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Review Article

Available Pharmacological Options and Symptomatic Treatments of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis is an autoimmune disease that targets the central nervous system and exposes the patients to a higher risk of various disabilities that impair their normal daily life activities. Different approaches take a part in the management of multiple sclerosis, in which pharmacological drug therapy is the corner stone and the central player in the treatment of multiple sclerosis. The pharmacological therapy can be categorized into; disease modifying therapies, symptomatic treatments, and relapse management. The discussed disease modifying therapies include; alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, teriflunomide and beta Interferon-1B, that have been found to share a characteristic feature of altering the immune system baseline functions in order to limit multiple sclerosis complications and deaccelerate its progression. The frequently occurring symptoms of multiple sclerosis are; depression, fatigue, general pain, spasticity, muscle spasm and other symptoms, that need to be carefully managed. Patients with multiple sclerosis face "on and off" episodes of aggravated symptoms known as a relapse that may last for days, weeks or even months. The National Institute for Health and Care Excellence guidelines have recommended the use of high corticosteroid doses as the gold-standard practice in managing a relapse episode. This review article will provide an overview of the different pharmacological therapies and their major role in the management of multiple sclerosis; via exploring the most recent published scientific evidence. In the end, a general discussion is added, focusing on the role of pharmacists and other medical experts in the clinical management of multiple sclerosis and patient support.

Key words: Multiple sclerosis, Multiple sclerosis pharmacological options, Multiple sclerosis symptomatic management, Disease modifying therapies.

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INTRODUCTION

Multiple Sclerosis (MS) is defined as an autoimmune neurological disorder that has massive debilitating impacts and serious complications on the patients' quality of life which exposes them to a wide range of disabilities.[1] Individuals with MS frequently suffer from a set of symptoms, such as limb numbness, partial/complete vision loss, general fatigue, tremor, dizziness, slurred speech, electric-shock feeling and tingling sensation in body parts.[1] MS is also suggested to precipitate a number of complications; for instance, muscles stiffness, muscle spasm, sexual dysfunction, disturbed bowel movement, uncontrolled urination, mood fluctuations, oblivion and elevated risk of developing depression and epilepsy, which may all coexist in the patient of MS resulting in a dreadful life.[2] MS major cause is yet to be verified; however, the disease mechanism involves the destruction of myelin sheaths that surround and protect the neuronal fibers in the central nervous system; thus, leading to disrupted neuronal signaling and potential neuronal death.[3] Nevertheless, a number of environmental and gene related risk factors are thought to contribute to the development of MS; for example, age, ethnicity, smoking, family history, climate, certain infections, and other autoimmune diseases.[4] Epidemiological studies show significant variations in the prevalence of MS worldwide. An MS epidemiological forecast in 2017 showed that Europeans and North Americans have a larger number of MS cases (>1.3 per 1000) compared to the Middle East and African countries (<0.1 per 1000).[5] In addition, the study pointed that the relapsing-remitting subtype of MS was spotted in the majority of the cases; 80% in South America and 63% in Europe.[5] MS course of treatment varies among patients according to different subtypes of MS. The commonly identified subtypes of MS are; clinically isolated syndrome, relapsing-remitting, benign, secondary progressive, and primary progressive MS.[6] These different subtypes are mainly divided based on the disease state; in other words, they differ in the disease severity, progression and number of relapse.[6] Therefore, proper diagnosis and detection of the specific subtype of MS is the key step in choosing the ideal medical intervention. The pharmacological options available for MS can be classified into three main groups; disease modifying therapies (DMTs), symptomatic treatments and MS relapse management. Each group includes a number of medical agents that would be discussed and clinically reviewed later in this article.

DISEASE MODIFYING THERAPIES

DMTs are mainly used for a long period of time in MS patients with a frequently occurring relapse episodes, as DMTs participate in reducing relapse severity, frequency and delaying their occurrence; thereby, slowing down the disease progression.[7] DMTs are found to be primarily efficacious in relapsing-remitting MS, and in a number of secondary progressive MS cases.[7] In contrast, no DMT has been observed to have any potential in the management of primary progressive MS yet.[8] However, DMTs mechanism of action is based on the pathophysiological hypothesis of inflammation and immune system attacks on the neurons and myelin sheaths.[9] Therefore, altering the immune system functions would potentially result in a lowered number of invasions on neurons; hence, reducing the disease progression.

Alemtuzumab

In 2014, alemtuzumab was approved by the Food and Drug Administration (FDA) as a DMT for the treatment of MS.[10] alemtuzumab is a monoclonal antibody that targets CD52 antigens found on the surface of the mature lymphocytes and marks them for destruction.[10] Since CD52 antigen exists only on mature lymphocytes, alemtuzumab will not have any effect on the lymphocytes stem cells.[11] Alemtuzumab unique mode of action makes it more selective than other DMTs in suppressing any potential immune response that may trigger a relapse. Latest studies have shown that alemtuzumab improves clinical outcomes in patients with relapsing-remitting MS over 4 years after discontinuing treatment with

other DMTs;[12] in addition, it is observed to reduce loss in the brain volume over 6 years of treatment course.[13] In 2017, a cohort study on the post-treatment adverse events of alemtuzumab concluded that alemtuzumab is safe and effective; nevertheless, the study faced a number of issues regarding the patients' compliance to the monitoring procedures.[14]

Dimethyl fumarate

In 2013, dimethyl fumarate was approved in the European countries as on oral medical agent for the treatment of MS.[15] Despite the fact that its mechanism of action is yet to be fully understood, it is thought to exert its activity via the activation of the Nrf2 pathway, which participates in suppressing inflammation and fighting oxidative stress.[16] Newer investigations have shown that dimethyl fumarate significantly lowers B cells expression of IL-6, TNF-α, and GM-CSF, which massively modulates the B cells inflammatory properties.[16] Thus, leading to the assumption that this might be a novel mechanism by which dimethyl fumarate regulates MS. The use of dimethyl fumarate is mainly a risk vs. benefit decision due to the unwanted severe side effects associated with its use, such as hepatotoxicity.[17]

Fingolimod

Fingolimod was first introduced as an anti-rejection agent in organ transplantation; however, it has failed to illustrate any efficacy in clinical trials.[18] Fingolimod mechanism of action in suppressing immune responses is generally via modulating sphingosine-1-phosphate receptor.[19] This modulation is found to sequester lymphocytes in the lymph nodes, preventing occurrence of an immune response.[19] Fingolimod is used in the management of relapsing MS and other inflammatory mediated medical conditions, such as chronic inflammatory demyelinating polyneuropathy.[20] A number of adverse events were attached to the use of fingolimod, such as lymphopenia, elevated liver enzymes, and mild cardiac events;[21] nevertheless, clinical studies suggest the use of an alternate dosing regimen might aid in reducing these events.[22]

Glatiramer acetate

Glatiramer acetate mechanism of action is not fully understood. Glatiramer acetate consists of four different amino acids; alanine, tyrosine, glutamic acid, and lysine, which are all found in the protein structure of neuronal myelin sheaths.[23] This tetra-amino acid oligomer seems to camouflage the myelin structure; thus, tricking the immune system to reduce its attacks on myelin.[23] MS patients receiving glatiramer acetate usually experience flu-like symptoms.[24] Lumps and other skin reactions at the site of injection are also common and observed frequently.[25] Recent investigations have shown that glatiramer acetate significantly reduces MS MRI-measured burden and activity.[26] Furthermore, glatiramer acetate use was not found to be associated with cortex gray matter [27] or spinal cord atrophy compared to other DMTs.[28]

Natalizumab

Natalizumab is a humanized monoclonal antibody that targets the α4-integrin cellular molecule.[29] Its mechanism of action is to block the α4β1-integrin receptor found on the surface of the immune system cells, which would result in preventing its migration into the central nervous system.[29] Thus, reducing the immune responses in the brain and lowering the risk of relapse. Natalizumab adverse events observed in post marketing surveillance include; liver toxicity, fatigue, allergic reactions, nausea, headache, high risk of infections and it is also suggested to increase the risk of melanoma.[30] Recent evidence has confirmed the sustained efficacy of natalizumab over the course of two years in MS treatment;[31] however, it has been linked to a significant loss in brain volume due to changes in the gray matter.[32] In a 2017 case report on a 21 years old pregnant female patient with relapsing MS, natalizumab was given to the patient as a rescue treatment after the deterioration of the case.[33] The recovery occurred after the treatment with natalizumab and the infant survived with no signs of treatment complications or teratogencity.[33] However, the study concluded that the use of natalizumab in pregnancy is a risk vs benefit decision and further clinical investigations need to be undertaken to evaluate the use of natalizumab in pregnant women.[33]

Teriflunomide

Teriflunomide is an immuno-regulatory agent that blocks the activity of the dihydroorotate dehydrogenase enzyme, which inhibits the de novo synthesis of pyrimidine.[34] Nevertheless, it is still not certain if this mechanism is involved in MS management. Teriflunomide is found to suppress highly dividing cells, such as activated T cells, which are thought to play a role in the pathogenesis of MS.[34] Teriflunomide is observed to have consistent safety and efficacy throughout the course of treatment in a study of 423 patients with relapsing MS over a period of 7 years.[35] Teriflunomide should be avoided in pregnant women and proper contraception should be maintained; however, in the case of unexpected pregnancy teriflunomide should be eliminated directly in order to avoid any potential harm to the fetus.[36] Rebound MS relapse after the discontinuation of teriflunomide is a major issue; therefore, corticosteroids use is well recommended to control the rebound (i.e. relapse) symptoms until the case is stabilized on other long-term DMTs treatments.[37]

Beta Interferon-1B

Beta Interferon-1B creates a balance between the pro-inflammatory and anti-inflammatory mediators in the central nervous system.[38] It is also responsible for reducing the number of inflammatory cells that cross the blood-brain barrier; moreover, it is observed to promote the activity of the nerve growth factor, which enhances the overall neuronal survival.[38] Skin reactions at the site of injection are commonly reported with beta Interferon-1B administration, the skin reactions can range from mild skin irritation and bruising to more severe events, such as cutaneous necrosis.[39] The issues associated with beta Interferon-1B injection are suggested to be responsible for inducing anxiety and stress in MS patients.[40] Depression and fatigue are other common symptoms facing MS patients; however, symptomatic management might increase patients' adherence to beta Interferon-1B treatment.[40] For decades, beta Interferon-1B treatment has proved to be effective in the management of relapsing MS, and it has been used in several clinical trials as a reference treatment to test the efficacy of newer MS DMTs.[41]

SYMPTOMATIC TREATMENTS OF MS

Patients with MS frequently suffer from a number of symptoms that might potentiate the disease progression, reduce treatment adherence, precipitate disabilities, and ultimately lower the patients' quality of life. Those symptoms could be either related to MS itself or the drug treatment. Symptomatic treatment is an essential part in the process of MS management, which may include; drug therapies, lifestyle modifications, and other medical interventions, according to the nature of symptoms. The most common symptoms and their suggested therapies are mentioned below:

Depression

Major depression frequently occurs in patients with MS compared to the general population. Approved and commonly prescribed drugs for depression treatment in MS are; fluoxetine, imipramine, and paroxetine.[42] Psychological therapy may also be an option in the management of depression.

Fatigue

Clinical investigations suggest the use of the medical agent amantadine that might benefit in the management of MS associated fatigue.[43] Non-pharmacological options may include; regular exercise and physiotherapy.

Generalized Neuropathic Pain

A wide list of medical agents could be beneficial in relieving MS pain. Amitriptyline, carbamazepine, gabapentin, clonazepam, lamotrigine, pregabalin, and phenytoin, are all used for pain management in MS patients.[44]

Spasticity and Muscle Spasm

Pharmacological management includes; baclofen, diazepam, clonazepam, carbamazepine, tizanidine, and gabapentin.[45] Other management options that may also participate include; physical exercise, hippotherapy, physiotherapy, and transcutaneous electrical nerve stimulation.

Other Symptoms

MS patients may experience other less frequent symptoms that need to be managed. The list below includes a summary of these symptoms and their current proposed management options:

- Swallowing difficulties: percutaneous endoscopic gastrostomy.
- Bladder issues (i.e. uncontrolled urination): desmopressin.[46]
- Sexual dysfunction: sildenafil, vardenafil.[47]
- Walking difficulties: fampridine,[48] exercise.
- Foot drop: functional electrical stimulation.
- Pseudobulbar affect: dextromethorphan and quinidine combination (Nuedexta®).[49]

MS Relapse Management

MS relapse can be defined as an episode of distressed and aggravated symptoms of the disease that limit patients' normal life activities.[50] Usually, a relapse episode is characterized by the worsening of the old MS symptoms accompanied with the appearance of other new symptoms.[50] For a patient to be identified with MS relapse requires the symptoms to last for at least 24 hours. Relapse episodes' duration vary between individuals, which can last for days, weeks or even months in some cases.[51] One of the serious complications of a relapse is optic neuritis; an inflammation that targets the optic nerve which transmits optical signals from the eye to the brain.[52] Other relapse symptoms may include; sensory complications, walking issues, weakness, fatigue, muscle stiffness, and altered thinking, which are quite similar to MS symptoms, since a relapse is an exacerbated state of MS. During an MS relapse episode, patients should receive high doses of corticosteroids. Corticosteroids are observed to reduce inflammation, limit the symptoms and increase recovery rate.[53] On the other hand, corticosteroids neither improve the outcomes of a relapse nor participate in preventing any possible disability that occur during a relapse.[54] Clinical investigations have recommended the use of methylprednisolone in the management of MS relapse.[55] According to the NICE guidelines, if the patient is not facing swallowing difficulties, 0.5 gram/day orally methylprednisolone for 5 days is recommended. In contrast, in hospitalized patients, 1 gram/day intravenously for 3 to 5 days is recommended. To be noted, patients should not receive a dose lower than 0.5 gram/day in the management of MS relapse.[55]

GENERAL DISCUSSION AND PHARMACISTS' ROLE IN MS MANAGEMENT

MS control requires proper cooperation and coordination between different medical experts; neurologists, general practitioners, nurses, and pharmacists, in order to provide suitable patient support and enhance treatment outcomes. Pharmacists have critical roles in the management of MS, as they do not only have a direct contact with patients but may also serve as final reviewers of the treatment plan. In general, pharmacists can significantly lower the risk of any avoidable medical errors and drug-drug interactions that could possibly occur; moreover, be responsible for patient education about the medical therapy, such as drug dosage, administration, potential side effects, contraindications, and other drug-specific instructions. In the case of MS, continuous patients' follow-up and monitoring are essential, especially with the use of newly approved medical agents, to sustain symptomatic control of the disease and lessen its progression. Professionally trained pharmacists usually referred to as specialty pharmacists, have extensive knowledge in MS and are well qualified to provide necessary patient support and education. In other words, clarifying, explaining and discussing different MS approaches; for example, MS definition, role of DMTs, symptoms management, organizing medical plans, means of communication with medical experts, and the addressing of any legal requirements, that are mentioned in the NICE guidelines as key points intended to elevate patients' awareness about MS.[56] Furthermore, pharmacists have a major role in collecting data about treatment progress, outcomes, and report on any major adverse events. Thus, enriching the databases of MS medications with phase IV post-marketing data, which in turn may aid in optimizing MS treatment strategies. Pharmacists may also interfere with the treatment plan in a number of patient-specific cases; for instance, an immediate stop of DMTs is a must during pregnancy or in women considering it; thus, the pharmacist can alarm the patient and notify the medical supervisors in order to take any necessary actions.[56] Patients receiving DMTs and require vaccination, which is recommended to be avoided especially live-attenuated ones, is another example in which a pharmacist may take an action to stop any potential harm that may occur to the patient. In addition to drug therapy, pharmacists may also aid and support the patient in modifying any negative lifestyle habits that could have a major impact on the disease state. For example, MS patients with a sedentary life routine are encouraged to exercise on regular basis, which is strongly suggested to have beneficial outcomes with no harmful effects. Moreover, smokers with MS are advised to consult their doctors or pharmacists on smoking cessation in order to reduce the detrimental effects of tobacco consumption. Pharmacists could also provide a number of humanitarian services in some special cases, such as helping the patients who may face complications with their health insurance that may be responsible for hindering the reception of treatment on the time needed, friendly frequent calls to check on the patients, aid in delivering the treatments to patients who live in remote areas or patients with disabilities, and many other examples that would overall improve treatment outcomes and patient adherence. Lastly, major roles of pharmacists can be summarized as the following:

- Patient education about MS and the drug therapy.
- Case monitoring.
- Data collection.
- Treatment optimization.
- Formation of an important communication ring between patients and medical supervisors.
- Providing patient support.

On the other hand, away from the pharmacological drug therapies of MS, the complementary and alternative medicine (i.e. CAM) research has accelerated in the past years, which may have a potential in the treatment of multiple sclerosis and several other autoimmune diseases. For

instance, *Cakile maritima* extract,[57] *Cammiphora molmol* oleo-resin,[58] and *Duboisia leichhardtii*[59] are found to suppress the activity of a number of bacteria that are suggested to trigger an immune response; thus, may have a potential in the management of MS. *Fumaria indica* is another interesting natural product, which is found to act centrally and exert an anxiolytic effect; in addition to, suppressing cytokines count in the brain.[60] Nevertheless, these natural extracts and resins are still in the experimental and preclinical stages. Ultimately, pharmacists and other medical experts are in need to keep their scientific information updated to the latest research findings; this review highlighted the latest advances in MS pharmacological treatments and discussed a number of clinical concerns and pharmacists' role in the management of MS.

CONCLUSION

MS is a debilitating disease that significantly lowers the patients' quality of life and leading to lifelong disabilities. It is also becoming a major trend and a challenge due to aging populations and wider exposure to risk factors. On the other hand, pharmacological agents that are well known for playing a critical role in any disease management protocol are gaining momentum with promising outcomes in MS management. The accumulating evidence stresses on the importance of combining DMTs with symptomatic management in order to provide sufficient control of MS. Non-pharmacological options, life style modifications, and patient support can also enhance the treatment outcomes. Pharmacists and other health care providers should cooperate together to optimize patient care plans and support.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVIATION USED

CD52: CAMPATH-1 antigen, DMTs: Disease Modifying Therapies, **GM-CSF:** Granulocyte macrophage colony-stimulating factor, **IL-6:** Interleukin-6, **MS:** Multiple Sclerosis, **NICE:** The National Institute for Health and Care Excellence, **Nrf2:** (Erythroid-derived 2)-like 2, **TNF-α:** Tumor Necrosis Factor-alpha.

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