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A review of treatment of relapsing-remitting type of multiple sclerosis (RRMS)

Arkadiusz Bydliński*, student

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

<https://orcid.org/0009-0001-4230-661X>, bydliniskiarkadiusz@gmail.com

Aleksandra Brożyna*, student

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

<https://orcid.org/0009-0000-9403-6212>, ola.brozyna@icloud.com

Natalia Małek, MD

Central Clinical Hospital in Warsaw, Banacha 1a, 02-097 Warsaw, Poland

<https://orcid.org/0009-0005-9602-2929>, n.malek2609@gmail.com

Sara Emerla, student

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

<https://orcid.org/0009-0007-2229-9145>, emerlasara@gmail.com

Anita Kwiatkowska, MD

Military Institute of Medicine - National Research Institute, Szaserów 128, 04-141 Warsaw, Poland

<https://orcid.org/0009-0009-7250-6194>, aw.kwiatkowska@gmail.com

Konrad Karłowicz, MD

Central Clinical Hospital in Warsaw, Banacha 1a, 02-097 Warsaw, Poland

<https://orcid.org/0009-0008-4610-6456>, konrad.karlowicz@uckwum.pl

Maria Hermanowska, student

Jan Kochanowski University, Collegium Medicum, al. IX Wieków Kielc 19A, 25-317 Kielce, Poland

<https://orcid.org/0009-0007-5673-6403>, marysia05@gmail.com

Julia Lubomirska, student

Jan Kochanowski University, Collegium Medicum, al. IX Wieków Kielc 19A, 25-317 Kielce, Poland

<https://orcid.org/0009-0008-8557-5108>, lubek1999@poczta.onet.pl

Patrycja Figurowska, MD

Independent Public Healthcare Center in Mińsk Mazowiecki, Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

<https://orcid.org/0009-0003-7269-6916>, patrycja.figurowska@gmail.com

Łukasz Ciulkiewicz, MD
Independent Public Healthcare Center in Mińsk Mazowiecki, Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

<https://orcid.org/0009-0005-4531-7532>, lukasz.ciulkiewicz@onet.eu

Patryk Pluta, MD

Stanisław Rybicki Regional Polyclinical Hospital in Skierniewice, Rybickiego 1,
96-100 Skierniewice, Poland

<https://orcid.org/0009-0005-3251-2267>, patrykpluta15@gmail.com

*These two authors are equal contributors to this work and designated as co-first authors.

Corresponding author: Arkadiusz Bydliński, student, bydlińskiarkadiusz@gmail.com

ABSTRACT

Introduction

Multiple sclerosis (SM) is the most common chronic inflammatory-demyelinating disease of the Central Nervous System. In its course, a multifocal damage is done to a nervous tissue - myelin sheaths surrounding axons become disintegrated. This process leads to a dysfunction of the electrical impulses passage along nerve fibers which occurs as various symptoms that hinder the functioning of the patients.

Aim of the study

This review aims to summarize treatment methods of relapsing-remitting type of multiple sclerosis (RRMS). Following information will be presented: groups of medications, mechanism of its action, its most important side effects and its effectiveness.

Material and method

This review presents the current state of knowledge about relapsing-remitting type of multiple sclerosis (RRMS) treatment - it is based on Pubmed database and was carried out using keywords concerning the issues of multiple sclerosis. Cited articles were selected in order to base on up-to-date investigation results.

Summary

A wide range of therapeutic options let neurologists treat their patients accurately, but the basic knowledge about each substance should be assimilated to choose the best individual therapy. Patients suffering from multiple sclerosis differ from each other and a personal approach is needed to implement appropriate treatment as soon as possible. Early start allows patients to not to lose their everyday functioning areas, as the neurodegenerative process is stopped at the initial stage. If some changes in brain tissue structure are permanently done, neurologists should know the options of symptomatic treatment to alleviate a patient's suffering.

Keywords

multiple sclerosis, SM, RRMS, multiple sclerosis treatment, SM treatment, RRMS treatment

INTRODUCTION

Multiple sclerosis (SM) is a neurological syndrome that affected 2.8 million patients in 2020 with its global prevalence of 35.9 per 100,000 people according to the Atlas of MS [1]. It can occur at any age, however the most exposed are patients between 20 and 40 years of

age [2]. Risk of being affected stands at 0.1% in the general population and having an affected first-degree relative increases the risk to 2-4% [3].

Although many risk factors were discovered throughout the years, there was not identified one particular causative agent. Presumably, multiple sclerosis occurs as a result of the series of interactions between genetic predispositions and environmental factors [4]. It has been proven that immunological dysfunctions are involved in the pathophysiology of this syndrome [5], including such immune cells as regulatory T cells (Tregs) [6], T helper cells [7] and B cells [8].

The diagnostic process is based on McDonald criteria (recently modified in 2017) and includes searching for lesions that fulfill requirements of dissemination in time (DIT) and dissemination in space (DIS) - proven by clinical presentation, magnetic resonance imaging (MRI) and the presence of oligoclonal bands in cerebrospinal fluid (CSF) [9].

Observing the course of multiple sclerosis, it can be assigned to one of four typical variants described by The International Advisory Committee on Clinical Trials of MS (also known as Lublin Classification) [10]:

- 1) Clinically isolated syndrome (CIS)
- 2) Relapsing-remitting multiple sclerosis (RRMS)
- 3) Primary progressive multiple sclerosis (PPMS)
- 4) Secondary progressive multiple sclerosis (SPMS)

85-90% of patients suffering from MS present the relapsing-remitting type (RRMS) [11].

AIMS OF TREATMENT

Actions undertaken in order to provide help to patients that are diagnosed with RRMS include:

- 1) treatment of acute relapses
- 2) disease-modifying treatment
- 3) reduction of associated symptoms

Symptomatic attacks worsen the general condition of patients and can be the cause of new signs of disease activity - implementing acute treatment allows patients to suppress immunological reaction and in consequence re-enter (mainly partially) to the state before the attack [12].

Chronic management includes disease-modifying therapy that has significantly developed in recent years. It ought to be introduced as early as possible, as high-efficacy

disease modifying therapies (HE-DMTs) can delay the progression of pathological process - the formation of new lesions in the central nervous system. Deceleration in demyelination causes patients' disease develop slower and the number of attacks are limited - in consequence they are able to remain their functioning status for a longer time [13]. Moreover, it prevents intense brain tissue atrophy, which is the cause of progressing patient's destabilization [13]. Therapeutic goals that are measurable include clinical state assessment (number of relapses and their intensity - annualized relapse rate - ARR) and observing disease activity in MRI defined by new/enlarging T2-hyperintense lesions and/or Gd-enhancing lesions [14].

When treating multiple sclerosis as a whole, eliminating the effects of formed lesions should not be ignored. Neurologists' attention has to embrace symptoms like: spasticity, muscle weakness, tremor, pain, bladder dysfunction, constipation, fatigue, paraesthesia, depression, cognitive impairment and sexual dysfunction. If primary treatment of multiple sclerosis is not able to eliminate earlier formed lesions, patients should be additionally treated to decrease dysfunctions hindering their daily functioning. In certain cases, symptomatic treatment is the only way to reduce patients' suffering. Choice of pharmacological and non-pharmacological symptomatic treatment depends on the personal needs of each patient individually [15].

TREATMENT OF ACUTE RELAPSES

Relapses of multiple sclerosis are defined as acute episodes of new neurologic dysfunctions or recurrence of the ones that resolved in the past. They have to be differentiated from pseudo-relapses that can be caused by fever, infection and chronic stress. The management should be focused on three pillars: 1) improvement of functioning of neurons affected by inflammatory demyelination - by expediting their recovery 2) reduction of current attack severity 3) decreasing or fully eliminating clinical symptoms caused by the attack [16].

Corticosteroids (CS) appeared to be an effective choice of therapy of acute MS exacerbations because of their immunosuppressive and immunomodulatory activity [17]. CS were proven to affect matrix metalloproteinases (MMPs) - proteolytic enzymes that take part in cell migration through an extracellular matrix. The fact that CS decrease the level of MMP-9 and increase the level of MMP inhibitors results in strengthening the blood-brain barrier and in consequence decreases the amount of immune cells entering brain tissue [18]. Another effect is related to CS surface receptors occurring on many cells, including immune cells.

The signal triggered by connection between CS and their receptors leads to lymphocytes death by apoptosis [19].

Short-term treatment using high-dose corticosteroids is a considered practice. The most common is parenterally administered methylprednisolone - 1g/day for 3-5 days [17]. Indicated method has been proved to decrease the intensity of exacerbation, improve patients' mobility and promote recovery phase [17]. As the therapy does not last a long time, adverse effects of CS are not frequent. If so, patients may mainly suffer from depression, anxiety, weakness, sleeping disorder, hypertension, gastritis and reflux. Usually neurologists add potassium supplementation and proton pump inhibitors during acute attack treatment to minimize the associated risk.

DISEASE-MODIFYING TREATMENT

Nowadays, the amount of disease-modifying therapies (DMTs) increases. Neurologists can offer patients suffering from MS a wide range of medications that are chosen on the basis of individual factors among which the most important are: age, comorbidities, plans for pregnancy, number and location of lesions, side effects and efficiency [20]. Therapeutics should be used one at a time, the combination therapy was not proven to be more effective [20]. If it is necessary to convert one therapy into another (as its individual efficiency is not satisfactory or adverse effects are intensified), neurologists should always be vigilant on the process of change. The therapy is obviously carried out as a step-up approach, but opposite situations occur too - in some cases a step-down approach is also implemented, especially when a patient's disease is stable for a long time and adverse effects of therapy begin to emerge.

Due to its mechanism of action, DMTs can be divided into 3 categories: [20]

- 1) Immunomodulatory agents
- 2) Continuous lymphocyte depleting agents
- 3) Time-limited immunosuppression followed by immune repopulation

Treatment aiming at various levels of RRMS is a result of numerous studies carried out over the past recent years and allows to choose individual therapy for each patient having regard to their needs.

Effectiveness of each therapy is presented as a reduction in annualized relapses rate (ARR) and reduction of disease activity in MRI (GdE lesions).

1) Immunomodulatory agents

Interferon β -1a, peginterferon β -1a, interferon β -1b - their action mechanisms are based on down-regulation of expression of MHC molecules on antigen-presenting cells, preventing immune cells passage through blood-brain barrier and also influencing on cytokines expressed as decreasing pro-inflammatory and increasing anti-inflammatory ones [21]. Clinical trial results in comparison to placebo: IFN β -1a administered subcutaneously revealed reduction in ARR: 32% and in GdE lesions: 67%; intramuscular administration resulted in reduction in ARR: 18% and in GdE lesions: 32% [22]; PEGylated IFN β -1a resulted in reduction in ARR: 27% and in GdE lesions: 86% [23]; IFN β -1b resulted in reduction in ARR: 34% and in GdE lesions: 83% [24]. Dose and route of administration: IFN β -1a (Rebif) 44 μ g 3x/week subcutaneously, IFN β -1a (Avonex) 30 μ g 1x/week intramuscularly, PEGylated IFN β -1a 125 μ g 1x/2weeks subcutaneously, IFN β -1b 250 μ g every other day subcutaneously [25]. Notable adverse effects include mainly flu-like symptoms and injection-site reactions. During IFN therapy neurologists should take care of monitoring such parameters as full blood examination (FBE) and liver function tests (LFTs) - at one, three and six months after first dose and then once a year [20]. Some patients may not respond to IFN treatment due to the presence of neutralizing antibodies (NAB) [20].

Glatiramer acetate is a synthetic polypeptide composed of 4 amino acids. Its mechanism of action might involve blocking myelin antigen presentation to T cells [20]. Clinical trial results in comparison to placebo - reduction in ARR: 29% and reduction in GdE lesions was not adequately assessed [26]. Glatiramer acetate is administered subcutaneously, 20 mg 1x/day or 40 mg 3x/week [25]. Adverse effects are not common and are connected with injection. It should be noticed that every patient develops antibodies to glatiramer but it is not associated with less therapeutic effectiveness [20].

Dimethyl fumarate (DMF) is a fumaric acid ester that activates erythroid-derived 2 nuclear factor (NRF2) and consequently has antioxidative activity. It also reduces neuronal excitotoxicity (a process that leads to neuron cells death) and modulates immune cells passage through the blood-brain barrier [27]. Clinical trial results in comparison to placebo - reduction in ARR: 44-53% and reduction in GdE lesions: 74-90% [28]. DMF is administered orally - the titration dose is 120 mg 2x/day x 7 days and the maintenance dose is 240 mg 2x/day [25]. The most common adverse effects are flushing and gastrointestinal symptoms - both of them tend to improve within one month of therapy. Standard monitoring during DMF

treatment should involve full blood examination (FBE) every 3-6 months, liver function tests (LFTs) every 6-12 months and urinalysis once a year [20].

Teriflunomide - an active metabolite of leflunomide - selectively and reversibly inhibits dihydroorotate dehydrogenase and therefore de novo pyrimidine synthesis is suppressed, which results in inhibition of proliferation of activated and autoreactive T and B lymphocytes [25]. Clinical trial results in comparison to placebo - reduction in ARR: 32% and reduction in GdE lesions: 80% [30]. Teriflunomide is administered orally, 14 mg 1x/day [25]. The most common adverse effects include nausea, diarrhea, hair thinning, hepatotoxicity and teratogenicity (applies to both men and women, an effective contraception is necessary) [25]. If needed, a washout therapy with cholestyramine is available - mainly used in case of pregnancy [29]. Standard monitoring during therapy involves full blood examination (FBE) and liver function tests (LFTs) once a month for six months and then every 4-8 weeks and regular measurement of blood pressure [20].

Sphingosine-1-phosphate receptor modulators - a group that includes fingolimod, siponimod, ozanimod and ponesimod. Their mechanism of action is related to a blockade of lymphocyte egression from a lymph node, which causes that the number of central memory and naive T and B lymphocytes is reduced so is their recirculation to the central nervous system [31]. Fingolimod has also an anti-inflammatory and neuroprotective influence due to its interaction with astrocytes and binding with S1P5 receptors on oligodendrocytes [32]. Siponimod and ozanimod are second-generation S1P receptor modulators that bind to S1P1 and S1P5 receptors [33,34]. Preclinical data also suggests that siponimod decreases axonal demyelination and increases axonal remyelination via oligodendrocytes [35]. Ponesimod is the newest one in the S1P receptor modulators group, it highly selectively binds to S1P1 receptor [36]. Clinical trial results in comparison to placebo - fingolimod revealed reduction in ARR: 54% and in GdE lesions: 82% [37]; siponimod revealed reduction in ARR: 55% and in GdE lesions: 82% [38]. Ozanimod revealed reduction in ARR: 48% and in GdE lesions: 63% in comparison to IFN β -1a [39]. Ponesimod revealed reduction in ARR: 31% in comparison to teriflunomide [40]. Every S1P receptor modulators are administered orally: fingolimod 0,5 mg 1x/d, siponimod 2 mg 1x/d after initial uptitration, ozanimod 0,92 mg 1x/d after initial uptitration and ponesimod 20 mg 1x/d after initial uptitration [25]. Adverse effects optionally caused by this therapy include lymphopenia, macular oedema, infections and first-dose bradycardia [25]. Standard monitoring should involve: lymphocyte count, liver function

tests (LFTs), blood pressure measurement and also every patient should have their visual acuity examined and skin cancer screening done every year [20].

Natalizumab is a humanized monoclonal antibody that inhibits $\alpha 4\beta 1$ integrin (an adhesion molecule that is expressed on the lymphocytes' surface) and thereby prevents autoreactive lymphocytes from crossing the blood-brain barrier [41]. Clinical trial results in comparison to placebo - reduction in ARR: 68% and in GdE lesions: 92% [42]. Natalizumab was the first therapy that was approved as an intravenous infusion form - the dose is 300 mg, the procedure of administration lasts over one hour and the patient gets its treatment every 4 weeks [20]. Adverse effects include headache, fatigue or gastrointestinal symptoms. An issue that limits the use of natalizumab is related to progressive multifocal leukoencephalopathy (PML) among patients who were exposed to JCV in the past. In general, the rate of John Cunningham virus (JCV) infection is not rare - more than half of the population is seropositive [43]. Every patient during natalizumab therapy should be checked for PML risk factors, which involves: the presence of JCV antibodies, more than two years of natalizumab therapy and prior use of any immunosuppressive therapy [44]. The risk of PML in patients who fulfill all the three criteria was estimated at 11.1 cases per 1000 patients [44]. A pivotal factor is positive JCV antibody serostatus - it was not proven that greater treatment duration would contribute to a greater PML risk among patients who are seronegative. The antibody titer has a great influence too - according to data, the lowest risk of PML is among patients whose JCV antibody index is $\leq 0,9$ and who are on natalizumab treatment for 1-24 months (0.1 PML cases per 1000 patients), when the highest risk is among patients whose index is $>1,5$ and who are on treatment >48 months (5.4 PML cases per 1000 patients) [45]. In view of the above, standard monitoring involves brain MRI every 6-12 months and JCV antibody testing every 6 months [29].

2) Continuous lymphocyte-depleting agents

Ocrelizumab is a humanized anti-CD20 monoclonal antibody. Antigen CD20 is expressed on the surface of B lymphocytes - its role is to enable proper B-cell immune response. The effects of ocrelizumab involve: selective depletion of CD20-expressing B lymphocytes what halts the preexisting humoral immunity and prevents their reconstitution, blockage of B cells passage from the periphery to the CNS, reduction of antigen presentation by B cells to T cells, reduction of B cells activation and differentiation to forms of plasmablast that secrete immunoglobulins and B cells secretion modulation what reduces the

level of proinflammatory cytokines [46, 47]. Clinical trial results in comparison to IFN β -1a - reduction in ARR: 46% and 47% and reduction in GdE lesions: 94% and 95%, additional analysis (that was not an endpoint described in study protocol) revealed also a reduction in loss of brain tissue volume [48]. The maintenance dose of ocrelizumab is 300 mg administered intravenously every 6 months after initial uptitration [25]. Combined safety analysis revealed that ocrelizumab is usually well-tolerated, the most appearing adverse effects include infusion-related reactions and neutropenia that can result in mild infections like urinary tract or upper-respiratory tract infections (though some serious infections like pneumonia or cellulitis were also noticed) [49]. Some serious complications were also noticed - there have been several cases of PML in patients on ocrelizumab treatment but most of them were previously on natalizumab treatment [50]. Hepatitis B reactivation can also occur. There was some suspicion of an increased risk of malignancy (<1%) among patients on natalizumab treatment (mainly breast cancer) but further trial-extension suggests that the risk is comparable with a population risk and the routine screening should be age-appropriate [51]. Standard monitoring should involve full blood examination (FBE) and comprehensive metabolic panel (CMP) periodically, HBV panel, immunoglobulin level initially and then periodically [25].

Ofatumumab is the first fully human monoclonal antibody directed against the CD20 molecule on B cells' surface. Its mechanism of action is comparable to ocrelizumab - ofatumumab depletes CD20-expressing B lymphocytes [52]. Clinical trials were conducted in comparison to teriflunomide and the results of the study were as follows - reduction in ARR: 51% and 58% and reduction in GdE lesions: 97% and 94% [53]. Ofatumumab is administered subcutaneously - initial dosing is 20 mg at weeks 0, 1 and 2 and the maintenance dosing is 20 mg 1x/month [25]. Its safety profile is similar to ocrelizumab - treatment can be associated with injected-related reactions and mild infections but there is also a risk of some serious infections or HBV reactivation [25]. As this therapy is quite new, its safety requires long-term monitoring in further studies. Standard monitoring should be focused on the same components as in the case of ocrelizumab [25].

3) Time-limited immunosuppression followed by immune repopulation

Alemtuzumab is a humanized anti-CD52 monoclonal antibody. The CD52 molecule is present on the surface of many B and T lymphocytes. Alemtuzumab causes depletion of CD52 positive cells in the mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC)

and complement-dependent cytotoxicity (CDC) [54]. After some time the repopulation process slowly starts - hematopoietic precursor cells are the base for new cells which begin to grow by following a distinct temporal pattern [54]. Clinical trial results in comparison to IFN β -1a - reduction in ARR: 55% and 49% and in GdE lesions: 63% and 61% [55]. Alemtuzumab therapy consists of two courses of intravenous infusions 12 months apart. During the first course a patient is given 12 mg daily for 5 days and in the second course the dose is also 12 mg but the procedure lasts 3 days [25]. If needed, a third course can be provided [25]. Due to the fact that adverse effects of alemtuzumab therapy can be major, patients undergo a strictly monitoring through the Risk Evaluation Mitigation Strategy program, which involves blood tests and urinalysis - its aim is to capture potential autoimmune disorders, as there occurred cases of thyroid dysfunction (30-40% of patients), immune thrombocytopenic purpura or anti-glomerular basement membrane disease [20]. The monitoring should also involve annual skin and gynecological cancers screening [25]. It is recommended to undergo Herpes virus prophylaxis - acyclovir 200-400 mg twice daily - from the start of every alemtuzumab course for 2 months (the level of CD4 lymphocytes should be >200 cells/ μ l) [56].

Cladribine is an analog of deoxyadenosine that mechanism of action is targeted to interfere with DNA synthesis and thereby to deplete immune cells (it preferentially leads to apoptosis of peripheral B and T lymphocytes) [57]. Clinical trial results in comparison to placebo - reduction in ARR: 58% and in GdE lesions: 86% [58]. Cladribine is administered orally in two courses - the cumulative dose is 3.5 mg/kg, so at one cycle the patient gets 1.75 mg/kg [25]. Adverse effects include lymphopenia, so there is a potential risk of infections or reactivation of VZV. During cladribine therapy, patients should have their full blood examination (FBE) with differential checked - before every course, 2 and 6 months after [25]. If the lymphocytes count is <200 cells/mm³, Herpes virus prophylaxis should be considered [20].

REDUCTION OF ASSOCIATED SYNDROMES

Multiple sclerosis is a disease with a wide range of symptoms - nowadays we know that it is mainly determined by the localisation of demyelinating lesions. As the neurodegenerative process may occur in different parts of CNS, symptoms may vary from mild fatigue to complete quadriplegic [10]. Actions undertaken by neurologists in order to alleviate symptoms and facilitate patients' everyday activities should not only be focused on

DMTs but also on symptomatic treatment, as not every lesion and its consequences can be cured completely.

Spasticity is presented as an increased muscle stiffness. It is one of the most vexing ailments - according to data, it may affect daily living activities of 44% patients with MS [59]. A very important part of preventing spasticity is avoiding the triggering and aggravating factors which include: infections, stress, constipation, excessive fatigue, fever and certain medicines (some antidepressants and DMTs like interferon) [60]. Non-pharmacological actions that are effective should comprise physiotherapy - it was proven that it decreases the spasticity and also improves the overall response to disease-modifying treatment [61]. Physical exercises are also useful when patients suffer from muscle weakness that is caused by their atrophy. Pharmacological therapies - baclofen, tizanidine, dantrolene and diazepam - are also recommended to be considered as studies have shown their effectiveness [59].

Tremor occurs in 25-60% of MS patients [62]. It can affect only one part of the body or have a severe form that can be highly disabling. So far, none of the studied therapies have been proven to be effective to a satisfactory degree. Some relief can be provided by high doses of isoniazid, propranolol, carbamazepine and glutethimide [62]. Some surgical procedures were reported to decrease tremor - studies were focused on stereotactic thalamotomy and thalamic stimulation - though the groups were small and the long-term functional outcome is not fully known [62].

Many patients with multiple sclerosis have to struggle with chronic pain that dramatically reduces their quality of life. The most common form is chronic neuropathic pain [63]. It leads patients to the next problem, as the treatment offered by modern medicine is not always effective and even if it is, it can face patients with potential adverse effects of another substances they have to take to exist. Using the proposed division, neurologists can offer MS patients three lines of pain-relieving therapy [63]. The first-line treatment includes gabapentin, tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors (SSRI/SNRI) and topical lidocaine. The second-line therapy involves opioid analgesics or tramadol (alone or combined with adjuvant substances from the first-line therapy). Third-line treatment is based on antiepileptic drugs (lamotrigine, carbamazepine, oxcarbazepine, valproic acid or topiramate), mexiletine and topical capsaicin [63]. The choice of appropriate drug should be in the hands of both doctor and patient to decide which of the following will be the best solution for current problems individually.

Fatigue is a common problem that patients suffering from multiple sclerosis have to face, but it is also a type of issue that entails other struggles. Muscle weakness and decreased endurance make patients feel fatigue faster, so they reduce their physical activity, which exacerbates the problem [64]. Studies showed that aerobic exercise (such as swimming, jogging, cycling), although in some cases very tough for patients, has a great impact on their fatigue level and general functioning. Regularly undertaken physical effort (adjusted for patients' ability) increases muscle strength, endurance and cardio-respiratory fitness, decreases the level of fatigue, improves patients' motor coordination and enables them to maintain their ability in performing daily tasks for a longer time [64].

Depression is a serious problem among patients suffering from neurological diseases, so do multiple sclerosis. Its intensity can be partially reduced by actions undertaken for other purposes (such as physical exercise, as mentioned before, that decreases fatigue) but additional treatment should be implemented if the mental condition of the patient requires it. As a first-line in pharmacological therapy, use of selective serotonin uptake inhibitors (SSRI) is recommended [65]. An extra caution should be exercised when using sedating or anticholinergic drugs, such as tricyclic antidepressants, as they can decrease patients' balance and increase cognitive impairment or bladder problems [65]. Patients' mental well-being can also be supported by attending psychotherapy. Providing patients with cognitive-behavioral therapy (CBT) is proved to be beneficial for them - it helps in correcting distorted perception of environment that the disease brought them, changing their core beliefs so that they are more motivated to participate in everyday life and improving their coping skills, which also impacts on cognitive dysfunctions and chronic fatigue [65].

Cognitive impairment is the issue that hinders daily functioning of many patients suffering from multiple sclerosis. Depending on the studies, the percentage of patients struggling with this problem is 34-65% [66]. The most affected cognitive domains are memory and information processing [67]. The first noticeable disorders depend on the affected area - some may be mild and patients may be able to compensate for it, while some may be very severe and may disturb patients' everyday functioning. Treatment of cognitive dysfunction is not easy, as it is a wide range of deficits. The most important step in the treatment process is an accurate assessment, patients should be examined by a neuropsychologist - specialist in this field. A variety of specially prepared tests can be carried out to capture the cognitive area that is affected by neurodegenerative process. As precise

information is collected, the patient may start a treatment process focused on their individual needs, utilizing therapeutic and behavioral techniques [66].

Sexual dysfunctions (SD) affect many patients with multiple sclerosis. Both men and women may have problems in their sexual sphere. The most common complaints about male SD relate to: erectile dysfunction (50-75%), ejaculatory/orgasmic dysfunction (50%), reduced libido (39%) and anorgasmia (37%), while female SD may involve: difficulty in achieving orgasm (37,1%), vaginal dryness (35,7%) and reduced libido (31,4%) [68]. Sexual dysfunctions should not be ignored, as they are an important part of quality of life (QoL) reported by patients. Pharmacological agents available in SD treatment involve: phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil), prostaglandin E1, dopamine agonist (apomorphine), adrenoceptor antagonists (phentolamine, yohimbine) or hormone therapy. Non-pharmacologically, patients can attend psychotherapy or use special items that facilitates their sexual relations [68].

Bladder dysfunction is an issue that is especially embarrassing for MS patients. An interdisciplinary assessment should be conducted by a neurologist and urologist. The problem can be divided into two categories: urinary incontinence and urinary hesitancy. Pharmacological treatment that may be effective include oxybutynin or solifenacin (in case of incontinence) and doxazosin or alfuzosin (in case of hesitancy) [69].

Neurogenic bowel dysfunction is one of the most common problems experienced by MS patients. It comprises two different conditions: constipation (caused by sensorimotor neuropathy that leads to fecal retention as the desire to defecate is decreased) and fecal incontinence (caused by anal sphincter weakness) [70]. Strategies used in order to help patients with constipation are both non-pharmacological and pharmacological. To prevent constipation, patients should firstly increase the amount of liquids and follow a high-fiber diet. Pharmacological agents that were proved to impact on bowel movements involve prucalopride, linaclotide, tegaserod and bisacodyl. Lactulose and bulk laxatives are also effective [70]. Fecal incontinence can also be treated pharmacologically - loperamide and codeine appeared to decrease the symptom of urgency and improved consistency of a stool [71].

CONCLUSIONS

Multiple sclerosis, a disease that years ago was perceived as a death sentence, still remains incurable, but modern medicine offers a wide range of medicines allowing patients to

keep living as usual. Disease-modifying therapies can be chosen individually for every patient according to their needs. Early implementation of treatment stops the progression of MS and thereby makes it possible to stay efficient physically and mentally for many years in most patients. Newer and newer therapeutics appearing on the neurological stage give hope for patients who do not respond to the previous treatment. Deepening the knowledge and understanding the process standing behind multiple sclerosis create new opportunities for next treatment methods.

Disclosures

Author's contribution:

Conceptualization: Arkadiusz Bydliński, Aleksandra Brożyna;

Methodology: Natalia Małek, Julia Lubomirska;

Formal analysis: Patryk Pluta, Sara Emerla, Anita Kwiatkowska;

Investigation: Maria Hermanowska, Patrycja Figurowska;

Writing-rough preparation: Łukasz Ciulkiewicz, Konrad Karłowicz;

Writing-review and editing: Arkadiusz Bydliński, Aleksandra Brożyna;

Supervision: Arkadiusz Bydliński, Aleksandra Brożyna;

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