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Progressive forms of multiple sclerosis: disease-modifying therapy review

**Klaudia Sapko, Anna Szczepańska-Szerej, Anna Jamroz-Wiśniewska,
Marcin Kulczyński, Michał Marciniak*, Konrad Rejdak**

Chair and Department of Neurology, Medical University of Lublin, Lublin, Poland

*E-mail address: lekmarciniec@gmail.com

ABSTRACT

Multiple sclerosis (MS) is a demyelinating, inflammatory, autoimmune disease of the central nervous system which affects most commonly young adults. It has wide spectrum of clinical and radiological presentations with relapses or steady progression. Recent years have brought new reports on the pathogenesis of MS. This systematized the current MS classification and created new parameters describing the course of the disease, such as activity and progression. Attention has been paid to the need for new drugs that focus on the treatment of progressive MS. Until now, the primary and secondary progressive MS have been somewhat forgotten, and most of modifying-disease drugs have been registered in the treatment of relapsing-remitting subtype. In recent years, not only new drug has been registered for the treatment of progressive MS (ocrelizumab) and another one is planned to be approved soon (siponimod), but also indications of old medicines (interferon-beta1b, cladribine, mitoxantrone, cyclophosphamide, azathioprine) have been extended. Despite intensive development, there is still a great need to seek new drugs that will stop the progression of disability in MS patients.

Keywords: Multiple sclerosis, Disease-modifying drugs, Primary-progressive MS, Secondary-progressive MS, New therapy

1. INTRODUCTION

Multiple sclerosis (MS) is a multifocal, demyelinating, chronic syndrome of the central nervous system of inflammatory nature. It mostly affects young people between ages 20 and 40 [1]. The disease attacks myelin sheath of neurons causing their inflammation and, finally, degeneration of axon. Currently, it has been elucidated that the disease is autoimmune and occurs in people with genetic predisposition [2]. Disease is characterized by the occurrence of periods of relapses and remissions or steady progression. The course of the disease may vary from silent lesions on magnetic resonance imaging (MRI) to the full clinical syndrome with severe neurological deficits. MS can cause various symptoms, such as sensory abnormalities including hyperaesthesia, hypaesthesia, paraesthesia, movement disorders, muscle weakness, muscle cramps, difficulties in movement, sphincter dysfunction. There may be visual disturbances caused by retrobulbar optic neuritis, which may be the first manifestation of the disease, diplopia, nystagmus, speech disorder, cognitive impairment. The main tool to assess the degree of disability is Expanded Disability Status Scale (EDSS) [3]. The list of MS symptoms is extensive, and the progress of disability in many patients is very dynamic, which is why early diagnosis is of great importance for the beginning of treatment. The basic diagnostic tool in MS is brain MRI, that is used to detect demyelinating lesions. MRI combined with clinical analysis helps to determine the phenotype of the disease [2].

2. CLASSIFICATION OF PHENOTYPES

In 1996 the Advisory Committee on Clinical Trials in Multiple Sclerosis of the American National Multiple Sclerosis Society (NMSS) defined 4 clinical subtypes of MS: relapsing-remitting (RRMS), primary progressive (PPMS), secondary-progressive (SPMS) and progressive-relapsing (PRMS) (Table 1.) [4]. The description of these types has been in use in clinical practice for many years, but progress in knowledge about disease has led to a revision of the descriptors. In 2011, the Committee and other experts re-examined the phenotypes of MS based on imaging, biomarkers and clinical advances. The basic assumptions of the previous classification have been maintained, however, changes have been introduced [5]. First, Clinically Isolated Syndrome (CIS) was included in the new classification. Currently CIS is considered the first manifestation of the disease, where clinical symptoms may indicate signs of inflammatory demyelination but are not a confirmation of the disease because the dissemination criteria in time must still be met [6]. A different situation concerns the Radiologically Isolated Syndrome (RIS), which was not included in the previous classification and the current criteria support these provisions. In RIS, accidental changes detected radiologically of a potentially demyelinating nature do not correspond with clinical symptoms [7,8].

Nevertheless, it motivates to be vigilant and to observe prospectively a patient who may develop a full-blown MS. The concept of RRMS, PPMS and SPMS phenotypes remained unchanged (Table 2). However, new modifiers were introduced such as disease activity and disease progression. The basic forms of MS can be classified as recurrent or progressive. Additionally, MS can be described by the activity measured by new lesions in neuroimaging or by the relapses. The progression expresses the increase of patient's disability. Inclusion of disease activity, resulted in elimination of the PRMS subtype [5].

The introduction of new modifiers enables better assessment of disease progression and therapeutic plan. The greater the activity and the progression of the disease expressed by the lesions on MRI, the number of relapses or the degree of disability, the greater the need to intensify the treatment.

Table 1. Multiple sclerosis clinical subtypes – 1996 description [4].

Subtype	Clinical course
Relapsing-remitting disease (RRMS)	Full recovery after relapse
	Partial recovery/residual deficit
Primary progressive disease (PPMS)	Progression of disability from the beginning
Secondary progressive disease (SPMS)	Progression of disability after relapsing onset
Progressive-relapsing disease (PRMS)	Progression of disability from the beginning, relapses with or without full recovery

Table 2. Multiple sclerosis clinical phenotypes - 2013 description [5].

Phenotype	Modifiers
Clinically isolated syndrome (CIS)	Active* or not active
Relapsing -remitting disease (RRMS)	Active* or not active
Primary progressive disease (PPMS)	Active* and progressive** Active* but not progressive Not active but progressive** Not active and not progressive
Secondary progressive disease (SPMS)	

*Activity assessed based on lesions on MR imaging (new or increasing lesions in CNS in T2-weighted images or enhancing after contrast) and on clinical relapses observed at least once a year.

**Progression determined based on the clinical evaluation of disability assessed at least once a year.

3. PROGRESSIVE PHENOTYPES OF MS

The progressive form of MS is characterized by gradual accumulation of disability regardless of relapses. In PPMS neurological deficits constantly increase from the beginning of the disease. On the other hand, gradual progress of disability may occur after the period of relapses. Then it is classified as SPMS phenotype [9]. In both cases activity and progression are taken under consideration. We assess activity based on lesions on MR imaging in form of new or increasing lesions in the central nervous system (CNS) in T2-weighted images or enhancing after contrast and based on clinical relapses observed at least once a year. In turn, the disease progression is estimated based on the clinical evaluation of disability assessed at least once a year [5]. The progressive form of MS can be specified, regardless of the primary or secondary character, based on activity and progression, while the two factors can occur together, independently of one another or not at all (Table 2). These features allow to establish a therapeutic schedule and determine the intensity of treatment in patients with progressive MS. Immediate implementation of the treatment should be applied in patients with high activity and disease progression [5,10].

4. MEDICATIONS FOR THE TREATMENT OF MS

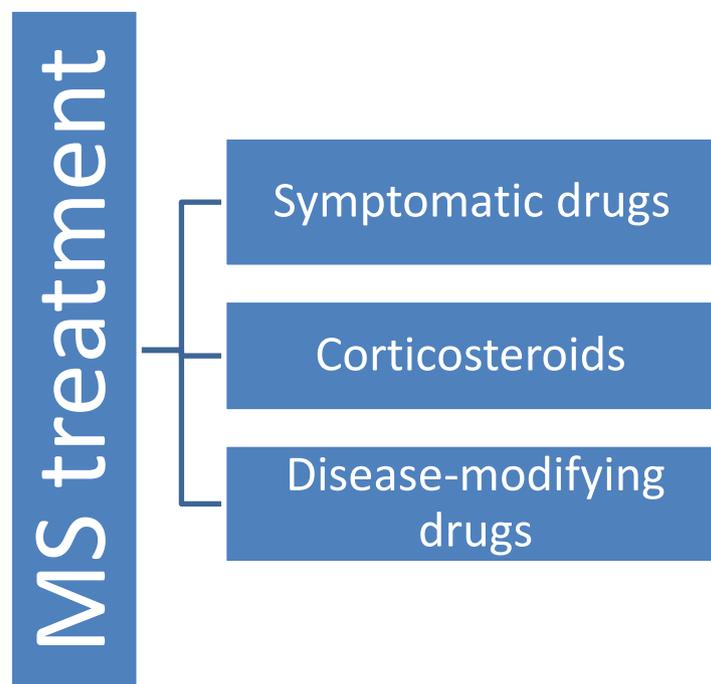


Figure 1. Groups of drugs used to treat MS.

Among the medications applied in MS, we can distinguish symptomatic drugs that are used to combat signs and symptoms of the disease such as paresis, spasticity, sphincter disorders, tremors, dizziness or paraesthesia, corticosteroids to treat relapses and disease-

modifying drugs (DMDs) that are designed to prevent relapses and to stop the progression of the disease (Figure 1). The treatment of progressive forms of MS is difficult and has so far been limited mainly to symptomatic medications. DMDs were mainly dedicated to treat RRMS [11]. However, recent years have brought many changes. Currently, among the drugs that modify the course of the disease in the treatment of progressive forms, we distinguish ocrelizumab, siponimod, interferon-beta 1b, cladribine and the other old, immunosuppressive drugs, such as, mitoxantrone, cyclophosphamide and azathioprine (Figure 2).

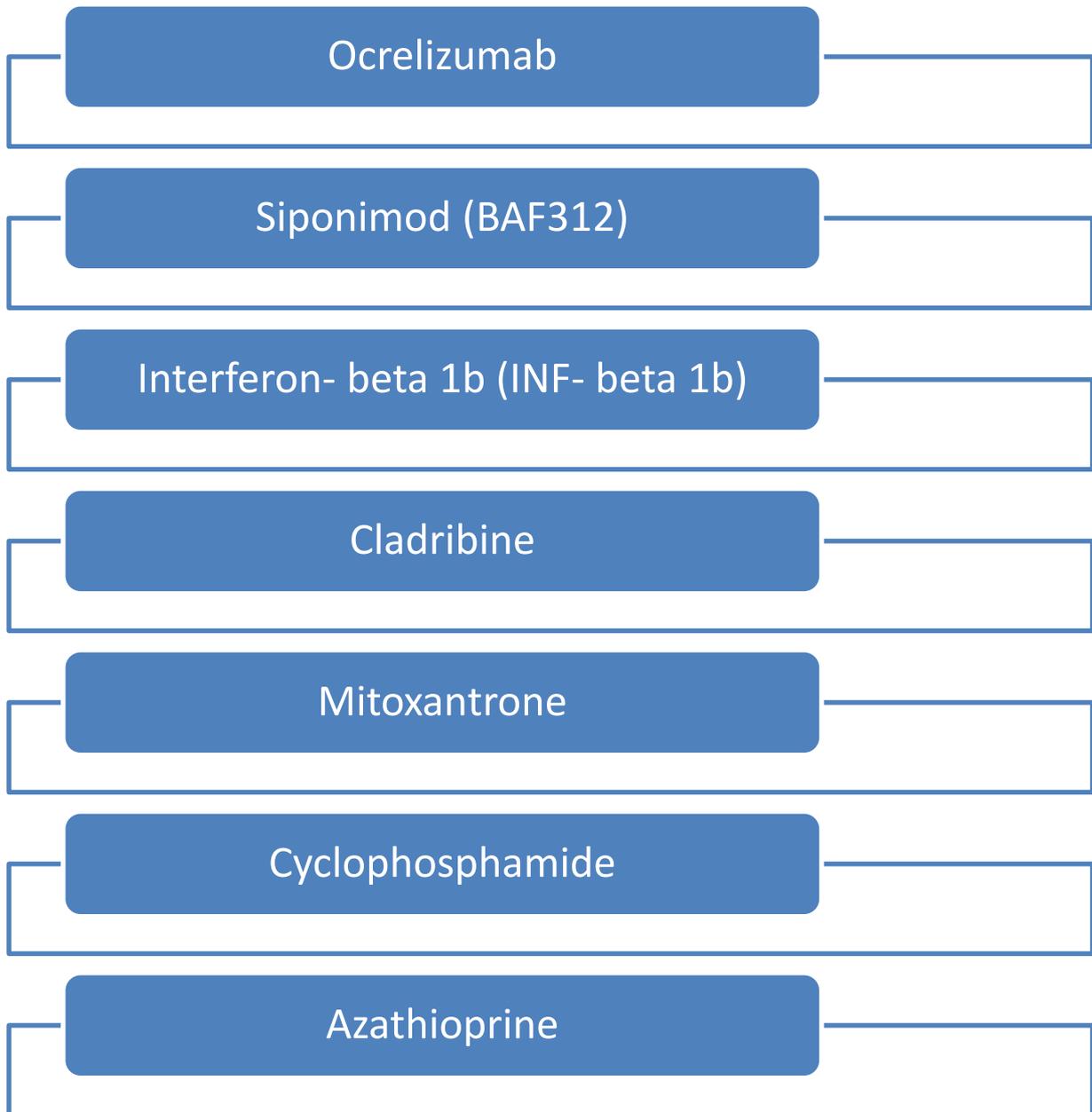


Figure 2. Disease-modifying drugs in the treatment of progressive forms of MS.

4. 1. Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody directed against CD20 antigen located on B lymphocytes that play important role in the pathogenesis of MS. They participate in the production of proinflammatory cytokines, autoantibodies that destroy myelin and activation of T cells, which intensify inflammatory reactions [12]. In addition, B lymphocytes form aggregates in the meninges, contributing to neurodegeneration and disability progression [13]. The uniqueness of ocrelizumab is that it is the first drug that has been approved for the treatment of not only RRMS but also a PPMS by the American Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) respectively in March and November 2017 (Table 3.) [12]. The efficiency of ocrelizumab in PPMS was investigated as part of the ORATORIO study, the results of which confirmed the beneficial effects of ocrelizumab in reducing the progression of disability in patients with MS [14]. Among the adverse reactions in patients receiving anti-CD20 antibodies, reactivation of hepatitis B virus (HBV) was observed, which later could lead to fulminant inflammation, hepatic failure and finally to death. Therefore, it is recommended to test the immunization status against HBV in patients treated with ocrelizumab and to register vaccinations against HBV. There are also reports of increased susceptibility to infection and incidence of cancer due to ocrelizumab treatment [12,15]. Nevertheless, ocrelizumab is a drug that sets a new direction in the treatment of MS.

4. 2. Siponimod (BAF312)

Siponimod (BAF312) is a new drug from the group of selective modulators of 1-phosphate sphingosine receptors (S1P), which has immunomodulatory and neuroprotective effect through the sequestration of B and T lymphocytes in lymphoid organs [16,17]. This group of substances also includes fingolimod, ponesimod, ozanimod and ceralifimod. Fingolimod was the first drug in this group registered for the treatment of MS. Its use is most often associated with the risk of bradycardia, hypertension, macular oedema, cough, dyspnoea or diarrhoea [16]. Siponimod, as a selective drug for the S1P and S5P receptor, differs from fingolimod with a slightly lower rate of side effects, but the therapeutic effect of these drugs is similar. The recently completed phase III EXPAND study also demonstrated the efficiency of siponimod in reducing the progression of disability in patients with SPMS (Table 3.) [17].

4. 3. Interferon-beta 1b (INF- beta 1b)

Interferon-beta 1b (INF- beta 1b) belongs to a group of substances called interferons, produced as glycoproteins in mammalian cells. They have immunomodulatory, anti-proliferative and antiviral effects. Among interferons, we distinguish alpha, beta and gamma interferon. INF-beta 1b was the first drug used as a disease-modifying therapy that was approved for the treatment of MS [18]. The primary indication was treatment of RRMS, approved in the USA in 1993, and in Europe in 1995 [18,19]. Long-term studies on the influence of interferon on patient's health confirmed its effectiveness and led to extension of indications for INF-beta 1b to the other forms of MS [20]. Currently, INF-beta 1b is indicated for patients with CIS, with active inflammation, who are at high risk of progression to full-blown MS, in patients with the form of RRMS and SPMS (Table 3) [18]. This drug is chosen as the first-line therapy in MS because of its confirmed effectiveness and the convenience of use. The INF-beta 1b method of administration has evolved over the years from the

subcutaneous injection kit to an automatic injection device that makes it easier for patients to undergo therapy [21]. Numerous injections are associated with an adverse reaction in the form of injection site reaction (ISR). Side effects include leukopenia, flu-like symptoms, headaches and increased liver enzymes. For many patients, numerous self-injections may be cumbersome and discouraging, but INF-beta 1b is still eagerly chosen by clinicians due to the long history of safe use [20].

4. 4. Cladribine

Cladribine is a drug that mimics the adenosine nucleoside. It is a purine analogue (2-chloro-2'-deoxyadenosine) whose metabolites are resistant to adenosine deaminase. It penetrates to the CNS and has a depleting effect on B and T lymphocytes [22,23]. Metabolites accumulate in cells causing their death [24]. Cladribine, not activated, undergoes rapid excretion from the body, and its activation occurs only with the participation of lymphocytes. Due to selective affinity for leukocytes and effective suppression of the immune response, cladribine has been used in the treatment of MS. It has been recently registered in the treatment of RRMS, but it has also been used in progressive types of MS (Table 3). The efficiency of this drug is compared to fingolimod. However, it is characterized by a more favourable biological profile and the occurrence of fewer side effects [23]. Nonetheless, cladribine should be associated with the risk of severe lymphopenia [24].

4. 5. Mitoxantrone

Mitoxantrone acts by intercalating the functioning of DNA, which affects and modulates the immune system. It has been approved by FDA for the treatment of SPMS and RRMS. The use of mitoxantrone is associated with many potential side effects such as cardiotoxicity, leukopenia, acute leukaemia, renal failure, depression, alopecia, nausea, vomiting, teratogenicity [25]. It is estimated that acute leukaemia's occur in 1% of patients treated with mitoxantrone, cardiac dysfunction in approximately 10% of patients [26]. Due to side effects profile, the use of mitoxantrone should be cautious and patients carefully monitored by check-ups of blood morphology and echocardiography examination.

4. 6. Cyclophosphamide

Cyclophosphamide belongs to the group of immunosuppressive drugs. As multiple sclerosis is treated according to the theory as an autoimmune disease, immunosuppressive drugs have been used in the therapy of MS since 1966 [25]. Cyclophosphamide is a prodrug that, when converted into active metabolites in the liver, causes cell death. It also reduces the level of immunoglobulins by reducing the level of lymphocytes in the blood and in the cerebrospinal fluid. There have been suggestions that cyclophosphamide causes a reduction in the level of Th1 lymphocytes, that are harmful in MS, and an increase in Th2 lymphocytes that cause visible benefits from the drug [27,28]. Cyclophosphamide is used for the treatment of progressive forms of MS. Because it penetrates the blood-brain barrier there is a justification for its use in severe exacerbations that are resistant to steroid therapy. What's more, this drug has been used successfully in paediatric MS [29]. Side effects of treatment with cyclophosphamide include haemorrhagic cystitis, bladder cancer, nausea, vomiting, alopecia and infertility. Nevertheless, more than 80% of patients assessed that they could tolerate treatment with cyclophosphamide, and its side effects can be controlled [25].

4. 7. Azathioprine

Azathioprine is a purine analogue. It causes immunosuppression through competition with other nucleotides of DNA [25,30]. In addition to the treatment of MS, it is indicated for the prevention of transplant rejection, myasthenia gravis and the other autoimmune diseases. People treated with azathioprine are at risk of side effects, such as macrocytic anaemia, leukopenia and abnormal liver function. The efficacy of azathioprine in MS has been confirmed by past studies. Numerous comparisons showed even greater efficacy than INF-beta 1b in MS therapy [31, 32]. Nonetheless, after the approval of INF-beta 1b for the treatment of MS, azathioprine is no longer used in the treatment of RRMS, but it can be still used in the treatment of progressive forms of MS (Table 3) [33].

Table 3. Drugs used in primary and secondary progressive MS.

Primary progressive MS (PPMS)	Secondary progressive MS (SPMS)
Ocrelizumab	Siponimod (BAF312) ***
	Interferon-beta 1b (INF-beta 1b)
	Cladribine
	Mitoxantrone
	Cyclophosphamide
	Azathioprine

*** Preregistered for the use in SPMS in the USA and is waiting for the approval by EMA.

5. CONCLUSIONS

Management in progressive MS is one of the new challenges. Progress in the studies on MS pathogenesis and emphasizing the severity of the disease in form of its clinical activity and increasing disability determines a new direction of research. Over the years, many drugs modifying the course of the disease have been registered for the treatment of MS, however, most of them are addressed for use in RRMS. There is still a relative lack of effective treatment for the progressive forms of the disease that would stop the build-up of disability. A challenge is the PPMS, for which ocrelizumab is only registered.

This drug is undoubtedly a pioneer in the treatment of PPMS and it sets many therapeutic and scientific challenges for the future. Another drug, siponimod, has been preregistered for the use in SPMS in the USA and is waiting for the approval by EMA in late 2018.

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