GUIDELINES

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Disease-modifying therapy in multiple sclerosis: recommendations of Multiple Sclerosis and Neuroimmunology Section of Polish Neurological Society

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ABSTRACT

The treatment of multiple sclerosis (MS) has undergone significant changes since the first disease-modifying therapy (DMT) drug was introduced. Currently, 19 original DMT drugs are registered in the European Union. The choice of optimal therapy is becoming increasingly challenging in the absence of reliable biomarkers on the basis of which disease progression and prognosis can be determined. In addition, longer availability and a growing number of drugs used in MS mean that doctors and patients may have to change therapy when the treatment is ineffective or is associated with the occurrence of adverse effects. The ageing of the MS population, comorbidities, and administration of other drugs during DMT should also be considered. This paper presents recommendations for initiating, monitoring, changing and possibly discontinuing DMT.

Keywords: multiple sclerosis, relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, disease-modifying therapy, clinically isolated syndrome, radiologically isolated syndrome, recommendations

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Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) of unclear aetiology. It is mostly diagnosed in adults aged 20–40. The disease is autoimmune-mediated [1, 2]. Observations of its natural course indicate that it is a severe and chronic disease which can lead to significant disability and shorten life expectancy in untreated patients. Recent advances in the treatment of MS have significantly improved the prognosis and offered the chance to substantially reduce disease activity, thus slowing disability progression in patients undergoing treatment [3].

Currently, there are therapies that favourably modify the relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) phenotypes. The increasing number of DMTs, the lack of reliable biomarkers that would allow the selection of the optimal drug for a particular patient, and the need for long-term therapy with drugs associated with the risk of adverse effects, mean that the use of DMT in practice is becoming increasingly difficult and complicated.

These recommendations are based on available scientific data and the clinical experience of the experts of the Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society. They are not the same as the current drug programme for the treatment of MS in Poland [1]. For the purposes of this paper, we used the most recent updates of the McDonald criteria [4] and the diagnostic criteria for Radiologically Isolated Syndrome (RIS) [5]. Our recommendations were established between May 2022 and March 2023. Seven co-authors (AKuł., DM-G, HB-P, AKal., WB, MS and MA-S) prepared a draft of the recommendations, which was discussed with other co-authors. Finally, the unanimously approved version was determined. These recommendations should be treated as guidelines to be implemented depending on clinical data, the results of additional tests, and the individual patient profile. This paper shows innovative DMTs according to their mechanism of action and the order of registration in European Union (EU) countries unless there were other important reasons for positioning the drugs.

Management of clinically isolated syndrome

Clinically isolated syndrome (CIS) is the first monophasic clinical episode that may suggest MS. During CIS, neurological symptoms are observed, which can be a monofocal or a multifocal inflammatory demyelinating process in the CNS [4, 6–8]. This can be acute or subacute, with symptoms lasting at least 24 hours, without fever or other signs of infection. CIS is usually characterised by a complete remission of symptoms [4–9].

In appropriate cases, the initiation of DMT may be considered as early as possible to inhibit disease activity and prevent brain volume loss [10] in patients with CIS who do not meet the criteria for the diagnosis of MS [11, 12]. Treatment with interferon beta or glatiramer acetate may be proposed for patients with CIS and CNS lesions on magnetic resonance imaging (MRI) suggestive of MS but not meeting the diagnostic criteria [13].

However, in such cases a careful differential diagnostic work-up is crucial, excluding other antibody-mediated CNS demyelinating diseases, such as aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders (NMOSD), where beta-interferons could be potentially harmful [14].

Patients with CIS who meet the McDonald 2017 diagnostic criteria for RRMS should immediately start DMT [13]. Currently, DMT is not reimbursed in Poland for patients with CIS without a diagnosis of MS.

Recommendations

- The initiation of DMT with interferon beta or glatiramer acetate may be considered in appropriate cases in patients with CIS who do not meet the criteria for the diagnosis of MS. This is particularly relevant for patients with CIS and CNS changes on MRI suggestive of MS.

Management of radiologically isolated syndrome

Radiologically isolated syndrome (RIS) was defined in 2009 by Okuda et al. [15]. It can be diagnosed if MRI shows lesions typical of MS. However, patients will not have presented with any neurological symptoms suggestive of the disease. Other causes of lesions mimicking MS should be excluded. The diagnostic management in patients with RIS is discussed in the diagnostic guidelines of the Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society [9]. Until now, RIS has not been considered a separate MS phenotype [16]. However, this is likely to change considering the recently proposed novel McDonald criteria [17], where RIS would fulfill diagnostic criteria for MS provided that: (i) dissemination in space and time are fulfilled; or (ii) dissemination in space is fulfilled and the presence of intrathecal oligoclonal bands is confirmed; or (iii) dissemination in space is fulfilled and at least six central vein sign (CVS) lesions are present on MRI. The proposed update stems from the fact that about two thirds of patients with RIS show radiological progression [18], and c.50% of patients develop neurological symptoms during a 10-year follow-up [19]. Moreover, it has been shown that two DMTs approved for MS, namely dimethyl fumarate and teriflunomide, reduce the risk of the first demyelinating event in RIS patients by 82% and 63%, respectively [20, 21]. The decision to initiate DMT in patients with RIS at high risk of developing MS should be made on a case-by-case basis [16, 22]. In Poland, DMT is not reimbursed for patients with RIS.

Recommendations

- Currently, there is no data that clearly warrants the initiation of DMT in patients with RIS. More data is needed to be able to select patients with a higher risk of conversion to clinically definite MS, who would benefit most from DMTs.

Treatment of relapsing-remitting multiple sclerosis

Relapsing-remitting multiple sclerosis (RRMS) is the most common phenotype of MS [23]. Scientific evidence indicates that the earlier the DMT starts, the more effective it is [24, 25]. It should be implemented immediately after the diagnosis of RRMS and used in patients with active RRMS. Disease activity is defined as the occurrence of clinical relapses and/or radiological activity (active Gadolinium-enhancing [Gd (+)] lesions on MRI, new or enlarging T2 lesions) assessed during one year [13, 22].

DMT should be managed by a neurologist with knowledge and clinical experience related to MS. The team should also include a nurse and a coordinator of care for patients with MS. Only well-organised MS comprehensive care units with a multidisciplinary team providing constant communication with patients can meet the requirements of comprehensive MS therapy. The concept of establishing such units was developed by ECTRIMS/EAN experts [13, 26], and is supported by the Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society.

Disease-modifying therapy drugs in RRMS

Disease-modifying therapy (DMT) drugs differ in their mechanisms of action, dosage and routes of administration, as well as a detailed description of indications and contraindications included in the Summary of Product Characteristics (SmPC) (Tab. 1) [27–42].

There have been very few head-to-head studies on the efficacy and safety of particular DMTs. However, data obtained indirectly from comparing different clinical trials using the propensity score matching method (which is always associated with the risk of error), real world data (RWD), and expert experience indicate that monoclonal antibodies (natalizumab, alemtuzumab, ocrelizumab, ofatumumab), sphingosine-1-phosphate (S1P) receptor modulators (fingolimod, ozanimod, ponesimod) and cladribine tablets are highly effective therapies, while beta interferons, glatiramer acetate, dimethyl fumarate, diroximel fumarate and teriflunomide are considered to be moderately effective [43–47]. It should be noted that even a drug with potentially high effectiveness may prove ineffective in some patients, while another with theoretically lower potency may show long-term effectiveness in specific cases. The use of drugs with higher efficacy may be associated with a higher risk of severe adverse effects. Therefore, DMT can be classified as:

— moderately effective therapy with a low risk of severe adverse effects
— highly effective therapy (HET) with a higher risk of severe adverse effects.

In the course of the disease, the benefit-risk ratio of DMT may change with age or due to the occurrence of new comorbidities.

Due to the mechanism of action determining the maintenance of the therapeutic effect and dosing mode, DMTs can be administered continuously (maintenance therapy) or intermittently (reconstitution, induction therapy) [48]. Maintenance therapy drugs must be administered continuously at regular intervals because their effect is short-lasting and occurs only during regular administration of the drug. Immune reconstitution therapies in the form of several repeated cycles induce long-term remission, which persists after drug discontinuation. There are non-selective reconstitution therapies, such as autologous hematopoietic stem cell transplantation (AHSCT), mitoxantrone and alemtuzumab and more selective therapies (cladribine).

Treatment strategies for RRMS

Two therapeutic strategies are applied for RRMS treatment, i.e. a strategy to intensify treatment if necessary (escalation therapy) and early intense therapy (early HET). The basis of the concept of escalation consists of starting treatment with drugs of lower efficacy and changing to a higher efficacy drug if this is ineffective. The concept of early intense therapy is associated with the administration of a highly effective drug at an early stage of the disease, which may be warranted by high clinical and radiological activity during this period [49, 50].

Currently, there is no clear scientific data that shows which therapeutic strategy is more beneficial. However, more reports indicate that using HET as the first-line treatment of RRMS allows a rapid clinical effect and offers better long-term effects [51–53]. However, further research is warranted in this respect.

Escalation therapy is based on continuous drug administration (maintenance therapy) at least in the initial period. In turn, the early HET strategy may involve the use of drugs included in maintenance therapy (natalizumab, fingolimod, ozanimod, ponesimod, ocrelizumab, ofatumumab) and reconstitution therapy (cladribine tablets, alemtuzumab).

Selection of first DMT

Currently, there are no biomarkers that would allow fully personalised treatment in clinical practice i.e. the choice of the optimal drug in terms of efficacy and safety for a specific patient. When RRMS therapy is started, the choice of DMT is based mainly on disease activity and the prognostic profile of its further course.

Table 1. Disease-modifying therapy drugs — basic information and selected common or significant adverse effects

International nonproprietary name	Trade names*	Dosage	Selected common/significant adverse effects
Beta-Interferons • Interferon beta-1b • Interferon beta-1a • Interferon beta-1a • Peginterferon-beta-1a	 Betaferon® Rebif® Avonex® Plegridy®	Depending on the drug: 250 µg *s.c.* every other day 44 µg *s.c.* three times a week 30 µg *i.m.* once a week 125 µg *s.c.* every 2 weeks	injection site reactions, flu-like symptoms, leukopenia, lymphopenia, elevated liver enzymes, depressed mood (depression)
Glatiramer acetate	Copaxone®	20 mg *s.c.* once daily or 40 mg *s.c.* three times a week	injection site reactions and rarely lipoatrophy and skin necrosis, transient systemic reaction to the drug immediately after administration: vasodilatation (flushing), dyspnea, chest pain, palpitations or tachycardia
Natalizumab	Tysabri®	300 mg *i.v.* every 4 weeks** or 300 mg *s.c.* every 4 weeks	infusion-related reactions during i.v. administration, pain at the injection site during s.c. administration, for both ways of administration: hypersensitivity reactions, rhinopharyngitis, urinary tract infection, opportunistic infections (e.g. PML)
Fingolimod	Gilenya®	0.5 mg *p.o.* daily	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. *Herpes zoster*, PML, cryptococcosis), macular edema, basal cell carcinoma, elevated liver enzymes, liver damage and PRES
Siponimod	Mayzent®	CYP2C9 genotyping should be performed prior to initiation of the treatment; dose depending on CYP2C9 genotype; during the first 5 days of treatment, the dose is increased from 0.25 mg/d to 1.25 mg/d; from Day 6, a main-tenance dose of 2 mg/d or 1 mg/d, depending on the genotype	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. Herpes zoster, cryptococcosis), macular edema, basal cell carcinoma, elevated liver enzymes Observation for PML and PRES
Ozanimod	Zeposia®	dose gradually increased from 0.23 mg *p.o.* once daily (days 1 to 4), then 0.46 mg *p.o.* once daily (days 5 to 7) to the target dose of 0.92 mg *p.o.* once daily	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. Herpes zoster, PML, cryptococcosis), hypertension, macular edema, basal cell carcinoma, elevated liver enzymes, PRES
Ponesimod	Ponvory®	dose gradually increased from 2 mg *p.o.* once daily (Days 1 and 2), 3 mg *p.o.* once daily (days 3 and 4), 4 mg *p.o.* once daily (days 5 and 6), then increase by 1 mg *p.o.* every day to 10 mg *p.o.* once daily (days 12, 13 and 14), from day 15 the target the of dose 20 mg *p.o.* once daily	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. Herpes zoster, cryptococcosis), hypertension, macular edema, basal cell carcinoma, elevated liver enzymes Observation for PML and PRES
Dimethyl fumarate	Tecfidera®	initially 120 mg *p.o.* twice daily, then 240 mg *p.o.* twice daily	immediately after drug administration: transient redness of the skin, burning sensation, flushing, gastrointestinal symptoms; long-term adverse effects: gastroenteritis, lymphopenia, leukopenia, opportunistic infections (e.g. PML), elevated liver enzymes, drug-induced liver injury
Diroximel Fumarate	Vumerity®	initially 231 mg *p.o.* twice daily, then 462 mg *p.o.* twice daily	immediately after drug administration: transient redness of the skin, burning sensation, flushing, gastrointestinal symptoms; long-term adverse effects: gastroenteritis, lymphopenia, leukopenia, opportunistic infections (e.g. PML), elevated liver enzymes, liver injury Observation for opportunistic infections (e.g. PML)
Teriflunomide	Aubagio®	14 mg *p.o.* once daily	leukopenia, infections, elevated liver enzymes, acute hepatitis, drug-induced liver injury, hair loss, hypertension, polyneuropathy
Alemtuzumab	Lemtrada®	12 mg *i.v.* for 5 days in year 1 and 12 mg *i.v.* for 3 days in year 2 of therapy	infusion-related reactions, infections (including opportunistic infections), leukopenia, immune reactions, including late autoimmune reactions (thyroiditis, hepatitis, ITP, MGN, Anti-GBM disease), vascular complications (e.g. myocardial ischemia, myocardial infarction, stroke, cervicocephalic arterial dissections)

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Table 1 cont. Disease-modifying therapy drugs — basic information and selected common or significant adverse effects

International nonproprietary name	Trade names*	Dosage	Selected common/significant adverse effects
Cladribine tablets	Mavenclad®	10 mg tablets; cumulative dose of 3.5 mg/kg body weight over 2 years. The drug is administered for 4–5 days in the first and second month in the first year and 4–5 days in the first and second month in the second year of the treatment	lymphopenia, infections (including opportunistic infections), elevated liver enzymes, symptomatic hepatitis, liver damage
Ocrelizumab	Ocrevus®	the dose is administered as two separate *i.v.* infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion; then a single 600 mg *i.v.* infusion every 6 months	(systemic) infusion-related reactions, decreased IgM and IgG levels, infections (including opportunistic infections); observation for reactivation of hepatitis B infection
Ofatumumab	Kesimpta®	20 mg administered by *s.c.* injection at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4 (20 mg *s.c.*)	injection-related reactions (systemic, e.g. flu-like) and injection site reactions, infections, decreased IgM Note: Attention should be paid to opportunistic infections and hepatitis B reactivation
Mitoxantrone	Mitoxantron Sandoz®	12 mg/m^2 of body surface area, given as an *i.v.* dose every 3 months; the maximum lifetime cumulative dose should not exceed 72 mg/m^2 of body surface area	anemia, leukopenia, granulocytopenia, acute leukemia, infections, cardiac arrhythmias, cardiomyopathy, circulatory failure, amenorrhea, hair loss

s.c. — subcutaneous(ly); i.m. — intramuscular(ly); *i.v.* — intravenous(ly); *p.o.* — orally; PML — progressive multifocal leukoencephalopathy; PRES — posterior reversible encephalopathy syndrome; ITP - immune thrombocytopenia; MGN — membranous glomerulonephritis; anti-GBM — goodpasture syndrome
*Preparations of innovative medicinal products registered in Poland.
In the coming years, further generic preparations and new biosimilars equivalent to biological medicinal products should be expected to be introduced to the market. Although it may raise uncertainty about the effectiveness and safety of treatment, it is worth noting that the registrations of generics and biosimilars are carried out under strictly defined rules, in accordance with the requirements of national and European regulatory authorities (the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland and the European Medicines Agency in Europe) and adequate legal regulations. Verification in real clinical practice requires confirmation of maintaining the effectiveness and safety of therapy when biological and biosimilar drugs are interchanged, including multiple replacements. For this purpose, further research and follow-up are warranted also within the framework of appropriate registries [94].
#Selection based on the Summary of Product Characteristics (SmPC) and expert experience. When making therapeutic decisions, it is necessary to follow current SmPCs and safety information.
**Possible regimen with an extended dosing interval (approximately 6 weeks on average) to reduce the risk of PML, as initially demonstrated in a retrospective analysis (TOUCH program). At the same time, the effect of such a change in the dosing regimen on the efficacy of treatment has not been established. Therefore, the definitive benefit-risk ratio of therapy with the modified dosing regimen remains unknown. Statistical modelling results indicate that the risk of relapse of MS in patients who switched to a dose regimen with an extended dosing interval may be higher if their body weight is > 80 kg or the dosing interval is ≥ 7 weeks

The following show unfavourable prognostic significance [54–56]:

- clinical factors, including a high annualised relapse rate (≥ 2 relapses/year), a short interval between the first and the second relapse, incomplete resolution of symptoms after relapse, and multifocal signs and symptoms at the onset of the disease, especially the occurrence of cerebellar, pyramidal and sphincter disorders
- radiological factors: at least 2 Gd(+) or ≥ 9 hyperintense lesions on T2 MRI, the presence of demyelinating lesions in the spinal cord or brainstem
- demographic and other factors: male sex, older age of patient (> 40), obesity, smoking.

Other patient-dependent factors also play an important role in the choice of DMT. These include reproductive plans, comorbidities and their treatment, seropositivity for John Cunninghan (JC) virus or hepatitis B virus (HBV), the need/necessity for preventive vaccinations, the patient's lifestyle, and their reluctance to take the risk of therapy (a strong fear of adverse drug effects) and the patient's preferences for the route and frequency of drug administration. In practice, the availability of DMT is also crucial, which can result from the rules of therapy reimbursement (the provisions of the drug programme in Poland).

The decision to start therapy and the choice of drug should be discussed with the patient during another appointment, specially planned for this purpose, which should take place at the right time (preferably 1–4 weeks after the patient is informed about the diagnosis). The patient's participation in therapeutic decisions determines further effective cooperation, including compliance with the therapy. The patient should be informed that DMT will not cure MS and may not bring about a significant clinical improvement. However, it is aimed at inhibiting disease progression. The patient should also know that DMT is associated with a risk of adverse effects and requires regular monitoring of the clinical condition, laboratory parameters and MRI examinations. Before starting each DMT, additional tests should be performed as indicated in the SmPC (Tab. 2). To achieve adequate immunity after vaccination, immunisation should be conducted before starting immunosuppressive DMT.

Proposed algorithm for initiating RRMS treatment with DMT

Patients with low/moderate disease activity (1 clinical relapse or 1 active (Gd+) lesion or 1–2 new T2 lesions on MRI in the last 12 months) can start treatment with any of the following: interferon beta, glatiramer acetate, dimethyl fumarate, diroximel fumarate, teriflunomide, ocrelizumab, ofatumumab, ozanimod or ponesimod. The important factor when choosing the first drug from among those listed above is as follows:

— a prognostic profile of the disease course

If unfavorable prognostic factors are present (see above), initiation of HET should be considered with consideration given to comorbidities and their treatment.

— reproductive plans

They should always be discussed with the patient at the time of starting DMT. Women of childbearing age who plan pregnancy or do not want to use contraception should be offered treatment with interferon beta or glatiramer acetate, which can be used until conception and even during pregnancy and breastfeeding, after considering the benefit-risk ratio.

— the route of administration and dosing regimen preferred by the patient.

Patients with high disease activity

There is no universally recognised definition of highly active disease in the case of RRMS. Even so, there is a consensus among experts that it is a broader concept than 'rapidly evolving severe RRMS' (RES-RRMS).

According to most experts [57–59], high disease activity is evidenced by:

— ≥ 2 relapses/year, especially with pyramidal and/or cerebellar signs and symptoms
— incomplete resolution of relapse symptoms
— > 9 T2 lesions on MRI, especially located in the spinal cord and/or brainstem
— several active (Gd+) lesions on MRI.

Patients with high disease activity should initiate therapy with highly effective drugs, i.e. natalizumab, fingolimod, ozanimod, ponesimod, ocrelizumab, ofatumumab, cladribine tablets or alemtuzumab in accordance with the indications and in the absence of contraindications to their use included in the SmPC. The choice of drug should be based on the patient's individual profile in each case. When considering the choice among HETs, a test for (latent) infections should be performed.

In patients with high disease activity, moderate-efficacy drugs may be introduced (interferon beta preferably in a high dose, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate) if indicated by clinical findings (e.g. contraindications to the use of HET, pregnancy, breastfeeding). As in the case of patients with low/moderate disease activity, the choice of drug is also influenced by other factors, including reproductive plans, comorbidities and their treatment, the safety profile of the DMT, and patient preferences.

Recommendations

- DMT should be initiated in patients with active RRMS immediately after the diagnosis. RRMS activity is defined clinically and/or radiologically
- The decision to start DMT and the choice of drug should be discussed with the patient during another appointment. The patient should be informed that DMT will not cure MS, and may not even bring about a significant clinical improvement. The patient should also be informed about the risk of adverse effects and the necessity of regular monitoring of therapy
- When starting DMT for RRMS, choice of the drug should be mainly based on disease activity and the prognostic profile of its further course. The following should be considered: reproductive plans, comorbidities and their treatment, drug safety profile, and patient preferences
- Patients with RRMS and low/moderate disease activity (1 clinical relapse or 1 active (Gd+) lesion or 1–2 new T2 lesion(s) on MRI within the last 12 months) may start therapy with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab, ozanimod, or ponesimod. The choice of drug should be based on the patient's individual profile
- Patients with RRMS with high disease activity should start therapy with highly effective drugs such as natalizumab, ocrelizumab, ofatumumab, fingolimod, ozanimod, ponesimod, cladribine tablets or alemtuzumab. The choice of drug should be based on the individual profile of the patient
- Females of childbearing age who are not using contraception or who are breastfeeding are encouraged to initiate treatment with interferon beta or glatiramer acetate. More safety data is needed with regards to other DMTs. However, this should be discussed on an individual basis, especially in cases with high disease activity
- In patients with high risk of disease reactivation post-partum who decide to breastfeed, the use of highly effective monoclonal antibodies, the amount of which that pass into breastmilk is expected to be low, should be discussed on an individual basis. More safety data is needed in this area
- Continuation of treatment with interferon beta or glatiramer acetate may be considered in pregnant patients after evaluating the benefit-risk ratio. If natalizumab is used, continuation of therapy until the end of the 34th week of gestation may be taken into account
- In patients with RRMS with high disease activity who plan pregnancy, reconstitution therapies (cladribine tablets, alemtuzumab) may be considered to stabilise the disease before pregnancy

Table 2. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis#

	Laboratory parameters	Clinical parameters	Radiological parameters
Beta interferons	1 Before starting the therapy and then at regular intervals (more often in the case of abnormalities in laboratory findings or individual clinical indications): 1. complete blood count with differential; 2. biochemical parameters of liver function; parameters of kidney function: urinalysis 3. TSH	1. Before starting the therapy and then at regular intervals: a. medical interview to check for current symptoms of severe depression and/or suicidal ideation; b. medical interview to check for and observation for possible signs symptoms of decompensated liver failure* 2. Regular observation of injection sites 3. Regular medical interview to check for flu-like symptoms	No need to monitor from the perspective of the safety of the therapy
Glatiramer acetate	Periodic monitoring of liver and kidney function tests is required	Points 1b and 2 as above	No need to monitor from the perspective of the safety of the therapy
Dimethyl fumarate and diroximel fumarate	1. Complete blood count with differential before starting the treatment and then every 3 months **NOTE:** In the case of lymphopenia, more frequent monitoring of blood count with differential is recommended, especially if lymphocyte count < 800/mm^3; if lymphopenia is present below this level for > 6 months — the benefit—risk ratio of the therapy should be reconsidered (eg determination of anti–JCV antibodies) Dimethyl fumarate should be discontinued if lymphopenia persists < 500/mm^3 for > 6 months 2. Biochemical parameters of renal function and urinalysis before the therapy, after 3 and 6 months, and then every 6—12 months, depending on clinical indications 3. Biochemical parameters of liver function: before starting treatment and then depending on clinical indications 4. If PML is suspected, JCV DNA should be determined by PCR in the cerebrospinal fluid	1. Medical interview to check for gastrointestinal symptoms before starting the therapy and then at regular intervals 2. Medical interview to check for flushing symptoms (at each visit) 3. In the case of persistent lymphopenia, medical interview to check for and observation for infection, including the symptoms of varicella–zoster virus infection and PML**	1. Usually no need to monitor from the perspective of the safety of the therapy 2. In appropriate cases with persistent lymphopenia between 500 and 800/mm^3 and a high anti–JCV antibody index and/or previous immunosuppression, increased frequency of MRI scans examinations (every 3–6 months) should be considered using a short protocol (ie FLAIR, T2, DWI) for the preclinical stage of PML
Teriflunomide	1. Before starting the therapy and then at regular intervals (as clinically indicated; more often in the case of abnormalities in findings): — complete blood count with differential — liver function tests: • for the first 6 months of therapy — ALT assessment every 4 weeks, and then at regular intervals; • in patients on other drugs with hepatotoxic potential OR who have concomitant liver disease OR clinical signs and symptoms of liver failure — ALT assessment every 2 weeks for 6 months, then at least once every 8 weeks for at least 2 years from the start of therapy; • if ALT > 2–3x the upper limit of normal (ULN), ALT should be assessed weekly; • if ALT > 3x ULN, therapy should be discontinued	1. Before starting the therapy and then at regular intervals: — medical interview to check for hypertension and periodic blood pressure monitoring, at least once every 3 months; — medical interview to check for and observation for possible symptoms of decompensated liver failure* 2. Medical interview to check for pregnancy and contraception before starting the therapy and at each visit	No need to monitor from the perspective of the safety of the therapy
Natalizumab	1. Before starting therapy: • test for anti–JCV antibodies (anti–JCV antibody index); • complete blood count with differential; • biochemical parameters of liver function; parameters of renal function: at least urinalysis 2. During the therapy: • determination of the anti–JCV antibody index every 6 months; • complete blood count with differential and liver function test and urinalysis with microscopic examination of sediment — at regular intervals, depending on clinical indications 3. If PML or JCV GCN is suspected, JCV DNA should be determined by PCR in the cerebrospinal fluid	1. Medical interview to check for and observation for PML symptoms** 2. Medical interview to check for decreased visual acuity, redness and eye pain (retinal examination should be performed for ARN)	More frequent MRI scans (every 3–6 months) using a short protocol (ie FLAIR, T2, DWI) should be performed in patients at a higher risk of PML Such patients include: a) those with all three risk factors for PML (ie the presence of anti–JCV antibodies and on natalizumab for > 18 months and previously on immunosuppressive drugs) OR b) those with a high anti–JCV antibody index treated with natalizumab > 24 months and with no history of immunosuppressive treatment Available data suggest that the risk of PML is low at ≤ 09 and increases significantly at > 15 in patients treated with natalizumab > 24 months MRI should also include a T1 sequence before and after contrast administration in the case of suspected PML

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Table 2. cont. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis[#]

	Laboratory parameters	Clinical parameters	Radiological parameters
Fingolimod — information also applies to other S1P receptor modulators (ozanimod/ /ponesimod/ /siponimod) unless indicated otherwise	1. Before starting the therapy: • complete blood count with differential; • liver function tests: at least ALT, AST and bilirubin; • kidney function tests: at least creatinine and urinalysis; • determination of antibodies against varicella zoster virus (VZV) In the absence of the antibodies, vaccination is mandatory at least one month before the therapy; • CYP2C9 genotyping (in the case of siponimod) 2. During the therapy: • complete blood count at Month 3, then periodically and in the case of symptoms of infection (for fingolimod at least once a year) — confirmed absolute lymphocyte count < 200/mm^3 x109/l should result in treatment discontinuation until recovery to baseline values (fingolimod, ozanimod — recovery to 500/mm^3 is sufficient to restart therapy, ponesimod — required level > 800/mm^3); • ALT, AST and bilirubin tests at 1, 3, 6, 9 and 12 months of treatment, and then at least every 6 months and up to 2 months after the discontinuation of therapy or as clinically indicated (in the case of siponimod — periodically or if the symptoms of hepatic impairment occur): — if transaminases are > 3x ULN but < 5x ULN without clinical symptoms and without an increase in bilirubin, more frequent monitoring is recommended, including determination of bilirubin and alkaline phosphatase levels; in the case of an increase in transaminases ≥ 5x ULN or > 3x with the increase in bilirubin, the drug should be discontinued (fingolimod); — treatment should be discontinued if significant liver injury is reported, eg, increase in ALT > 3x ULN or total bilirubin 2x ULN (ponesimod); — treatment should be discontinued if transaminases > 5x ULN (ozanimod); — in patients who develop symptoms of hepatic impairment during treatment, liver enzymes should be tested and treatment should be discontinued if significant liver impairment is confirmed (siponimod); • Periodic urinalysis; • Regular cervical smear according to the standards of practice (in the case of fingolimod)	1. Before starting the therapy: • ECG and blood pressure measurement; • cardiology consultation in patients on drugs that may slow the heart rate and in patients with a history of arrhythmias and conduction disorders, heart failure, cardiogenic syncope, or other significant heart disease and sleep apnea; • ophthalmology consultation — in the case of ponesimod — in all patients in whom the drug is planned; — in the case of ozanimod – in patients with a history of diabetes, uveitis or retinal disease; — in the case of fingolimod and siponimod — in patients with a history of diabetes or uveitis; • Dermatology consultation within 6 months before treatment (fingolimod and siponimod) 2. In connection with the first drug administration: For fingolimod: • ECG monitoring for 6 hours after the drug intake, additionally blood pressure and heart rate measurement every hour; additional 2–hour ECG monitoring is recommended if the heart rate reached the lowest levels 6 hours after the drug intake; • ECG monitoring should be prolonged if the heart rate decreases < 45/min in adults OR if QTc is prolonged > 500 ms OR the at least second–degree atrioventricular block is present; • the patient should be hospitalized at least until the next day and until the symptoms have resolved FOR ozanimod, ponesimod and siponimod: — ECG monitoring is recommended only in patients with a history of cardiac disease 3. During the therapy: • Medical interview to check for cardiac arrhythmias and blood pressure disorders (at each visit) and periodic blood pressure monitoring; • Medical interview to check for vision disorders (at each visit) and ophthalmology consultation: — in the case of fingolimod and siponimod: ophthalmology consultation is necessary 3–4 months after the start of treatment to exclude macular edema, and then at least once a year, depending on the ophthalmologist's opinion; ophthalmology consultation is also necessary if any visual disturbances occur during the treatment; — in the case of ozanimod — ophthalmology consultation during treatment is recommended in patients with a positive history of uveitis or retinal disease and in patients with diabetes AND in those with the symptoms of macular edema (therapy should be discontinued if the diagnosis is confirmed); — in the case of ponesimod – regular ophthalmology consultations in patients with a history of uveitis or diabetes AND if the patient reports any visual disturbances during the therapy; • Medical interview to check for new/enlarging skin nevi (at each visit) and dermatology consultation during therapy: — in the case of fingolimod and siponimod — every 6–12 months; — in the case of ponesimod — patients with pre–existing skin diseases and with new or changing skin nevi should be referred to a dermatologist for monitoring of the lesions; — in the case of ozanimod — patients should be warned against unprotected exposure to sunlight and against the use of phototherapy • If clinically indicated, spirometric assessment of respiratory function should be performed during treatment (ponesimod) • Medical interview to check for and observation for symptoms of infection, including opportunistic infections and neuroinfections (at each visit) • Medical interview to check for and observation for possible symptoms of decompensated liver failure*	No need to monitor from the perspective of the safety of the therapy unless the patient develops symptoms of opportunistic infections with possible CNS involvement (eg, cryptococcal meningitis, PML, meningitis and/or encephalitis caused by Herpes simplex virus or VZV)

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Table 2. cont. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis[#]

	Laboratory parameters	Clinical parameters	Radiological parameters
Alemtuzumab	1. Before starting the therapy: • Biochemical tests, including liver, kidney and thyroid function tests; • Complete blood count with differential; • Urinalysis with microscopic examination of sediment; • Screening tests for HIV infection (HIV Ag/Ab) and HBV (HBsAg, anti–HBc), HCV (anti–HCV), TBC (Quantiferon TB Gold Plus, IGRA test and chest X–ray) — if necessary, consultation with an infectious disease specialist or lung specialist 2. During the first cycle of treatment with infusions: — Platelet count should be determined immediately after the infusion on Days 3 and 5 of the first cycle, and immediately after the infusion on Day 3 of each subsequent cycle Clinically significant thrombocytopenia should be monitored until resolution Consultation with a hematologist should be considered 3. During the therapy between the infusion cycles: • complete blood count with differential, serum creatinine, urinalysis with microscopic assessment of sediment, liver function tests (transaminases) every month; • serum TSH every 3 months; • annual screening for HPV infection in female patients Tests should be continued up to 48 months after the last course of alemtuzumab 4. Assessment before the next infusion cycle: — HIV test, qualitative determination of HBV and HCV viral load, and chest X–ray should be repeated	Before starting the therapy: 1. ECG monitoring; 2. Measurement of heart rate and blood pressure; 3. Medical interview to check for autoimmune diseases, cardiovascular disease and immunodeficiencies; Premedication (before the infusion): — patients should be premedicated with glucocorticoids (1000 mg methylprednisolone for the first 3 days of each treatment cycle) during the first 3 days of each treatment cycle, immediately before the infusion; — premedication with antihistamines and/or antipyretics may also be considered; — all patients should be treated with oral prophylaxis of herpes virus infection from the first day of each treatment cycle and it should be continued for at least 1 month after the discontinuation of treatment (acyclovir 200 mg twice daily or equivalent); — patients should avoid ingestion of uncooked or undercooked meats, blue cheese and unpasteurized dairy products two weeks prior to, during, and for at least one month after LEMTRADA infusion to reduce the risk of infection caused by Listeria During the intravenous infusion: — monitoring of heart rate, blood pressure and general clinical status of patients at least every hour; — if severe infusion reactions occur, the intravenous infusion should be discontinued immediately (if the patient develops clinical signs and symptoms suggestive of myocardial ischemia, hemorrhagic stroke, cervicocephalic arterial dissections or pulmonary alveolar hemorrhage) Assessment immediately after the intravenous infusion: — observation for infusion reactions is recommended for at least 2 hours after the infusion; — patients with clinical signs and symptoms suggestive of a serious adverse event temporarily associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervicocephalic arterial dissection and alveolar hemorrhage) should be closely monitored until the symptoms are completely resolved (hospitalization) During the therapy: 1. Medical interview to check for signs and symptoms of myocardial infarction, stroke, intracerebral artery dissection, pulmonary hemorrhage (may occur up to one month after alemtuzumab infusion) 2. Medical interview to check for signs and symptoms of hyperthyroidism or hypothyroidism (at each visit) 3. Medical interview to check for and observation for symptoms of infection, including opportunistic infections and neuroinfections (at each visit)	No need to monitor from the perspective of the safety of the therapy unless patients develop signs and symptoms of opportunistic infection with possible CNS involvement (eg, cryptococcal meningitis, PML)
Ocrelizumab and ofatumumab	1. Before starting the therapy: • complete blood count with differential; • liver function tests: at least ALT and AST; • kidney function tests: at least creatinine and urinalysis; • screening tests for HBV (anti–HBc, HBsAg) and, if necessary, consultation with an infectious disease specialist/hepatologist; • screening for immunodeficiency (eg HIV Ag/Ab); • standard breast cancer screening based on local guidelines (in the case of ocrelizumab) 2. During the therapy, before each administration of ocrelizumab: • blood count before each drug administration; • urinalysis before each administration of the drug; • kidney and liver function tests before each administration of the drug; • HBsAg and anti–HBc before each administration of the drug 1. During ofatumumab therapy — complete blood count with differential, assessment of liver and kidney function tests and urinalysis after 3 months, and then at least twice a year, depending on the patient's clinical condition	1. Medical interview to check for and observation for symptoms of infection, including opportunistic infections and neuroinfections (at each visit) 2. Medical interview to check for and observation for possible symptoms of decompensated liver failure * in patients with a history of hepatitis B or C 3. Regular observation of injection sites and medical interview to check for injection–related reactions (in the case of ofatumumab) Premedication for ocrelizumab infusion–related reactions: The following premedication must be administered prior to each ocrelizumab infusion: • 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each infusion; • antihistamine approximately 30–60 minutes prior to each infusion In addition, premedication with an antipyretic (eg, paracetamol) may also be considered approximately 30–60 minutes prior to each infusion	No need to monitor from the perspective of the safety profile of the therapy unless patients develop signs and symptoms of opportunistic infection with possible CNS involvement (eg PML)

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Table 2. cont. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis[#]

	Laboratory parameters	Clinical parameters	Radiological parameters
Cladribine tablets	1. Before starting the therapy: • complete blood count with differential; • biochemical parameters of liver function: ALT, AST, alkaline phosphatase and total bilirubin; • biochemical parameters of kidney function and urinalysis; • determination of antibodies against varicella zoster virus (VZV) In the absence of the antibodies, vaccination is mandatory at least one month before the therapy; • Screening tests for HIV infection (HIV Ag/Ab) and HBV (HBsAg, anti–HBc), HCV (anti–HCV), TBC (Quantiferon TB Gold Plus, IGRA test and chest X–ray); if necessary, consultation with an infectious disease specialist or lung specialist 2. During the therapy: • complete blood count with differential 2 months and 6 months after initiation of the treatment in each year of the therapy; • If the lymphocyte count decreased < 500/mm^3, it should be actively monitored until it increases to at least 800/mm^3; • regular monitoring of liver enzymes and bilirubin based on clinical signs and symptoms Before the next treatment course: • complete blood count with differential; • ALT, AST, alkaline phosphatase and total bilirubin before the next treatment course; • serum creatinine level; • screening tests for HIV (HIV Ag/Ab) and HBV (anti–HBc, HBsAg), HCV (anti–HCV), TBC (Quantiferon TB Gold Plus, IGRA test and chest X–ray)	1. Medical interview to check for and observation for symptoms of infection, including opportunistic infections (especially varicella zoster virus) and neuroinfections (at each visit)	No need to monitor from the perspective of the safety profile of the therapy unless patients develop signs and symptoms of opportunistic infection with possible CNS involvement (eg PML)

PML — progressive multifocal leukoencephalopathy, JCV — JC virus, SmPC — summary of product characteristics, MRI — magnetic resonance imaging, PCR — polymerase chain reaction, ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGTP — gamma–glutamyl–transpeptidase, TSH — thyroid–stimulating hormone, ARN — acute retinal necrosis, GCN – JC virus granule cell neuronopathy, FLAIR — fluid attenuated inversion recovery, DWI — diffusion weighted imaging, CNS — central nervous system

#In each case, attention should be paid to the detailed recommendations in the current SmPC of a given medicinal product

*The signs and symptoms of decompensated liver failure include palmar erythema, yellowing of the sclera, ascites, Medusa's head sign, hepatosplenomegaly, pruritus, stellate angiomas (telangiectasia) on the abdomen and chest

**Signs and symptoms suggestive of PML: cognitive and behavioral disorders as well as other new neurological symptoms to be differentiated in the case of a suspected MS relapse

- Tests for (latent) infections should be performed to select the optimal drug before initiating a highly effective and immunosuppressive DMT. Particular attention should be paid to the JC virus, HBV, HIV, *Mycobacterium tuberculosis* and varicella zoster virus (VZV). If necessary, an infectious disease specialist should be consulted
- Before initiating treatment with natalizumab, the anti-JCV antibody index should be determined and the risk of progressive multifocal leukoencephalopathy (PML) should be stratified. During treatment with natalizumab, monitoring the anti-JCV antibody index is recommended. Extending the interval between the doses to six weeks may be considered after stabilisation of the disease to reduce the risk of PML development
- Preventive vaccinations should be performed before starting immunosuppressive DMT
- Drug dosing and additional tests before starting DMT and during treatment monitoring should be determined based on the current version of drug characteristics (SmPC).

Treatment of secondary progressive multiple sclerosis

Secondary progressive multiple sclerosis (SPMS) is characterised by gradual, relapse-independent disability progression after an initial relapsing-remitting course. In the early phase of SPMS, relapses and/or radiological activity (active SPMS) may occur. Currently, there are no unified diagnostic criteria for SPMS [9]. Siponimod, IFN-beta 1b, or mitoxantrone are recommended in active SPMS [13]. The choice of DMT should be individual and based on disease activity and progression, the adverse effect profile, and patient preferences.

Recommendations

- Siponimod or INF-beta 1b should be offered to patients with SPMS with signs and symptoms of inflammatory activity (relapses and/or radiological activity).

- Mitoxantrone may be considered in patients with active SPMS when there is no other therapy available. However, potential adverse effects should be taken into account.

Treatment of primary progressive multiple sclerosis

Primary progressive multiple sclerosis (PPMS) is characterised by the progression of disability from the onset of the disease without evident relapses [9]. Ocrelizumab has been approved for the treatment of PPMS based on clinical trials [60]. Its efficacy and safety have been confirmed in a clinical trial in patients at age < 55 years with disease duration < 15 years and a lower level of disability (EDSS < 6.5). Ocrelizumab is used in the treatment of adult patients with early PPMS assessed based on disease duration and the level of disability, as well as radiological features characteristic of inflammatory activity [35].

Initiation of treatment must be preceded by a thorough analysis of the benefit-risk ratio associated with the use of ocrelizumab [61, 62], which is particularly relevant in the case of older patients with PPMS without disease activity, in whom symptomatic treatment alone may be most appropriate.

Recommendations

- Ocrelizumab is recommended for patients with early and (clinically and/or radiologically) active PPMS
- Treatment effectiveness should be evaluated every 12 months. Treatment discontinuation should be discussed with the patient if there is significant disease progression.

Monitoring and change of DMT

Monitoring of MS treatment has two aims:

1. ensuring the safety of the therapy (monitoring clinical, laboratory and radiological parameters that may indicate adverse effects)
2. rapid detection of the ineffectiveness of therapy to modify it (monitoring of clinical and radiological disease activity).

Monitoring DMT safety

Monitoring of MS therapy for safety is mainly defined for individual drugs based on their SmPCs [27–42, 63]. Table 2 sets out clinical, laboratory and radiological parameters that must be regularly monitored to avoid, or early detect, possible adverse effects of individual DMTs. They are developed based on the provisions of the SmPCs and international recommendations [13, 22]. It should be noted that the monitoring of therapy in women also includes performing a pregnancy test each time pregnancy is suspected and in accordance with the SmPC.

The occurrence of adverse effects may be the basis for changing the therapy to a drug with a different safety profile. Severe adverse reactions require discontinuation of therapy, regardless of its duration, followed by a decision to reintroduce DMT. Serious adverse reactions of DMT include:

- anaphylactic reaction requiring immediate discontinuation of treatment
- liver failure or alanine transaminase (ALT) and aspartate transaminase (AST) > 3–5 x the upper limit of normal (ULN)
- leukopenia, particularly grade 3 and 4 neutropenia (< 1,000/mm^3 and < 500/mm^3, respectively) [64] and grade 3 (< 500/mm^3) and grade 4 lymphopenia (< 200/mm^3) (except for therapy with sphingosine receptor modulators, during which lymphocyte count may decrease to 200/mm^3, but not below this level) [65]
- thrombocytopenia, especially < 50,000/mm^3 [66]
- progressive multifocal leukoencephalopathy (PML) requiring immediate discontinuation of treatment
- severe skin complications due to injection therapy (abscess, necrosis).
- Highly effective therapies (HETs) may need to be discontinued and switched to a therapy with no immunosuppressive potential when the patient presents with:
- malignant neoplasm
- hepatitis B or C
- tuberculosis
- HIV
- another severe infection.

If pregnancy is confirmed, immediate discontinuation of DMT is usually recommended. Treatment with glatiramer acetate, beta-interferons, and natalizumab (until the 34th week of gestation) may be continued during pregnancy provided that the maternal benefit outweighs the potential risk to the foetus [67].

If teriflunomide is discontinued and switched to another therapy, regardless of the reason for treatment modification, the patient should undergo the standard procedure, i.e. accelerated drug elimination using oral cholestyramine (8 g 3 x day, or in the case of poor tolerance of the dose, 4 g 3 x day for 11 days) or oral activated charcoal (50 g every 12 hours for 11 days) before initiating a new therapy. If teriflunomide is discontinued due to planned pregnancy, the efficacy of drug elimination should be confirmed by the assessment of blood drug levels twice, with an interval of at least 14 days. The target concentration of the drug should be less than 0.02 mg/l [34, 67].

Monitoring effectiveness of DMT

Monitoring the effectiveness of MS therapy does not differ for individual drugs and should include [68]:

- regular neurological examination with assessment of the EDSS score at least once a year

– assessment of the radiological activity of the disease using brain MRI (new and/or enlarging T2 lesions and/or Gd(+) lesions) should be performed at least once a year. In the first year of treatment (3–6 months after the start of therapy), a contrast MRI (the so-called re-baseline MRI) may be considered to which subsequent MRI scans can be compared. In the absence of relapsing activity and new radiological lesions, another MRI without contrast administration may be considered.

If a relapse occurs, the following should be performed:

– a neurological follow-up examination during the relapse and c.90 days after the onset of relapse symptoms
– (if possible) a follow-up/comparative MRI examination before and after contrast administration (preferably before administration of high doses of glucocorticoids)
– a follow-up MRI examination of the relevant section of the spinal cord and a comparison of this examination with the baseline MRI in the case of spinal cord relapse.

The lack of effectiveness of the therapy can be found at least 6-9 months after its initiation and usually after 12 months. Change of treatment due to its ineffectiveness may occur earlier in exceptional cases i.e. due to high disease activity/aggressive course of the disease, and especially disease activity higher than before the start of therapy [9, 69, 70].

Definition of DMT ineffectiveness

There is no uniform definition of DMT ineffectiveness [13, 22, 68]. There is currently no therapy for complete recovery from MS. Therefore, residual clinical and/or radiological activity during DMT is highly possible.

Therapy is usually considered ineffective if one of the following conditions is met mostly after 12 months of therapy:

– at least 1 relapse
– at least 1 MRI lesion enhancing after contrast administration
– at least 2 new/enlarging T2 lesions on MRI
– a significant increase in disability (EDSS) lasting for 3–6 months (an increase of 0.5 or 1 point, depending on the baseline EDSS score).

DMT switching

A change in treatment can be related to an escalation strategy (escalating from moderate efficacy to higher efficacy) or a lateral switch (within the same category of DMT efficacy). If a DMT is ineffective, it should be escalated or changed to any other highly effective drug (lateral switch) if the patient is already treated with a highly effective DMT. However, lateral switching is usually recommended when adevrse reactions occur (see above and Tab. 2).

Regardless of the reason for changing treatment, the choice of another DMT should depend on similar factors as in the choice of the first therapy (see above) [22]. When switching DMTs, the duration of action of individual drugs should be considered to avoid the potential consequences of combining different therapies. Recommendations on time intervals to be maintained between therapies (wash-out) are given in Table 3.

Recommendations

- During DMT use, clinical and radiological parameters should be monitored by assessing the patient's neurological status and performing an MRI examination at least once a year
- MRI examination without contrast administration may be considered in the absence of relapse activity and new radiological lesions
- A more effective DMT should be used if disease activity occurs during therapy with a moderately effective drug
- Switching to a highly effective drug with a different mechanism of action should be made if disease activity occurs during highly effective DMT
- Therapy with another highly effective drug should be considered immediately if it is necessary to discontinue DMT affecting lymphocyte migration (natalizumab, S1P receptor modulators) due to the high risk of disease reactivation
- Scheduled administration of the next treatment cycle should be primarily considered based on the approved regimen if disease activity occurs before administration of the full therapeutic dose (before the second treatment cycle) of reconstitution therapies (cladribine tablets, alemtuzumab)
- In patients on reconstitution therapies (cladribine tablets, alemtuzumab), additional treatment cycles should be considered after assessing the benefit-risk ratio if disease activity recurs after a stabilisation period induced by the standard dose of the drug (two cycles)
- De-escalation of treatment should be considered: a highly effective DMT should be replaced with a moderately effective DMT in some cases – e.g. during pregnancy or due to patient safety
- If adverse reactions occur during DMT, another drug should be administered based on its safety profile, or, if the adverse reaction is due to the route of administration, the route should be changed if possible.

Completion of disease-modifying therapy

With the long-term course of MS, age-related changes to the immune system are observed (immunosenescence). The consequence of this process is associated with a change in the nature and severity of inflammatory reactions underlying the

Table 3. Recommended time intervals between the use of disease-modifying drugs in multiple sclerosis [95]

Switching from to	Beta-interferons	Glatiramer acetate	Dimethyl Fumarate, Diroximel Fumarate	Teriflunomide	S1P receptor modulators	Natalizumab	Alemtuzumab	Anti-CD20 (ocrelizumab, ofatumumab, rituximab*)	Cladribine tablets
Beta-interferons		Not required	Not required	Not required	Not required	Not required	Not required	Not required	Not required (provided that the lymphocyte count is normal prior to the first administration of cladribine)
Glatiramer acetate	Not required		Not required	Not required	Not required	Not required	Not required	Not required	Not required (provided that the lymphocyte count is normal prior to the first administration of cladribine)
Dimethyl fumarate°, Diroximel fumarate °	Not required	Not required		Not required	Not required	Not required	Not required	Not required	Not required (provided that the lymphocyte count is normal prior to the first administration of cladribine)
Teriflunomide	Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure		Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure (provided that the lymphocyte count is normal prior to the first administration of cladribine)
S1P receptor modulators° *	Optimally #^ ≥ 4 weeks	Optimally#^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks		Optimally #^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks	Optimally # ≥ 4 weeks provided that the lymphocyte count is normal prior to the first administration of cladribine
Natalizumab *&	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks		Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks provided that the lymphocyte count is normal prior to the first administration of cladribine
Alemtuzumab°	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months		Optimally # ≥ 6 months	Optimally # ≥ 6 months provided that the lymphocyte count is normal prior to the first administration of cladribine
Anti-CD20 - ocrelizumab - ofatumumab	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months		Optimally # ≥ 6 months provided that the lymphocyte count is normal prior to the first administration of cladribine Optimally # ≥1-3 months provided that the lymphocyte count is normal prior to the first administration of cladribine
Cladribine tablets °	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	

*the possibility of a severe rebound after treatment discontinuation; °before starting another DMT drug, it should be verified whether the lymphocyte count meets the criteria for the inclusion of another DMT (complete blood count with differential should be performed); &before starting another DMT drug, the possibility of carry-over PML should be considered; #related to individual decision making, depending on the clinical and immunological status of the patient; ^related to individual decision making, depending on the S1P receptor modulator due to significant differences in pharmacokinetic parameters

disease, as well as higher susceptibility to infections and cancer [71–73]. Clinically, a reduction in the frequency of relapses and a reduction in disease activity on imaging studies are observed. However, an accelerated accumulation of neurological disability independent of relapses is found [71, 74, 75].

Most of the data obtained in clinical trials is related to patients up to 55–60. The amount of information on the drug action, including efficacy and safety, for people over 60 is limited [76]. The potential decrease in the efficacy of DMT with age, combined with increasing susceptibility to infections/cancer and comorbidities, means that some patients may experience an unfavorable change in the benefit-risk ratio of DMT, which may result in decision on therapy discontinuation [77].

Currently, there are no methods that could reliably predict disease progression and the risk of disease reactivation after DMT is discontinued. Available studies were concentrated mainly on discontinuation of moderately effective DMT. The results suggest that older age (most often defined as > 50–60 years), a longer period of clinical stabilisation, and the absence of signs of disease activity on imaging studies are associated with a lower risk of recurrence of MS activity [78–88]. There is no consensus on the progression of neurological disability after stopping of moderately effective DMT [11, 13, 22, 23]. Completion of a highly effective DMT, especially as regards drugs that affect lymphocyte migration (natalizumab, S1P receptor modulators) is associated with a high risk of disease reactivation [89,90]. Currently, there is insufficient data to reliably assess the risk [82, 91].

The DISCO-MS trial to assess the effect of discontinuation of DMTs on MS course did not yield conclusive results [92]. Further clinical trials in this respect are being conducted in patients with RRMS (DOT-MS) and SPMS (STOP-I-SEP). Different studies have also been performed on the development of adequate prognostic tools [93].

Recommendations

- DMT should be continued in patients during clinical and radiological stabilisation of the disease if there are no contraindications related to the safety of therapy or treatment tolerance.
- If DMT is discontinued, the patient should be informed of all aspects of the situation, including the need to remain under the constant care of a neurologist and regular follow-up for early detection of possible disease reactivation.

Author's comment:

During the publication process additional monoclonal antibody – ublituximab (Briumvi®) was registered in European Union countries, including Poland.

Article information

Conflicts of interest: *AKulakowska received honoraria for lectures and contributions to Advisory Board from pharmaceutical companies i.e. Biogen, Novartis, Bayer, Teva, Sanofi, Merck, Bristol-Myers-Squibb, Janssen-Cilag, UCB and GSK. None of the consulting agreements are relevant to the submitted work.*
DM-G received compensation for speaking and consulting services from Biogen, Novartis, Roche, Merck, Teva, BMS, GSK, Bayer, Shire and Sanofi. None of the consulting agreements are relevant to the submitted work.
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MSiger declared no conflict of interest relevant to the submitted work.
AS received compensation for speaking and consulting services from Biogen, Sanofi, Novartis, Teva, and Merck. None of the consulting agreements are relevant to the submitted work.
SW received honoraria for lectures and contributions to Advisory Board from pharmaceutical companies i.e. Bayer, Biogen, Merck,

Novartis, Roche, Sanofi, and Teva. None of the consulting agreements are relevant to the submitted work.
JZ declared no conflict of interest relevant to the submitted work.
BZ-P received honoraria for lectures and contributions to Advisory Board or as investigator in clinical trials from pharmaceutical companies i.e. Biogen, Novartis, TEVA, Sanofi, Merck, Bayer, Roche, Allergan, CHUGAI, and BMS. None of the consulting agreements are relevant to the submitted work.
MA-S received honoraria for lectures and contributions to Advisory Board from pharmaceutical companies i.e. Biogen, Novartis, Bayer, Teva, Sanofi, Merck, Bristol-Myers-Squibb, Janssen-Cilag, Roche, UCB and GSK. None of the consulting agreements are relevant to the submitted work.

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