molecules.

Clinical studies have shown reduction in the annual relapse rate by 44-53%, and of the risk for sustained progression of disability by up to 38%. The risk for Gd+ lesions is reduced by 74% to 90%, and the risk of developing new or newly enlarging T₂ hyperintense lesions is reduced by 71% to 85%.

The most common adverse reactions are flushing, diarrhea, nausea, abdominal pain, which occur early in the course of treatment (in the first month), but may continue to occur intermittently throughout the treatment period. The risk of lymphopenia cannot be ruled out and 4 cases of PML, associated with prolonged lymphopenia, have been reported. Temporary dose reduction to 120 mg twice a day may reduce the adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed.

The drug is *contraindicated* in patients with persisting severe lymphopenia and severe renal and hepatic impairment.

There is no data on the development of anti-drug *neutralizing antibodies*.

Teriflunomide (Aubagio®) is a purine analogue with immunosuppressive properties. The recommended dose is 14 mg once daily orally in patients aged 18-65 years. Approved for the treatment of relapsing-remitting multiple sclerosis by FDA and EMA in 2012 and 2013, respectively.

Teriflunomide is an active metabolite of leflunomide, which is used for the treatment of rheumatoid arthritis. It selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, engaged in the *de novo* synthesis of pyrimidines, required for the proliferation of dividing B- and T-lymphocytes. Consequently, teriflunomide inhibits the abnormal proliferation and activation of pathogenic T- and B-cells. Through this cytostatic effect, teriflunomide inhibits the immune responses associated with disease activity. Resting lymphocytes are not damaged, so they can still divide and proliferate at a low level, using available pyrimidines. As a result, the previously acquired cell immunity is preserved and the risk of infectious diseases does not increase.

Clinical studies in patients with relapsing-remitting multiple sclerosis have shown a 30% reduction in the annual relapse rate, 60% reduction in the number of active and new lesions on MRI, and 80% reduction of gadolinium-enhanced lesions.

The side effects include upper respiratory tract infections, headache, diarrhea, nausea, alopecia or hair thinning, high blood pressure or alanine aminotransferase (ALT) increase. Isolated cases of toxic hepatic necrosis, pancytopenia and teratogenic effects have been reported.

The clinical efficacy of the first-line therapy glatiramer acetate 20 and 40 mg/ml and teriflunomide is similar to that of beta interferons. The clinical efficacy of dimethyl fumarate is higher than that of the other first-line therapy drugs.

Despite Avonex's lower efficacy compared to other beta interferons, given the fewer side effects, more convenient administration as well as less frequent antibodies production, Avonex and Plegridy, may be used in young active patients with shorter duration and lower activity of the disease.

In cases of unsatisfactory clinical efficacy or increased disease activity, switching to betaferon (Extavia®), Rebif®, glatiramer acetate, teriflunomide or dimethyl fumarate is recommended. However, it has to be considered that betaferon (Extavia®) is associated with frequent development of antibodies and the highest incidence of adverse reactions. In the presence of clinical evidence of development of antibodies to beta interferons switching to glatiramer acetate, teriflunomide or dimethyl fumarate is advised. Patients with unsatisfactory clinical response to a certain drug might respond well to another one. When all first-line treatment options have been used-up, second-line therapies should be prescribed.

Switching from intravenous to oral therapy for patient's convenience only, without a medical reason (unsatisfactory efficacy or intolerance), is not recommended.

Treatment of different forms of multiple sclerosis has its specifics.

Patients with **clinically isolated symptoms**, who do not fulfil the criteria for multiple sclerosis, are at a high risk of a second relapse, after which the diagnosis will be definitive. Treatment of such patients delays onset of further relapses and definitive diagnosis. In patients with very high MRI activity manifested in multiple lesions (10-20 lesions) and multiple contrast-enhancing lesions, initiation of disease-modifying therapy is recommended. In patients with moderate MRI findings, suggesting lower disease activity, further clinical relapse may be awaited to make a final diagnosis and initiate treatment.

In the beginning of the disease, in patients with clinically isolated symptoms:

- First line disease modifying drugs are recommended

Treatment of relapsing-remitting form of the disease with first-line disease modifying drugs should be initiated as soon as diagnosis is made, to prevent new lesions. This is of particular importance in patients with high clinical and MRI activity of the disease. Early treatment can change the natural course of the disease by reducing the rate and severity of relapses, delaying the disease progression, disability and incapacity for work (by an average of 18 months), improving patients' quality of life, and prolonging their life.

- The neurologist should determine the form of disease and decide on the initiation and type of treatment during a period outside relapse.
- The treatment should continue for 1 year, thereafter the neurologist should assess the treatment efficacy (Appendix 6).
- In the presence of evidence of decreased clinical efficacy, assessed by the criteria for treatment efficacy, a change in therapy should be considered. It is recommended that clinical evidence is corroborated by testing for neutralizing antibodies.
- Whenever possible, testing for neutralizing antibodies with predictive value should be performed in all patients 18 months after initiation of interferon therapy.

Treatment of newly diagnosed relapsing-remitting multiple sclerosis

- **First line treatment** – Beta interferons (including pegylated beta interferon), glatiramer acetate, teriflunomide or dimethyl fumarate;
- **Second line treatment** - S₁P receptor modulators, the selective immunosuppressor cladribine or monoclonal antibodies;
- Hygiene and dietary regimen;
- Symptomatic treatment;

The treatment of multiple sclerosis **in children** (under 16 years of age) still presents a great challenge. Corticosteroid therapy can be used for relapse management.

The use of disease modifying therapies in children is limited, due to lack of clinical trials. Most of the drugs do not have an issued marketing authorization, although the results from small scale studies have shown clinical efficacy and safety similar to that in adult patients. Due to the high relapse rate in adolescence leading to earlier disability, the use of disease modifying therapies can be

recommended. The benefits of an early treatment, immediately after a definitive diagnosis had been made, are undeniable.

Based on limited published data, it might be assumed that the safety profile of betaferon (Extavia®), Avonex® and glatiramer acetate are given at doses recommended for adults in adolescents between 12 and 16 years of age, and Rebif® given to children and adolescents (12 to 17 years old) would be similar to that in adult patients. Treatment of pediatric patients follows a titration schedule based on the patient's body weight and should be under the physician's responsibility.

Fingolimod (Gilenya®) is the first and, for the time being, the only disease modifying therapy, approved in 2018 for treatment of children above 12 years of age and body weight above 40 kg with relapsing-remitting MS. The administered dose is 0,5 mg. Fingolimod reduces the annual relapse rate by 82% and the number of active lesions on MRI by 66%. The safety profile is similar to the one in adults, but requires increased caution. There is no data on long-term safety. Before treatment initiation, it is recommended all vaccinations to be performed.

Criteria for treatment of multiple sclerosis with fingolimod in children with relapsing-remitting disease

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria
2. Ages of 12 to 18 and body weight over 40 kg
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. Patients with severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year and with 1 or more Gadolinium enhancing lesions on brain MRI or with increased relapse rate (at least 2 relapses in the previous year) despite treatment with first-line drugs
5. Significant increase in T₂ lesions compared to the latest MRI scan during the last 12 months

II. Exclusion criteria

1. Patients with immunodeficiency syndrome or receiving immunosuppressive therapy
2. Active acute or chronic infections (hepatitis, tuberculosis)
3. Neoplasms, except cutaneous cell skin carcinoma
4. Severe hepatic impairment
5. Patients with an AV block II degree Mobitz 2 type or higher, sick sinus syndrome or sinoatrial block, history of symptomatic bradycardia or recurrent syncope, significant QT prolongation (> 470 ms in pediatric female patients and > 450 ms in pediatric male patients)

6. Treatment with class IA antiarrhythmic agents (quinidine, disopyramide) or class III (amiodarone, sotalol), beta-blockers, heart rate-lowering calcium channel blockers (verapamil, diltiazem or ivabradine) or other substances that can lower heart rate (digoxin, anticholinesterase agents or pilocarpine)

7. Pregnancy

III. Treatment is not administered, or discontinued (if initiated) in cases of:

1. Pregnancy.
2. Serious adverse drug reactions.
3. High level of non-adherence to the therapy.
4. Lack of clinical efficacy of the therapy (2 or more relapses per year).
5. Disability progression to EDSS = 5.

**Criteria for beta-interferon and glatiramer acetate therapy in patients
with relapsing-remitting multiple sclerosis**

I. Inclusion criteria:

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria)
2. Age > 16 years (>18 years for glatiramer acetate and pegylated beta-interferon)
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])

II. Exclusion criteria

1. Concomitant chronic conditions/diseases that shorten life expectancy (alcohol abuse, dementia, psychotic disorders, active malignancies)
2. Patients with severe depression and suicide attempts during treatment (beta interferons only)
3. Pregnancy (at physician's discretion based on specific therapy and term of pregnancy)

III. Treatment is not administered or discontinued (if initiated) in cases of:

1. Pregnancy (at physician's discretion based on specific therapy and term of pregnancy)
2. Serious adverse effects of treatment
3. High patient non-compliance
4. Lack of clinical efficacy of the therapy (2 or more relapses in a year)
5. Patients treated with beta-interferons without clinical effect and/or in the presence of neutralizing antibodies, might be switched to other first- or second-line therapies, depending on the disease activity

6. First-line treatment failure; Switching to second-line therapies for such patients may be considered
7. Disability progression to EDSS = 5
8. Reaching the age of 59, and absence of disease activity in the last 2 years

Criteria for dimethyl fumarate therapy in patients with relapsing-remitting multiple sclerosis

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria)
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])

II. Exclusion criteria

1. Pregnancy or planning for pregnancy
2. Patients with immunodeficiency syndrome or receiving immunosuppressive therapy
3. Active acute or chronic infections (hepatitis, tuberculosis)
4. Neoplasms, except cutaneous cell skin carcinoma
5. Severe hepatic impairment

III. Treatment is not administered, or discontinued (if initiated) in cases of:

1. Pregnancy
2. Serious adverse drug reactions
3. High level of non-adherence to the therapy
4. Lack of clinical efficacy of the therapy (2 or more relapses per year)
5. Failure of first-line treatment; Switching to second-line therapies might be considered depending on the disease activity
6. Disability progression to EDSS = 5
7. Reaching the age of 59, and absence of disease activity in the last 2 years

Laboratory tests and follow-up evaluations required during dimethyl fumarate therapy

I. Prior to treatment initiation:

1. A recent complete blood count (within 1 month), serum aminotransferases and bilirubin, blood urea nitrogen and creatinine.

II. During treatment:

1. Assessment of renal function (creatinine, blood urea nitrogen, and urinalysis) and serum aminotransferases at 3 and 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated
2. Regular assessment every 6 months of complete blood count with monthly differential blood count (DBC) monitoring in lymphocyte counts $<0,8 \times 10^9/L$ and treatment discontinuation in lymphocyte counts $<0,5 \times 10^9/l$ until recovery.
3. Patients should be instructed to inform the physician of any signs and symptoms of infection.

Criteria for teriflunomide therapy in patients with relapsing-remitting multiple sclerosis

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria)
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])

II. Exclusion criteria:

1. Severe immunodeficiency
2. Severe active infection until recovery
3. Significant bone marrow disorder or significant anemia, leukopenia, neutropenia or thrombocytopenia
4. Severe hepatic impairment
5. Dialysis
6. Severe hypoproteinemia
7. Pregnancy or lactation

III. Treatment is not administered, or discontinued (if initiated) in cases of:

1. Pregnancy. Accelerated elimination procedure is recommended to reduce plasma concentrations below 0.02 mg/L.
2. Serious adverse drug reactions
3. High level of non-adherence to the therapy
4. Lack of clinical efficacy of the therapy (2 or more relapses per year)
5. In case of first-line treatment failure, switching to other therapies of first or second-line might be

considered, depending on the disease activity. Over a period, equal to 5 half-lives (3.5 months), starting another therapy leads to an additive effect on the immune system and requires increased caution.

6. Disability progression to EDDS = 5

7. Reaching the age of 59, and absence of disease activity in the last 2 years

Laboratory tests and follow-up evaluations required during teriflunomide therapy

I. Prior to treatment initiation:

1. A recent complete blood count (within 1 month) (including differential WBC count and platelet count), alanine aminotransferase (ALT/SGPT) levels and blood pressure.

II. During treatment:

1. Regular assessment of liver enzymes ALT (SGPT) – every 4 weeks during the first 6 months of treatment and periodically thereafter. When administered in patients with previous liver impairment, assessment of liver enzymes should be performed every 2 weeks during the first 6 months of treatment and at least every 8 weeks thereafter, for 2 years from treatment initiation. In ALT/SGPT elevations between 2 and 3-fold the upper limit of normal, liver function assessment should be performed every week. For elevations 3 times the upper limit of normal, discontinuation of therapy should be considered.

2. Complete blood cell counts should be performed based on signs and symptoms (e.g. infections) during treatment.

3. Monitoring and management of the hypertension.

Strict hygiene and diet regimen are recommended in patients with multiple sclerosis:

- Sufficient rest and avoidance of physical and mental exertion
- Protection against over-cooling and overheating
- Protection against common colds
- Reduction of dietary intake of salt and animal fats in favor of foods rich in polyunsaturated fatty acids (linoleic acid) and Vitamin D, and cessation of tobacco smoking
- Medical exercise therapy

The drugs for second-line treatment in patients with relapsing-remitting disease include the S₁P-receptor modulator fingolimod, the selective immunosuppressant cladribine or the monoclonal

antibodies natalizumab, alemtuzumab and ocrelizumab. Currently, these drugs are the most efficient agents for the treatment of relapsing-remitting multiple sclerosis. They are used when first-line therapies fail or are contraindicated. They are used as the second line disease modifying treatment in patients with highly active relapsing-remitting form of multiple sclerosis, despite at least one-year treatment with first-line medications. The lack of clinical efficacy is defined as the occurrence of at least two relapses or increased frequency and severity of relapses, as compared to the previous year. Treatment with second line drugs may also be considered in cases with a significant increase in T2 lesions (at least 2 new lesions), as compared to a previous MRI scan. Patients should have at least 9 hypertensive T2 lesions in cerebral cortex.

Second-line treatment drugs are contraindicated during pregnancy and during planned conception.

It is highly recommended to have a baseline MRI scan prior to initiation of second-line treatments and switching between them in order to assess the risk of PML. The potential risk of PML in patients treated with natalizumab, fingolimod and ocrelizumab has to be considered. There is an increased risk of opportunistic infections and malignancy, especially with prolonged use. In patients treated with fingolimod cryptococcal or herpes infections may appear and in natalizumab-treated patients herpes infections may occur. The risk of basal cell carcinoma is increased in patients treated with fingolimod.

S₁P receptor modulator fingolimod (Gilenya[®]) has been found to have immune-modulating properties. The recommended dose in patients aged 18-65 is one 0.5 mg capsule taken orally once daily. It has been approved for the treatment of multiple sclerosis in 2010 (for the USA) and in 2011 (for the EU).

Fingolimod is a structural analogue of sphingosine 1-phosphate (S₁P), a modulator of sphingosine 1-phosphate receptors which play a role in the processes of inflammation and regeneration. S₁P receptors are expressed in lymphoid tissues, and S₁P₅ receptors – in the white matter of the central nervous system.

The drug converts endogenous sphingosine to a phosphate form, which binds to sphingosine 1-phosphate receptors 1 (S₁P₁) located on the lymphocytes. This promotes receptor internalization and deprives lymphocytes of their capability to recognize the signal for egression from lymphoid tissues. The capacity of lymphocytes to egress from lymph nodes and thymus gland and their migration to the CNS is blocked. As a result, T- and particularly B-lymphocyte counts in peripheral blood decrease (by 25% from baseline). The functions of lymphocytes, which remain in secondary lymphoid organs and peripheral blood, are not affected. The drug crosses the blood-brain barrier and stimulates central

nervous system receptors leading to inhibition of neurodegenerative and promotion of regenerative processes. It induces thymocyte apoptosis, inhibits brain capillary permeability mediated by the vascular endothelial growth factor (VEGF), stabilizes the blood-brain barrier integrity, shifts cytokine production from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) cytokines and reduces macrophage transmigration to brain parenchyma.

Fingolimod reduces the annual relapse rate by 50% and the number of active lesions on MRI by 60%. Fingolimod delays the progression of sustained disability by 37%.

Serious adverse reactions are associated with infections, macular edema and AV block. Less serious adverse reactions include flu-like symptoms, headache, diarrhea, depression, back pain, cough, hypertension, lymphopenia, leukopenia, and increased serum transaminases.

Contraindicated in patients with immunodeficiency syndrome receiving immunosuppressive therapy, active infection (hepatitis, tuberculosis) cardiac rhythm and conduction disturbances, AV block, sick-sinus syndrome, sinoatrial block, symptomatic bradycardia, recurrent syncope, prolonged QT-interval, patients receiving anti-arrhythmic and heart-rate reducing drugs, patients with uncontrolled hypertension, chronic obstructive pulmonary disease, pulmonary fibrosis, neoplasm, hepatic impairment and pregnancy.

Criteria for treatment of multiple sclerosis with fingolimod in patients with relapsing-remitting disease

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria)
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. Aggressive disease course with increased relapse rate (at least 2 relapses in the previous year), despite treatment with first-line drugs
5. Significant increase in T₂ lesions compared to the latest MRI scan during the last 12 months

II. Exclusion criteria

1. Patients with immunodeficiency syndrome or receiving immunosuppressive therapy
2. Active acute or chronic infections (hepatitis, tuberculosis)
3. Neoplasms, except cutaneous cell skin carcinoma
4. Severe hepatic impairment

5. Patients with an AV block II degree Mobitz 2 type or higher, sick sinus syndrome or sinoatrial block, history of symptomatic bradycardia or recurrent syncope, significant QT prolongation (> 470 ms in women and > 450 ms in men)

6. Treatment with class Ia antiarrhythmic agents (quinidine, disopyramide) or class III (amiodarone, sotalol), beta-blockers, heart rate-lowering calcium channel blockers (verapamil, diltiazem or ivabradine) or other substances that can lower heart rate (digoxin, anticholinesterase agents or pilocarpine)

7. Pregnancy

III. Treatment is not administered, or discontinued (if initiated) in cases of:

1. Pregnancy.

2. Serious adverse drug reactions.

3. High level of non-adherence to the therapy.

4. Lack of clinical efficacy of the therapy (2 or more relapses per year).

5. Patients can switch to cladribine, alemtuzumab, natalizumab or ocrelizumab after a 1-month wash-out period.

6. Disability progression to EDDS = 5.

7. Reaching the age of 59, and absence of disease activity in the last 2 years.

Laboratory tests and follow-up evaluations required during fingolimod therapy

I. Prior to treatment initiation:

1. A recent complete blood count (within 1 month) and transaminase and bilirubin levels.

2. Testing for antibodies to varicella zoster virus (VZV). Vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment.

3. Ophthalmological evaluation.

II. At treatment initiation:

1. ECG, consultation with an internist, and blood pressure measurement before and 6 hours after the first dose of fingolimod.

2. Monitoring for a period of 6 hours for symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring is recommended.

III. During treatment:

1. Ophthalmological assessment is recommended at 3-4 months after treatment initiation.

2. Liver transaminases should be monitored at 1, 3, 6, 9, and 12 months after initiation of therapy, and every 6 months thereafter.
3. Periodic follow-up every 6 months of complete blood count and discontinuation of treatment when the lymphocyte count drops below $0,2 \times 10^9/l$, until recovery.
4. Patients must report visual disturbances or signs and symptoms of infection at any time while on therapy.
5. If treatment is interrupted for more than 2 weeks, patients should be monitored for 6 hours upon the resumption of treatment.

Cladribine (Mavenclad) is a selective immunosuppressor. The product was approved by EMA in August 2017 for the treatment of adult patients with highly active relapsing multiple sclerosis.

Orally administered at a cumulative dose of 3.5 mg / kg body weight for 2 years, administered as 1 treatment cycle of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. Following completion of the 2 treatment cycles, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.

Cladribine is a nucleoside analogue of deoxyadenosine. The mechanism by which cladribine exerts its therapeutic effects in MS is not fully elucidated, however its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS. Cells of the innate immune system are less affected than cells of the adaptive immune system. Treatment with cladribine leads to rapid reductions in circulating CD4+ and CD8+ T cells. CD8+ T cells have a less pronounced decrease and a faster recovery than CD4+ T cells, resulting in a temporarily decreased CD4 to CD8 ratio. Cladribine reduces CD19+ B cells and CD16+/CD56+ natural killer cells, which also recover faster than CD4+ T cells.

Cladribine reduces the annual relapse rate by 58% and the mean number of T1 Gd+ lesions on MRI by 86%. The reduction of the risk of disability progression with cladribine compared to placebo is 47%. In patients with highly active disease, cladribine reduces the annual relapse rate by 66-68%, and the risk of disability progression by 82%.

The strength of its efficacy for reducing relapse rate and delay of disability progression is sustained during years 3 and 4 without need for further treatment.

Adverse drug reactions of highest clinical relevance are lymphopenia and herpes zoster. Transient grade 3 or 4 lymphopenia has been seen in up to 25% of patients mainly 2 months after the first cladribine dose in each treatment year. Transient grade 4 lymphopenia has been seen in less than 1% of patients. Most patients recover to either normal lymphocyte counts or grade 1 lymphopenia within 9 months.

This drug is contraindicated in: infection with human immunodeficiency virus (HIV), active chronic infection (tuberculosis or hepatitis), in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy, active malignancy, moderate or severe renal impairment (creatinine clearance <60 mL/min), pregnancy and breast-feeding.

Criteria for treatment of multiple sclerosis with cladribine tablets in patients with relapsing-remitting disease

I. Inclusion criteria:

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria)
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. Aggressive disease course with increased relapse rate (at least 2 relapses in the previous year), despite treatment with first-line drugs
5. Significant increase in T₂ lesions compared to the latest MRI scan during the last 12 months

II. Exclusion criteria

1. Severe comorbidities – moderate or severe hepatic impairment (Child-Pugh score >6), moderate or severe renal impairment (creatinine clearance < 60 ml/min)
2. Human immunodeficiency virus (HIV) infection
3. Immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy
4. Active chronic infection (tuberculosis or hepatitis)
5. Pregnancy and breast feeding
6. Active malignancy

III. Treatment is not administered, or discontinued (if initiated) in cases of:

1. Pregnancy of a female patient
2. Serious adverse drug reactions

3. High level of non-adherence to the therapy
4. Lack of clinical efficacy of the therapy (2 or more relapses per 1 year)
5. The patient can switch to treatment with fingolimod, natalizumab, alemtuzumab or ocrelizumab
6. Disability progression to EDDS = 5
7. Reaching the age 59 year and absence of disease activity during the last 2 years

**Laboratory tests and follow-up evaluations required during therapy
with cladribine tablets**

I. Prior to treatment initiation (first cycle):

1. Complete blood count with differential: lymphocytes counts must be normal $\geq 1,000$ cells/mm³
2. Serum transaminases, bilirubin, blood urea nitrogen, creatinine
3. Screening for latent infections, in particular hepatitis B and C and tuberculosis (T-spot test).
Initiation of cladribine should be delayed until the infection is fully controlled
4. Testing for anti-VZV antibodies in patients without a history of chickenpox or without varicella zoster virus (VZV) vaccine. VZV vaccination of antibody-negative patients should be considered prior to treatment initiation.

II. During the first and up to 6 months after the last (second) treatment cycle:

1. Complete blood count with differential:
 - a) at 2 and 6 months of treatment initiation in each year of treatment
 - b) Before initiating cladribine in year 2, the lymphocyte counts should be at least 800 cells/mm³. If necessary, the year 2 treatment cycle can be delayed for up to 6 months to allow recovery of lymphocytes.

Monoclonal antibodies have caused a revolution in the treatment of autoimmune diseases. Recent advances in monoclonal antibody technology have enabled the development of quite specifically targeted immunotherapies. The problem is that such specific therapies may not be appropriate for diseases without fully elucidated underlying immunopathology, because of the risk of unforeseeable and undesirable effects.

Natalizumab (Tysabri®) is the first humanized monoclonal antibody, approved by FDA for the treatment of relapsing-remitting multiple sclerosis. Administered at a dose of 300 mg as a 1-hour intravenous infusion once monthly (every 4 weeks). A second-line therapy in younger patients with early and active disease course with prevailing inflammatory changes. Given the risk of severe side effects, natalizumab should be used as monotherapy only in patients with aggressive relapsing-

remitting disease who are preferably negative for JC (John Cunningham) virus antibodies and do not respond to first-line therapy. Should not be combined with other disease modifying drugs because of the risk of severe complications. The half-life of natalizumab is 11 days.

Natalizumab is a recombinant anti- α 4-integrin antibody, targeting the α 4-subunit (CD49d) of α 4- β 1 and α 4- β 7 (VLA-4) of integrin receptors on the surface of activated T cells. Natalizumab binds the integrin T-cell specific receptor antigen VLA-4 (Very Late Appearing Antigen-4), which mediates binding to brain endothelium adhesion molecule-1 (VCAM-1) and promotes transmigration of circulating T cells into the CNS. In this way, it blocks the interaction of lymphocyte integrin receptors with VCAM-1 receptors on the vascular endothelial membrane. Partially inhibits leukocyte activation, proliferation and migration to the sites of inflammation.

Natalizumab reduces the relapse rate by approximately 60% and MRI lesions by 90%. It also reduces the number of new MRI lesions and their conversion to “black holes” associated with axonal loss. Improves inflammatory demyelination-mediated visual disorders. Reduces the risk of disability progression by 25-40%. Natalizumab’s efficacy increases during the second year of treatment.

The *biological markers* of natalizumab activity are not studied yet, but drug concentrations, easily measured with ELISA, are objective markers of its bioavailability.

Neutralizing antibodies to natalizumab develop in about 10% of patients as soon as after the third infusion. Although it is a humanized monoclonal antibody, a small part of it, which is produced from mice, is susceptible to antibodies. In 6% of patients, neutralizing antibodies persisting over time reduce the clinical efficacy of the drug and increase its allergic side effects. In some patients, NABs disappear within about 2 years.

The adverse reactions are associated with fatigue, headache, depression, joint pain, urinary and pulmonary (bronchopneumonia) infections, and abdominal discomfort. Less than 1% of patients experience serious hypersensitivity reactions. Because of reported cases of hepatotoxicity, the medication is contraindicated in patients with evidence for hepatic disease.

Progressive multifocal leukoencephalopathy (PML) is the most severe treatment complication. The risk is up to 4 cases per 1000 treated patients. The risk is higher at a higher level of anti JCV antibodies, longer treatment and concomitant immunosuppressive therapy. It is a result of disturbance of the T lymphocyte-mediated immunity (dramatic decrease of T cells) and premature development of pre-B cells in the bone marrow. Natalizumab increases the level of circulating B cells which carry the JC polyomavirus which causes PML. The number of CD4 cells, which play an important role in the control of the infection, is also reduced. However, the treatment benefits exceed the risk of potential life-threatening PML.

The risk of PML development is determined by screening for the presence of anti-JC virus antibodies, prior to treatment initiation. Repeat testing on a yearly basis is recommended, since every year 2% of the population are likely to experience spontaneous seroconversion of the antigen status. The risk of development of leukoencephalopathy is highest during the third year of treatment. In JCV antibody-positive patients who have received one or two years of treatment with natalizumab a change of therapy should be considered. It should be considered that such a change is likely to increase the frequency of relapses.

If PML occurs, the immune effector response should be promptly restored by restoring the capability of leukocytes to migrate across the blood-brain barrier suppressed by natalizumab. This is achieved by plasma exchange, which reduces $\alpha 4$ integrin saturation.

Criteria for treatment of multiple sclerosis with the monoclonal antibody natalizumab in patients with relapsing-remitting disease

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. Aggressive disease course with increased relapse rate (at least 2 relapses during the preceding year), despite treatment with first-line drugs
5. Significant increase in T₂ lesions compared to the latest MRI scan during the last 12 months

II. Exclusion criteria

1. Severe comorbidities – cardiac diseases, pulmonary diseases, renal or hepatic disorders and infections
2. Pregnancy or planning for pregnancy

III. Treatment is not administered, or discontinued (if initiated) in cases of:

1. Pregnancy
2. Serious adverse drug reactions:
 - In case of onset of new neurological symptoms, the assumed causes are PML or another opportunistic infection until condition is clarified.
 - MRI scan and lumbar puncture for JCV testing should be considered
 - In case of negative test results, it is assumed that the new symptoms are a result from disease attack and appropriate treatment should be initiated

- Is symptoms resolve following treatment, dosing of natalizumab may resume
3. High level of non-adherence to the therapy
 4. Lack of clinical efficacy of the therapy (2 or more relapses per 1 year)
 5. Patients may switch to fingolimod, cladribine, alemtuzumab or ocrelizumab after a 2-month wash-out period
 6. After a 2-year treatment, in JCV-positive patients, a benefit/risk assessment should be performed and in case of continuation of natalizumab therapy, JCV-index assessment and MRI screening should be performed at least every 6 months.
 7. Disability progression to EDSS = 5
 8. Reaching the age 59 years and absence of disease activity during the last 2 years
 9. PML has been reported following discontinuation of natalizumab. Monitoring is recommended especially in patients who have switched to other therapies with potential risk of PML development

Laboratory tests and follow-up evaluations required during natalizumab therapy

I. Prior to treatment initiation:

1. MRI scan
2. Testing for anti JCV antibodies. In patients negative for anti-JCV antibodies at baseline a new test may be performed every 6 months.

II. During the treatment:

1. Annual testing for anti-JCV antibodies
2. Monthly monitoring for changes in neurological status
3. Evaluation of ALAT, ASAT and bilirubin every 6 months
4. MRI screening every 6 months and laboratory JCV-index assessment for JC-positive patients

Alemtuzumab (Lemtrada®) is a humanized monoclonal antibody for the treatment of B-cell chronic lymphocytic leukemia. In 2013, this medicinal product was approved by FDA for first-line treatment of relapsing-remitting multiple sclerosis. In 2014, FDA approved its use only as second-line treatment in patients with aggressive disease course who have not responded to first-line therapy. The drug is not efficient in secondary progressive multiple sclerosis.

The drug is administered once a year at a dose of 12 mg/day by 4-hour intravenous infusion on 5 consecutive days (60 mg total dose), followed by three consecutive infusions (36 mg total dose) given 12 months after the initial treatment cycle. The benefits and risks of more than 2 treatment cycles have not been fully established, but the safety profile does not appear to change with additional courses.

Alemtuzumab binds to CD52, a cell surface glycoprotein receptor antigen presents on lymphocytes (T and B cells) and on natural killer cells, monocytes, and macrophages. It causes apoptosis and depletion of lymphocytes with CD52 receptors via antibody-mediated cell toxicity. Lymphocytes repopulate over time with B-cell recovery usually completed within 6 months, while T-cell repopulation takes longer. CD8⁺ T cell counts rise to normal within about 30 months, but CD4⁺ T cell counts – not earlier than 5 years post-treatment. Due to B cell activation and transient elevation of cytokine levels after treatment initiation, a temporary neurological decline might be observed. There is no evidence that the drug affects the immunological memory for antibodies to common viruses and vaccines. The ability of generation of humoral immune responses against new antigens is also preserved.

Clinical trials in patients with relapsing-remitting multiples sclerosis have shown reduction of the annual relapse rate by 55% versus subcutaneous interferon β -1a, and reduction in contrast-enhancing T₂ lesions and brain atrophy on MRI, but no significant effect on disability progression. In patients with unsatisfactory outcome from previous IFN beta treatment, alemtuzumab reduced the relapse rate and risk of disability progression by 40%. In patients with early-phase disease improvement of disability and brain volume increase have been observed, probably due to the release of neurotrophic factors from immune cells recovering after treatment.

Inhibitory antibodies have been found in 85% of patients, but are not associated with decrease in efficiency and adverse reactions.

Adverse reactions include infusion reactions such as chills, rash, headache, nausea and vomiting; upper respiratory tract and urinary tract infections, lymphopenia, leukopenia, flushing, nausea, fatigue, as well as transient neurological decline (for several hours) due to the release of cytokines. For their control, premedication with corticosteroids (methylprednisolone 1,000 mg) is given for the first 3 days of each treatment cycle.

There is a possibility for rare serious adverse reactions occurring within 1 to 3 days after infusion of each dose during the first year of treatment, as well as after the second treatment course. Such reactions are unpredictable and affect different organs and systems, have an acute course of development and can be fatal. They also include complications not associated with a concomitant condition or known underlying medical risk for the patient.

Hemorrhagic stroke in the days after the infusion might occur in patients below 50 years of age, without history of hypertension, coagulation disorders or concomitant anticoagulant or antiplatelet therapy.

Myocardial ischemia (including myocardial infarction) is an infusion complication, which is not associated with accompanying risk factors. Part of the patients reported were below 40 years of age and had no risk factors for ischemic heart disease.

Arterial dissections of branches of the vertebral and carotid arteries, including multiple dissections, have been reported both within the first days after alemtuzumab application or later on, within the first month after the infusion.

Pulmonary alveolar hemorrhage might occur spontaneously, without temporal or causal relationship to anti-GBM disease (Goodpasture syndrome).

Thrombocytopenia as an infusion complication might occur within the first days after the infusion (unlike immune (idiopathic) thrombocytopenic purpura, ITP). It is often self-limiting and relatively mild.

Secondary autoimmune complications, occurring within 5 years after treatment but reaching a peak in the second-year post-treatment, are a major issue.

Autoimmune hyperthyroidism (Graves's disease) develops in 30% of patients as a result of development of antibodies to thyrotropin receptors. Autoimmune hyperthyroidism occurs within 48 months following first alemtuzumab exposure. Most complications are mild to moderate in severity and serious events occur in less than 1% of patients.

Idiopathic immune thrombocytopenic purpura occurs in 2% of patients between 14 and 36 months after first exposure.

Nephropathies, including anti-glomerular basement membrane disease, have been observed in 0.3% of patients within 39 months after the last dose.

Prophylaxis with an oral anti-herpes agent (acyclovir 200 mg BID) should be initiated in all patients starting on the first day of each treatment cycle and continuing for at least 1 month.

Criteria for treatment of multiple sclerosis with alemtuzumab in patients with relapsing-remitting disease

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. Aggressive disease course with increased relapse rate (at least 2 relapses during the preceding year), despite treatment with first-line drugs

5. Significant increase in T2 lesions compared to the latest MRI scan during the last 12 months
6. The medicine's application should only be done in a hospital with ready access to intensive care

II. Exclusion criteria

1. Sever active infection until complete resolution.
2. Uncontrolled hypertension.
3. History of arterial dissection of the cervicocephalic arteries
4. Stroke history.
5. History of angina pectoris or myocardial infarction
6. Known coagulopathy, concomitant anti-platelet or anti-coagulant therapy
7. Other concomitant autoimmune diseases (besides MS)
8. Human immunodeficiency virus (HIV) infection
9. Pregnancy and breast feeding

III. Treatment is not administered or discontinued (if initiated) in cases of:

1. Pregnancy of female patients
2. Serious adverse drug reactions
3. High level of non-adherence to the therapy
4. Lack of clinical efficacy of the therapy (2 or more relapses per 1 year)
5. The patient can switch to treatment with fingolimod, cladribine, natalizumab or ocrelizumab
6. Disability progression to EDSS = 5
7. Reaching the age 59 years and absence of disease activity during the last 2 years

Laboratory tests and follow-up evaluations required during alemtuzumab therapy

I. Prior to treatment initiation:

1. Complete blood count with differential
2. Serum creatinine levels
3. Serum levels of liver transaminases
4. Urinalysis with microscopy
5. Thyroid function evaluation – thyroid stimulating hormone (TSH) levels
6. Screening for active and latent tuberculosis with T-spot test. In patients with active infection initiation of treatment is delayed until the infection is fully controlled

7. Testing for anti-VZV antibodies in patients without a history of chickenpox or without varicella zoster virus (VZV) vaccine. VZV vaccination of antibody-negative patients should be considered prior to treatment initiation
8. Screening for hepatitis B and C viruses
9. Treatment should not be initiated in case of any active infection
10. Prior to initiation and re-administration of therapy, MRI scan should be performed and evaluated for PML signs

II. During treatment and for 48 months following the last treatment course:

1. Complete blood count with differential (monthly)
2. Serum creatinine levels (monthly)
3. Serum levels of liver transaminases (monthly)
4. Urinalysis with microscopy (monthly)
5. Thyroid function evaluation – thyroid stimulating hormone (TSH) levels – every 3 months)

Ocrelizumab (Ocrevus) is a recombinant humanized anti-CD20 monoclonal antibody. Ocrelizumab was approved by FDA for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) in 2017. In 2018 Ocrelizumab received EMA approval for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) as well as for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion for 2,5 hours, followed 2 weeks later by a second 300 mg infusion. Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg intravenous infusion for 3,5 hours every 6 months. If patients did not experience a serious infusion-related reaction (IRR) with any of the previous Ocrevus infusions, a shorter (2-hour) infusion can be applied for subsequent doses. Premedication must be administered prior to each ocrelizumab infusion to reduce the frequency and severity of infusion related reactions (IRRs): 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion and antihistamine approximately 30-60 minutes prior to each ocrelizumab infusion. In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes prior to each infusion.

Ocrelizumab selectively targets CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. The capacity of B-cell reconstitution and preexisting humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Clinical trials in patients with relapsing forms of MS show reduction in annual relapse rate by 47% compared to interferon β -1a 44 mg, s.c., reduction in MRI Gd+T1 lesions by 94 % and reduction in new and/or enlarging T2 hyperintense lesions by 80%, as well as reduction in brain atrophy. Ocrelizumab reduces the risk of disability progression by 40% compared to interferon β -1a 44 mg s.c.

Clinical trial in patients with primary progressive MS shows that Ocrelizumab significantly delays the 12 weeks confirmed disability progression by 24% and reduces deterioration in walking speed compared to placebo. Ocrelizumab treatment reduces the volume of MRI T2 hyperintense lesions and loss of brain volume.

Inhibitory antibodies were detected in 1% of patients, but they were not associated with changes in the efficacy or safety of the drug.

Adverse events with the highest clinical relevance are infusion-related reactions (IRR) and infections. IRR include but are not limited to itching, rash, urticaria, erythema, redness, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnea, laryngeal or pharyngeal edema, nausea, tachycardia. Among the infections, leading are the upper respiratory tract, nasopharyngitis, influenza, sinusitis, bronchitis, oral herpes, gastroenteritis, viral infection, herpes zoster, conjunctivitis, cellulitis, etc. Blood immunoglobulin M levels were decreased. There is a potential risk for PML occurrence.

Ocrelizumab *is contraindicated* in patients with active infection (e.g. hepatitis, tuberculosis), until the infection is fully controlled, severely immunocompromised patients (lymphopenia, neutropenia, hypogammaglobulinemia), known active malignancies, progressive multifocal leukoencephalopathy (PML) or suspected PML, pregnancy and breastfeeding.

**Criteria for treatment of multiple sclerosis with ocrelizumab in patients
with relapsing-remitting disease**

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria
2. Age >18 years
3. Disability score of up to 4.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. Aggressive disease course with increased relapse rate (at least 2 relapses during the preceding year), despite treatment with first-line drugs
5. Significant increase in T₂ lesions compared to the latest MRI scan during the last 12 months

II. Exclusion criteria

1. Severe comorbidities: patients in a severely immunocompromised state (e.g. with lymphopenia, neutropenia, hypogammaglobulinemia); known active malignancies;
2. It is forbidden to use other immunosuppressives concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses
3. Planned pregnancy, pregnancy and breast feeding

III. Treatment is not administered or discontinued (if initiated) in cases of:

1. Pregnancy of female patients
2. Serious adverse drug reactions: life-threatening infusion related reactions or serious hypersensitivity reactions, during any previous infusion with ocrelizumab.
3. Active infection other than a fungal nailbed infection. The re-treatment should be delayed until the active infection is treated and patient fully recovered
4. CD4 cell count < 250/ μ L
5. Active Hepatitis B virus (HBV) infection or Hepatitis B virus reactivation
6. Progressive multifocal leukoencephalopathy (PML)
7. Active tuberculosis infection – new or reactivated
8. High level of non-adherence to the therapy
9. Lack of clinical efficacy of the therapy (2 or more relapses per 1 year)
10. The patient can switch to treatment with fingolimod, cladribine, natalizumab or alemtuzumab
11. Disability progression to EDSS = 5
12. Reaching the age 59 years and absence of disease activity during the last 2 years

Laboratory tests and follow-up evaluations required during ocrelizumab therapy

I. Prior to treatment initiation:

1. Complete blood count with differential, lymphocytes counts must be normal and CD4 cell count $\geq 250/\mu$ L

2. Serum transaminases, bilirubin, blood urea nitrogen, creatinine
3. Screening for latent infections, in particular hepatitis B and C, HIV and tuberculosis (T-spot test).
Initiation of ocrelizumab should be delayed until the infection is fully controlled
4. Patients who require vaccination with live or live attenuated vaccines should complete their immunization at least 6 weeks prior to initiation of ocrelizumab.

II. Prior each following ocrelizumab infusion, i.e. every six months:

1. Complete blood count with differential, CD4 cell count $\geq 250/\mu\text{L}$.
2. Serum transaminases, bilirubin, blood urea nitrogen, creatinine
3. Screening for latent infections, in particular hepatitis B and C, HIV and tuberculosis (T-spot test).
Initiation of ocrelizumab should be delayed until the infection is fully controlled.

Conversion from relapsing-remitting to secondary progressive multiple sclerosis is defined in case of gradual progression (>1 point EDSS score increase within 1 year) without evidence of relapsing activity or in case of propulsive aggravation of MS symptoms.

Treatment of active secondary progressive multiple sclerosis is conducted with siponimod (Mayzent). Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Criteria for siponimod therapy in patients with SPMS

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. McDonald diagnostic criteria
2. Age > 18 years
3. Disability score of up to 5.0 (Kurtzke Expanded Disability Status Scale [EDSS])
4. 6 months duration of progression and possible propulsive aggravation of MS symptoms
5. MRI data confirmatory for inflammatory disease activity – Gd-enhancing T₁ lesions and/or active (new or enlarging) T₂ lesions.

II. Exclusion criteria

1. Patients with immunodeficiency syndrome or patients on immunosuppressive therapies.
2. History of progressive multifocal leukoencephalopathy or cryptococcal meningitis
3. Active malignancies
4. Severe liver impairment (Child-Pugh class C).

5. Patients who in the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or heart failure NYHA class III/IV.
6. Patients with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sinoatrial heart block or sick-sinus syndrome, if they do not have a pacemaker.
7. Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser).
8. During pregnancy and in women of childbearing potential not using effective contraception

III. Treatment is not administered or discontinued (if initiated) in cases of:

1. Pregnancy
2. Serious drug adverse events
3. Consistent non-adherence to the therapy
4. Progressive multifocal leukoencephalopathy or cryptococcal meningitis
5. Disability progression to EDSS = 6
6. Reaching age of 59 years and absence of disease activity during the last 2 years
7. Previous treatment with alemtuzumab

Laboratory tests and follow-up evaluations required during siponimod therapy:

I. Prior to treatment initiation:

1. A recent complete blood count (within 1 month), serum transaminases and bilirubin levels.
2. Testing for antibodies against varicella zoster virus (VZV). VZV vaccination of antibody-negative patients should be done prior to treatment initiation.
3. Genetic testing to determine CYP2C9 genotype status
4. Ophthalmological evaluation.

II. At treatment initiation:

1. In patients with sinus bradycardia (heart rate <55 bpm), first- or second-degree [Mobitz type I] AV block or history of myocardial infarction in the previous 6 months or heart failure: monitoring for a period of 6 hours for symptoms of bradycardia with hourly heart rate and blood pressure measurement.
2. Serum transaminases, bilirubin, blood urea nitrogen, creatinine
3. If a dose is missed during the first 6 days of treatment initiation, treatment needs to be reinitiated with a new titration pack.

III. During treatment:

1. Ophthalmological evaluation 3-4 months after treatment initiation.

2. Regular complete blood count assessment every 6 months; in case of absolute lymphocyte counts $<0.2 \times 10^9/L$, the dose should be reduced to 1 mg. Confirmed absolute lymphocyte counts $<0.2 \times 10^9/L$ in patients already receiving siponimod 1 mg should lead to interruption of siponimod therapy until the level reaches $0.6 \times 10^9/L$ when re-initiation of siponimod can be considered.
3. Patients should be instructed to report to their physician all visual disturbances or symptoms of infection.
4. If treatment is interrupted for more than 4 consecutive days, it must be re-initiated with a new titration pack

Treatment of the secondary progressive phase of the disease in patients with frequent relapses and disability progression (**progressive-relmitting MS**) can also be conducted with Interferon's beta-1b therapies (Betaferon, Extavia®). At present this therapy for treatment of secondary progressive MS is not widely used in clinical practice. Despite the lack of efficacy data from recent clinical trials, interferon beta-1b shows decrease of superimposed relapses' frequency & intensity in patients with secondary progressive course of multiple sclerosis. Disability progression time is increased by 12 months for 2 years & the number of new MRI lesions decreases. Treatment is given to patients with more rapid progression; pharmacological treatment is not required in slow disease progression.

Criteria for multiple sclerosis treatment with interferons beta-1b therapies (Betaferon, Extavia®) in SPMS patients with frequent superimposed relapses

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria
2. Age > 18 years
3. EDSS score of up to 4.0

II. Exclusion criteria

1. Concomitant chronic diseases which shorten life expectancy (alcohol abuse, dementia, psychotic disorders, active malignancies).
2. Patients with severe depression and suicide attempts during treatment
3. Pregnancy

III. Treatment is not administered or discontinued (if initiated) in cases of:

1. Pregnancy

2. Serious adverse drug reactions
3. Lack of clinical efficacy of the therapy – progressive deterioration of patient's condition by more than 1 point in EDSS score within 1 year.
4. High level of non-adherence to the therapy
5. Disability progression to EDSS = 5
6. Reaching the age of 59 years and the absence of disease activity during the last 2 years

In patients with secondary progressive multiple sclerosis and frequent superimposed relapses the neurologist must decide for initiation of:

1. Siponimod therapy
2. Interferon beta-1b therapy (Betaferon, Extavia)
3. Symptom management

Ocrelizumab (Ocrevus) **is used for the treatment of primary progressive multiple sclerosis.** Ocrelizumab is used for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Criteria for multiple sclerosis treatment with ocrelizumab in patients with primary progressive disease

I. Inclusion criteria

1. Multiple sclerosis diagnosed according to 2017 revision of Thompson et al. to the McDonald diagnostic criteria
2. Age > 18 years
3. EDSS score of up to 4.0
4. Disease duration from the onset of symptoms more than 1 year and less than 3 years.
5. Lack of relapses from the disease onset with concomitant progressive symptoms worsening.
6. MRI data confirmatory for inflammatory disease activity- T1 Gd-enhancing lesions and/or active (new or enlarging) T2 lesions.

II. Exclusion criteria

1. Severe comorbidities: patients in a severely immunocompromised state (e.g. with lymphopenia, neutropenia, hypogammaglobulinemia); known active malignancies;

2. It is forbidden to use other immunosuppressives concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses

3. Planned pregnancy, pregnancy and breast feeding

III. Treatment is not administered or discontinued (if initiated) in cases of:

1. Pregnancy of female patients

2. Serious adverse drug reactions: life-threatening infusion related reactions or serious hypersensitivity reactions, during any previous infusion with ocrelizumab.

3. Active infection other than a fungal nailbed infection. The re-treatment should be delayed until the active infection is treated and patient fully recovered

4. CD4 cell count $< 250/\mu\text{L}$

5. Active Hepatitis B virus (HBV) infection or Hepatitis B virus reactivation

6. Progressive multifocal leukoencephalopathy (PML)

7. Active tuberculosis infection – new or reactivated

8. High level of non-adherence to the therapy

9. Lack of clinical efficacy of the therapy - progressive deterioration of patient's condition by more than 1 point in EDSS score within 1 year.

10. Disability progression to EDSS = 5

11. Reaching the age 59 years and absence of disease activity during the last 2 years

Laboratory tests and follow-up evaluations required during ocrelizumab therapy

I. Prior to treatment initiation:

1. Complete blood count with differential, lymphocytes counts must be normal and CD4 cell count $\geq 250/\mu\text{L}$

2. Serum transaminases, bilirubin, blood urea nitrogen, creatinine

3. Screening for latent infections, in particular hepatitis B and C, HIV and tuberculosis (T-spot test). Initiation of ocrelizumab should be delayed until the infection is fully controlled

4. Patients who require vaccination with live or live attenuated vaccines should complete their immunization at least 6 weeks prior to initiation of ocrelizumab.

II. Prior each following ocrelizumab infusion, i.e. every six months:

1. Complete blood count with differential, CD4 cell count $\geq 250/\mu\text{L}$.

2. Serum transaminases, bilirubin, blood urea nitrogen, creatinine

3. Screening for latent infections, in particular hepatitis B and C, HIV and tuberculosis (T-spot test).
Initiation of ocrelizumab should be delayed until the infection is fully controlled

Stem cell transplantation is used to achieve rapid, complete and long-lasting immunosuppression. Peripheral blood stem cell transplantation is performed after development of deep immunosuppression. It might be efficient in patients with malignant MS, however its toxicity with a mortality rate of 5-10% should be considered. To date, there have been few published studies with up to 2-year follow-up in which 80% of patients with relapsing-remitting MS were relapse-free compared to only 40% of patients with primary progressive MS. Maintenance immunosuppressive therapy is not required. The use of stem cell transplantation in clinical practice requires studies with significantly longer duration. The Movement Disorders and Multiple Sclerosis Society, and the Bulgarian Society of Neurology do not recommend this therapy until its efficacy and safety have been established in controlled studies.

Percutaneous transluminal endovascular angioplasty or extracranial venous stenting for treatment of chronic cerebrospinal venous insufficiency should not be used in patients with multiple sclerosis. Chronic cerebrospinal venous insufficiency has no role in the pathogenesis of multiple sclerosis.

**Patients are admitted by a neurologist to a neurological unit or
outside UCDM-MS for:**

- Relapse management
- Pharmacological treatment initiation outside of clinical relapse
- Onset of other threatening symptoms

**The neurologist at UCDM-MS should see the patient once every 6 months, whenever
deterioration occurs and monitor for signs of:**

- Onset of new relapse
- Progressive neurological decline with an increase in EDSS score of 1 or more points sustained over one year
- Increased relapse rate – more than 2 relapses per year
- Treatment side effects outside of clinical relapse
- Treatment efficacy outside of clinical relapse

- Depression, fatigue, cognitive, sexual or pelvic floor disorders
- Need for symptomatic management

The optimization of treatment control requires clinical assessment of patients at least once every 6 months. Follow-up evaluations should include relapse rate, severity and duration of relapses and degree of recovery from the relapse. This allows for the patient's optimal response to the administered immunomodulatory therapy to be determined. A reduction in relapse rate by 30% to 45% from baseline is a criterion for treatment efficacy. Evaluation of treatment efficacy can be performed 6 months after initiation of therapy. Relapses have different significance for patients depending on the associated clinical symptoms. Signs of motor and cerebellar system dysfunction and symptoms of pelvic bowel and bladder disorders, particularly with involvement of several systems during relapse, are predictors of poorer outcome. Relapses requiring corticosteroid treatment are significant. Relapses in the early stages of the disease that are unresponsive to corticosteroid treatment are also associated with poorer prognosis. Refractoriness to steroid therapy is common in more advanced stages of the disease. An immunomodulatory therapy may be considered not sufficiently effective if recovery from previous relapse is incomplete or lasts several months. Disability progression measured by EDSS (Appendix 6) is another sign of lack of efficiency of immunomodulatory therapy. Treatment efficacy evaluation is also based on MRI findings. This includes evidence of new or enlarged T₁ and T₂ lesions, gadolinium-enhanced lesions, brain atrophy and total MRI burden of the disease. Assessments of cognitive function, fatigue, depression, social activities and quality of life are also important in determining the efficacy of treatment. Based on evidence for immunomodulatory therapy impact on cognitive disturbances, cognitive decline is considered an indicator of suboptimal treatment efficacy.

- **Treatment should be reconsidered in evidence of worsening of relapses, disability progression and MRI findings (Appendix 6):**
 - Evidence of low level of significance for all three parameters
 - Evidence of moderate level of significance for 2 parameters
 - Evidence of high level of significance for one parameter
 - Treatment of a patient with relapsing-remitting or secondary progressive MS should be continued until disability EDSS score 5 (6.0 for siponimod, respectively) is reached.

- After this degree of disability relapse rate reduction has no impact on disability progression

Conventional treatment is not efficient in a certain portion of patients. Currently used medications mainly address inflammation and have a moderate effect on the relapse rate. In one-third of patients on average, the relapse rate remains unchanged. Better clinical outcomes observed in patients with more relapses are explained with more prominent inflammatory rather than degenerative component of the disease. No drugs are available yet that can influence the neurodegenerative process. If case of therapy inefficiency, the patient should be offered enrolment in clinical trials of new drugs.

To avoid any disappointment, it should be explained to the patients that the treatment aims at reducing the rate of subsequent relapses, but it does not have any effects on the current symptoms of the disease. Reduction in the relapse rate by 30%, and possible delay of disability progression is what can be expected.

Symptomatic treatment is necessary because new symptoms appear, while old symptoms become worse, which has a negative impact on the patients' quality of life. In order to determine whether a certain symptom has to be treated, symptoms have to be classified into degrees such as mild, moderate and severe. Mild symptoms are those that do not interfere with the patient's everyday activities and do not require treatment. Moderate symptoms interfere with every day and social activities of the patient, and cause discomfort. Such symptoms require pharmacological treatment. Severe symptoms lead to disability, and limit to a serious extent the patient's everyday activity. These symptoms usually cannot be managed by pharmacological treatment and require more specific measures and care.

Fatigue is managed by different non-pharmacological methods, such as aerobic exercises, physical therapy, behavioral therapy and others. The administration of amantadine – 200 mg daily, fluoxetine – 10 to 40 mg daily, and modafinil – 100-400 mg in the morning relieves fatigue.

Cognitive disorders are managed with donepezil 10 mg daily, although treatment efficacy is relatively low.

Affective disorders – depression is managed with tricyclic antidepressants and serotonin and noradrenaline reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs). Lithium and anticonvulsants are used for the treatment of bipolar disorders and tricyclic antidepressants (amitriptyline 25 mg daily) – for the management of pathological laughter and crying.

Pain syndromes are relieved using tricyclic antidepressants and SNRIs (amitriptyline, venlafaxine, moclobemide, mirtazapine, duloxetine, milnacipran), anticonvulsants (carbamazepine, gabapentin, phenytoin, topiramate, gabapentin and pregabalin) and skeletal muscle relaxants.

Muscle weakness is best managed by physical therapy and physical exercises. Patients should be encouraged to be physically active. Preventive measures to minimize muscle contracture development and preserve passive joint movements of affected limbs are recommended.

Gait disturbances are improved using the potassium channel blocker fampridine (Fampyra®). By blocking potassium channels, fampridine reduces the leakage of ionic current through these channels which prolongs re-polarization and enhances action potential formation in demyelinated axons. It is thought that by enhancing action potential formation, more impulses might be conducted in the central nervous system. Fampyra® should be prescribed and used under the supervision of a clinician experienced in the treatment of multiple sclerosis. The recommended dose is one 10 mg tablet twice daily. Tablets should be taken without food. The initial prescription should be for no more than 2 weeks of therapy, and should be followed by evaluation of the clinical efficacy of the drug, determined by a T25FW (timed 25-foot walk) test. Fampyra® should be discontinued if there is no benefit or worsening is reported by the patient.

Spasticity (increased muscle tone) is well managed by physical therapy and muscle relaxants. Tizanidine (Sirdalud®) – up to 24 mg daily, and baclofen – up to 70 mg daily can be used.

Vertigo might be a symptom of relapse in which case it can be well managed by a course of corticosteroids. In case it is a residual symptom, dimenhydrinate 75-150 mg/day, betahistine 48 mg/day, and combined therapy with cinnarizine/dimenhydrinate (Arlevert®), 3x1 tablet daily can be used.

Tremor is difficult to manage but in some cases treatment with clonazepam 2-4 mg/day, propranolol 50-100 mg, isoniazid 1,200 mg/day, glutethimide 1,000-4,000 mg/day or primidone 250 mg/day is effective.

Paroxysmal symptoms respond to anticonvulsants, tricyclic antidepressants and benzodiazepines. Carbamazepine (up to 1,200 mg daily) is the drug of choice. Epileptic seizures can be well managed by the use of conventional anticonvulsants such as carbamazepine and phenytoin, and valproates.

Pelvic floor disorders can seriously affect the quality of patients' lives. Overactive bladder is improved by anticholinergic agents (oxybutynin 10 mg daily or tolterodine (Detrusitol®) 4 mg daily), the β_3 -adrenergic receptor agonist mirabegron (Betmiga®) 25-50 mg and tricyclic antidepressants, while intermittent catheterization is a method of choice in the treatment of underactive bladder. In less severe cases vibration devices are used on the abdominal wall above the bladder to stimulate bladder emptying. The patient should be observed for symptoms of incontinence or urinary infections and if necessary antibiotic treatment should be considered. Patients with nocturia are prescribed

desmopressin nasal spray (10-40 µg per night), an antidiuretic hormone, which reduces urination for 6-8 hours, but may cause hyponatremia. In patients with detrusor sphincter dyssynergia skeletal muscle relaxants and alpha-2 agonists can be used.

Sexual disorders are treated with antidepressants and erectile dysfunction is managed through administration of a phosphodiesterase type 5 inhibitor – sildenafil (Viagra®) 50 to 100 mg, vardenafil (Levitra®) 5-10 mg orally, 1 hour prior to sexual activity, and tadalafil (Cialis®) 20 mg.

Gastrointestinal disorders (constipation) require complex management. Above all, it has to be clarified whether the constipation is caused by any of the medications received and if so, their doses should be reduced. Increased physical activity, dietary changes by eating fibre-rich food, and the avoidance of chocolate products, hydration and warm drinks for stimulation of gastrointestinal reflexes are recommended. If dietary measures are insufficient mild laxatives may be used.

Dysphagia is managed by dietary modification and changes in the way of eating. In severe cases a nasogastric tube might be used.

Visual disorders (diplopia) are corrected with prism eyeglasses. Nystagmus is treated with baclofen, clonazepam, scopolamine, gabapentin and other drugs.

Respiratory disorders are managed through treatment of respiratory infections, regulation of body temperature to improve axonal conductivity and vaccines for anti-flu prophylaxis.

Rehabilitation is a very important part of health care delivery for patients with multiple sclerosis. They should be referred to physical therapy and rehabilitation when their everyday activities are already restricted and symptomatic management is no longer effective. At a certain time of his/her life the patient shall need crutches, a walking aid or a wheelchair, which requires a thorough assessment by a physiotherapy specialist.

Comprehensive care in MS patients has certain specific features.

Fever and infections should be prevented and promptly treated. Demyelinated fibres are extremely sensitive to minimal changes in body temperature or mild acidosis. Exposure to high temperatures on beaches, in saunas, tubs or swimming pools or even a slight elevation of 1-2 degrees in body temperature caused by infection may lead to disease deterioration. This is the reason for frequent relapses occurring even after mild respiratory infections. Management of fever in infections is extremely important and contributes significantly to the improvement of neurological symptoms.

Surgical interventions and anesthesia have a minimal impact on patient's condition, so they can be used if clinically indicated. Intrathecal and spinal anesthesia should be avoided; epidural anesthesia is well tolerated.

During *pregnancy* the risk of relapse decreases dramatically, especially during the third trimester, as corroborated by MRI findings. The risk increases considerably during the postpartum period. If the two periods are considered together, pregnancy carries no real risk of deterioration. Female patients with multiple sclerosis not only have no contraindications to pregnancy and delivery, but also disease prognosis is not worsened but rather improved by pregnancy. The risk of disease conversion to secondary progressive form is decreased. However, prognosis in patients who have already progressed to secondary progressive form of the disease is not so favourable. There is no evidence to suggest that MS affects in any way fertility, conception, fetal viability or birth. No increased risk of ectopic pregnancy, spontaneous abortion, stillbirth and congenital malformations has been observed. The only consideration that may need to be made in pregnancy planning is the patient's disability which might make child-bearing difficult. Children of a parent with MS have a low genetic risk of MS (about 3% to 5%), however in the very rare cases of both parents having MS, the risk will increase to 31%.

Safe prophylaxis should be considered in women planning pregnancy since MS is diagnosed primarily in reproductive age and 2/3 of affected individuals are women.

The demonstrated relative safety of *glatiramer acetate*, *interferons β -1a and β -1b* during pregnancy has made possible their label extension. All remaining preventive MS therapies are not recommended during pregnancy. Nevertheless, since none of the approved therapies have demonstrated absolute safety at the time of conception and during pregnancy, the general recommendation for contraception during immunomodulation remains valid.

Some disease-modifying drugs should be stopped prior to planned pregnancy because they are contraindicated during this period. The use of *glatiramer acetate*, *interferons β -1a and β -1b* during pregnancy is admissible only in aggressive forms of the disease when the benefits to the mother outweigh the potential risks to the fetus.

Monitoring of the use of *glatiramer acetate* 20 mg/ml and 40 mg/ml during the entire period of pregnancy has not shown risk of malformations, spontaneous abortions or feto/neonatal toxicity. The contraindication against the use of *glatiramer acetate* in pregnancy has been removed from the updated SmPC by EMA in 2016. Nevertheless, as a precautionary measure, it is preferable to avoid the use of *glatiramer acetate* during pregnancy, unless the benefit to the mother outweighs the risk to the fetus.

If clinically justified, the use of *interferon beta* may be considered before contraception and during the first trimester of pregnancy as there is no data indicative of increased risk of congenital fetal anomalies. Since experience with exposure during the second and third trimester is very limited

and the risk of spontaneous abortions cannot be adequately evaluated, treatment with interferon beta is contraindicated during this period of pregnancy.

There is no need of termination of unplanned pregnancy during therapy with interferons beta and glatiramer acetate. If treatment with these drugs is discontinued during the pregnancy and re-initiated after delivery, full treatment effect shall be achieved within several months and not during the risk period immediately following delivery.

There is no evidence for teratogenic effects of beta-interferons and glatiramer acetate, so mutagenicity is not increased even after long-term exposure of the mother and there is no risk for the child. Both glatiramer acetate and beta-interferon are big molecules and would not be expected to excrete in breast milk, so they are probably safe during breastfeeding.

Beta-interferons and glatiramer acetate do not interact with hormonal contraceptives and have no impact on their efficacy. There is no data available for reduced fertility associated with their use both in men and women.

Dimethyl fumarate does not interact with oral contraceptives and does not relate to their efficacy, it does not alter human fertility. It should be known that during the first weeks of the use of dimethyl fumarate patients may experience lower dyspeptic syndrome leading to reduced absorption and compromised efficacy of oral contraceptives. Dimethyl fumarate is not associated with increased risk of congenital malformations of the fetus and miscarriage. Strict adherence to contraception is recommended during therapy. Treatment should be discontinued 1 month prior to conception. Dimethyl fumarate should be avoided during lactation.

Teriflunomide is contraindicated in pregnancy due to teratogenicity. Reliable contraception is required during therapy, as well as for 2 years after discontinuation of treatment or at least 6 weeks after plasma concentration of teriflunomide is determined to be below 0.02 mg/l in 2 consecutive measurements. Teriflunomide plasma concentrations should be measured before a woman begins to attempt to become pregnant. In men the treatment may result in oligospermia. The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low. In case of unplanned pregnancy an accelerated elimination procedure with cholestyramine or active charcoal is required. Pregnancies occurring during therapy with teriflunomide should be considered as high risk ones and closely monitored by an experienced obstetrician-gynaecologist and a specialist in fetal morphology. Teriflunomide is not recommended during lactation. It does not interact with hormonal contraception and does not impact its efficacy.

During *fingolimod* therapy and 2 months after its discontinuation pregnancy should be avoided due to a risk of harmful effects to the fetus, although there is no data available for congenital

fetal malformations. Female patients must use effective contraception while on fingolimod therapy. In case of occurrence of unplanned pregnancy treatment with fingolimod should be stopped immediately. Pregnancies occurring during therapy with fingolimod should be considered as high-risk ones and closely monitored by an experienced obstetrician-gynaecologist and a specialist in fetal morphology. Fingolimod should not be used during lactation. There is no available data that fingolimod is associated with an increased risk of reduced fertility or interactions with hormonal contraception and its efficacy.

Natalizumab should be stopped 2 months prior to pregnancy, although there is no evidence that a wash-out period is required prior to conception. Natalizumab does not cross the placenta during the first trimester, but is increasingly transported via the placental barrier during the second & third trimester of pregnancy. Treatment should be discontinued in case of unplanned pregnancy during therapy. Routine MRI monitoring for PML should be continued during natalizumab exposure in pregnancy. Natalizumab therapy is not associated with reduced fertility or congenital fetal malformations. Re-initiation of treatment should be considered as early as possible after delivery due to a risk of relapse. Not recommended during lactation. Does not interact with hormonal contraception and has no impact on its efficacy.

Alemtuzumab therapy requires effective contraception during treatment and for 4 months after the last infusion. The thyroid function should be monitored for at least 4 years after the last infusion because of its connection to the foetal wellbeing. Pregnancies occurring within 1 month after administration of alemtuzumab should be closely monitored. In pregnant women previously treated with alemtuzumab routine monthly laboratory monitoring is required for at least 4 years after the last infusion. Female patients are at risk of autoimmune conditions such as thyroid disorders, immune thrombocytopenic purpura, nephropathies and others. Development of drug induced autoimmune disorders during pregnancy might affect both the mother and fetus (mostly neonatal thyrotoxicosis). Breast-feeding should be discontinued during each course of treatment and for 4 months following the last infusion of each treatment course. There is no data for interaction of alemtuzumab with hormonal contraceptives or impact on their efficacy.

Cladribine is contraindicated in pregnant women. In women of childbearing potential, pregnancy must be excluded before initiation of cladribine in year 1 and year 2, and prevented by using effective contraception during cladribine treatment and for at least 6 months after the last dose. In addition, both a hormonal and barrier contraceptive method should be considered because of serious potential risk to the foetus in case of unplanned pregnancy. Women who become pregnant during therapy with cladribine must discontinue treatment. Male patients treated with cladribine

should also take strict precautions to prevent pregnancy of their partners during treatment and for at least 6 months after the last dose. Breast-feeding is contraindicated during treatment and for 1 week after the last dose. Cladribine does not impact hormonal contraceptive efficacy.

Ocrelizumab therapy requires effective contraception both during treatment and for 12 months after the last infusion. B-cell number monitoring is recommended in infants of mothers who have been exposed to ocrelizumab during pregnancy. Vaccination of those infants with live or live-attenuated vaccines should be delayed until B-cell levels have recovered. Ocrelizumab therapy is not recommended during breast-feeding. There is no data for interaction of ocrelizumab with hormonal contraceptives or impact on their efficacy.

Siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception due to risk to the fetus. Before initiation of treatment, women of childbearing potential must be informed about existing risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after treatment discontinuation.

The use of corticosteroids or other drugs for symptomatic management should also be discontinued during pregnancy. Short courses (3-5 days) of prednisolone or methylprednisolone treatment can be administered for relapse management only during the second and third trimesters of pregnancy.

There is no data to suggest a short-term increase of the risk or rebound activity of the disease following discontinuation of disease modifying drugs, while on the other hand the female patient will enter a period when the disease is suppressed by the pregnancy. After delivery, however when the risk of relapses increases, immediate initiation of DMTs is advised. In such cases breast-feeding is not recommended and the baby should be fed by formula feeding. If the patient does not receive medications, breastfeeding not only should not be avoided, but it might also prevent an increase in disease activity.

There are no specific requirements for the childbirth method except for unconfirmed considerations about avoiding spinal anaesthesia.

The use of oral contraceptives does not affect the disease course, so they are not contraindicated in multiple sclerosis. Exceptional cases are patients with a rare form of multiple sclerosis, whose relapses are closely related to the menstrual cycle and contraception, and in such cases oral contraception may have a beneficial effect on the disease.

There are no contraindications to hormone replacement therapy in menopausal women either. HRT has a beneficial effect on disease symptoms which tend to become worse during menopause.

Nutrition and physical activity have been largely studied. Normal physical activity, aerobic exercises and sports enjoyed by the patient are recommended but overheating, dehydration, excessive exertion and activities associated with potential risk of injury should be avoided. Elevation of body temperature during physical activity may cause transient symptoms (paresthesia, blurred vision) that do not lead to sustained complications and are not a contraindication to sporting activities. Swimming is not contraindicated if the water is warm enough. Patients with lower extremity weakness can participate in sports engaging the upper limbs (yoga).

There is no evidence that any of the proposed diets has a beneficial effect on the course of the disease. A low-fat diet is very popular but its clinical benefit has not been confirmed yet. Still, patients should be recommended a diet rich in polyunsaturated fatty acids and vitamin D, and poor in animal fats, as well as cessation of tobacco smoking.

Vaccinations are safe in MS patients. Some data even suggest that flu vaccine and antitubercular BCG vaccine reduce relapse rate. Exceptions are vaccinations during relapses or in very active disease stages. Patients are recommended to receive influenza vaccines as 25% of all relapses are caused by flu or other viral infections. All vaccinations are safe in patients receiving DM therapies as well. Immunizations are also safe in patients receiving immunosuppressive therapy with the exception of live virus vaccines (varicella, measles, rubella, and mumps). Individual benefit-risk ratio assessment and coordination of vaccination timing with the timing of the DMT dose are recommended to ensure higher efficacy of the vaccination.

Vaccinations for Covid 19 should be consistent with the used disease modifying therapies (Appendix 8).

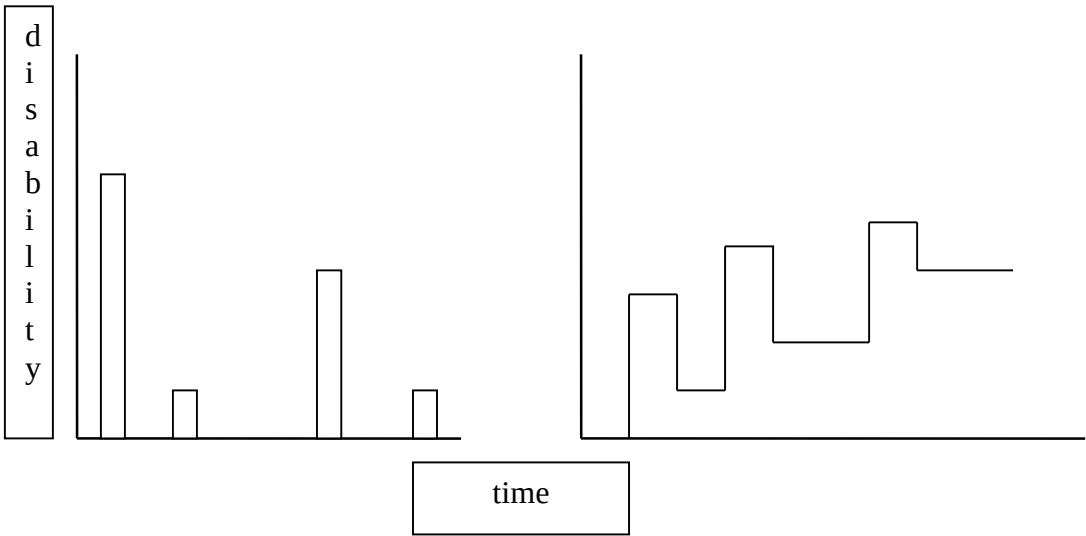
The social and psychological aspects of the disease are of crucial importance. Initially, when patients learn about their poor prognosis and uncertain future, they need emotional support. With the progression of their disability however, patients can no longer keep up to their habitual duties, and eventually quit working. Later on, they become dependent on caregivers' help in their everyday activities. They are often abandoned by their partners and have to take care of themselves alone. They are faced with different problems in the course of the disease stages and must be prepared by timely education.

The education of patients should start with their being diagnosed. The patient should be made familiar with the nature of the disease, and the chances for a favorable outcome. Patients should also be advised to observe proper hygiene and dietary regime, and avoid “alternative” methods of treatment. In the beginning of the disease patients should not be encouraged to join “MS societies” because they are likely to meet many patients with severe neurological deficits there, for which they

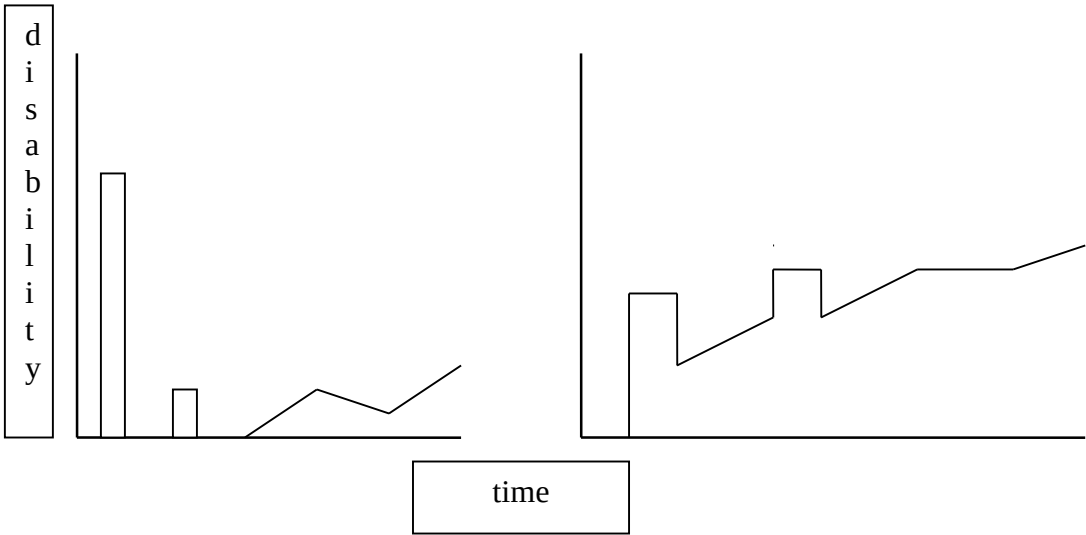
are not emotionally prepared yet. Most brochures are also intended for patients in the advanced stages of the disease. The support a patient could get at a later stage from different associations and communities is of extreme importance.

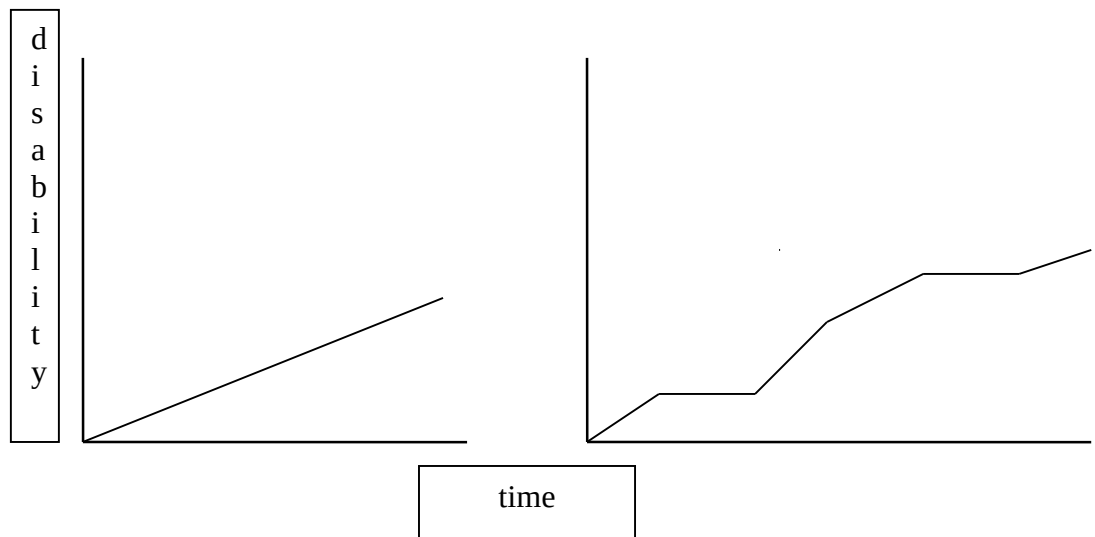
Appendix 1. Clinical course forms of MS, depending on time profile

Relapsing-remitting MS



Secondary-progressive MS



Primary –progressive MS

Appendix 2. 2017 Revised McDonald Diagnostic Criteria for MS

Clinical symptoms	Number of lesions with objective clinical evidence	Additional data needed for MS diagnosis
2 or more attacks	2 or more	None
2 or more attacks	1 + clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location	None
2 or more attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 attack	2 or more	Dissemination in time demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands
1 attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands
• If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. • If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis.		

If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis.

- No additional tests are required to demonstrate dissemination in space and time in first two cases, however brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered, unless MRI is not possible.
- In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered.
- Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.
- The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Appendix 3. Revised in 2017 MRI McDonald criteria

Dissemination in space of lesions in the CNS (DIS)	Dissemination in time of lesions in the CNS (DIT)
Dissemination in space can be demonstrated by one or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in two or more of four areas of the CNS: • Periventricular • Cortical or juxtacortical • Infratentorial brain regions • Spinal cord * For demonstration of dissemination of the demyelinating process in time and space, no distinction between symptomatic and asymptomatic MRI lesions is required	Dissemination in time can be demonstrated 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 *For some patients (eg, individuals older than 50 years or those with vascular risk factors) it might be prudent for the clinician to seek a higher number of periventricular lesions, than to trust only lesion.

Appendix 4. Corticosteroid treatment of MS relapses

Corticosteroid dosage forms	Administration	Indication
1. Methylprednisolon amp. 125 mg; 250 mg	500–1000 mg i.v. B serum glucosae 500 ml over 1 – 1,5 hours for 5 days	Pulse therapy – for 5 days in relapse and optic neuritis In very severe (with possible brain stem symptoms) attack and acute MS 1000 mg i.v.
2. Methylprednisolon amp. 20 mg; 40 mg	- 80 mg i.m. for 3 days - 60 mg a total of 12 days - 40 mg in the morning - 20 mg single dose	I option – oral tapering following intravenous pulse therapy
3. Prednisolone F tabl. 0,5 mg	12 tabl. = 6 mg 10 tabl. = 5 mg for 2-3 days, 8 tabl. = 4 mg in the morning 6 tabl. = 3 mg single dose 4 tabl. = 2 mg after breakfast 2 tabl. = 1 mg	II option – oral tapering following intravenous pulse therapy
4. Prednisolone tabl. 5 mg	12 tabl. = 60 mg 10 tabl. = 50 mg for 2-3 days, 8 tabl. = 40 mg in the morning 6 tabl. = 30 mg single dose 4 tabl. = 20 mg after breakfast 2 tabl. = 10 mg	III option – oral tapering following intravenous pulse therapy

Appendix 5. Symptomatic pharmacological treatment in multiple sclerosis

Symptom	Drug, pharmaceutical form mg	Daily dose mg
Muscle tone spasticity	Tizanidine (Sirdalud) tabl. 2, 4 Baclofen tabl. 10, 25	2 – 32 50 – 100
Intention tremor	Isoniazid (Rimicid) tabl. 100 mg β -blockers (Propranolol) tabl. 25 and 40 Primidone (Mysolin, Liskantin) tabl. 250 Glutethimide tabl. 250	800 – 1200 50 – 120 125 – 750 1000 - 4000
Gait disturbance	Fampridine (Fampyra) tabl. 10	20
Pelvic-floor disturbances <i>Imperative urges and incontinence</i>	Galanthamin (Nivalin) tabl. 5; 10; amp. 2,5; 5; Nivabex sir. fl. Tolterodine (Detrusitol) tabl. 1; 2 Oxybutynin (Driptane) tabl. 5; 10 Desmopressin (Adiuretin) fl. 500 μ g/5ml Mirabegron (Betmiga) 25; 50	10 – 30 2 – 4 10 – 20 1-4 nasal drops 2-3 times daily 25-50
<i>Urinary retention</i>	Baclofen tabl. 10; 25 Diazepam tabl. 5; 10	20 – 40 10 – 15
Nystagmus	Baclofen tabl. 10; 25 Clonazepam (Rivotril) tabl. 0,5; 2 Gabapentin (Neurontin) tabl. 300; 400; 800; caps. 600	50 – 100 0,5 – 4,0 2 – 3 g
Pain, paresthesia and paroxysmal attacks	Amitriptyline dr. 25 mg Gabapentin (Neurontin) tabl. 300; 400; 800; caps. 600 Pregabalin (Lyrica, Brieka) caps. 25; 50; 75; 100; 150; 200; 300 Carbamazepine (Tegretol) tabl. 200 Clonazepam (Rivotril) tabl. 0,5; 2 Phenytoin (Epilan, Phenhydan) tabl. 100 Lamotrigine (Lamictal) tabl. 5; 25; 50; 100 Topiramate (Topamax) tabl. 50; 100; 200; 300; 400	25 – 75 2 – 3 g 300-600 200 – 1200 0,5 – 4,0 300 – 400 100 – 300 100 – 200

Fatigue	Amantadine sulfat (PK-Merz) tabl. 100	200 – 300
	Modafinil (Aspendos) tabl. 100	100-400
Depression and neuropathic pain	Amitriptyline dr. 25	25 – 75
	Venlafaxine (Laroxine, Effectin) tabl. 75; 150	75 – 300
	Mirtazapine (Remirta) tabl. 30; 45	30 – 60
	Duloxetine (Dulsevia, Aritavi) caps. 30; 60	30 – 60
Cognitive impairment	Galanthamin (Nivalin) tabl. 5; 10	10 – 30
	Donepezil (Aricept) tabl. 5; 10	5 – 10
Vertigo	Dimenhydrinat (Dimenhydrinat) tabl. 50	75 – 150
	Betahistine (Betaserc, Vertisan) tabl. 16	48
	Cinnarizine/Dimenhydrinat (Arlevert 20 mg/40 mg)	60 mg/120 mg

Appendix 6. Levels of clinical significance by therapy efficacy criteria

Parameter	Low significance	Moderate significance	High significance
Relapses			
Frequency/severity	1 mild relapse per year	1 moderate relapse per year	More than 1 moderate or 1 severe relapse per year
Recovery	Fast recovery, following corticosteroid treatment	Slow recovery, following corticosteroid treatment	Incomplete recovery, following corticosteroid treatment
Progression			
EDSS<3,5	< 2 point change	2 point change	>2 point change
EDSS>4	<1 point change	1 point change	>1 point change
Clinical progression	No motor symptoms, minimal sensorial symptoms	Moderate motor symptoms, cognitive or more pronounced sensory symptoms	Pronounced motor, cognitive and other symptoms
MRI			
New gadolinium-enhanced lesions	Changes in 2 categories	Changes in 3 categories	Changes in >3 categories
New T₂ lesions			
Enlarging T₂ lesions (burden)			
New T₁ lesions			
Enlarging T₁ lesions			
Increasing atrophy			

Appendix 7.

J. F. Kurtzke Scale (1983) for Quantitative Assessment of Neurological Impairment in Multiple Sclerosis – Expanded Disability Status Scale (EDSS)

A. Pyramidal Functions

0 – Normal;

1 – Abnormal signs without disability (asymmetrical hyperreflexia, decreased or missing abdominal reflexes, pathological reflexes from the Babinski group, etc.);

2 – Minimal disability (latent paresis);

3 – Mild or moderate paraparesis or hemiparesis; severe monoparesis;

4 – Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia;

5 – Paraplegia, hemiplegia, or marked quadriparesis;

6 – Quadriplegia;

V – Unknown.

B. Cerebellar Functions.

0 – Normal;

1 – Abnormal signs without disability (coordination disorders seen only in coordination testing, no gait disturbance or interference with everyday activities);

2 – Mild truncal or limb ataxia;

3 – Moderate truncal or limb ataxia;

4 – Severe ataxia in all limbs, but with certain effective movement;

5 – Unable to perform coordinated movements due to ataxia;

V – Unknown;

X– Placed after each number to denote that limb weakness interferes with testing.

C. Brainstem Functions

0 - Normal;

1 – Abnormal signs without disability (e.g. listlessness sensory symptoms);

2 – Moderate nystagmus or other mild disability;

3 – Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves;

4 – Marked dysarthria or other marked disability (facial diplegia or ophthalmoplegia);

5 – Inability to swallow or speak;

V – Unknown.

D. Sensory function

0 – Normal;

1 - Vibration or figure-writing decrease only in 1-2 limbs;

2 – Mild decrease in touch, pain or position sense, and/or moderate decrease in vibration in 1-2 limbs; or vibratory decrease alone in three or four limbs;

3 – Moderate decrease in touch, pain or position sense, and/or lost vibration in one or two limbs; or mild decrease in touch, pain and/or moderate decrease in all proprioceptive tests in three or four limbs;

4 – Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch, pain and/or severe proprioceptive decrease in more than two limbs;

5 – Loss of sensation in one or two limbs; or moderate decrease in touch, pain and/or loss of proprioception for most of the body below the head;

6 – Sensation essentially lost below the head;

V – Unknown.

E. Bowel and Bladder Function:

0 – Normal;

1 – Mild urinary hesitance, urgency, rarely retention;

2 – Moderate hesitance, urgency, retention or rare urinary incontinence;

3 – Frequent urinary incontinence;

4 – In need of almost constant catheterization;

5 – Loss of bladder function;

6 – Loss of bladder and bowel function;

V – Unknown.

F. Visual Function:

0 – Normal;

1 – Scotoma with visual acuity (corrected) better than 20/30;

2 – Worse eye with scotoma with maximal visual acuity (corrected) of 20/30-20/59;

3 – Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60-20/99;

4 – Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100-20/200; grade 3 plus maximal acuity of better eye of 20/60 or less;

5 – Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less;

6 – Grade 5 plus maximal visual acuity of better eye of 20/60 or less;

V – Unknown;

X – Added to grades 0 to 6 in presence of temporal pallor.

G. Mental Functions:

0 – Normal;

1 – Mood alteration only (euphoria or depression);

2 – Mild decrease in mentation with regard to abstract thinking or mathematical operations.

3 – Moderate decrease in mentation, disturbance in judgments and conclusions.

4 – Marked decrease in mentation with certain disorientation.

5 – Dementia.

V – Unknown.

H. Other functions:

0 – Normal.

1 – Define finding if any.

V – Unknown.

Kurtzke Expanded Disability Status Scale (1986)

0 – Normal neurological exam (all grade 0 in all functional system (FS) scores); possible mental grade 1.

1 – No disability, minimal signs in one FS (i.e., grade 1) without mental grade 1; all grade 0 in remaining systems.

1.5 – No disability, minimal signs in more than one FS (more than 1 FS grade 1; with or without mental grade 1).

2 – Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 – Minimal disability in two FS (two FS grade 2, others 0 or 1).

3 – Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 – Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grades 2 (others 0 or 1).

4 – Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.

4.5 – Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.

5 – Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (one FS grade 5, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).

5.5 – Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (one FS grade 5, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).

6 – Intermittent or unilateral constant assistance (cane or crutch) or intermittent bilateral intermittent assistance required to walk about 100 meters with or without resting; (more than two FS grade 3+).

6.5 – Constant bilateral assistance (canes, crutches) required to walk about 20 meters without resting; (more than two FS grade 3+).

7 – Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

7.5 – Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (FS equivalents are combinations with more than one FS grade 4 +).

8 – Essentially restricted to bed or chair or perambulated in wheelchair; can move limbs and has effective use of arms; (FS equivalents are combinations, generally grade 4+ in several systems).

8.5 – Essentially restricted to bed; has some effective use of arm(s); (FS equivalents are combinations, generally 4+ in several systems).

9 – Helpless bed patient; can only communicate and swallow; (FS equivalents are combinations, mostly grade 4 +).

9.5 – Totally helpless bed patient; unable to communicate effectively or swallow; (FS equivalents are combinations, almost all grade 4 +).

10 – Death due to MS

Appendix 8. MS prophylaxis and the risk of COVID-19

Appendix to the National Consensus for Diagnosis and Treatment of Multiple Sclerosis

A summary of the leading global experience and practical treatment recommendations for the use of immunotherapies for treatment of MS on the background of an increased risk of COVID-19 infection.

COVID-19 (coronavirus disease 2019) is a novel strain from the Corona viridae family, isolated for the first time in China. Multiple sclerosis itself is not expected to increase the risk for infection with COVID-19 or the predisposition to occurrence of clinical symptoms after exposure to the virus.

The risk of complications of the infection is increased in different conditions that could be divided into two groups:

Unmodifiable risk factors: age, chronic cardiovascular and pulmonary diseases, neoplastic processes, underlying non-iatrogenic immunodeficiencies. Cautious use of active immunotherapies in MS patients at more advanced age is expected to ensure better immunity against the virus.

Relatively modifiable risk factors: diabetes, hypertension, drug induced immunosuppression/reduced lymphocyte count.

The above mentioned modifiable risk factors point to the responsibility of MS specialists to ensure adequate risk management during immunomodulation therapy in a complicated epidemic setting. Due to the lack of sufficient evidence for each of the used therapies the recommendations at this early stage are rather theoretical. Furthermore, the immune response at COVID-19 exposure has not been fully studied yet, but based on the already known from the experience with SARS (Severe acute respiratory syndrome-related coronavirus) it could be assumed that T-lymphocytes play a central role in this antiviral response.

MS treatment affects the adaptive immune system. The innate immune system is less affected with the exception of NK cells. The circulating immune cells are either modulated or destroyed. Practice has shown that MS therapies do not lead to an increased infection risk or more severe course of **Covid infection. Abrupt discontinuation of MS treatment (as a preventive measure against infection or during COVID-19 illness)** can cause worsening of the disease.

Following **high-dose corticosteroid** therapy patients are encouraged to observe strict self-isolation for at least 2 weeks.

First line therapies as **interferon beta 1a, interferon beta 1b, glatiramer acetate, teriflunomide and dimethyl fumarate** can be prescribed and administered as usually, without

significant risk of compromising the antiviral immunity. They have no negative impact on the severity of Covid-19. Mild forms of Covid-19 can continue treatment & new patients' treatment can be initiated.

During **dimethyl fumarate** therapy the recommendation for monitoring of the lymphocyte count should be considered, especially during the first six months of therapy, when its impact on the absolute lymphocyte count is unclear. In lymphocyte count ≤ 500 mm³ treatment should be temporarily discontinued while in values between 500 mm³ and 800 mm³ it can be continued with regular monitoring of the absolute lymphocyte count. The treatment can be safely administered in lymphocyte counts over 800 mm³.

Fingolimod therapy is associated with certain risks in view of free T-lymphocytes retention within the peripheral lymph nodes and respective reduction in circulating immune cells numbers, which probably compromises the anti-viral immunity. On the other hand, fingolimod is a drug for treatment of active relapsing MS and discontinuation of therapy is often associated with disease re-activation. Therefore, continuation of treatment is justifiable following individual benefit-risk assessment.

Natalizumab therapy is considered to be safe in the present epidemic setting due to its ability to limit the penetration of circulating immune cells into the CNS. Another consideration is the risk of re-activation of MS as a result of possible missed dose provided the patient has no access to the hospital for the next infusion. Patients are without high risk of severe COVID-19 and initiation of treatment is not contraindicated. The risk of severe COVID-19 with natalizumab is the lowest among high-efficacy therapies. If the treatment is stopped in case of severe COVID-19 illness, it should be resumed within 8 weeks to avoid a rebound effect.

Therapies suppressing the lymphocyte cell line are considered to be relatively more risky during the epidemic period.

Ocrelizumab, despite its target anti-CD20 activity affects B-cell and T-cell responses and IL-6 production. It might also compromise the anti-viral response. At the same time, the drug is indicated for treatment of active MS and the risks of worsening of the disease as a result of delay of therapy should not be underestimated. Temporary delaying the initiation of ocrelizumab or the administration of the next infusion could be considered to avoid immediate risk of infection (direct contact with a COVID-19 patient) or during illness.

Patients with primary progressive MS should be individually considered in the context of the higher mean age in the subgroup, as well as the lower risk of significant disability progression in case of temporary infusion delay.

Treatment with **alemtuzumab** и **cladribine** is associated with a relatively higher risk of development of severe Covid-19 infection. Individual benefit-risk assessment in initiation and subsequent administration of these therapies during the epidemic period is recommended. Patients, who have received the first course of treatment and are subject to a second administration of the drugs are considered to be relatively protected against activation of MS for a period of 18 months after the previous course of treatment. Following administration of alemtuzumab, patients should follow strictly the general anti-epidemic measures for at least 4 months, accompanied by monitoring of blood parameters as stated in the SPC. Following administration of cladribine, because of its long-term effects on the lymphocyte cell line, patients should observe most strictly the anti-epidemic measures till immune recovery.

MS patients, using disease modifying drugs, with confirmed **Covid-19 infection**, require special attention by the treating neurologist and an infectious disease specialist. People with **mild** symptoms of COVID-19 can continue treatment with interferons, glatiramer acetate, teriflunomide, dimethyl fumarate or fingolimod, since they are not at a higher risk of infection complications. The administration of second line therapies during illness from Covid-19 should depend on the severity of the symptoms of infection.

In cases of severe Covid-19 infection an individual assessment is recommended. Infusions of second line therapies and cladribine administration can be delayed till resolution of symptoms. Treatment with fingolimod and natalizumab should be resumed within 8 weeks to avoid a rebound effect.

Patients with progressive forms of MS and high degree of disability (EDSS >6,0) are at increased risk of more severe course of Covid-19.

Vaccines against COVID-19 are safe for people with MS and are not likely to trigger a relapse or to worsen chronic MS symptoms. Getting the COVID-19 vaccine while on any MS therapy is safe, still some DMTs may make the vaccine less effective. People with relapsing or progressive forms of MS should be vaccinated. In addition, members of the same household and close contacts should also be vaccinated against COVID-19. The vaccine can cause fever or may lead to temporary worsening of MS symptoms.

Treatment with **interferon beta 1a, interferon beta 1b, glatiramer acetate, teriflunomide, dimethyl fumarate and natalizumab** does not affect the effectiveness of the vaccine. The vaccination is not contraindicated and the timing does not need to be coordinated with the timing of the DMT dose.

Fingolimod therapy could reduce the response to the vaccine but discontinuation of treatment is not recommended. The patient can be vaccinated without stopping the treatment. The treatment should be initiated 4 to 6 weeks after vaccination with both doses of BioNTech/Pfizer or Moderna vaccines. The first dose of the AZ/Oxford vaccine is administered 2 to 4 weeks before initiation of treatment and the second dose – at least 3 months after start of treatment.

Treatment with alemtuzumab, cladribine and ocrelizumab requires coordination of vaccination timing with the timing of the DMT dose.

Before starting treatment with **alemtuzumab and cladribine** the full vaccination course should be completed at least 4 to 6 weeks before treatment initiation. If the patient already receives treatment, there should be an interval of at least 6 months between the last treatment course and the vaccination and the lymphocyte count should be recovered. The next treatment course could be delayed till completion of vaccination. Vaccination should be avoided during cladribine treatment and until normalization of white blood cell count after it.

In patients treated with the anti-CD20 drug **ocrelizumab**, the first dose of the vaccine must be administered before initiation of treatment, and the second dose – at least 4 weeks before starting therapy. The treatment might reduce the response to some vaccines by up to 50%. During ongoing therapy, the vaccine should be administered 4 to 5 months after the last dose of the drug. After administration of 2 vaccine doses and recovered lymphocyte count, the next treatment dose should be delayed for at least 4 weeks. After administration of the second vaccine dose the next treatment course could be delayed or treatment could be resumed after the first dose of the vaccine (and the second dose to be delayed). The first dose of the AZ/Oxford vaccine is administered 5 months after the last infusion of the drug and at least 2 weeks before the next infusion. The second dose of the vaccine is administered at least 3 months after the next infusion and at least 2 weeks before the subsequent infusion. The first dose of the BioNTech/Pfizer or Moderna vaccines is administered 4 months after the last drug infusion, and the second dose – 3 to 4 weeks later and at least 2 weeks before the subsequent infusion.